Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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F. HOFFMANN-LA ROCHE LTD / GENENTECH, INC

CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER WO20698/TOC4129G

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PROTOCOL APPROVAL

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Name	Reason for Signing	Date and Time (Eastern USA - New York)
Rowell,Lucy	Project Statistician	14-Sep-2007 11:29:27
Ross, Graham	Clinical Science Leader	14-Sep-2007 11:44:53

This protocol is intended for use in a life-threatening indication: Yes ☑ No ☐

SYNOPSIS OF PROTOCOL TOC4129g/WO20698

TITLE	A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated Her2-Positive Metastatic Breast Cancer
SPONSOR	F. Hoffmann-LaRoche Ltd. and Genentech, Inc.
CLINICAL PHASE	III
INDICATION	Patients who have HER2-positive metastatic breast cancer (MBC) and have not received chemotherapy or biologic therapy for their metastatic disease
OBJECTIVES	**Primary Objectives** The primary objective of this study is to compare progression-free survival (PFS) based on tumor assessments by an independent review facility (IRF) between patients in the two treatment arms: placebo + trastuzumab + docetaxel vs. pertuzumab + trastuzumab + docetaxel. **Secondary Objectives** • To compare overall survival (OS) between the two treatment arms • To compare PFS between the two treatment arms based upon investigator assessment of progression • To compare the overall objective response rate between the two treatment arms • To compare the duration of objective response between the two treatment arms • To compare the safety profile between the two treatment arms • To compare time to symptom progression, as assessed by the FACT Trial Outcome Index - Physical Functional Breast (TOI-PFB) • To evaluate if biomarkers from tumor tissues or blood samples (e.g., HER3 expression, Fcγ, and serum ECD/HER2 and/or HER ligands concentrations) correlate with clinical outcomes
TRIAL DESIGN	Phase III, randomized, double-blind, placebo-controlled
NUMBER OF PATIENTS	The study will enroll 800 patients from approximately 250 sites worldwide.
TARGET POPULATION	The study population for this trial is patients with HER2-positive MBC who have not previously been treated with chemotherapy and/or biologic therapy for their MBC. Patients with Stage IV disease at initial disease presentation as well as those who have progressed following either neo-adjuvant or adjuvant therapy with a disease-free interval of at least 12 months will be included, and they may have received trastuzumab and/or taxanes in the adjuvant setting.

LENGTH OF STUDY	A total of approximately 800 patients (approximately 400 per arm) will be enrolled. It is estimated that the accrual will be approximately 40 patients per month after a 9-month ramp-up period over an approximate 26.5-month timeframe. An Interactive Voice Response System (IVRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.
INVESTIGATIONAL DRUG	**Blinded Pertuzumab/Placebo** Pertuzumab/placebo will be administered as an IV loading dose of 840 mg for Cycle 1, and 420 mg for subsequent cycles. Pertuzumab/placebo will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed. If the patient misses a dose of pertuzumab/placebo for 1 cycle (i.e., the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab/placebo (840 mg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.
COMPARATOR DRUGS	**Trastuzumab** Trastuzumab will be administered as an IV loading dose of 8 mg/kg for Cycle 1, and 6 mg/kg for subsequent cycles. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline. Trastuzumab will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed. If the patient misses a dose of trastuzumab for 1 cycle (i.e. the 2 sequential administration times are 6 weeks or more apart), a re -loading dose of trastuzumab (8 mg/kg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1 and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later. **Docetaxel** Docetaxel will be administered as an IV dose of 75 mg/m^2 every 3 weeks for at least 6 cycles until investigator-assessed radiographic or clinical progressive disease or unmanageable toxicity. At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for >5 days or ANC < 100/µL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

TREATMENT SCHEDULE	For the first cycle of treatment, blinded pertuzumab/placebo will be given on Day 1 over 60 minutes followed by a 60-minute observation period. Trastuzumab and docetaxel will be administered on Day 2 of Cycle 1 using the labeled guidelines for administration. If the administrations of all three agents are well tolerated in Cycle 1, they may be given sequentially on Day 1 in subsequent cycles thereafter. If a subject cannot tolerate all three drugs given on the same day, the Cycle 1 dosing schedule (pertuzumab/placebo on Day 1, trastuzumab and docetaxel on Day 2) will be followed. If one or both of the monoclonal antibody study drugs needs to be permanently discontinued or is held for more than two cycles, the subject will be taken off the study treatment. However, if docetaxel needs to be permanently discontinued for reasons related to toxicity, the subject can continue on monoclonal antibody study drugs.
INCLUSION CITERIA	Disease-Specific Inclusion Criteria: 1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy Locally recurrent disease must not be amenable to resection with curative intent. Note: Patients with de-novo Stage IV disease are eligible. 2. HER2-positive (FISH-positive or IHC 3 +) MBC confirmed by a Sponsor-designated central laboratory. It is strongly recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.) General Inclusion Criteria: 3. Age ≥ 18 years 4. Left Ventricular Ejection Fraction (LVEF) ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (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 7.4.2 of the protocol, page 96) 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 6. For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) and to continue its use for the duration of study treatment and for 6 months after the last dose of study treatment 7. Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure

EXCLUSION CRITERIA	**Cancer-Related Exclusion Criteria:** 1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC). This includes any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC. 2. History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting 3. History of systemic breast cancer treatment in the neo-adjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months 4. History of persistent Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy 5. Current peripheral neuropathy of NCI-CTCAE, Version 3.0, Grade ≥ 3 at randomization 6. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell carcinoma 7. Current clinical or radiographic evidence of central nervous system (CNS) metastases 8. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases. 9. 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 (e.g., liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin) • If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin. **Hematological, Biochemical, and Organ Function** 10. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina 11. History of CHF of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia) 12. History of myocardial infarction within 6 months of randomization 13. History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy 14. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy

EXCLUSION CRITERIA Cont'd	**General Exclusion Criteria** 15. Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization: • Absolute neutrophil count < 1,500 cells/mm^3 • Platelet count < 100,000 cells/mm^3 • Hemoglobin < 9 g/dL • Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome) • AST (SGOT) and ALT (SGPT) > 2.5 × ULN • AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN (unless bone metastases are present) • Serum creatinine > 2.0 mg/dL or 177 μmol/L • International normalized ratio (INR) and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless on therapeutic coagulation) 16. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures) 17. Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment 18. Pregnant or lactating women 19. History of receiving any investigational treatment within 28 days of randomization 20. Current known infection with HIV, HBV, or HCV 21. Receipt of IV antibiotics for infection within 14 days of randomization 22. Current chronic daily treatment with corticosteroids (dose of > 10 mg/ day methylprednisolone equivalent) (excluding inhaled steroids) 23. Known hypersensitivity to any of the study drugs 24. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol
ASSESSMENTS: • Efficacy	The primary endpoint is PFS based on IRF evaluations. PFS is defined as the time from randomization to the first documented radiographical progressive disease, as determined by the IRF using current RECIST (Therasse et al. 2000), or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions. Overall survival is the key secondary endpoint, and is defined as the time from the date of randomization to the date of death from any cause.

• Safety	Safety outcome measures are as follows: • Incidence of Congestive Heart Failure (CHF) and asymptomatic left ventricular ejection fraction (LVEF) events • LVEF measurements over the course of the study • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Laboratory test abnormalities
• Pharmacokinetics/ QT (Substudy)	A **subset** of principal investigators and patients will participate in a pharmacokinetic, drug–drug interaction, and QTc interval substudy as detailed in a separate protocol. Separate IRB/IEC approval and Informed Consent Form will be required for participation in the substudy.
• Quality of Life/ Pharmacoeconomics	**Patient-Reported Outcomes Assessments** This study will use the Functional Assessment of Cancer Therapy-Breast (FACT-B), Version 4. The FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer (see Appendix 6 of the protocol, page 130). Patients will rate all items on a five-point scale ranging from "not at all" to "very much." The FACT-B provides supplemental domain valuative ratings or utility weights, thus providing an estimate of the relative importance of each quality of life domain to an individual patient. The FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. The FACT-B has been used extensively and has demonstrated reliability, validity, and sensitivity to change over time. Only female patients on this study will be asked to complete the FACT-B questionnaire. **Pharmacoeconomic Assessments** An economic assessment comparing various costs between the two treatment arms will be conducted by evaluating hospitalizations while on study treatment. The number of hospital visits, number of days admitted, and type of visits (emergency room vs. inpatient care) will be collected. This information will be collected from information submitted on AE and SAE electronic case report forms (eCRFs).
OPERATIONAL PROCEDURES	This protocol will be co-sponsored by Genentech, Inc., and F. Hoffmann-La Roche, Inc. These Sponsors will oversee the management of this study and will be responsible for clinical operations including site management and source data verification. Genentech and Roche will identify potential sites for participation in this study. Study networks will be assessed by Genentech and Roche and, where necessary, a Corporate Compliance Group–approved risk mitigation plan will be implemented. The Sponsors will perform pre-trial evaluations at individual sites. The Sponsors will oversee selection, approval, and monitoring of all clinical study sites. Patient eligibility verification will be conducted on all patients identified for enrollment into the study. Overall monitoring will be managed by the study Sponsors. Statistical analyses and clinical study report preparation will be managed by the Roche staff. A **central IRB** will be utilized when possible to ensure timely submission and approval of site regulatory documents for sites not required to use a local IRB.

OPERATIONAL PROCEDURES Cont'd	An **Interactive Voice Response System (IVRS)** will be utilized for collection of patient screening information, randomization, and drug management. Unblinding will not be permitted during the study except for safety issues that arise during study treatment. An **Independent Review Facility (IRF)** will be used to determine tumor response. Images (CT/MRI) will be acquired according to a standard protocol and will be transmitted to the independent reviewers. In addition, relevant clinical information such as results from tumor-marker assessments will be forwarded, as needed, to the independent reviewers to aid with assessment of disease progression and response. Full details will be listed in the Independent Imaging Review Charter. **The central independent review of MRI and CT scans will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.** Investigators' tumor assessments will not be reconciled with IRF tumor assessments. An independent **Data Monitoring Committee** (**DMC)** will monitor safety, review results from the interim analyses, and make recommendations regarding continuation of the study. The DMC will meet periodically to review safety summaries prepared by an independent Data Coordinator Center (DCC). The safety summaries will provide adequate information to assess overall safety in addition to cardiac-specific concerns. Members of the DMC will be external to Genentech and Roche, and will follow a charter that outlines their roles and responsibilities. Enrollment will not be deferred while the DMC performs a review. An independent **Data Coordinating Center (DCC)** will perform all safety and efficacy analyses that will be reviewed by the DMC during the trial. An independent **Cardiac Review Committee (CRC)** will evaluate potential congestive heart failure events during the study for an independent central determination of CHF rates for reporting to the DCC and DMC. The CRC will follow a charter that outlines their roles, responsibilities, and processes.
SAMPLE COLLECTION	Archival tumor samples from the primary tumor (or metastatic sites, if the primary tumor is not available) will be submitted from all subjects during screening and submitted to a central pathology laboratory for assessment of HER2 status via IHC and FISH for study eligibility, as well as for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 25 unstained freshly cut slides of 4 µm will be submitted (the number of slides submitted may be reduced pending on the regulatory and or IEC requirements of some counties). The slides must be sent to the central lab within 2 days of being cut. From submitted tumor blocks, at the central laboratory a maximum of 15 slides will be cut and 2 cores will be removed in order to construct tissue microarrays (TMAs) for later analysis. The remaining part of the tumor block will be returned to the institution. HER2 testing will be prioritized and the tissue will subsequently be used for assessment of biomarkers.

SAMPLE COLLECTION Cont'd	For the assessment of tumor tissue biomarkers, a variety of analysis methodologies may be used, including but not limited to, qRT-PCR, IHC, in-situ hybridization, and gene expression profiling. At the end of the collection process, the most suitable analytical methodologies will be selected and employed. **Tissue Microarray (TMA) Construction** The tumor blocks will also be used to set up a TMA: a maximum of 2 tissue cores of 1.5 mm each will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissue cores from different patients. This process protects the tissue against oxidation and allows for long-term storage and later analysis. For later analysis, tissue sections can be generated using the latter tissue microarray. This technology will allow a high throughput (many patient samples on one glass slide) analysis of biomarkers. **DNA/RNA Extraction** The submitted tumor blocks will be used to generate sections on glass slides for the extraction of tumor DNA and RNA for later analysis. These slides will be prepared in a central lab to ensure the same quality for all samples and in later studies. Note that as tumorigenesis is a multiple-step process linked to somatic events, DNA analysis will focus on sporadic mutations specifically found in tumor tissue but not inherited changes found in the whole body. For this purpose, some sections containing tumor will be taken from the block and used for the extraction process. The tumor tissue samples will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed. **Metastatic Tumor Tissue Samples for Biomarker Analysis (Optional)** If a biopsy of the patient's metastatic tumor tissue is available, it will be submitted from consenting patients at baseline (after the patient has been determined to be eligible for the study, but before the first administration of study medication) for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Biopsy samples should be submitted and processed as described in Section 5.4.7.1 of the protocol, page 70 . **Serum Samples for ECD/HER2 and HER Ligands Analysis** For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment. Biomarker assessments with these samples will include levels of ECD/HER2, selected HER ligands, and/or markers thought to be important for HER family signaling or response to HER inhibitors and HER activation. At this time the significance of ECD/HER2 is not known, but because of its potential importance it will be measured as part of the panel of potential biomarkers of therapeutic effect. Leftovers of samples may be used for re-testing or developing and validating existing and/or new diagnostic tests related to pertuzumab or trastuzumab, or both.

SAMPLE COLLECTION Cont'd	**Whole Blood Sample for Fcγ Polymorphism Analysis (Clinical Genotyping)** A whole blood sample (3 mL) for assessment of Fcγ polymorphism will be collected from patients at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication). An analysis of Fcγ-receptor polymorphism will be correlated with clinical outcome in order to further evaluate the mechanism of action of both trastuzumab and pertuzumab. Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the individual countries. **Serum and Plasma for Biomarker Sample Repository (BSR) Research (Optional)** Blood samples for extraction of serum and plasma samples (approximately 5 mL per sample) for biomarker discovery, validation, and application will be collected from consenting patients. These samples are collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study every 9 weeks at the time of every tumor assessment until IRF-determined progressive disease. If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18. The collected BSR samples will be stored with the study Sponsor's facility or a contract laboratory facility for up to 15 years after the end of the associated study (database closure), at which time the samples will be destroyed. These samples will be used only for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and will help to better understand the pathogenesis, course, and outcome of breast cancer and related diseases and adverse events. The collected blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data related to HER2-positive breast cancer disease or response to pertuzumab and/or trastuzumab. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined.

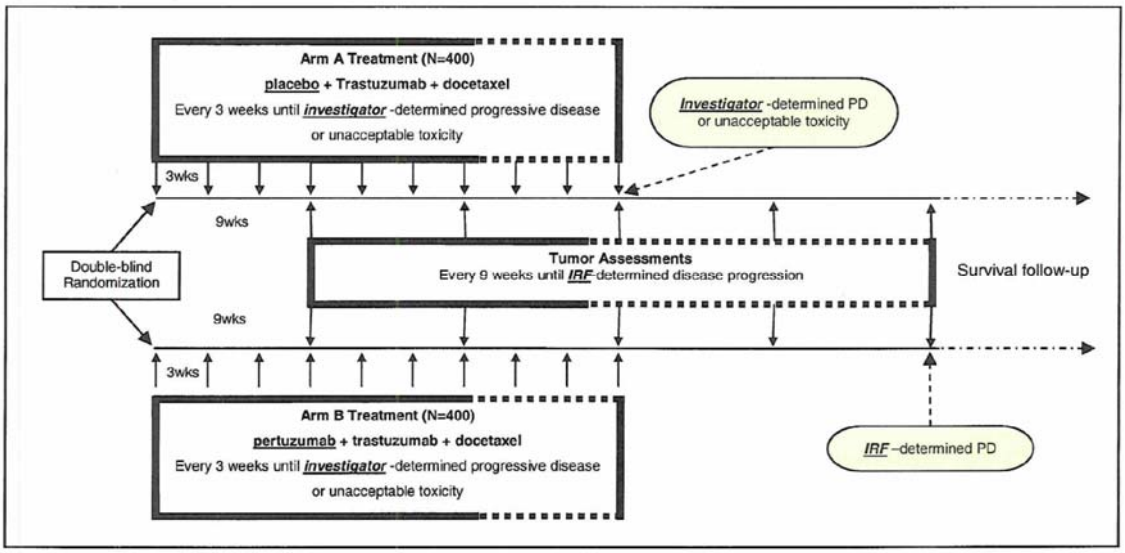
STUDY DURATION	Patients should remain in the treatment phase of the study until investigator-assessed radiographic or clinical progressive disease, unmanageable toxicity, or study termination by Genentech and Roche. Patients will not receive open-label pertuzumab after discontinuation from study treatment. After discontinuation of study treatment, tumor assessments will continue until IRF-assessed progression. In addition, patients will be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and Roche. Tumor assessments will be conducted every 9 weeks from the date of randomization. Delays in treatment administration will not impact the timing of the tumor assessments. If a tumor assessment must be performed early/late, subsequent assessments will be conducted according to the original schedule of every 9 weeks from the date of randomization. Tumor assessments must be conducted until IRF-determined progressive disease (PD), even if treatment has been discontinued due to an investigator-determined PD or unacceptable toxicity. After termination of study treatment, patients will continue be followed for survival until death, loss to follow-up, or study termination by Genentech and Roche.
SAFETY PROCEDURES	There have been reports of CHF with trastuzumab and pertuzumab treatment. Because of this, left ventricular systolic dysfunction is a potential safety concern for patients who receive the treatments outlined in this study. While on study treatment, patients will be monitored for cardiac events with regular assessments of left ventricular function with either Echocardiography or MUGA. (Echocardiography is the preferred method. The same assessment method, ECHO or MUGA, the same institution/facility, and the same assessor should be used throughout the study, to the extent possible.) For patients who experience Grade 1 or 2 left ventricular systolic dysfunction (i.e., asymptomatic decrease in LVEF), an algorithm is provided in Section 7.3.1.1 of the protocol, page 90 , outlining under which circumstances treatments have to be held and LVEF assessed prior to treatment continuation. Patients who experience CHF (NCI-CTCAE Grade ≥ 3) will have study treatment discontinued. CHF will be reported in an expedited manner to the Sponsors for timely monitoring. Clinical studies have demonstrated a higher incidence of myelosuppression when trastuzumab is administered with chemotherapy. Limited, non-comparative data from Phase I/II studies suggest that the combination of pertuzumab and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic AEs while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor support will be allowed in this protocol.

SAMPLE SIZE	A sample size of 800 patients is needed to provide 80% power to detect a 33% improvement in OS (HR=0.75) at the two-sided significance level of 5%. Since both PFS and OS analyses are event-driven, and to avoid prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial is designed to enroll sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of the final PFS analysis. Assuming that the median OS in the control arm is 36 months and OS is exponentially distributed, one interim analysis at 50% of total required deaths, and a Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary, approximately 385 deaths will be required. In addition, assuming that the accrual rate is approximately 40 patients per month after a 9-month ramp-up period, 800 patients will need to be enrolled and followed for an additional 29.5 months to obtain 385 deaths. The enrollment period is estimated to be 26.5 months, and 50% of the required deaths will be reached at around 33.5 months. Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it is estimated that 381 IRF-assessed PFS events, corresponding to approximately 448 investigator-assessed events, will have occurred when 50% of the required deaths (193 deaths) is reached. Table 6 in the protocol, page 107, lists the power for final PFS analysis at the two-sided significance level of 5% with 381 IRF-assessed PFS events. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.
STATISTICAL METHODS	**Efficacy Analyses** Analyses of PFS, OS, and time to symptom progression will be based on the intent-to-treat (ITT) population, defined as patients who have been randomized. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only responders will be included in the analysis. All efficacy analyses will be based on the treatment arm to which patients were randomized. **Analysis of Primary Variable** The primary endpoint is PFS based on IRF assessments. For patients who discontinue study treatment due to reasons other than death or IRF-assessed progression, every effort will be made to continue tumor assessments until IRF-determined progressive disease or patient death. 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 IRF-evaluable tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day). For patients whose IRF-determined progression event is not available, surrogating death at any time as a progressive event can artificially prolong the PFS time because of a much longer life expectancy in this patient population compared with PFS. Therefore, only deaths within 18 weeks of the last tumor assessments will be included as an event in the primary analysis. However, a sensitivity analysis will be performed including all deaths as an event.

STATISTICAL METHODS Cont'd	The log-rank test, stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia), will be used to compare PFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis. The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazard model, stratified by prior treatment status and region, will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% confidence interval (CI). **Secondary Variables** **Overall survival.** Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. 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. To minimize the chance of a biased OS estimate resulting from scheduled survival follow-up every 18 weeks, immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.) **PFS based on investigator assessments.** 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 investigator tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day). Analysis methods are the same as those described for the primary endpoint. **Objective response.** Only patients with measurable disease at baseline will be included in the analysis of the objective response. Patients without a post-baseline tumor assessment will be considered to be non-responders. Analysis of objective response will be based on IRF assessments. An estimate of the objective response rate and its 95% CI will be calculated for each treatment arm. The difference in objective response rate will also be provided with 95% CIs. The Mantel-Haenszel χ^2 test stratified by prior treatment status and region will be used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test result will also be provided as a sensitivity analysis. **Duration of objective response.** Only patients with an objective response will be included in the analysis of duration of objective response. The method for handling censoring is the same as that described for the primary endpoint. Analysis of duration of objective response will be based on IRF assessments. Duration of objective response will be estimated using the Kaplan-Meier approach. Comparisons between treatment arms using the unstratified log-rank test and estimation of hazard ratio using Cox regression will also be made.

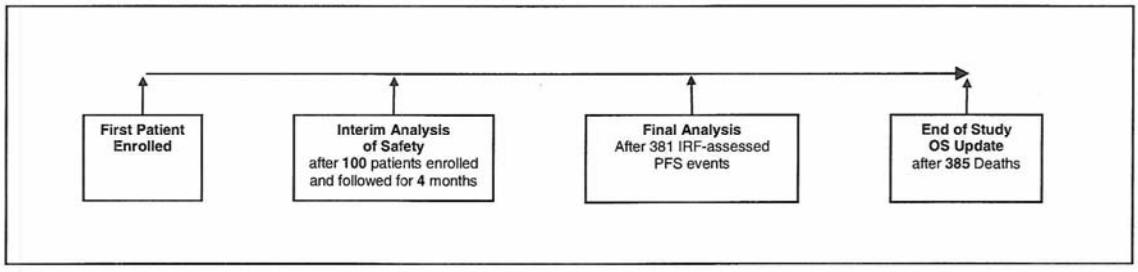
STATISTICAL METHODS Cont'd	**Time to symptom progression.** A decrease of five points in TOI-PFB is considered symptom progression. Data for patients who do not have an observed symptom progression will be censored at the last observed TOI-PFB assessment date. If baseline TOI-PFB assessment is unavailable, or if there is no post-baseline TOI-PFB assessment performed, data will be censored at the time of randomization plus 1 day. Analysis methods are the same as those described for the primary endpoint. **Biomarker analyses.** To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes will be summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers. Markers to be considered include the status of HER receptors, HER ligands, Fc-γ, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis will be put on markers that have shown association with clinical outcome in patients treated with pertuzumab in previous studies: qRT-PCR markers: tumor gene expression profiles associated with HER2 activation Baseline serum markers: levels of ECD/HER2 and HER ligands Efficacy outcomes considered for this analysis will include PFS, objective response rate, and OS. The PFS and objective response will be based on the IRF assessments. The biomarker analyses at the time of protocol development do not take the form of testing fixed hypotheses involving specific cutoffs or other pre-specified prediction rules. It is planned for the Statistical Analysis Plan (to be generated prior to unblinding of this trial) to use all available scientific evidence from independent studies or publications to specify testable prediction rules. In addition, this plan will specify in due detail how data-adaptive prediction rules will be derived (e.g., systematic cutoff search) and how the inherent multiplicity/bias will be corrected in order to prevent biased conclusions. The difference in treatment benefit across biomarker statuses defined by a suitable prediction rule will be evaluated by testing the interaction effect of treatment and the prediction status using Cox regression for PFS and OS, and using logistic regression for response rate. These models involving an interaction term will also be used to estimate the conditional efficacy outcomes, conditional on biomarker prediction status or treatment arm, including and excluding the stratification factors into the model. Clinical covariates can be of prognostic value and could interact with treatment benefit and with biomarker status. Candidates here are baseline variables of prognostic value describing tumour properties and morbidity status or common lab values. Biomarker prediction will be checked involving relevant clinical covariates, which could be part of the biomarker prediction function, if necessary. **Safety Analyses** The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, cardiac-specific AEs, LVEF measurements, and laboratory test results. Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually receive.

Figure 1 Study Design: Patient Treatment and Assessment



PD=progressive disease; IRF=Independent Review Facility.

Figure 2 Study Design: Analysis Timing



IRF=Independent Review Facility; PFS=progression-free survival.

Table 1 Schedule of Assessments

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit[b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Informed Consent	× [c]					
Complete Medical History, including Demographics	×					
Review of Inclusion and Exclusion Criteria	×					
Complete Physical Examination, and Vital Signs	×					
Symptom-directed Physical Exam, and Vital Signs			× [d]	×		
12-Lead Electrocardiogram (ECG)	×		If clinically indicated	× [e]	If clinically indicated	
Chest X-ray	×		If clinically indicated	× [e]	If clinically indicated	
ECOG Performance Status	×		×	×	Every 9 weeks at the time of each tumor assessment [f, g]	
FACT-B- Quality of Life (Females ONLY)		×	Every 9 weeks within 3 days <u>prior</u> to each tumor assessment [g]			
Tumor Assessments	×		Perform every 9 weeks from randomization until IRF-confirmed progressive disease [g]			
LVEF by ECHO or MUGA	× [h]		Perform every 9 weeks from randomization until 18 Weeks post-treatment [i]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit[b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Bone Scan	×		If clinically indicated	× [e]	If clinically indicated until IRF-confirmed progressive disease [g]	
Adverse Events	× [j]		Ongoing [k]		Ongoing [k]	
Concomitant Meds and Cancer-related Surgery/Procedures			Ongoing			
Pertuzumab/placebo Administration			× [l]			
Trastuzumab Administration			× [m]			
Docetaxel Administration			× [n]			
Samples						
Tumor for HER2 Eligibility & Biomarkers, to central lab	× [c]					
Hematology and Blood Chemistry, at local lab		× [o]	× [o]	×		
INR and aPTT, at local lab		×	× [p]			
Pregnancy Test, at local lab *(If applicable)*		× [q]	× (q3cycles) [q]	× [q]		
Serum for Trastuzumab PK, to central lab		× [r, s]				
Serum for Antibodies to Pertuzumab, to central lab		× [s]		×		
Serum for HER2 ECD & HER Ligands, to central lab		× [s]	Every 9 weeks at the time of each tumor assessment [g]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Whole Blood for Fcγ Polymorphism (clinical genotyping), to central lab		× [s,t]				
Samples requiring separate informed consent						
Metastatic Tumor for Biomarkers, to central lab		× [s]				
Serum & Plasma for Biomarker Sample Repository (BSR), to central lab		× [s]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post –treatment) [g, u]			
Record Post Study Treatment Cancer-related Medical or Surgical Procedures and Therapies				Ongoing [v]		
Survival Information					×	× [v]

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Symptom-directed physical examination including vital signs and weight will be assessed every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

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

[f] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[g] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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.

Table 1 Schedule of Assessments (Cont.)

[h] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization.

[i] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever occurs first.

[j] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[k] See Section 7.2 in protocol, page 86 , for adverse event reporting and follow-up requirements.

[l] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[m] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[n] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity).

[o] See Section 5.4.3 in protocol, page 66 , for specific required tests. 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.

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

[q] For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline. During the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[r] Collect and submit only for patients that have received prior trastuzumab.

[s] Collect and submit only if patient is determined to be eligible and will be randomized onto the study, but prior to the first study drug dose.

[t] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[u] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18**.

[v] Collect post–study treatment cancer-related medical or surgical procedures and therapies and survival information until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep).

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase
BSR	Biomarker Sample Repository
CHF	Congestive heart failure
CI	Confidence interval
C_{max}	Maximum plasma concentration
CR	Complete response
CT	Computed tomography
DFI	Disease-free interval
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EEG	Electroencephalogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organization for Research and Treatment of Cancer
ESF	Eligibility Screening Form

GLOSSARY OF ABBREVIATIONS

EU	European Union
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
GGT	Gamma-glutamyl transferase
HER2	Human Epidermal Growth Factor Receptor 2
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	Independent Review Facility
ITT	Intent to treat
IV	Intravenous
JVP	Jugular Venous Pressure
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MBC	Metastatic breast cancer
MDASI	M.D. Anderson Symptom Inventory
MRI	Magnetic resonance imaging
MUGA	Multigated angiogram
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

GLOSSARY OF ABBREVIATIONS

NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PS	Performance status
aPTT	Activated partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
TOI-PFB	Trial Outcome Index-Physician Function Breast
ULN	Upper limit of normal

1.1 Background

1.1.1 Breast Cancer

Breast cancer is the most common cancer in women, with a global prevalence of more than 1 million patients and a mortality rate of approximately 400,000 deaths per year (International Agency for Research on Cancer; http://www-dep.iarc.fr; Globocan 2002). While improved early detection and advances in systemic therapy for early stage disease have resulted in a small decline in breast cancer mortality since 1989, metastatic breast cancer (MBC) remains largely incurable with a median survival of approximately 24 months (www.seer.cancer.gov). Factors associated with poor survival include age $\geq$ 50 years, visceral disease, shorter disease-free interval (DFI), aneuploid tumors, tumors with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor receptor 2 (HER2) status (Chang 2003).

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

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

With the growing understanding of the biology of breast cancer, multiple new targets for anti-cancer therapies are being identified. Trastuzumab, which targets the HER2 receptor, is approved for use as monotherapy or in combination with chemotherapy in the metastatic setting, and in combination with chemotherapy as adjuvant treatment for HER2-positive breast cancer. The optimal management of MBC now takes into account not only a patient's general condition, medical history, tumor burden, and receptor status, but also the HER2 status.

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and non-overlapping toxicity, which can be combined with established treatments for breast cancer.

1.1.2 Human Epidermal Growth Factor Receptors (HER)

Evidence suggests that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. The HER tyrosine kinase receptor family is comprised of four receptors: HER1 (EGFR), HER2, HER3, and HER4. These receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers. Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signalling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase (MAPK) pathway for cellular proliferation.

HER2 and HER3 have unique characteristics compared with HER1 and HER4. HER2 has no known ligand and, in a state of overexpression, can form active homodimers and initiate tyrosine kinase signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors is also increased, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using micro-array technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate tyrosine kinase signaling through several mechanisms (Jones et al. 2006).

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

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

HER2 has emerged as an important prognostic and potential predictive factor in breast cancer. Approximately 25% of patients overexpress HER2 (also known as c-*erb*B2 or *neu*). In the laboratory, HER2 overexpression results in oncogenic transformation and more aggressive tumor behavior. Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER), absence of *bcl2*, and absence of lobular architecture. Despite associations with other known negative prognostic factors, HER2 overexpression has

been independently associated with poorer disease-free survival (DFS) and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000).

1.1.3 Trastuzumab (rhuMAb HER2, Herceptin®)

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

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

A randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first-line treatment for HER2-positive MBC (Marty et al. 2005). A total of 186 patients received at least one dose of protocol therapy. The addition of trastuzumab to 100 mg/m^2 docetaxel for at least six cycles resulted in superior clinical efficacy with improved overall response rates (61% vs. 34%; P = 0.0002), overall survival (median, 31.2 vs. 22.7 months; P = 0.0325), time to progressive disease (median, 11.7 vs. 6.1 months; P = 0.0001), time to treatment failure (median, 9.8 vs. 5.3 months; P = 0.0001), and duration of response (median, 11.7 vs. 5.7 months; P = 0.009). There was little difference in the number and severity of adverse events between the arms. Grade 3 to 4 neutropenia was seen more commonly with the combination (32%) than with docetaxel alone (22%), and there was a slightly higher incidence of febrile neutropenia in the combination arm (23% vs. 17%). More patients in the combination arm had left ventricular ejection fraction (LVEF) decreases ≥ 15% compared with the docetaxel alone arm (17% vs. 8%), and 1 patient (1%) in the combination arm experienced symptomatic heart failure. An additional patient who was assigned to the trastuzumab + docetaxel treatment arm experienced congestive heart failure (CHF) after discontinuation of study treatment and during treatment with an investigational anthracycline. The CHF event in this second patient was attributed by the investigator as related to the investigational anthracycline (Marty et al. 2005).

Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy for breast cancer (Cobleigh et al. 1998; Slamon et al. 2001). The most significant adverse event observed in patients who receive trastuzumab is cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic congestive heart failure (CHF). Risk factors for cardiac failure in

the setting of trastuzumab treatment include co-administration with anthracycline-based chemotherapy, increasing age, a declining LVEF during treatment to below the lower limit of normal (LLN), and the use of anti-hypertensive medications (Tan-Chiu et al. 2005).

1.1.4 Trastuzumab Pharmacokinetics

Analyses in clinical studies showed that trastuzumab has dose-dependent, non-linear pharmacokinetics, with faster clearance and shorter half-life at doses of < 100 mg. The volume of distribution approximates the serum volume. Early studies of the recommended dose indicated that the half-life was approximately 6–10 days. However, based on recent data from pharmacokinetic re-analysis, the half-life is approximately 28.5 days (95% confidence interval, 25.5–32.8 days). The washout period is up to 24 weeks (95% confidence interval, 18–24 weeks). Steady state pharmacokinetics should be reached by approximately 20 weeks (95% confidence interval, 18–24 weeks). The estimated mean AUC was 578 mg/day/L and the estimated peak and trough concentrations were 110 mg/L and 66 mg/L, respectively.

Overall, the pharmacokinetic (PK) profile probably reflects a composite of 1) interaction with tumor cell-bound HER2; 2) complexing with shed HER2 antigen extracellular domain (ECD); and 3) non-specific elimination similar to that observed with endogenous IgG. Serum concentrations are decreased in the presence of shed antigen and this is probably related to a faster clearance of the antibody-antigen complex than of free trastuzumab. Importantly, however, baseline shed antigen concentrations in the clinical studies did not show any correlation with clinical efficacy.

The approved dose of trastuzumab is a 4-mg/kg initial dose followed by a 2-mg/kg dose given every 7 days. This dosing regimen was based upon clinical efficacy in a randomized Phase III study (Slamon et al. 2001). Since the initial approval, the half-life of trastuzumab has been determined to be approximately 28.5 days, which supports a dosing of every 3 weeks vs. weekly. PK data are available from two studies evaluating the safety, tolerability, and pharmacokinetics of trastuzumab administered every 3 weeks to women with HER2-positive (IHC 3+ or FISH+) metastatic breast cancer (Baselga et al. 2005; Leyland-Jones et al. 2003).

All patients in these two studies received trastuzumab every 3 weeks by IV infusion. The initial infusion was given over 90 minutes at a dose of 8 mg/kg. All subsequent infusions were given over 90 minutes at a dose of 6 mg/kg. Data from Baselga et al. (2005) indicate that serum concentrations of trastuzumab increased, and steady state concentrations (in the range 50–60 ng/mL) were achieved after approximately eight to ten doses. Serum trough levels appeared to be comparable over the study period, although trough concentrations were slightly lower with the every-3-week regimen compared with previous studies of the weekly regimen.

In one study (Leyland-Jones et al. 2003), the cumulative dose during an every-3-week regimen arm interval was identical between the every-3-week regimen arm and the weekly regimen arm. As expected, data show that mean trough trastuzumab concentrations were approximately 20% lower at the end of each cycle than those

concentration levels at the same time point using weekly dosing. However, the average exposure at any time during the treatment is comparable between the two regimens.

1.1.5 Pertuzumab (rhuMAb 2C4)

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

Like trastuzumab, pertuzumab is produced in Chinese hamster ovary (CHO) cell cultures and purified by protein-A column affinity chromatography, followed by ion-exchange column chromatography. Because of the high degree of homology between pertuzumab and trastuzumab, procedures similar to those developed for trastuzumab are used for the manufacturing process, the in-process controls, and the characterization of pertuzumab. No bovine-derived raw materials are used in the manufacture of pertuzumab.

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

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

Both pertuzumab and trastuzumab target the HER2 receptor but bind at distinct epitopes on the receptor. Consequently, ligand-activated downstream signaling is blocked by pertuzumab but not by trastuzumab. Pertuzumab, therefore, may not require HER2 overexpression to exert its activity as an anti-tumor agent. In addition, there is a potential role for the combination of pertuzumab and trastuzumab in HER2-overexpressing diseases, due to their complementary modes of action.

1.1.5.1 Summary of Non-Clinical Studies

In Vitro Studies

In vitro studies show that pertuzumab blocks ligand-activated HER2 signaling, whereas trastuzumab does not. In the breast carcinoma cell line MCF-7, pertuzumab, but not trastuzumab, blocked heregulin-induced activation of the PI3-kinase cell survival pathway, as indicated by a lack of activation of a key enzyme (Akt) in this pathway (Agus et al. 2002). The ability of pertuzumab to inhibit ligand activation of HER2 has also been demonstrated in transfected cell lines of fibroblast origin and with purified soluble receptors (Sliwkowski et al. 1994; Fitzpatrick et al. 1998).

Furthermore, pertuzumab blocks heregulin-dependent *in vitro* growth of a number of breast cancer cell lines as well as cell lines derived from other solid tumors (Lewis et al. 1996; Schaefer et al. 1997; Mann et al. 2001). For example, in the heregulin-secreting MDA-MB-175VII breast carcinoma cell line, which expresses low to moderate levels of HER2 protein (1+ by immunohistochemistry), cell proliferation was inhibited in a dose-dependent fashion by both pertuzumab and trastuzumab, but the magnitude of the inhibition was far greater with pertuzumab (Schaefer et al. 1997). The calculated pertuzumab concentration at which half-maximal growth inhibition (IC_{50}) occurred was 120 ng/mL or 0.8 nM, and is consistent with biochemical measurements of pertuzumab inhibition of heregulin binding or receptor activation (Agus et al. 2002; Fitzpatrick et al. 1998; Lewis et al. 1996). The combination of trastuzumab and pertuzumab was shown to have a synergistic growth–inhibiting effect on BT474 breast tumor cells, which express high levels of HER2, underscoring the complementary mechanism of action of the two drugs (Nahta et al. 2004).

In Vivo Studies

The effects of pertuzumab on cell lines derived from a number of human solid tumors have been investigated in murine xenograft models. Pertuzumab was tested for its antitumor activity either as a single agent or in combination with various cytotoxic or biologic therapies.

Single-Agent Studies: Pertuzumab shows activity in xenograft models of lung adenocarcinoma, breast carcinomas, and both androgen-dependent and androgen-independent prostate (Agus et al. 2000; Fiebig 2003a; Fiebig 2003b; Fiebig 2003c). For example, growth inhibition ranging between 50% and 70% compared with control was observed with pertuzumab in six out of 18 non–small cell lung cancer (NSCLC) xenografts (Fiebig 2003b). Similar studies using six different human mammary tumor explants revealed one clear responder with more than 90% growth inhibition (Fiebig 2003a) while one out of four ovarian tumor explants was inhibited by more than 70% (Fiebig 2003c). A dose of 6 mg/kg pertuzumab administered once per week produced maximal growth inhibition of human tumor xenografts in mice, which could not be augmented by higher doses (Friess et al. 2002).

Combination Therapy Studies: Pertuzumab can augment the therapeutic effect of cytotoxic agents regardless of their mode of action, as shown in various human lung, breast, and ovarian tumor xenograft models in immunodeficient mice. This was shown with the tubulin inhibitor paclitaxel, the topoisomerase inhibitor irinotecan, the alkylating agent cisplatin, and the antimetabolite drugs gemcitabine and capecitabine, respectively (Friess 2002a; Friess 2002b; Friess 2003; Hasmann et al. 2003; Hasmann and Dettmar 2004; Metz 2004). The augmentation by pertuzumab of the chemotherapeutic effects of various agents with differing modes of action is possibly explained by the deprivation of PI3-kinase–mediated cellular survival signals after inhibition of HER2 activation.

Pertuzumab enhances the antitumor activity of other HER pathway inhibitors. For example, pertuzumab augmented the activity of the EGFR kinase inhibitor erlotinib (Tarceva®) in human lung cancer xenograft models (Friess et al. 2003; Friess 2003;

Friess et al. 2005). The combination of pertuzumab and trastuzumab synergistically inhibits the growth of xenografts derived from HER2-overexpressing NSCLC Calu-3 cells (Friess 2005) and from KPL-4 breast cancer cells (Friess et al. 2006). The synergistic action of pertuzumab and trastuzumab may be explained by their complementary modes of action: while pertuzumab prevents the ligand-activated formation of HER2 heterodimers and homodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Furthermore, as the two antibodies are not competing for the same binding epitope on HER2, their combination may lead to a higher antibody load, resulting in increased tumor-cell killing via antibody-dependent cell-mediated cytotoxicity (ADCC).

In conclusion, these results justify further clinical evaluation of pertuzumab in combination with chemotherapy drugs such as paclitaxel, gemcitabine, and capecitabine, and other HER pathway inhibitors with complementary mechanisms of action.

1.1.5.2 Summary of Clinical Studies

Pertuzumab has been studied in several Phase I or II clinical trials in solid tumors, including breast, prostate, ovarian, and lung cancer. Unlike trastuzumab, pertuzumab in all studies except one was administered as fixed doses of 840 mg IV as the initial dose followed by 420 mg IV every 3 weeks, or as fixed doses of 1050 mg IV every 3 weeks. This dose was established through population-based PK modeling and analysis in female patients (Ng et al. 2006). Pertuzumab was given until evidence of progressive disease or toxicity.

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

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

Modest clinical activity has been observed in patients with HER2-negative tumors who have received pertuzumab either as a single agent or in combination with cytotoxic chemotherapy. Partial responses (PRs) have been observed in < 5% of patients with ovarian cancer and HER2-negative breast cancer. No objective tumor responses were observed in patients with hormone-resistant prostate cancer or in patients with advanced non–small cell lung cancer. Stable disease (SD) of at least 6 months has been observed in approximately 5–7% of patients.

Pertuzumab has been evaluated in Phase II studies in combination with trastuzumab in patients with HER2-positive MBC who have previously received trastuzumab for metastatic disease. One study, conducted by the National Cancer Institute (NCI), enrolled 11 patients with previously treated HER2-positive MBC. Two out of the 11 patients exhibited a PR (Portera et al. 2007). In the second study, BO17929, 66 enrolled patients that had previously been treated with trastuzumab for HER2-positive MBC received the combination of pertuzumab and trastuzumab every 3 weeks until disease progression. Of the 66 patients enrolled, 42 were included in the most recent preliminary analysis of the data. One patient is reported to have a complete response (CR), 5 patients had PRs, and 17 patients had SD of at least two cycles in duration in this preliminary analysis (Baselga et al. 2007).

The overall safety data suggest that the combination of pertuzumab and trastuzumab is well tolerated. The preliminary Phase II study data suggest that the incidence of clinical cardiac toxicity is similar to that reported for trastuzumab-based treatments. One patient who received the combination in the NCI trial (n=11) experienced Grade III CHF (Portera et al. 2007). Asymptomatic decreases in LVEF have also been observed in 4 other patients; 3 patients' LVEF were back to normal within 3 months after discontinuation of pertuzumab and trastuzumab. It should be noted that 2 of these patients reported by Portera et al. had experienced LVEF decline during a previous trastuzumab treatment. The most common adverse events observed when pertuzumab is given with trastuzumab include diarrhea, nail changes, allergic reactions, anemia, and thrombocytopenia. The majority of adverse events reported in these trials are of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Grade 1–2 in severity. One patient had a Grade 3 allergic reaction. In study BO17929, of the 42 patients treated with pertuzumab and trastuzumab, 1 patient has experienced an LVEF decrease of greater than 10 percentage points from baseline to an absolute value less than 50%. This patient remained asymptomatic and discontinued treatment after Cycle 3 due to disease progression (Baselga et al. 2007).

Currently there are insufficient data available to determine cardiac toxicity risk-factors for the combination of pertuzumab and trastuzumab. Because current preliminary data suggest that the incidence of clinical cardiac toxicity in patients receiving combination pertuzumab/trastuzumab–based treatments is similar to that reported for trastuzumab-based treatments, this study will include regular cardiac LVEF monitoring of all patients, and will implement the treatment delay/stopping algorithm for LVEF decline as is the standard for patients receiving trastuzumab-based regimens (see Section 7.3.1.1.

1.1.6 Docetaxel

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

1.1.6.1 Docetaxel Pharmacokinetics

The pharmacokinetics of docetaxel has been evaluated in cancer patients in a variety of studies and in a population PK analysis. For details, please refer to the currently approved prescribing information.

1.1.6.2 Combination Studies with Anti-HER2 Monoclonal Antibodies

Both trastuzumab and pertuzumab have been administered with docetaxel in doses ranging between 60 mg/m^2 and 100 mg/m^2. Currently, no single chemotherapy regimen is considered to be the global standard of care for women with HER2-positive MBC that has progressed following trastuzumab administered in the adjuvant setting.

See Section 1.1.3 for a summary of a randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first-line treatment for HER2-positive MBC.

Patients with a range of tumor types received pertuzumab with docetaxel every 3 weeks until progressive disease or unacceptable toxicity (Study BO17021). No tumor responses were observed in this study of 19 patients. The maximum tolerated dose of docetaxel when given with pertuzumab was determined to be 75 mg/m^2. Dose-limiting toxicities (DLTs) were observed, including one case of Grade 4 febrile neutropenia and one case of Grade 3 fatigue.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare PFS based on tumor assessments by an independent review facility (IRF) between patients in the two treatment arms.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To compare overall survival (OS) between the two treatment arms
- To compare PFS between the two treatment arms based upon investigator assessment of progression
- To compare the overall objective response rate between the two treatment arms
- To compare the duration of objective response between the two treatment arms
- To compare the safety profile between the two treatment arms

- To compare time to symptom progression, as assessed by the FACT Trial Outcome Index - Physical Functional Breast (TOI-PFB)
- To evaluate if biomarkers from tumor tissues or blood samples (e.g., HER3 expression, Fcγ, and serum ECD/HER2 and/or HER ligands concentrations) correlate with clinical outcomes

3. STUDY DESIGN

3.1 Overview of Study Design

This study is a Phase III, randomized, double-blind, placebo-controlled, multicenter international clinical trial. 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 study. Patients could have received one prior hormonal treatment for MBC. Patients may have received systemic breast cancer treatment in the neo-adjuvant or adjuvant setting, provided that the patient has experienced a DFI of ≥ 12 months from completion of adjuvant systemic treatment (excluding hormonal therapy) to metastatic diagnosis. Patients may have received trastuzumab and/or a taxane during the neo-adjuvant or adjuvant treatment. HER2-positive status using archival paraffin-embedded tumor tissue will be confirmed in a central laboratory by IHC and/or FISH.

A total of 800 patients will be randomized in a 1:1 ratio to one of two treatment arms:

Arm A:

- **Pertuzumab placebo:** every 3 weeks until progressive disease or unacceptable toxicity
- **Trastuzumab:** 8 mg/kg IV loading dose, followed by 6 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity
- **Docetaxel:** 75 mg/m^2 IV every 3 weeks for at least 6 cycles until progressive disease or unacceptable toxicity (at the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3])

Arm B:

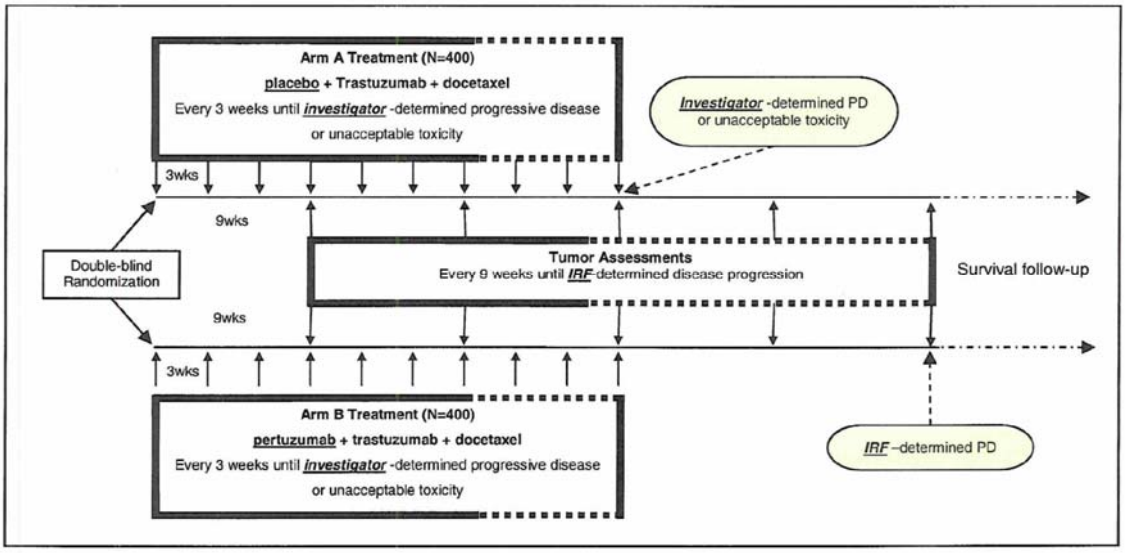
- **Pertuzumab:** 840 mg IV loading dose, followed by 420 mg IV every 3 weeks until progressive disease or unacceptable toxicity
- **Trastuzumab:** 8 mg/kg IV loading dose, followed by 6 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity
- **Docetaxel:** 75 mg/m^2 IV every 3 weeks for at least 6 cycles until progressive disease or unacceptable toxicity (at the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any

of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/µL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3])

Patients should remain in the treatment phase of the study until investigator-assessed radiographic or clinical progressive disease, unmanageable toxicity, or study termination by Genentech and Roche. Patients will not receive open-label pertuzumab after discontinuation from study treatment. After discontinuation of study treatment, tumor assessments will continue until IRF-assessed progression. In addition, patients will be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and Roche.

Tumor assessments will be conducted every 9 weeks from the date of randomization. Delays in treatment administration will not impact the timing of the tumor assessments. If a tumor assessment must be performed early/late, subsequent assessments will be conducted according to the original schedule of every 9 weeks from the date of randomization. Tumor assessments must be conducted until IRF-determined progressive disease (PD), even if treatment has been discontinued due to an investigator-determined PD or unacceptable toxicity (see Figure 1).

Figure 1 Study Design: Patient Treatment and Assessment



PD=progressive disease; IRF=Independent Review Facility.

A Data Monitoring Committee (DMC) will monitor patient safety. In addition to the DMC, an independent Cardiac Review Committee (CRC) will review cardiac data generated during the course of the study and report their findings to the DMC for review every 6 months beginning 9 months after the first patient is enrolled and at the safety interim analysis.

An Independent Review Facility (IRF) will evaluate progressive disease and overall tumor response through a periodic review of all radiographic (e.g., MRI, CT, bone scans,

chest x-ray, etc.), as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and photographic data, if available, generated from all patients.

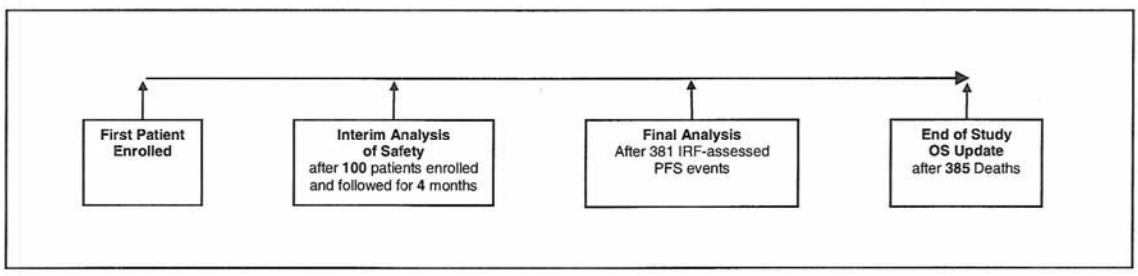
No interim analysis of efficacy is planned for this study. One safety-only interim analysis will occur after 100 patients have been enrolled and followed for at least 4 months. If the DMC does not recommend stopping the trial due to safety concerns at the interim analysis, the final primary efficacy analysis will take place when approximately 381 IRF-assessed PFS events (corresponding to approximately 448 investigator-assessed events) have occurred. The primary efficacy analysis will be based on tumor assessments by the IRF.

At the time of the final PFS analysis, it is expected that 193 patients will have died. An analysis of Overall Survival (OS) will be conducted at the same time as the primary efficacy analysis of PFS. Patients who are still on study will continue to be followed for safety and survival (see Figure 2).

3.1.1 End of Study

The trial will end when approximately 385 deaths have been reported or the trial is terminated by the Sponsors. An OS update will be provided at the end of the study (see Figure 2).

Figure 2 Study Design: Analysis Timing



IRF=Independent Review Facility; PFS=progression-free survival.

3.2 Number of Patients/Assignment to Treatment Groups

A total of approximately 800 patients (approximately 400 per arm) will be enrolled. It is estimated that the accrual will be approximately 40 patients per month after a 9-month ramp-up period over an approximate 26.5-month timeframe. An Interactive Voice Response System (IVRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.

A complete block randomization scheme will be applied to achieve balance in treatment assignment within each of the eight strata, as defined by prior treatment status (de novo vs. prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia). Unblinding of treatment assignment will not be permitted during the study except for safety issues that may arise during study treatment. An

approval from the Sponsor‘s medical monitor(s) must be obtained prior to any unblinding of treatment code.

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.

3.3 Centers

A total of approximately 800 patients will be enrolled from approximately 250 sites worldwide.

4. STUDY POPULATION

4.1 Overview

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

4.2 Inclusion Criteria

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

Disease-Specific Inclusion Criteria:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy

   Locally recurrent disease must not be amenable to resection with curative intent.
   Note: Patients with de-novo Stage IV disease are eligible.

2. HER2-positive (FISH-positive or IHC 3 +) MBC confirmed by a Sponsor-designated central laboratory. It is strongly recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.)

General Inclusion Criteria:

3. Age ≥ 18 years

4. Left Ventricular Ejection Fraction (LVEF) ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (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 7.4.2)

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1

6. For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) and to continue its use for the duration of study treatment and for 6 months after the last dose of study treatment
7. Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure

4.3 Exclusion Criteria

Cancer-Related Exclusion Criteria:

1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC).

   This includes any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC.
2. History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting
3. History of systemic breast cancer treatment in the neo-adjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months
4. History of persistent Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy
5. Current peripheral neuropathy of NCI-CTCAE, Version 3.0, Grade ≥ 3 at randomization
6. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell carcinoma
7. Current clinical or radiographic evidence of central nervous system (CNS) metastases
8. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.
9. 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 (e.g., liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin)

- If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

Hematological, Biochemical, and Organ Function

10. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina
11. History of CHF of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia)
12. History of myocardial infarction within 6 months of randomization
13. History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy
14. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy

General Exclusion Criteria

15. Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization:
    - Absolute neutrophil count < 1,500 cells/mm^3
    - Platelet count < 100,000 cells/mm^3
    - Hemoglobin < 9 g/dL
    - Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)
    - AST (SGOT) and ALT (SGPT) > 2.5 × ULN
    - AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN (unless bone metastases are present)
    - Serum creatinine > 2.0 mg/dL or 177 μmol/L
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless on therapeutic coagulation)
16. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures)
17. Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment
18. Pregnant or lactating women

19. History of receiving any investigational treatment within 28 days of randomization
20. Current known infection with HIV, HBV, or HCV
21. Receipt of IV antibiotics for infection within 14 days of randomization
22. Current chronic daily treatment with corticosteroids (dose of > 10 mg/ day methylprednisolone equivalent) (excluding inhaled steroids)
23. Known hypersensitivity to any of the study drugs
24. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

4.4 Concomitant Medication and Treatment

Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, etc., according to standard of care when necessary.

All protocol-allowed medications taken by the patient for concomitant disease should continue as necessary during the study and be recorded on the electronic case report form (eCRF). The following list of allowed medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard of care practice.

The following treatments/procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions associated with pertuzumab and/or trastuzumab
- Medication to treat diarrhea (e.g., loperamide)
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for docetaxel and ASCO clinical guidelines (Smith et al. 2006).
- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site
- Inhaled steroids for asthma
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion
- Palliative surgical procedures. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings.
- As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start.

The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.

- Anti-coagulation therapy for maintenance of patency of permanent indwelling IV catheters is permitted.
- Palliative radiotherapy. Radiotherapy is only allowed during the study treatment period for the indication of bone lesions present at baseline. If a patient requires radiation therapy to a new lesion, that new lesion would, per Response Evaluation Criteria in Solid Tumors (RECIST), qualify as progressive disease.

The following treatments are not permitted:

- Treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy
- Concurrent investigational agents of any type
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

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

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

4.5 Criteria for Premature Withdrawal

Patients may withdraw from the study at any time for any reason. Investigators may withdraw patients from the study and/or from study treatment in the event of intercurrent illness, adverse events, protocol violation, administrative reasons, or for other reasons. Patients who prematurely withdraw from study treatment will continue being followed for post-treatment assessments unless patients withdraw from the study. Excessive patient withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

If a patient decides to withdraw, all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

In case a patient decides to prematurely discontinue study treatment ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.6 Replacement Policy

4.6.1 For Patients

Patients randomized into the study will not be replaced.

4.6.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 1 Schedule of Assessments

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit[b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Informed Consent	× [c]					
Complete Medical History, including Demographics	×					
Review of Inclusion and Exclusion Criteria	×					
Complete Physical Examination, and Vital Signs	×					
Symptom-directed Physical Exam, and Vital Signs			× [d]	×		
12-Lead Electrocardiogram (ECG)	×		If clinically indicated	× [e]	If clinically indicated	
Chest X-ray	×		If clinically indicated	× [e]	If clinically indicated	
ECOG Performance Status	×		×	×	Every 9 weeks at the time of each tumor assessment [f, g]	
FACT-B- Quality of Life (Females ONLY)		×	Every 9 weeks within 3 days <u>prior</u> to each tumor assessment [g]			
Tumor Assessments	×		Perform every 9 weeks from randomization until IRF-confirmed progressive disease [g]			
LVEF by ECHO or MUGA	× [h]		Perform every 9 weeks from randomization until 18 Weeks post-treatment [i]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit[b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Bone Scan	×		If clinically indicated	× [e]	If clinically indicated until IRF-confirmed progressive disease [g]	
Adverse Events	× [j]		Ongoing [k]		Ongoing [k]	
Concomitant Meds and Cancer-related Surgery/Procedures			Ongoing			
Pertuzumab/placebo Administration			× [l]			
Trastuzumab Administration			× [m]			
Docetaxel Administration			× [n]			
Samples						
Tumor for HER2 Eligibility & Biomarkers, to central lab	× [c]					
Hematology and Blood Chemistry, at local lab		× [o]	× [o]	×		
INR and aPTT, at local lab		×	× [p]			
Pregnancy Test, at local lab *(If applicable)*		× [q]	× (q3cycles) [q]	× [q]		
Serum for Trastuzumab PK, to central lab		× [r, s]				
Serum for Antibodies to Pertuzumab, to central lab		× [s]		×		
Serum for HER2 ECD & HER Ligands, to central lab		× [s]	Every 9 weeks at the time of each tumor assessment [g]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Whole Blood for Fcγ Polymorphism (clinical genotyping), to central lab		× [s,t]				
Samples requiring separate informed consent						
Metastatic Tumor for Biomarkers, to central lab		× [s]				
Serum & Plasma for Biomarker Sample Repository (BSR), to central lab		× [s]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post –treatment) [g, u]			
Record Post Study Treatment Cancer-related Medical or Surgical Procedures and Therapies				Ongoing [v]		
Survival Information					×	× [v]

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Symptom-directed physical examination including vital signs and weight will be assessed every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

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

[f] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[g] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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.

Table 1 Schedule of Assessments (Cont.)

[h] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization.

[i] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever occurs first.

[j] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[k] See Section 7.2 for adverse event reporting and follow-up requirements.

[l] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[m] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[n] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity).

[o] See Section 5.4.3 below for specific required tests. 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.

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

[q] For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline. During the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[r] Collect and submit only for patients that have received prior trastuzumab.

[s] Collect and submit only if patient is determined to be eligible and will be randomized onto the study, but prior to the first study drug dose.

[t] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[u] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18**.

[v] Collect post–study treatment cancer-related medical or surgical procedures and therapies and survival information until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

5.1 Screening Examination and Eligibility Screening Form

All patients must provide written Informed Consent (IC) before any study-specific assessments or procedures are performed.

An Eligibility Screening Form (ESF) documenting the patient's fulfillment of the entry criteria is to be completed by the investigator/designee for all patients considered for the study and subsequently included or excluded. Patients who are considered for study entry but fail to meet the eligibility requirements should also have an ESF completed with the reason for lack of eligibility given, since this provides information on the selected trial population. This screening information will be collected via the IVRS and will not be entered into the clinical trial database. All ESFs should be kept in the study files at the sites. Additionally, copies of records of all prior trastuzumab dosing and ECHO/MUGA reports should be retained with the study files at the investigative sites, for randomized and screen-failure patients.

5.2 Procedures for Enrollment of Eligible Patients

Patients will be randomly assigned to one of the two treatment groups. The patient identification numbers are to be allocated sequentially in the order in which the patients are enrolled using the IVRS.

The investigator or designee will then be able to enter the patients' data into the eCRF, which will be used for electronic data capture (EDC). A Patient Enrollment and Identification Code List must be maintained by the investigator.

The treatment randomization list will be generated by the Sponsor and incorporated into IVRS. The password-protected and/or encrypted electronic drug kit number randomization list will be kept in a central repository by the Sponsor's unblinding statistician. An open key to the code will not be available at the study site, to the Sponsor's monitors, project statisticians, or the project team at either Genentech or Roche (see Unblinding, Section 6.8).

5.3 Procedures for Screening and Baseline

- Tumor tissue for HER2 status and biomarker analyses. After signing an informed consent and before randomization into the study, patients must have HER2 positive breast cancer defined as 3+ by IHC or FISH amplification ratio ≥ 2.0 as determined by a designated central laboratory. Results obtained from the central laboratory will be recorded in the eCRF (e.g., IHC 0, 1+, 2+ or 3+; FISH Positive or Negative). The actual FISH amplification ratio will be obtained by the Sponsor directly from the designated central laboratory. The diagnosis may be made on the primary breast cancer specimen, or on a biopsy of a metastatic site if primary tumor is not available. It is highly recommended that FFPE tumor blocks are sent to the central laboratory; however, if this is not possible, 25 unstained and freshly cut slides per tumor specimen will be submitted. Blocks will be returned to the originating institution; slides sent to the central laboratory will not be returned (see Section 5.4.7.1).

The following screening tests and procedures must be completed between Day -28 days and Day -1 (except where indicated). Day -1 is defined as the day before the initiation of study treatment (i.e., there is no Day 0). The timing of all procedures is summarized in Table 1. (Specific data points to be collected will be detailed in the eCRF.)

- Complete medical history and demographics including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or therapies
- Review of inclusion and exclusion criteria
- Complete physical exam, including vital signs (blood pressure, pulse rate, and body temperature) and physical measurements (body weight and height). In the physical examination, particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated Jugular Venous Pressure (JVP), sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).
- 12-Lead ECG
- Chest X-ray
- ECOG performance status (see Appendix 2)
- Functional Assessment of Cancer Therapy-Breast Symptom Index (FACT-B) questionnaire must be administered to female patients within 7 days prior to initiation of study treatment (see Section 5.5).
- Tumor assessment should be performed as specified in Section 5.4.4. To ensure comparability, the techniques used for tumor assessment at screening/baseline should be consistent with those used subsequently in the study, e.g., MRI, CT, bone scans, etc., as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available. A CT or MRI brain scan is to be performed at screening only in patients with signs or symptoms suggesting CNS involvement or other unexplained neurological symptoms, and during the study, if clinically indicated. **The central independent review will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessment. All patients must have their LVEF assessed by 2D echocardiography (ECHO) or multigated-angiography (MUGA) as part of the screening procedure. The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. ECHO is the preferred method because it can detect wall-motion abnormalities. LVEF is to be calculated using the modified Simpson method, and must be ≥ 50% at baseline as determined by the local facility before a patient can be enrolled in the study. The investigator must decide which method of LVEF assessment (ECHO or MUGA scan) will be used for each patient at baseline, and the same method and the same institution/facility should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with the LVEF result.

- Bone scan

- Adverse events. Only serious adverse events (SAEs) related to study-specific procedures are to be collected during the screening/baseline period.

- Hematology, blood chemistry, INR, and activated partial thromboplastin time (aPTT) should be performed at a local laboratory **within 7 days** prior to the first administration of study medication (see Section 5.4.3 for specific tests required). Because the toxicity of docetaxel is influenced by liver function (see Section 7.3.2.5), no protocol exceptions/waivers will be granted for out-of-range liver function tests, as described in the inclusion criteria.

- Pregnancy Test. A serum β-HCG test should be performed for all women of childbearing potential and for all women < 2 years after the onset of menopause. Testing should be performed at a local laboratory **within 7 days** prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.4.3).

- Serum sample for trastuzumab pharmacokinetics should be collected **within 7 days** prior to the first administration of study medication, *only if the patient has received prior trastuzumab therapy* and is eligible for and will be enrolled into the study. The samples will be submitted to the central laboratory.

- Serum sample for testing for antibodies to pertuzumab should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study.

- Serum sample for HER2 family ECD and HER ligands should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.3).

- Whole blood sample for Fcγ polymorphism should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.4). Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the involved countries.

- Samples requiring supplemental informed consent
  If the patient has signed the appropriate supplemental informed consent(s), the following samples are required to be collected and submitted. Patients will be permitted to separately consent for each item individually. All samples will be collected **within 7 days** prior to the first administration of study medication. All samples should be collected only after the patient has been determined to be eligible for, and will enroll into the study, but prior to the first study drug dose:

  – Metastatic tumor tissue for biomarkers for pertuzumab/trastuzumab response (see Section 5.4.7.2)

  – Serum and plasma samples for Biomarker Sample Repository (BSR) research (see Section 5.4.7.5)

5.4 On-Study Clinical Assessments and Procedures

The following assessments and procedures will be completed for randomized patients according to the Schedule of Assessments (see Table 1). (Specific data points to be collected will be detailed in the e CRF.)

5.4.1 Treatment Period Assessments and Procedures

During the treatment period, a window of ± 3 days will apply to all visits and assessments, unless otherwise specified.

- Symptom-directed physical examination including vital signs and weight every cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG as clinically indicated

- Chest X-ray as clinically indicated

- ECOG performance status before administration of each study treatment (see Appendix 2)

- FACT-B questionnaire must be completed by female patients within 3 days prior to each tumor assessment.

- Tumor assessments (CT scans, MRI scans, etc.) will be performed as specified in Section 5.4.4 every 9 weeks after the date of randomization and will continue until IRF-confirmed progressive disease. 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. To ensure comparability, the techniques used for tumor assessment at Screening/Baseline should be consistent with those used subsequently in the study. Brain CT/MRI scans should be performed on patients with symptoms/signs suggestive of CNS involvement or other

unexplained neurological symptoms. **The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessment must be performed every 9 weeks after the date of randomization. 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. More frequent LVEF monitoring may be performed as needed for cardiac safety (see Section 7.3.1.1). The same method of LVEF assessment (ECHO or MUGA scan) and the same institution/facility used at baseline should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with each LVEF result.
- Bone scan as clinically indicated
- Adverse Events (AEs) including SAEs should be documented according to NCI-CTCAE, Version 3.
- Concomitant medications and cancer-related surgery or procedures should be documented at each visit; including prescription, over-the-counter, and herbal/homeopathic remedies and/or therapies, as well as any cancer-related diagnostic, therapeutic, or surgical procedures performed.
- Hematology and blood chemistry will be collected and submitted to a local laboratory within 3 days prior to administration of each study treatment, or when clinically indicated (see Section 5.4.3).
- INR and aPTT will be collected and submitted to a local laboratory for all patients receiving therapeutic doses of anti-coagulants before the start of every chemotherapy cycle, and when clinically indicated.
- Pregnancy test. A urine pregnancy test should be administered within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated). Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3). Pregnancy test results must be available prior to the drug infusion.
- Serum sample for HER2 family extracellular domain and HER ligands will be collected every 9 weeks at the time of each tumor assessment.
- Samples requiring supplemental informed consent
  - Serum and plasma samples for BSR Research will be collected every 9 weeks at the time of each tumor assessment.
- Pertuzumab/placebo administration every 3 weeks. The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered within 3 days of randomization. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity (see Section 6 for details).

- Trastuzumab administration every 3 weeks. The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity (see Section 6).

- Docetaxel administration every 3 weeks. The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity) (see Section 6).

5.4.2 Post–Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit)

During the post-treatment follow-up period, a window of ±3 days will apply to all visits and assessments, except for follow-up survival information collection which will have a window of ± 7 days. The treatment discontinuation visit should occur 4–6 weeks (28-42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last). (Specific data points to be collected will be detailed in the eCRF.)

- Symptom-directed physical examination and vital signs (pulse rate, blood pressure, body temperature, and weight) will be performed at the treatment discontinuation visit. Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and as clinically indicated through Week 18 post-treatment.

- Chest X-Ray will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and as clinically indicated through Week 18 post-treatment.

- ECOG performance status will be performed at the treatment discontinuation visit, and at the time of each tumor assessment, until IRF-determined progressive disease.

- FACT-B questionnaire must be completed by female patients within 3 days prior to each tumor assessment.

- Tumor assessments. For patients who discontinue study treatment for reasons other than death or IRF-determined progression events, efforts should be made to continue to collect scheduled tumor assessments every 9 weeks (63 Days) ± 3 days until patient death or IRF-determined progressive disease. 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. **The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessments. For all patients, LVEF assessments should be conducted at Week 9 and Week 18 post-treatment. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first. The LLN for the LVEF facility will be reported along with the LVEF results.

- Bone scan will be performed at the Treatment Discontinuation Visit (if not performed within the previous 28 days), and if clinically indicated until IRF-confirmed progressive disease.

- Adverse Events. All AEs and SAEs should be collected through the treatment discontinuation visit. Cardiac adverse events occurring up to 12 months after last administration of study medications must be reported irrespective of causal relationship or treatment assignment. See Section 7.2.4 for full details of post-treatment discontinuation visit AE reporting requirements.

- Hematology and blood chemistry will be collected and submitted to a local laboratory at the treatment discontinuation visit (see Section 5.4.3).

- Pregnancy test. A urine pregnancy test should be administered at the treatment discontinuation visit. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3) .

- Concomitant medications and cancer-related surgery or procedures should be collected through the time of the treatment discontinuation visit.

- Serum sample for testing for antibodies to pertuzumab should be collected at the treatment discontinuation visit.

- Serum sample for HER2 family extracellular domain and HER ligands will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease.

- Samples requiring supplemental informed consent
  - Serum and plasma samples for biomarker repository sample research will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18**.
- Post–study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be recorded including the dates and description of the procedure(s) or therapies, and any clinical findings.
- Survival information will be collected via telephone or clinic visits every 18 weeks ± 1 Week (7 Days) post-treatment until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Requests to withdraw consent must be documented in the source documents and signed by the investigator. Immediately prior to the data cutoffs for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

5.4.3 Local Laboratory Assessments

All local laboratory sample collection and testing will be scheduled as indicated in Table 1. Additional assessments may be performed as clinically indicated. Normal ranges for the local laboratory parameters must be supplied to the study Sponsors before the study starts.

The following tests will be performed at a local laboratory:

Hematology. Hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells). Additional tests may be performed per the institution's standard practice. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the treatment discontinuation visit, and when clinically indicated.

Blood chemistry. Na^+, K^+, bicarbonate, Cl^-, BUN/Urea, Ca^{++}, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, LDH, total bilirubin, creatinine, non-fasting blood glucose. Additional tests may be performed per institution's standard practice. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the treatment discontinuation visit, and when clinically indicated. For patients involved in the separate PK/DDI/QTc substudy, alpha-1-acid glycoprotein test will also be required, as detailed in that substudy protocol.

Coagulation. All patients will have INR and aPTT testing at baseline. Patients on therapeutic doses of anti-coagulants should have INR and aPTT measurements repeated during the study, at least before the start of every chemotherapy cycle, and when clinically indicated.

Pregnancy test. For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline. During the treatment period within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated) and at the treatment discontinuation visit, a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Treatment period pregnancy test results must be available prior to the drug infusion.

The relevant laboratory assessments should be available prior to each administration of study treatment for dose modification or delay requirements as specified in Section 7.3. These assessments must be performed within 3 days prior to the administration of study treatment at each cycle.

NOTE: Hematology, blood chemistry, coagulation and serum β-HCG tests are only valid as part of baseline eligibility screening if they have been performed within 7 days of randomization.

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. Any abnormalities that are discovered during patient assessment should be further investigated where clinically indicated, in order to ensure that patients are fit to be included in the study and to receive study medication.

5.4.4 Tumor Assessments

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

The minimum screening examinations should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals)
- CT or MRI scan of the brain and/or spine where there is clinical suspicion of CNS metastases
- An isotope bone scan (with bone X-ray[s] as necessary) at baseline. It should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions.
- Medical photography to monitor chest wall recurrences (i.e., subcutaneous skin lesions)

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.

The same assessment technique must be used throughout the study for evaluating a particular lesion (e.g., if a CT scan is used to assess metastatic lung lesions at baseline then a CT scan must be used at all subsequent tumor assessments to assess metastatic lung lesions). The same investigator should assess all tumor responses for each patient.

For patients with multiple measurable lesions, a maximum of five lesions per organ and 10 lesions in total that are representative of all involved organs should be designated as target lesions and recorded and measured at screening.

All other lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the treatment period and follow-up, if applicable, until confirmed evidence of progressive disease. Tumor lesions that are situated within a field of previous irradiation can be considered measurable if these lesions have shown clinical evidence of progression and can be reproducibly measured over time. Patients who have metastatic disease that is confined to the bone are not eligible for response evaluation but will be included in the PFS analysis if the criteria for progressive disease is satisfied (i.e., new bone lesions after treatment initiation).

Complete and partial responses should be confirmed between 4 and 6 weeks (28 and 42 Days) after response is observed. This confirmation should not cause the next planned regular tumor assessment to be delayed. The complete and partial responses can be also confirmed at the next scheduled tumor assessment if it occurs between 4 and 6 weeks (28 and 42 Days) after the initial response.

In case of SD, follow-up assessments must have met the RECIST SD criteria at least once after study entry at a minimum interval of 6 weeks.

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

Tumor assessments will be performed every 9 weeks after the date of randomization. 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. For patients who discontinue study treatment for reasons *other than* death or IRF-determined progression events, efforts should be made to continue to perform scheduled tumor assessments every 9 weeks (63 Days) until patient death or IRF-determined progressive disease.

After the cutoff date for the final PFS analysis, tumor assessments will no longer be collected.

5.4.4.1 Independent Review of MRI/CT Scans

The central independent review of tumor assessment scans, etc., will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.

The IRF will assess response, non-response, or progression (CR, PR, SD, or PD, according to current RECIST [Therasse et al. 2000]) during the study.

Images must be acquired according to an imaging protocol described in the Imaging Guidelines provided by the IRF and must be transmitted to the IRF. In addition, bone scans, x-rays, cytologic data (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and relevant clinical information including medical photography will be forwarded to the IRF to aid in the tumor response assessment. Full details are listed in the IRF Charter and in the Imaging Guidelines.

NOTE: At the end of the study, investigator RECIST data and the IRF RECIST data will NOT be reconciled.

5.4.5 Anti-Therapeutic Antibodies to Pertuzumab

Within 7 days prior to the first administration of study medication and at the time of the treatment discontinuation visit, serum samples (5 mL blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study Sponsors.

Serum samples will be assayed for anti-pertuzumab antibody titers using a bridging electro-chemi-luminescence assay (ECLA). This assay measures anti-pertuzumab antibodies at a titer of >1.0 (1:10 dilution), with a relative sensitivity equivalent to approximately 200 ng/mL of an affinity-purified CDR-specific antibody from a hyper-immunized cynomolgus monkey.

These samples will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and checked. This research may take several years to complete, at which time the samples will be destroyed.

5.4.6 Trastuzumab Serum Concentration

Within 7 days prior to the first administration of study medication, a single serum sample (5 mL blood draw) for testing of trastuzumab concentration will be collected from all patients who have received prior trastuzumab therapy and are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory.

These samples will be assayed for trastuzumab concentrations using a receptor-binding ELISA. The assay uses immobilized antigen HER2-ECD to capture trastuzumab from serum samples. The MQC for trastuzumab in human serum measured by this assay is 156 ng/mL.

These samples will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and checked. This research may take several years to complete, at which time the samples will be destroyed.

5.4.7 Tumor and Blood Biomarker Samples

The procedures for the collection, handling, and shipping of laboratory samples being submitted to the central laboratory for testing or subsequent shipment to the study Sponsors will be specified in a central laboratory manual. Biological samples taken from all patients may be infectious and will be classified as UN3373 Biological Substance, Category B, for shipping purposes.

The tumor tissue and blood samples described in Sections 5.4.7.1, 5.4.7.3, and 5.4.7.2 and 5.4.7.5 (if consented for and collected), will be used for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and/or prognostic for breast cancer. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined but may include determination of markers of tumor genesis pathways or mechanisms of response to anti-HER2 therapies. The collected tumor tissue and blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data. Tumor tissue and blood samples remaining after the pre-defined biomarker assessments (e.g., aliquots of tumor cell RNA or DNA) may be used for re-testing, developing, and validating diagnostic assays related to HER2 positive breast cancer or the prediction of response to pertuzumab and/or trastuzumab, or further assessment of the defined marker panels.

5.4.7.1 Tumor Tissue Samples for HER2 Status and Biomarker Analysis

Archival tumor samples from the primary tumor (or metastatic sites, if the primary tumor is not available) will be submitted from all subjects during screening and submitted to a central pathology laboratory for assessment of HER2 status via IHC and FISH for study eligibility, as well as for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction.

Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 25 unstained freshly cut slides of 4 µm will be submitted (the number of slides submitted may be reduced pending on the regulatory and or IEC requirements of some counties). The slides must be sent to the central lab within 2 days of being cut. From submitted tumor blocks, at the central laboratory a maximum of 15 slides will be cut and 2 cores will be removed in order to construct tissue microarrays (TMAs) for later analysis. The remaining part of the tumor block will be returned to the institution. HER2 testing will be prioritized and the tissue will subsequently be used for assessment of biomarkers.

For the assessment of tumor tissue biomarkers, a variety of analysis methodologies may be used, including but not limited to, qRT-PCR, IHC, in-situ hybridization, and gene expression profiling. At the end of the collection process, the most suitable analytical methodologies will be selected and employed.

Tissue Microarray (TMA) Construction

The tumor blocks will also be used to set up a TMA: a maximum of 2 tissue cores of 1.5 mm each will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissue cores from different patients. This process protects the tissue against oxidation and allows for long-term storage and later analysis.

For later analysis, tissue sections can be generated using the latter tissue microarray. This technology will allow a high throughput (many patient samples on one glass slide) analysis of biomarkers.

DNA/RNA Extraction

The submitted tumor blocks will be used to generate sections on glass slides for the extraction of tumor DNA and RNA for later analysis. These slides will be prepared in a central lab to ensure the same quality for all samples and in later studies.

Note that as tumorigenesis is a multiple-step process linked to somatic events, DNA analysis will focus on sporadic mutations specifically found in tumor tissue but not inherited changes found in the whole body. For this purpose, some sections containing tumor will be taken from the block and used for the extraction process.

The tumor tissue samples will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed.

5.4.7.2 Metastatic Tumor Tissue Samples for Biomarker Analysis (Optional)

If a biopsy of the patient's metastatic tumor tissue is available, it will be submitted from consenting patients at baseline (after the patient has been determined to be eligible for the study, but before the first administration of study medication) for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Biopsy samples should be submitted and will be processed as described in Section 5.4.7.1.

5.4.7.3 Serum Samples for ECD/HER2 and HER Ligands Analysis

For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment. Biomarker assessments with these samples will include levels of ECD/HER2, selected HER ligands, and/or markers thought to be important for HER family signaling or response to HER inhibitors and HER activation. At this time the

significance of ECD/HER2 is not known, but because of its potential importance it will be measured as part of the panel of potential biomarkers of therapeutic effect. Leftovers of samples may be used for re-testing or developing and validating existing and/or new diagnostic tests related to pertuzumab or trastuzumab, or both.

The serum samples for ECD/HER2 and HER ligand analysis will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed.

5.4.7.4 Whole Blood Sample for Fcγ Polymorphism Analysis (Clinical Genotyping)

A whole blood sample (3 mL) for assessment of Fcγ polymorphism will be collected from patients at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication). An analysis of Fcγ-receptor polymorphism will be correlated with clinical outcome in order to further evaluate the mechanism of action of both trastuzumab and pertuzumab. Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the individual countries.

Blood samples for Fcγ polymorphism analysis and the DNA extracted from them will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and has been checked. The research may take several years to complete, after which time the samples will be destroyed.

5.4.7.5 Serum and Plasma for Biomarker Sample Repository (BSR) Research (Optional)

Blood samples for extraction of serum and plasma samples (approximately 5 mL per sample) for biomarker discovery, validation, and application will be collected from consenting patients. These samples are collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study every 9 weeks at the time of every tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18.**

The collected BSR samples will be stored with the study Sponsor's facility or a contract laboratory facility for up to 15 years after the end of the associated study (database closure), at which time the samples will be destroyed. These samples will be used only for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and will help to better understand the pathogenesis, course, and outcome of breast cancer and related diseases and adverse events.

The collected blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data related to HER2-positive breast cancer disease or response to pertuzumab and/or trastuzumab. Since the identification of new markers that correlate with disease activity and the efficacy or

safety of treatment is rapidly developing, the definitive list of analyses remains to be determined.

5.4.7.6 Ethics Approval and Consenting Process for Optional Tumor and Blood Samples

Sampling for the above optional biomarkers is contingent upon the appropriate Institutional Review Board's approval or Independent Ethics Committee's approval of sampling for the optional exploratory biomarker assessments and written informed consent of the patient. If an Institutional Review Board/Independent Ethics Committee (IRB/IEC) does not approve the sampling for the optional assessments, those sections will not be applicable at that site.

Collection of optional blood and tumor samples requires a separate patient consent. Individual patients may refuse the collection, storage, and use of any of the optional samples above; however, this will *not* exclude them from participation in this study. If the subject consents, the samples must be collected and submitted as described above.

5.5 Quality of Life Assessments

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system under development since October 1987 began with the creation of a patient-reported general core questionnaire called the Functional Assessment of Cancer Therapy, or FACT-G. Today's FACIT System (Version 4) has been translated in over 40 languages and consists of the FACT-G questionnaire and numerous other patient reported body organ or site specific questionnaires (referred to as "Additional Concerns") developed by David Cella of the Center on Outcomes Research Education (Brady et al. 1997).

5.5.1 The FACT-B Subscale

This study will use the Functional Assessment of Cancer Therapy–Breast (FACT-B), Version 4. The FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer (see Appendix 6). Patients will rate all items on a five-point scale ranging from "not at all" to "very much". The FACT-B provides supplemental domain valuative ratings or utility weights, thus providing an estimate of the relative importance of each quality of life domain to an individual patient. The FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. The FACT-B has been used extensively and has demonstrated reliability, validity, and sensitivity to change over time.

Only female patients on this study will be asked to complete the FACT-B questionnaire.

5.5.2 Administration of the FACT-B

Paper FACT-B questionnaires will be utilized in this study and will be completed by female patients pre-treatment (at baseline) and within 3 days prior to each tumor assessment. (QoL data will not be collected via the eCRF system).

The QoL evaluations have been specifically linked to on-study tumor assessments (rather than treatment cycles) to avoid biased data collection. Patients should complete the QoL assessment on schedule prior to each tumor assessment even if protocol therapy is no longer being administered due to toxicities or investigator-determined progressive disease.

5.6 Pharmacoeconomic Assessments

An economic assessment comparing various costs between the two treatment arms will be conducted by evaluating hospitalizations while on study treatment. The number of hospital visits, number of days admitted, and type of visits (emergency room vs. inpatient care) will be collected. This information will be collected from information submitted on AE and SAE eCRFs.

5.7 Post-Study Provisional Care

Patients who discontinue this study for progressive disease or other reasons will receive treatment according to the local standard of care. Any post-study cancer treatment will be recorded. Information on patient outcomes and information on post-progression anti-cancer therapies will be captured as far as reasonably possible on a post-progression follow-up form.

5.8 Pharmacokinetic, Drug–Drug Interaction, and QTc Interval Substudy

A **subset** of principal investigators and patients will participate in a pharmacokinetic, drug–drug interaction, and QTc interval substudy as detailed in a separate protocol. Separate IRB/IEC approval and Informed Consent Form will be required for participation in the substudy.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Formulation of Pertuzumab/Placebo and Trastuzumab

Each lot of the recombinant antibodies produced for clinical purposes meets USP requirements for sterility and safety. In addition, each lot is extensively characterized and meets the required specifications for identity, purity, and potency.

6.1.1 Pertuzumab/Placebo

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

The formulation of the pertuzumab/placebo is equivalent to pertuzumab, without the active agent.

For further details, see the pertuzumab Investigator Brochure (IB).

6.1.2 Trastuzumab

In countries where permitted by local regulatory requirements, commercial Herceptin (trastuzumab) will be obtained directly by the site for use during this study. In other countries, investigational trastuzumab will be supplied by the study Sponsors.

Trastuzumab will be a freeze-dried preparation at a nominal content of either 440 mg or 150 mg per vial. Vial size will also vary by country.

Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

For further details, see the trastuzumab Summary of Product Characteristics and local prescribing information.

6.2 Labeling of Pertuzumab/Placebo and Trastuzumab

Pertuzumab/placebo and trastuzumab will be labeled according to the regulatory requirements in each country, as well as in accordance with International Conference of Harmonization (ICH) Good Clinical Practice.

6.2.1 Pertuzumab/Placebo

The study Sponsors will provide pertuzumab to all study sites labeled for investigational use only.

6.2.2 Trastuzumab

Where permitted by regulatory requirements, sites will obtain and utilize standard trastuzumab.

For sites that will not obtain trastuzumab due to regulatory requirements, the study Sponsors will provide trastuzumab labeled for investigational use only.

6.3 Storage, Preparation, and Administration of Pertuzumab/Placebo and Trastuzumab

6.3.1 Storage of Pertuzumab/Placebo and Trastuzumab

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

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

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

6.3.2 Preparation of Pertuzumab/Placebo and Trastuzumab

6.3.2.1 Blinded Pertuzumab/Placebo

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

The indicated volume of pertuzumab/placebo solution should be withdrawn from the vials and added to a 250-cc IV bag of 0.9% sodium chloride injection. Gently invert the bag to mix the solution. DO NOT SHAKE VIGOROUSLY. Visually inspect the solution for particulates and discoloration prior to administration. The entire volume within the bag should be administered as a continuous IV infusion. The volume contained in the administration tubing should be completely flushed using a 0.9% sodium chloride injection.

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

A rate-regulating device may be used for all study-drug infusions. When the study drug IV bag is empty, 50 mL of 0.9% Sodium Chloride Injection may be added to the IV bag or an additional bag will be hung, and the infusion may be continued for a volume equal to that of the tubing to ensure complete delivery of the study drug.

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

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

6.3.2.2 Trastuzumab

Each vial of trastuzumab 150 mg is reconstituted with 7.2 mL of Sterile Water for Injection (SWFI). This formulation does not contain a preservative and is suitable for single use only.

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

Use of other reconstitution solvents is not allowed.

Appropriate aseptic techniques should be used. Trastuzumab should be carefully handled during reconstitution. The following instructions have to be followed:

1. Using a sterile syringe, slowly inject the sterile water for injections in the vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.

2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

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

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

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

Determine the volume of the solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent dose of 6 mg trastuzumab/kg body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions, since it causes aggregation of the protein. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for a maximum of 24 hours from reconstitution (do not store above 30°C). No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Trastuzumab may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions. Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial.

6.4 Docetaxel

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

6.5 Study Treatment Administration Sequence

Study treatment cycles are 3 weeks (21 days) in length. The first dose of pertuzumab/placebo (Cycle 1, Day 1) should be administered within 3 days of the date of randomization. The first dose of trastuzumab should be administered 24 hours later

(Cycle 1, Day 2), followed by the first dose of docetaxel. If the initial infusions of all three agents are well tolerated as determined by the investigator, subsequent cycles of trastuzumab and docetaxel may also be administered on Day 1 of the cycle. When all drugs are given on the same day they will be administered in the following sequence:

Pertuzumab/Placebo → Trastuzumab → Docetaxel.

6.6 Dose and Schedule of Pertuzumab/Placebo, Trastuzumab, and Docetaxel

6.6.1 Pertuzumab/Placebo Dose and Schedule

Pertuzumab/placebo will be administered as an IV loading dose of 840 mg for Cycle 1, and 420 mg for subsequent cycles.

Pertuzumab/placebo will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of pertuzumab/placebo for 1 cycle (i.e., the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab/placebo (840 mg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

6.6.2 Trastuzumab Dose and Schedule

Trastuzumab will be administered as an IV loading dose of 8 mg/kg for Cycle 1, and 6 mg/kg for subsequent cycles. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline.

Trastuzumab will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of trastuzumab for 1 cycle (i.e. the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of trastuzumab (8 mg/kg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1 and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.

6.6.3 Docetaxel Dose and Schedule

Docetaxel will be administered as an IV dose of 75 mg/m^2 every 3 weeks for at least 6 cycles until investigator-assessed radiographic or clinical progressive disease or unmanageable toxicity. At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of

the following toxicities: febrile neutropenia, Grade 4 neutropenia for >5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

Table 2 Study Treatment Dose and Schedule

Cycle	Blinded Pertuzumab/Placebo	Trastuzumab	Docetaxel
Cycle 1	Day 1: 840mg loading dose over 60 min followed by a 60 minute observation period	Day 2: 24 hrs after pertuzumab 8 mg/kg loading dose over 90 min followed by a 60 minute observation period	Day 2: After trastuzumab obs. period 75 mg/m^2 over 1 hour observe according to institution standards
Cycle 2 [a)]	Day 1: 420mg over 60 min followed by a 30 min, or 60 min obs. period [e)]	Day 1: After pertuzumab observation period 6 mg/kg over 30 min, or 90 min [c)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After trastuzumab observation period 75 mg/m^2 (or 100 mg/m^2 [g)]) over 60 min observe according to institution standards
Other Cycles *(every 21 days)*	Day 1: 420mg [b)] over 30 min, or 60 min[d)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After pertuzumab observation period 6 mg/kg [f)] over 30 min, or 90 min [c)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After trastuzumab observation period 75 mg/m^2 (or 100 mg/m^2 [g)]) over 60 min observe according to institution standards for a total of 6 cycles or more

Table 2 Study Treatment Dose and Schedule (Cont.)

a) If the administrations of all three agents are well tolerated in Cycle 1, they may all be given on Day 1 in subsequent cycles in the following sequence: pertuzumab/placebo → trastuzumab → docetaxel. If a patient cannot tolerate all three drugs given on the same day, the Cycle 1 dosing schedule (pertuzumab/placebo on Day 1, trastuzumab + docetaxel on Day 2) will be followed.

b) Pertuzumab/placebo should be re-loaded (840mg) if the agent is interrupted for 1 cycle (i.e., the 2 sequential administration times are at least 6 weeks apart). If reloading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

c) If the first infusion of trastuzumab is tolerated without infusion-associated adverse events (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

d) If the first two infusions of blinded pertuzumab/placebo are tolerated without infusion-associated adverse events (fever and/or chills), the third and subsequent infusions may be delivered over 30 minutes.
e) If the first infusion of pertuzumab/placebo or trastuzumab is well tolerated without infusion-associated adverse events, the subsequent observational periods may be reduced from 60 minutes to 30 minutes.
f) Trastuzumab should be reloaded (8 mg/kg) if the agent is interrupted for 1 cycle (i.e., the 2 sequential administration times are at least 6 weeks apart). If reloading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.
g) At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/µL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

6.7 Dose Delays and Modifications

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

6.7.1 Pertuzumab/Placebo and Trastuzumab Dose Delays and Modifications

Pertuzumab/placebo and trastuzumab doses may be delayed due to toxicities. If pertuzumab/placebo or trastuzumab is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment, and the patient will continue to be followed post-treatment as described in Section 5.4.2.

Pertuzumab/placebo or trastuzumab dose modifications are not permitted.

6.7.2 Docetaxel Dose Delays and Modifications

Docetaxel may be delayed due to toxicities. If docetaxel is delayed for more than 3 weeks with no recovery the patient should be withdrawn from docetaxel treatment. If docetaxel needs to be permanently discontinued, the patient will continue on pertuzumab/placebo and trastuzumab.

At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle of 75 mg/m^2 without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for >5 days or ANC < 100/µL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

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

Table 3 Docetaxel Dose Adjustments

Docetaxel Dose	When

Docetaxel Dose	When
75 mg/m^2	Starting dose Administer only if neutrophil count is > 1500 cell/mm^3
100 mg/m^2	At the discretion of the treating physician, after at least 1 cycle of 75 mg/ m^2 without any of the following toxicities: Febrile neutropenia Grade 4 neutropenia for > 5 days ANC < 100/µL for more than 1 day Other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).
55 mg/m^2 (or 75 mg/m^2 if dose previously increased to 100 mg/m^2)	25% reduced dose in case of any of the following toxicities: Febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1,500 cells/mm^3) Platelet count < 100,000 cells/mm^3 (after recovering to a platelet count ≥ 100,000 cells/mm^3) Severe or cumulative cutaneous reactions
Permanently Discontinue Docetaxel	After any of the following toxicities: Severe hypersensitivity reactions (Section 7.3.2.2) Peripheral neuropathy > Grade 3 Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery Febrile neutropenia or neutrophils < 500 cells/mm^3 without recovery Platelet < 100,000 cells/mm^3 without recovery Total bilirubin > ULN without recovery Serum transaminase (AST/ALT) levels > 1.5 × ULN concurrent with serum alkaline phosphatase levels > 2.5 × ULN without recovery

ANC=absolute neutrophil count; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

See also Section 7.3.

6.8 Study Treatment Unblinding

As per regulatory reporting requirements, Genentech and Roche will unblind the identity of the study medication for all unexpected (as per the IB) serious adverse events that are considered by the investigator to be related to the blinded study drug (pertuzumab/placebo). Unblinding for other reasons is not permitted. All cases of safety unblinding require the approval of the Medical Monitor.

Unblinding for interim analysis, or ongoing safety monitoring by a DMC, will be performed through an independent Data Coordinating Center (DCC) to ensure integrity of the study.

All other individuals directly involved in this study will remain blinded until the final analysis of the primary efficacy endpoint.

6.9 Assessment of Compliance

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Dose reductions and titrations of docetaxel must be recorded.

Accurate records must be kept for each study drug provided by the Sponsors, pertuzumab and trastuzumab (investigational). These records must contain at least the following information:

- Documentation of drug shipments received from the Sponsors (date received and quantity)

A Drug Dispensing Log must be kept current and contain the following information:

- The study number of the patient to whom the study medication was dispensed
- The date(s), drug kit number, and quantity of the study medication dispensed to the patient

This inventory must be available for inspection by the monitor. All supplies, including partially used or empty vials of pertuzumab/placebo and trastuzumab (investigational), and copies of the dispensing and inventory logs, must be retained at the site for review by the Roche/Genentech Monitor, unless destruction has been authorized by Roche/Genentech or required by local or institutional regulations (see Section 6.10).

6.10 Destruction of Study Drug

All pertuzumab, trastuzumab, and docetaxel supplies, including partially used or empty vials, must be destroyed on site as per the site's specific procedures for handling and disposing of hazardous drugs. The specific procedures for destruction of investigational pertuzumab and trastuzumab are to be provided to the monitor who will verify them as acceptable and in line with the Sponsor's SOPs.

To assist with storage capacity and functionality, it is acceptable for sites to destroy the vials before inspection by the site monitor so that only the empty boxes stating the drug kit number and patient information and dispensing date written on the label can be used for reconciliation of destroyed supplies.

Unused pertuzumab/placebo and trastuzumab (investigational) drug supplies, including medication that has been exposed to storage temperatures outside of the protocol-specified range, may only be destroyed upon written approval from the Sponsors, provided that such disposition does not expose humans to risks from the drug.

Written authorization must be obtained from the Sponsors before destruction of pertuzumab/placebo and investigational trastuzumab. Written documentation of destruction must contain the following:

- Identity (drug kit numbers or patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed

- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsors with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of the responsible person who discarded the investigational product in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events and Laboratory Abnormality Definitions

7.1.1 Clinical AEs

Per the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that worsen during a study are to be reported as AEs.

7.1.1.1 Intensity

Intensity of all adverse events will be graded according to the NCI-CTCAE, Version 3.0 on a 5-point scale (Grades 1–5) and reported in detail on the eCRF.

Adverse events not listed on the NCI-CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening/disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.1.2 Adverse Event Relationship to Drug

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration
- Assessment that it may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappearance or decrease on cessation or reduction in dose
- Reappearance on re-challenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

7.1.1.3 Serious Adverse Events

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills one or more of the following criteria:

- It is fatal (i.e., results in death; NOTE: Death is an outcome, not an event).
- It is life threatening. (NOTE: The term "life threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.)
- It requires in-patient hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability/incapacity.
- It is a congenital anomaly/birth defect.
- It is medically significant or requires intervention to prevent one or other of the outcomes listed above.

The full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2,** will be adhered to (see Appendix 1).

7.1.1.4 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST, or other criteria as determined by the protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic clinical deterioration may occur in some patients. In this situation, progressive disease is evident in the patient's clinical symptoms but is not supported by the tumor measurements. Or, the progressive disease is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.2 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eForms of the eCRF.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE eForm in the eCRF:

- Accompanying clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

7.2 Reporting and Follow-Up of Adverse Events and Laboratory Abnormalities

7.2.1 Reporting of Non-Cardiac, Non-Serious Adverse Events

For all patients that have received at least one dose of study medication, all new non-cardiac, non-serious AEs (related and unrelated) must be collected during the study through the treatment discontinuation visit. These events will be reported via the eCRF.

7.2.2 Reporting of Serious Adverse Events (Immediately Reportable)

For all patients who have received at least one dose of study medication, any clinical AE or abnormal laboratory test value that is *serious* (as defined in Section 7.1.1.3 above) and which occurs during the course of the study, regardless of the treatment arm, must be reported to the Sponsors **within *one* working day** of the investigator becoming aware of the event (expedited reporting).

Related SAEs (cardiac and non-cardiac) ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated non-cardiac SAEs must be collected and reported during the study through the treatment discontinuation visit.

Adherence to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2** will be required. Complete information can be found in Appendix 1.

7.2.3 Reporting of Cardiac Adverse Events

All cardiac AEs occurring during the study and up to 12 months after last administration of study medications must be reported irrespective of causal relationship (related and unrelated) or severity (serious or non-serious).

***Symptomatic* Left Ventricular Systolic Dysfunction**

Symptomatic left ventricular systolic dysfunction should be reported as an **SAE** as congestive heart failure (CHF) and not as individual signs and symptoms thereof. CHF must also be reported on the Congestive Heart Failure eCRF. Specific related signs and symptoms will be entered on the eCRF. CHF should be graded according to NCI-CTCAE Version 3.0 for "left ventricular systolic dysfunction" and the NYHA classification (see Appendix 3).

***Asymptomatic* Left Ventricular Systolic Dysfunction**

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

- An asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50% must be reported as an AE

- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment must be reported in an expedited manner by using the SAE form and classifying the event as Non-Serious Event of Special Interest (see Section 3a on page 1 of the SAE form)

In both cases, it should be reported as left ventricular systolic dysfunction and graded according to NCI-CTCAE, Version 3.0.

The following table summarizes the reporting conventions for left ventricular systolic dysfunction:

Table 4 Reporting Conventions for Left Ventricular Systolic Dysfunction

Observation	How to report	Term to be reported	Grading
Asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50%	AE (eCRF AE eform)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE eform) and Non-Serious Event of Special interest (SAE form)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Symptomatic left ventricular systolic dysfunction (Congestive Heart Failure)	CHF eCRF and SAE (SAE form)	Congestive heart failure	NCI-CTCAE for "left ventricular systolic dysfunction" and NYHA criteria
Asymptomatic decline in LVEF to a value higher than 10 percentage points below Baseline, or Asymptomatic decline to a value 10 percentage points below baseline or lower, but ≥ 50%	Record on LVEF eCRF, not AE eCRF	N/A	N/A

LVEF=left ventricular ejection fraction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; AE=adverse event; SAE=serious adverse event; eCFR=electronic case report form.

Note: Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.

7.2.3.1 Cardiac Review Committee Document Review

Patients with potential cardiac events to be reviewed by the CRC will be identified from the study database according to the specifications detailed in the CRC charter.

In order for the CRC to adequately review potential cardiac events, copies of specific source documents will be required by the CRC: copies of chest X-ray reports, ECG readings, cardiac consultations, clinic visit notes, LVEF reports, documentation of medications received. The study Sponsors or designee will contact the study site to request the required source documents for identified patients. The CRC will review these source documents along with patient data profiles to independently determine whether or not the patient experienced a cardiac event according to the cardiac event definition defined in the CRC charter. The CRC cardiac event evaluations will be provided to the

DCC for submission to the DMC for review during the periodic safety reviews. The independent CRC cardiac event evaluations will not be provided to the study sites.

7.2.4 Follow-up of AEs and Post-Treatment AE Collection

During the treatment period through the treatment discontinuation visit, all AEs (regardless of seriousness or causality) should be reported and continue to be followed until one of the following occurs:

- Resolved or improved to baseline
- Investigator confirmation that no further improvement can be expected
- Death

AEs that are *ongoing* at the time of the treatment discontinuation visit should be followed depending on the event type:

- All Cardiac AEs (regardless of seriousness or causality), and all SAEs (regardless of causality) should be followed until resolution/stabilization/death up to 1 year after the last dose.
- Non-cardiac, non-serious AEs (regardless of causality) should be followed only until the Treatment Discontinuation Visit.

Only the following *new* adverse events that start *after* the treatment discontinuation visit should be reported:

- Cardiac events (regardless of causality or seriousness) that start up to 1 year after the last dose should be reported. These events should be followed until resolution/stabilization/death up to 1 year after the start of the event.
- Treatment-related SAEs should be reported at any time regardless of the start date. These events should be followed until resolution/stabilization/death up to 1 year after the start of the event.

7.2.5 Follow-Up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found, or until the test values are determined to be not clinically significant by the investigator. If a clear explanation is established, it should be recorded on the eCRF.

7.2.6 Pregnancy

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy. In patients of childbearing potential and women < 2 years after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment (e.g., birth control pills, barrier method [condoms, diaphragm]; intrauterine devices; surgical methods, or abstinence). Based on PK

considerations, contraceptive measures are recommended for at least 6 months following the last dose of either trastuzumab or pertuzumab.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to the Sponsor. The investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of study medication must also be reported to the investigator.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 6 months following the last dose of either monoclonal antibody.

7.3 Dose Modifications for Toxicity

The NCI-CTCAE Version 3.0 will be used to grade toxicity.

Pertuzumab/placebo, trastuzumab, and docetaxel will be given as specified in Section 6. Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections.

7.3.1 Pertuzumab/Placebo and Trastuzumab

Pertuzumab/placebo and trastuzumab administration may be delayed to assess or treat AEs such as cardiac adverse events, myelosuppression, or other events. No dose reduction will be allowed for pertuzumab/placebo or trastuzumab.

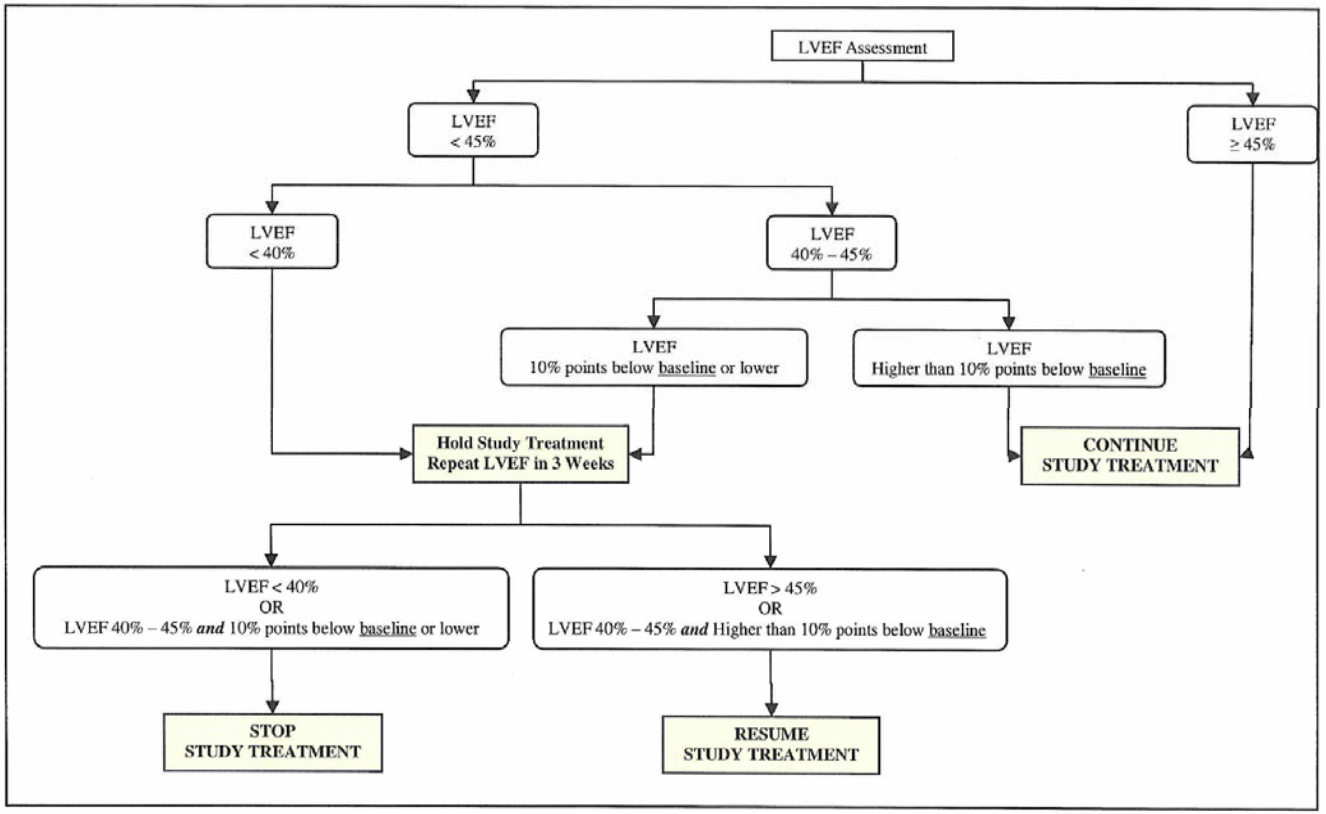
7.3.1.1 Cardiac Safety

All patients must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly according to the schedule of assessments. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Pertuzumab/placebo and trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting congestive heart failure, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. Congestive heart failure should be treated and monitored according to standard medical practice.

At the present time, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure the safety of patients in the trial, pertuzumab/placebo and trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented and confirmed with a repeat assessment within 3 weeks of the first assessment, using the same assessment method.

For patients whose LVEF drops to values lower than 45%, the decision to stop or continue study treatment is based on the algorithm shown in Figure 3.

Figure 3 Algorithm for Continuation and Discontinuation of Pertuzumab/Placebo and Trastuzumab Based on LVEF Assessments



LVEF=left ventricular ejection fraction.

Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.

7.3.1.2 Infusion-Associated Symptoms and Allergic Reactions

Administration of monoclonal antibodies, including pertuzumab and trastuzumab, may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rashes, headache, nausea, vomiting, or allergic reactions.

Patients with extensive pulmonary disease, e.g., lymphangitis, multiple metastases, recurrent pleural effusions, and those with pre-existing pulmonary compromise who are treated with trastuzumab, may be at increased risk of serious infusion-associated symptoms. Therefore, careful consideration must be made before enrolling patients with chronic lung disease into the study.

Study treatment will be administered in a setting with emergency equipment and staff that is trained to monitor for and respond to medical emergencies. Patients who experience an NCI-CTCAE grade 4 allergic reaction, acute respiratory distress syndrome, or bronchospasm will be discontinued from study treatment.

Patients who experience infusion-associated symptoms may be managed by:

- Slowing or stopping the trastuzumab or pertuzumab/placebo infusion
- Supportive care with oxygen, beta agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab or pertuzumab infusions at the investigator's discretion.

If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms.

7.3.1.3 Pertuzumab/Placebo or Trastuzumab: Incomplete Loading Dose

In case the whole loading dose of pertuzumab/placebo or trastuzumab could not be administered due to an infusion reaction or other reason, the following guidelines apply:

The patient should receive at least 50% of the loading dose in the first week. Therefore, if the patient receives less than 50% of the Cycle 1 dose, the patient should receive the remainder before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only approximately 50% of the scheduled loading dose (i.e., only 4 mg/kg instead of 8 mg/kg of trastuzumab; or only 420 mg instead of 840 mg of pertuzumab/placebo), the patient should receive the remaining dose (4 mg/kg of trastuzumab; or 420 mg of pertuzumab), preferably in the first week, and then regular maintenance doses (6 mg/kg of trastuzumab; 420 mg of pertuzumab/placebo) on Day 22, as routinely scheduled.

If the patient receives between 50–75% of the dose, the patient should receive the remainder before Day 22, preferably within the first two weeks of Cycle 1. For example, if a patient received only approximately 60% of the scheduled loading dose, the patient should receive the remaining 40%, within 2 weeks after the interrupted loading dose.

Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.

If the patient received ≥ 75% of the loading dose, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22.

7.3.2 Docetaxel

The recommendations given in the prescribing information for docetaxel should be strictly followed.

The first dose of docetaxel should be given at a dose of 75 mg/m^2 and dose reductions should be applied in the event of toxicity. If docetaxel is withheld for more than 3 weeks with no recovery the patient should be withdrawn from docetaxel treatment. If docetaxel has been withdrawn, investigators may continue with pertuzumab/placebo and trastuzumab, if clinically appropriate.

7.3.2.1 Hematotoxicity

Neutrophil count

Docetaxel should only be administered if the neutrophil count is ≥ 1,500 cells/mm^3.

If patients experience either febrile neutropenia or neutrophils < 500 cells/mm^3 for more than one week following docetaxel administration, docetaxel should be held until the patient is fully recovered and the neutrophil count is≥ 1,500 cells/mm^3. Treatment with docetaxel may be resumed with a 25% reduction in the dose. If patients continue to experience these reactions at a dose of 55 mg/m^2, docetaxel should be discontinued permanently.

Alternatively, prophylactic G-CSF may be used in patients who experienced febrile neutropenia or severe infection during the previous cycle, in order to maintain dose intensity as clinically indicated or according to the ASCO guidelines for growth factor support (Smith et al. 2006).

Platelet count

- Patients with a platelet count of ≥ 100,000 cells/mm^3 on the day of treatment may receive docetaxel.
- Patients with a platelet count < 100,000 cells/mm^3 should not be given docetaxel. Docetaxel may be delayed for a maximum of 3 weeks.
- If the platelet count recovers to ≥ 100,000 cells/mm^3 after a decline to < 100,000 cells/mm^3, the patient should receive further cycles of docetaxel with a 25% reduction in the dose.

- If the platelet count does not recover to a level ≥ 100,000 cells/mm^3, the patient should discontinue docetaxel.

7.3.2.2 Hypersensitivity

Patients should be observed closely for hypersensitivity reactions, especially during the first and second docetaxel infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel; thus, facilities for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. These patients should not be re-challenged with the docetaxel. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Minor symptoms such as flushing or localized cutaneous reactions generally do not require interruption of therapy.

7.3.2.3 Peripheral Neuropathy

Patients who develop ≥ Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

7.3.2.4 Fluid Retention

Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion, or ascites that is possibly related to docetaxel should be closely monitored and the decision to continue or discontinue study treatment is at the discretion of the Investigator.

7.3.2.5 Hepatic Impairment

Patients should have adequate baseline liver function as stated in the inclusion criteria in Section 4.2. Liver function should be measured before each cycle to avoid docetaxel-associated toxicity.

According to the manufacturer, docetaxel should not be administered to patients who have total bilirubin > ULN or to patients with serum transaminase (AST/ALT) levels > 1.5 × ULN concurrent with serum alkaline phosphatase levels > 2.5 × ULN, as there is a higher risk of developing adverse reactions such as toxic death, including sepsis; gastrointestinal hemorrhage, which can be fatal; febrile neutropenia; infections; thrombocytopenia; stomatitis; and asthenia.

7.3.2.6 Cutaneous Reactions

Localized skin erythema of the extremities with edema followed by desquamation has been observed. According to the manufacturer, patients who are dosed at 100 mg/m^2 of docetaxel and experience severe or cumulative cutaneous reactions during docetaxel therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions at a dose of 75 mg/m^2, the dose should be reduced to 55 mg/m^2 or the treatment should be discontinued.

7.3.3 Dose Adjustment for Changes in Body Weight

Baseline body weight is used to calculate required doses of trastuzumab and docetaxel.

The trastuzumab dose should be recalculated only if the patient's weight changes by more than ±10% from baseline.

Docetaxel dose adjustments due to changes in body weight should be based upon the investigative site's institutional standards.

The pertuzumab dose should not be adjusted for body weight.

7.4 Warnings and Precautions for Pertuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate, other than those noted in the Investigator's Brochure.

7.4.1 Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Associated Symptoms

Monoclonal antibodies may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during or very shortly after an infusion. In the pertuzumab single-agent Phase II studies, 41% of patients experienced treatment-related adverse events occurring during or within 24 hours of an infusion. The true rate of infusion-associated reactions may be considerably lower since approximately 5% of patients had such events during an infusion (data from two studies).

To date, 6 patients who have received pertuzumab (approximately 1%) have experienced serious events compatible with infusion-associated reactions or hypersensitivity reactions, or both. Two of these serious events occurred during a pertuzumab infusion (hypersensitivity, urticaria). The remaining four serious cases (pulmonary edema, ARDS, anaphylaxis, hypertension, and dyspnea) occurred following a pertuzumab infusion. In 3 cases, pertuzumab was given after administration of gemcitabine (anaphylaxis, pulmonary edema, hypertension, and dyspnea). Only two of the six cases occurred in the context of the first pertuzumab infusion.

Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each pertuzumab infusion and for 60 minutes following the completion of the infusion for any adverse effects. If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may subsequently be premedicated with acetaminophen, diphenhydramine, or meperidine.

Infusion of pertuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience an NCI-CTCAE Grade 3 or 4 allergic reaction or acute respiratory distress syndrome should not receive additional pertuzumab.

7.4.2 Risk of Cardiotoxicity

Like trastuzumab, pertuzumab is directed at the HER2 receptor and may be associated with a risk of cardiac dysfunction.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan. In pertuzumab single-agent Phase II studies, a fall in LVEF of $\geq 10\%$ to a LVEF value $< 50\%$ was observed in 7% of patients who had a post-baseline LVEF assessment. Nine of these patients had received prior anthracycline treatment. Overall, 3 symptomatic cardiac failure events have been reported in approximately 550 patients treated with pertuzumab across all studies. Two of these cases occurred in patients with MBC who had received prior anthracyclines.

Patients with significant cardiac disease or baseline LVEF below 50% are not eligible for this study. Risk factors for pertuzumab-associated cardiac dysfunction are not known at this time, and this risk should be carefully weighed against the potential benefit in patients who have received prior anthracyclines. During the screening/baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-related congestive heart failure, including all prior LVEF assessments.

Monitoring of LVEF is required while patients are receiving study treatment. If symptomatic left ventricular dysfunction develops (NCI-CTCAE Grade 3 or 4) with a drop in LVEF consistent with cardiac failure, the patient must discontinue study treatment. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice.

7.4.3 Risk of EGFR-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors. In the 7-week IV and 26-week toxicity studies in cynomolgus monkeys, there was a treatment-related increase in the incidence of diarrhea. Diarrhea has been observed in approximately 50% of patients being treated with pertuzumab in Phase II single-agent studies, and up to 70% of patients in combination therapy studies, and was NCI-CTC Grade 1 or 2 in the majority of cases. For patients experiencing diarrhea, early intervention with loperamide should be considered.

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

7.5 Warnings and Precautions for Trastuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for trastuzumab.

Trastuzumab therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Serious adverse reactions including cardiotoxicities, infusion reactions, hypersensitivity, allergic-like reactions, and pulmonary events have been observed in patients receiving trastuzumab therapy. These severe reactions were usually associated with the first infusion of trastuzumab and generally occurred during or immediately following the infusion. For some patients, symptoms progressively worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction.

7.5.1 Infusion Reactions, Allergic-Like Reactions, and Hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur, the trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients with dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

7.5.2 Pulmonary Events

Dyspnea, bronchospasm, asthma, and hypoxia can occur as part of an infusion reaction. These are most common with the first infusion, and their severity decreases with subsequent infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. Single cases of pulmonary infiltrates, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and respiratory insufficiency have been reported rarely. Acute respiratory distress syndrome (ARDS) has been reported with fatal outcome.

7.5.3 Cardiotoxicity

Heart failure (NYHA Class II–IV) has been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death.

Table 5 Incidence and Severity of Cardiac Dysfunction in Metastatic Breast Cancer

	Trastuzumab Alone [a] n=213	Trastuzumab + Paclitaxel [b] n=91	Paclitaxel Alone [b] n=95	Trastuzumab + AC [b] n=143	AC [b] n=135
Any cardiac dysfunction	7%	11%	1%	28%	7%
NYHA Class III–IV	5%	4%	1%	19%	3%

AC = anthracycline + cyclophosphamide; NYHA=New York Heart Association.

a) Open-label, single-agent Phase II study (94% received prior anthracyclines)
b) Randomized Phase III study comparing chemotherapy Herceptin to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel

Risk factors for trastuzumab-associated cardiotoxity include increased age, concomitant administration with anthracyclines, and declining LVEF while on trastuzumab treatment.

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with the standard medications for this purpose.

The half-life of trastuzumab is approximately 28.5 days (range, 25.5–32.8 days). Trastuzumab may persist in the circulation for up to 24 weeks (range, 18–24 weeks) after stopping trastuzumab treatment. Patients who receive anthracyclines during this period may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy up to 24 weeks after stopping trastuzumab. If anthracyclines are used then the patient should have careful cardiac surveillance.

Most patients who developed heart failure in the Phase III trials of trastuzumab in MBC improved with standard medical treatment. This included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

7.6 Warnings and Precautions for Docetaxel

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for docetaxel.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Efficacy Variable

The primary endpoint is PFS based on IRF evaluations. PFS is defined as the time from randomization to the first documented radiographical progressive disease, as determined by the IRF using current RECIST (Therasse et al. 2000), or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.

8.1.2 Secondary Efficacy Variables

The secondary efficacy variables are as follows:

Overall survival: OS is defined as the time from the date of randomization to the date of death from any cause.

PFS based on investigator assessment: PFS based on investigator assessment is defined as the time from randomization to the first documented radiographic progressive disease, as determined by the investigator using current RECIST (Therasse et al. 2000), or death from any cause, whichever comes first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.

Objective response: Objective response is defined as a CR or PR determined by the IRF using current RECIST (Therasse et al. 2000) on two consecutive occasions ≥ 4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response.

Duration of response: Duration of response is defined as the period from the date of initial confirmed PR or CR until the date of progressive disease or death from any cause. Tumor responses will be based on the IRF evaluations using current RECIST (Therasse et al. 2000).

Time to symptom progression: This is defined as the time from randomization to the first symptom progression in the FACT TOI-PFB. The TOI-PFB is a 24-item subscale generated using 3 subsections from the FACT-B questionnaire: Physical Well-being, Functional Well-being and Additional Concerns. A decrease of five points is considered clinically significant, and thus symptom progression.

Biomarker analysis: The relationship between molecular markers and efficacy outcomes will be evaluated.

8.1.3 Safety Variables

Safety of the treatment will be evaluated as follows:

- Incidence of CHF and asymptomatic LVEF events
- LVEF measurements over the course of the study
- Incidence and severity of AEs and SAEs
- Laboratory test abnormalities

8.2 Statistical and Analytical Methods

This study is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel relative to placebo + trastuzumab + docetaxel in patients with previously untreated MBC. The final analysis for the primary endpoint will take place when approximately 381 IRF-assessed PFS events have occurred. A data cutoff date will be determined when this number of events occurs, and the clinical data on or prior to the data cutoff date will be thoroughly cleaned. The treatment assignment will be unblinded, analyses will be performed, and a clinical study report will be prepared. Assuming there will be 15% fewer IRF-assessed PFS events compared to investigator-assessed events, it is estimated that approximately 448 investigator-assessed PFS events will have been reported at the data cutoff for final PFS analysis.

8.2.1 Statistical Model

The fixed-sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple statistical testing of IRF-assessed PFS, OS, objective response rate, and duration of response. The four variables will each be tested at an overall two-sided 5% significance level in the order specified. Additional details on the testing procedure will be specified in the statistical analysis plan.

8.2.1.1 Analysis of Primary Variable

The primary endpoint is PFS based on IRF assessments. For patients who discontinue study treatment due to reasons other than death or IRF-assessed progression, every effort will be made to continue tumor assessments until IRF-determined progressive disease or patient death. 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 IRF-evaluable tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day).

For patients whose IRF-determined progression event is not available, surrogating death at any time as a progressive event can artificially prolong the PFS time because of a much longer life expectancy in this patient population compared with PFS. Therefore, only deaths within 18 weeks of the last tumor assessments will be included as an event in the primary analysis. However, a sensitivity analysis will be performed including all deaths as an event.

The log-rank test, stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia), will be used to compare PFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazard model, stratified by prior treatment status and region, will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% confidence interval (CI).

8.2.1.2 Secondary Variables

Overall survival. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. 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. To minimize the chance of a biased OS estimate resulting from scheduled survival follow-up every 18 weeks, immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

PFS based on investigator assessments. 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 investigator tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day). Analysis methods are the same as those described for the primary endpoint.

Objective response. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Patients without a post-baseline tumor assessment will be considered to be non-responders. Analysis of objective response will be based on IRF assessments.

An estimate of the objective response rate and its 95% CI will be calculated for each treatment arm. The difference in objective response rate will also be provided with 95% CIs. The Mantel-Haenszel χ^2 test stratified by prior treatment status and region will be used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test result will also be provided as a sensitivity analysis.

Duration of objective response. Only patients with an objective response will be included in the analysis of duration of objective response. The method for handling censoring is the same as that described for the primary endpoint. Analysis of duration of objective response will be based on IRF assessments.

Duration of objective response will be estimated using the Kaplan-Meier approach. Comparisons between treatment arms using the unstratified log-rank test and estimation of hazard ratio using Cox regression will also be made.

Time to symptom progression. A decrease of five points in TOI-PFB is considered symptom progression. Data for patients who do not have an observed symptom progression will be censored at the last observed TOI-PFB assessment date. If baseline TOI-PFB assessment is unavailable, or if there is no post-baseline TOI-PFB assessment performed, data will be censored at the time of randomization plus 1 day. Analysis methods are the same as those described for the primary endpoint.

Biomarker analyses. To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes will be summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers. Markers to be considered include the status of HER receptors, HER ligands, Fc-γ, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis will be put on markers that have shown association with clinical outcome in patients treated with pertuzumab in previous studies:

- qRT-PCR markers: tumor gene expression profiles associated with HER2 activation
- Baseline serum markers: levels of ECD/HER2 and HER ligands

Efficacy outcomes considered for this analysis will include PFS, objective response rate, and OS. The PFS and objective response will be based on the IRF assessments.

The biomarker analyses at the time of protocol development do not take the form of testing fixed hypotheses involving specific cutoffs or other pre-specified prediction rules. It is planned for the Statistical Analysis Plan (to be generated prior to unblinding of this trial) to use all available scientific evidence from independent studies or publications to specify testable prediction rules. In addition, this plan will specify in due detail how data-adaptive prediction rules will be derived (e.g., systematic cutoff search) and how the inherent multiplicity/bias will be corrected in order to prevent biased conclusions.

The difference in treatment benefit across biomarker statuses defined by a suitable prediction rule will be evaluated by testing the interaction effect of treatment and the prediction status using Cox regression for PFS and OS, and using logistic regression for response rate. These models involving an interaction term will also be used to estimate the conditional efficacy outcomes, conditional on biomarker prediction status or treatment arm, including and excluding the stratification factors into the model.

Clinical covariates can be of prognostic value and could interact with treatment benefit and with biomarker status. Candidates here are baseline variables of prognostic value describing tumour properties and morbidity status or common lab values. Biomarker prediction will be checked involving relevant clinical covariates, which could be part of the biomarker prediction function, if necessary.

See also Section 8.2.5.1, Biomarker Analyses.

8.2.2 Hypothesis Testing

The difference in primary endpoint, IRF-assessed PFS, between the two treatment arms will be compared using a two-sided log-rank test at 5% significance level stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia). The null hypothesis is that the survival distributions of PFS in the two treatment groups are the same. The alternative hypothesis is that the survival distribution of PFS in the treatment and the control arm are different:

$$H_0: S_{<pertuzumab>} = S_{<placebo>} \quad \text{vs.} \quad H_1: S_{<pertuzumab>} \neq S_{<placebo>}$$

Additional tests will be performed to compare whether the distributions or the key summary statistics of the secondary endpoints between the two treatment arms are the same at a two-sided alpha level of 5%. The overall type I error rate for the primary and the OS analysis will be controlled using the fixed sequence testing procedure.

8.2.3 Types of Analyses

8.2.3.1 Efficacy Analysis

Analyses of PFS, OS, and time to symptom progression will be based on the intent-to-treat (ITT) population, defined as patients who have been randomized. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only responders will be included in the analysis. All efficacy analyses will be based on the treatment arm to which patients were randomized.

8.2.3.2 Exclusion of Data from Analysis

Intent-to-treat population:

All randomized patients will be included in the intent-to-treat population.

Other efficacy populations:

See Section 8.2.3.1 for patients who will be excluded from the analyses for objective response and duration of response.

Safety population:

All patients who received any amount of study medication (docetaxel, pertuzumab/placebo, and/or trastuzumab) and have at least one post baseline safety assessment will be included in the safety population. Analyses will be based on the treatment they actually receive.

8.2.3.3 Interim Safety Monitoring and Interim Safety Analyses

There have been reports of CHF with trastuzumab and pertuzumab treatment. Because of this, left ventricular systolic dysfunction is a potential safety concern for patients who receive the treatments outlined in this study. While on study treatment, patients will be monitored for cardiac events with regular assessments of left ventricular function with either Echocardiography or MUGA. (Echocardiography is the preferred method. The same assessment method, ECHO or MUGA, the same institution/facility, and the same assessor should be used throughout the study, to the extent possible.) For patients who experience Grade 1 or 2 left ventricular systolic dysfunction (i.e., asymptomatic decrease in LVEF), an algorithm is provided in Section 7.3.1.1 outlining under which circumstances treatments have to be held and LVEF assessed prior to treatment continuation. Patients who experience CHF (NCI-CTCAE Grade ≥3) will have study treatment discontinued. CHF will be reported in an expedited manner to the Sponsors for timely monitoring.

Clinical studies have demonstrated a higher incidence of myelosuppression when trastuzumab is administered with chemotherapy. Limited, non-comparative data from Phase I/II studies suggest that the combination of pertuzumab and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic AEs while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor support will be allowed in this protocol.

A DMC will be convened to monitor patient safety. In addition to the DMC, an independent CRC will review all suspected cases of left ventricular systolic dysfunction. This CRC will report their findings to the DMC every 6 months starting approximately 3 months after the first patient has been enrolled, and at the time of the interim analysis.

To closely monitor patient safety, the DMC will review serious adverse events and investigator-assessed CHF every month through the interim analysis, starting approximately 3 months after the first patient has been enrolled. After the interim safety review, the DMC will review serious AEs and investigator-assessed CHF every 3 months. Moreover, every 6 months, starting approximately 9 months after the first patient has been enrolled, the DMC will receive summaries of serious and non-serious AEs, incidence of CHF assessed by the CRC, and maximum decrease in LVEF measures, and will have a teleconference to discuss their safety findings (the Sponsors will not be allowed to participate in this teleconference).

In addition to the periodic safety monitoring, an interim safety analysis is planned. The interim safety analysis will take place after 100 patients have been enrolled and followed for at least 4 months. The DMC will review all safety data from all patients enrolled and may recommend stopping the study if, among the patients who have been followed for at least 4 months, the incidence of cardiac events (as defined in the CRC charter) based upon the CRC assessment is at least 9.3% higher in the pertuzumab arm compared with the control arm. The DMC may also recommend stopping the study if, in their opinion, the incidence of other clinically significant toxicities, such as neutropenia, neutropenic

sepsis, or severe pulmonary toxicity, is unacceptably high in the pertuzumab arm compared with the control arm.

Assuming that the cardiac event rate in the control arm is 5%, the stopping guidance for cardiac event rate is chosen so that the chance of falsely stopping the study at the interim analysis will be < 5% if there is no difference in event rate between two arms. If the event rate in the pertuzumab arm is 10%, the chance of stopping the trial at the interim analysis is approximately 19%. However, if the event rate in the pertuzumab arm is 15%; the chance of stopping the trial at the interim will increase to approximately 47%.

8.2.4 Safety Data Analysis

The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, cardiac-specific AEs, LVEF measurements, and laboratory test results. Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually receive.

Cardiac safety. The number and percentage of patients with CHF (NCI-CTCAE Grades 3, 4, and 5) and asymptomatic LVEF events (NCI-CTCAE Grades 1 and 2) at any time during the study will be summarized by treatment arm. The summary of CHF will be based on assessments by the independent CRC. LVEF can be measured by either MUGA or ECHO.

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 difference in the maximum absolute decrease in LVEF measure between the two treatment arms will be assessed by the Wilcoxon test. LVEF measurements and change in LVEF from baseline will be summarized by treatment arm and scheduled visits in graphical and tabular format.

For each ECHO/MUGA evaluation following the initiation of study drug, the number and percentage of patients who have had trastuzumab and pertuzumab held and ECHO/MUGA repeated will be summarized. In addition, the change in LVEF at that timepoint will be summarized using descriptive statistics.

In addition, Cox regression model of time to first CHF and time to first CHF or asymptomatic LVEF events will be utilized to explore risk factors for cardiac dysfunction. Optional blood samples for assessment of candidate markers indicative of cardiac dysfunction will be collected periodically from consenting patients for exploratory analysis.

Adverse events. Verbatim descriptions of treatment-emergent AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI-CTCAE, Version 3.0. All AEs, including SAEs, will be summarized by treatment arm and CTCAE grade. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Laboratory data. Clinical laboratory tests will be performed at local laboratories. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTCAE, Version 3.0. Select laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm.

8.2.5 Other Analyses

8.2.5.1 Exploratory Biomarker Analysis

The objective of the further statistical analyses of biomarkers is the identification of those markers or combinations of markers which show best association with positive or negative clinical outcome of pertuzumab treatment or safety issues. Special emphasis will be on the identification of markers that discriminate between patients (subgroups) that specifically benefit from the treatment. These biomarker analyses will be explorative. Data on markers (e.g., IHC scores, ISH scores on tumor gene amplification, and DNA mutation data of tumor target genes) will be analyzed, depending on their availability.

According to experience, many biomarkers show a skewed statistical distribution across patients and within patient. Frequently there is also some biochemical background of this skewness; the variation process has a multiplicative structure. Biomarkers with skewed distributions may cause problems when linear statistical approaches (e.g., regression) are to be used. When used as covariates in statistical models, these biomarkers as well can obscure the results. Therefore, suitable transformations need to be found that transform these measurements into distributions with an approximate Gaussian shape. Typical choices in the biomarker area are transformations of the form log $(x + c)$. These transformations do not change the order of the values, such that non-parametric analyses based on ranks or cutoffs remain unchanged by the transformation. Such transformations are also a prerequisite when linear multivariate approaches (e.g., discriminant analysis and principal component analysis) are employed.

The basic statistics and interdependencies of the different markers will be descriptively investigated. Methodological analyses comparing different measurement approaches, e.g., IHC and qRT-PCR, will be performed with regard to reliability and validity.

Exploratory Statistical and Analytical Methods

During the course of an explorative analysis, numerous statistical tests will be performed. The p-values emerging from these analyses will not (and cannot) be interpreted in a confirmative sense; they will be seen as a special descriptive tool in order to guide the analyses toward improved prediction rules.

Markers will be evaluated on a univariate level regarding their potential for prediction (e.g., search or adaptation of cutoffs) of the clinical endpoints. Further multivariate techniques (e.g., linear discriminant analysis, multiple logistic regression, principal component analysis with rotation, cluster analysis, CART methodology) will be employed in order to study combinations of markers.

Biomarker and response correlations with clinical covariates will be investigated. It will be checked whether covariates can improve the prediction and whether there is an interaction with the biomarkers. Relevant covariates could become a part of an explorative biomarker prediction rule.

Candidate groupings derived from biomarker prediction rules will be checked with time-to-event variables (Kaplan-Meier curves, Cox proportional hazard model, log-rank test).

8.2.5.2 Pharmacoeconomic Analysis

The number of hospital visits, number of days admitted, and type of hospital visits (emergency room vs. in-patient care) will be summarized by treatment arm. The Fisher's exact test will be employed to compare the difference in these outcomes between the two treatment arms.

8.3 Sample Size

A sample size of 800 patients is needed to provide 80% power to detect a 33% improvement in OS (HR = 0.75) at the two-sided significance level of 5%. Since both PFS and OS analyses are event-driven, and to avoid prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial is designed to enroll sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of the final PFS analysis.

Assuming that the median OS in the control arm is 36 months and OS is exponentially distributed, one interim analysis at 50% of total required deaths, and a Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary, approximately 385 deaths will be required. In addition, assuming that the accrual rate is approximately 40 patients per month after a 9-month ramp-up period, 800 patients will need to be enrolled and followed for an additional 29.5 months to obtain 385 deaths. The enrollment period is estimated to be 26.5 months, and 50% of the required deaths will be reached at around 33.5 months.

Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it is estimated that 381 IRF-assessed PFS events, corresponding to approximately 448 investigator-assessed events, will have occurred when 50% of the required deaths (193 deaths) is reached. Table 6 lists the power for final PFS analysis at the two-sided significance level of 5% with 381 IRF-assessed PFS events. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.

Table 6 Statistical Power for Final PFS Analysis

Effect size	Power for Log-Rank test of PFS
40% improvement in PFS	90%
33% improvement in PFS	80%

PFS=progression-free survival.

All sample size calculations were performed using East® Version 4 (Cytel, Inc., Cambridge, MA).

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

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

An electronic data capture (EDC) system using electronic Case Report Forms (eCRFs) will be utilized for all data capture required for this study. Exceptions to this include radiographic tumor assessment films (including but not limited to chest X-rays, CT scans, MRI, and bone scans), ECHO/MUGA cardiac assessments, and paper quality-of-life questionnaires completed by the patients. Local clinical laboratory data, including hematology and serum chemistry will be transcribed by the site from the paper laboratory reports onto the eCRF. **In no case is the eCRF to be considered as source data for this trial.**

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche database will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the investigator.

Throughout the study the study management team will review data according to the Data Review Plan as described in the Data Quality Plan.

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up to date version of MedDRA (medical dictionary for regulatory activities terminology) for AEs and diseases and the INN (international non-proprietary name) drug terms and procedures dictionary for treatments and surgical and medical procedures.

Unblinding will not be permitted during the study except for safety issues that arise during study treatment. Treatment unblinding will take place right before the final analysis for the primary endpoint or at the time the DMC recommends trial stopping.

10. STUDY COMMITTEES

This study consists of three independent review committees: an IRF, a CRC, and a DMC. The IRF will be used to independently assess tumor responses. The DMC will be employed to review accumulating safety data for the combination of pertuzumab + trastuzumab + docetaxel. Because cardiac toxicity is a potential safety concern for the pertuzumab + trastuzumab treatment, an independent CRC will be convened to review cardiac assessments and report their findings to the DMC and the Sponsors. An independent data coordination center (DCC) will be employed to perform analyses for DMC reviews.

Independent Review Facility. An independent imaging group will be used to evaluate tumor assessments for determination of progression free survival as a part of the primary objective of the trial. Imaging studies (CT/MRI/bone scans) will be acquired according to a standard protocol and will be transmitted to the independent reviewers. In addition, relevant cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data will be forwarded, if available, to the independent reviewers to aid with assessment of progressive disease and response. Full details are listed in the Independent Imaging Review Charter. Investigator tumor assessments will not be reconciled with the IRF tumor assessments.

Independent Data Monitoring Committee. The DMC will be composed of a group of independent experts including at least one statistician, three medical oncologists, and one cardiologist external to the Sponsors.

The DMC will be responsible for monitoring the safety of patients in the study (see Section 8.2.3.3) for a brief description of the monitoring plan). The DMC will make recommendations to the Sponsors regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study for excessive toxicity. A separate DMC Charter will outline the committee's composition and the members' roles and responsibilities.

Cardiac Review Committee. A group of independent experts will form the Cardiac Review Committee to determine the cardiac event rates. This group will consist of cardiologists who are not Principal Investigators, DMC members, or active (contracted) Genentech or Roche consultants.

The committee members will review patient data profiles and source documents from all potential cases of left ventricular systolic dysfunction, as specified in the CRC charter. The independent cardiac assessments will be provided to the DMC for review every 6 months starting approximately 9 months after the first patient has been enrolled, and at each of the interim analyses. The detailed review process, definition of cardiac events, committee composition, and the member roles and responsibilities will be documented in the CRC charter.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC). For studies conducted in the United States or under U.S. IND, the investigator will additionally adhere to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators," part 50, "Protection of Human Patients," and part 56, "Institutional Review Boards."

In other countries where "Guidelines for Good Clinical Practice" exist, Roche/Genentech and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

It is the responsibility of the investigator or a person designated by the investigator (if acceptable by local regulations) to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, anticipated benefits, objectives, and potential hazards of the study. Appropriate forms for obtaining written informed consent will be provided by the investigator or by Roche/Genentech/designee.

For patients not qualified to give or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his or her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients, including those already being treated, should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.3 Independent Ethics Committees/Institutional Review Board

Independent Ethics Committees (non-U.S. Sites): This protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the patient, will be submitted by the investigator to an IEC. Approval from the committee must be obtained before starting the study and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IEC approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

Institutional Review Board (U.S. Sites): It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures will be reviewed and approved by an IRB. This board must operate in accordance with the current U.S. Federal Regulations. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsors and the investigator. Protocol modifications must be prepared by a representative of the Sponsors and initially reviewed and approved by the Clinical Science Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies, if required. Approval must be received by the investigator before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsors and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche, Genentech, and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

15. STUDY DOCUMENTATION, eCRFs, AND RECORD KEEPING

15.1 Investigator's Files/Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) investigator's study file; and (2) patient clinical source documents.

The investigator's study file will contain the protocol and amendments, IRB/IEC and governmental approval with correspondence, sample Informed Consent Form, drug records, staff curriculum vitae, and authorization forms and other appropriate documents and correspondence, etc. In addition, at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the investigator's study file.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include patient hospital/clinic records; physician's and nurse's notes; appointment book; original laboratory reports; ECG, EEG, X-ray, pathology and special assessment reports; signed Informed Consent Forms; consultant letters; and patient screening and enrollment logs.

The investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, Roche/Genentech must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Roche or Genentech to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator, in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made before storing outside of the site.

15.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

15.3 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit, or Genentech GCP/Quality Assurance Group or its designees, or

to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

Data for this study will be captured via an EDC system by using an eCRF. An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change. For each patient randomized, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study treatment, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

This protocol will be co-sponsored by Genentech, Inc., and F. Hoffmann-La Roche, Inc. These Sponsors will oversee the management of this study and will be responsible for clinical operations including site management and source data verification.

Genentech and Roche will identify potential sites for participation in this study. Study networks will be assessed by Genentech and Roche and, where necessary, a Corporate Compliance Group–approved risk mitigation plan will be implemented. The Sponsors will perform pre-trial evaluations at individual sites. The Sponsors will oversee selection, approval, and monitoring of all clinical study sites. Patient eligibility verification will be conducted on all patients identified for enrollment into the study.

Overall monitoring will be managed by the study Sponsors. Statistical analyses and clinical study report preparation will be managed by the Roche staff.

The IVRS will be utilized for collection of patient screening information, randomization, and drug management. It is anticipated that a number of sites will be able to utilize a Central IRB (CIRB), and this will be managed by the Sponsors. Tissue and blood samples will be collected for this study and will be stored and assayed by a central analytical laboratory or the Sponsors. Data from central analytical laboratories will be sent directly to Roche electronically and will not be collected via CRF. Local clinical laboratory data including hematology and serum chemistry will be transcribed by the site from the paper source documents onto the eCRF**.**

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Roche/Genentech, e.g., patients' written Informed Consent Forms, in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

In accord with standard editorial and ethical practice, Roche/Genentech will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Roche/Genentech personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche/ Genentech personnel. Authorship will be determined by mutual agreement.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal (results in death) (NOTE: death is an outcome, not an event)
- is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- required in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For SAEs, possible causes of the event **are** indicated by selecting one or more options (check all that apply):

- Pre-existing/Underlying disease – specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (Cont.)

An SAE occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, an SAE that occurs after this time, if considered related to test "drug," should be reported.

Such preliminary reports will be followed by detailed descriptions later, which will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

For SAEs, the following must be assessed and recorded on the AEs page of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

For sites outside of the United States

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor (see attached gcp_for000227 for details of administrative and contact information).

ROCHE HEADQUARTERS CONTACT for SAEs: Clinical Operations/Clinical Science (see attached gcp_for000227 for details of administrative and contact information).

Weekends, holidays, and after 5:00 p.m., call the local emergency contact number provided by the Monitor.

For United States sites

GENENTECH HEADQUARTERS CONTACT for SAEs: Drug Safety

Fax: (650) 225-4682 or (650) 225-5288

Weekends, holidays, and after 5:00 p.m., call 1-800-526-6367 and ask for the physician on call.

Appendix 2 ECOG Performance Status Scale (with Karnofsky equivalent)

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90–100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work (Karnofsky 70–80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50–60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30–40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10–20)
5	Dead

Appendix 3 NYHA Classification

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997	

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000])

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable lesions – all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, Ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000]) (Cont.)

Response Criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (1)

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UA	Non-PD	No	UA
Non-PD	UA	No	UA

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000]) (Cont.)

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of progressive disease at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) that is defined in the study protocol.

Duration of Overall Response

- The duration of overall response is measured from the time-measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for progressive disease are met, taking as reference the smallest measurements recorded since the treatment started

Appendix 5 National Cancer Institute-Common Toxicity Criteria AE v3.0

The Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE v3.0) can be found in the Roche handout entitled: ”National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0” or on the following web-site:

http://ctep.cancer.gov

Appendix 6 FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

Appendix 6 FACT-B (Version 4) (Cont.)

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

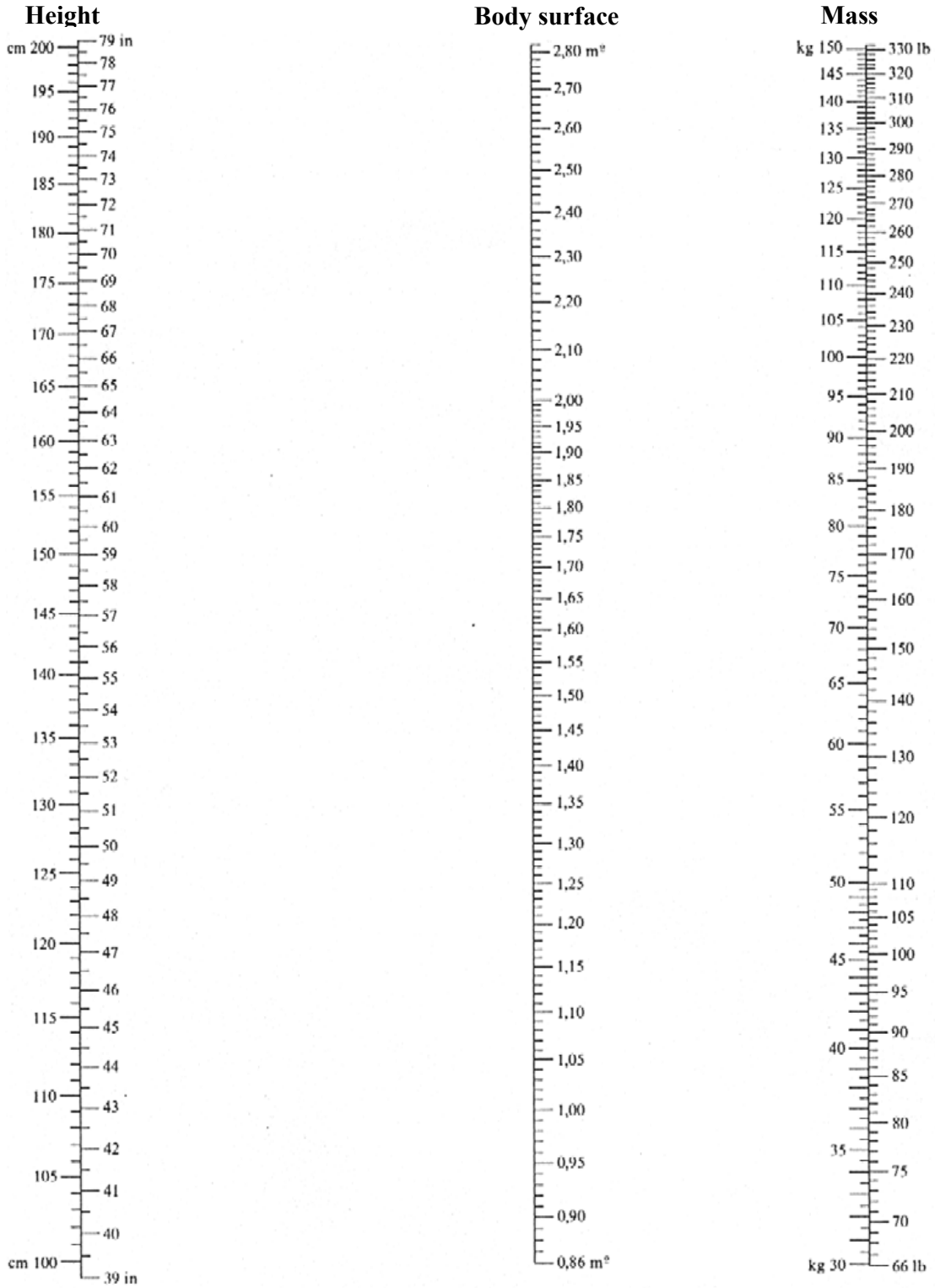
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

Appendix 6 FACT-B (Version 4) (Cont.)

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath.....	0	1	2	3	4
B2	I am self-conscious about the way I dress...	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive.....	0	1	2	3	4
B5	I am bothered by hair loss.....	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have.....	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix 7 Nomogram for the Determination of Body Surface Area



Based on the Formula from Du Bois and Du Bois, Arch.intern.Med., 17, 863 (1916): $0 = M^{0,425} \times L^{0,725} + 71,84$ resp. $\log 0 = \log M \times 0,425 + \log L \times 0,725 + 1,8564$
(0: Body surface [in cm2], M; Body mass [in kg]: L: Body length [in cm]

DATA REPORTING AND ANALYSIS MANUAL (DRAM)

CLINICAL STUDY REPORT (CSR) STUDY DRAM FOR WO20698

PART I

Version no: B

DRAM APPROVAL

Date: See last date in electronic signature manifestation below.

DRAM approved by: See electronic signature manifestation below.

Name	Reason for Signing	Date and Time (UTC)
Corte_Real_Correia,Helena	Documentation Specialist	01-Jul-2011 09:39:53
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Ross, Graham	Clinical Science Leader	01-Jul-2011 15:08:29

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AEGT	Adverse Event Group Terms
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
BML	Below Measurable Limit
BOR	Best Overall Response
BSA	Body Surface Area
CBR	Clinical Benefit Response
CI	Confidence Interval
CR	Complete Response
CHF	Congestive Heart Failure
COG	Clinical Operations Guidelines
CRC	Cardiac Review Committee
CSR	Clinical Study Report
CT	Computed Tomography
DCC	Data Coordinating Centre
DCS	Data Collection Specification
DFI	Disease Free Interval
DMC	Data Monitoring Committee
DRAM	Data Reporting and Analysis Manual
DRMP	Drug Risk Management Plan
ECD	Extracellular Domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form

GLOSSARY OF ABBREVIATIONS

EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen Receptor
FACT-B	Functional Assessment of Cancer Therapy-for patients with Breast Cancer
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence In Situ Hybridization
HAHA	Human Anti-Human Antibody
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INN	International Nonproprietary Names
INR	International Normalized Ratio
IRF	Independent Review Facility
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
MARS	Management, Analysis and Reporting of Safety data
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MUGA	Multigated Angiogram
NACT	Next-line anti-cancer therapy
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for

GLOSSARY OF ABBREVIATIONS

	Adverse Events
NYHA	New York Heart Association
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Safety Analysis Population
SD	Stable Disease
SI	Système International
SLD	Sum of Longest Diameters (of target lesions)
SMQ	Standardized MedDRA Queries
SMT	Study Management Team
TOI-PFB	Trial Outcome Index-Physical Functional Breast
UA	Unable to Assess
ULN	Upper Limit of Normal

1. GENERAL INFORMATION

This document provides details of the final statistical analysis for study WO20698/TOC4129g, a Phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (MBC).

1.1 Data Cut-off

Data cut-offs will be defined for each reporting event in the study. The data cut-off for the primary analysis will occur at the point when 381 PFS events have occurred according to the Independent Review Facility (IRF). The data cut should be applied keeping all dates on or before the data cut-off based on visit dates and start dates. If a start date is partial then the partial date imputation rules (in Section 4.5.1) will be used to decide whether to include in the data cut. (Note: in the case of partial date recorded for a death, the imputation rules will use 'last known date' (defined in Section 4.3.3). At the point of applying the data cut, last known date will not have been calculated, so deaths will be included in the data cut, based on the usual partial date rules for deaths (Section 4.5.1.2) except for the part relating to last known date. Therefore rules use the worst case scenario to include deaths in the data cut).

Dates that are after the data cut-off may be included in the datasets for the primary analysis in the following cases:

1. Adverse event end dates: events that started prior to the cut-off but resolved between the cut-off and Database Lock (DBL)
2. Other treatment end dates: other treatments that started prior to the cut-off and ended between the cut-off and DBL
3. Hospitalization date of discharge: hospitalizations that commenced prior to the cut-off, and the patient was discharged between the cut-off and DBL

Post data cut-off end dates will be handled in the following way within the analysis and reporting:

- Post data cut-off end dates will be included in the listings
- Durations as displayed in listings will be calculated from the start date to the end date
- Durations that are summarized in tables (duration of diarrhoea and rash, and hospitalizations) will be 'censored' such that the duration will be calculated from the start date to the last known date
- Post data-cut-off end dates will be excluded when there is a need to derive an analysis variable, such as a censoring date, the last known date in treatment period or the last known date
- The GDMs will include a flag to identify any records with a post data cut-off end date. The VADs will also include both the duration and the 'censored duration' for diarrhoea, rash and hospitalization, in the case of a post data cut-off end date

If a post data cut-off end date is partial, the imputation rules will be conservative such that there is no risk of a partial end date being imputed as a date after the data cut-off in error.

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of this study is to compare progression-free survival (PFS) between patients in the two treatment arms, based on tumor assessments by an Independent Review Facility (IRF).

1.2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To compare overall survival (OS) between the two treatment arms
- To compare PFS between the two treatment arms based upon Investigator assessment of progression
- To compare the overall objective response rate (ORR) between the two treatment arms
- To compare the duration of objective response between the two treatment arms
- To compare the safety profile between the two treatment arms
- To compare time to symptom progression, as assessed by the Functional Assessment of Cancer Therapy (FACT) Trial Outcome Index – Physical Functional Breast (TOI-PFB)
- To evaluate if biomarkers from tumor tissues or blood samples (e.g., HER3 expression, Fcγ, and serum ECD/HER2 and/or HER ligands concentrations) correlate with clinical outcomes

1.3 Study Design

This study is a Phase III, randomized, double-blind, placebo-controlled, multicenter, international clinical trial. Patients who have human epidermal growth factor receptor 2 (HER2)-positive MBC and have not received chemotherapy or biological therapy (including approved or investigational tyrosine kinase/HER inhibitors or vaccines) for their metastatic disease are eligible for the study. Patients could have received one prior hormonal treatment for MBC. Patients may have received systemic breast cancer treatment in the neo-adjuvant or adjuvant setting, provided that the patient has experienced a disease free interval (DFI) of ≥ 12 months, from completion of adjuvant systemic treatment (excluding hormonal therapy) to metastatic diagnosis. Patients may have received trastuzumab and/or a taxane as part of their neo-adjuvant or adjuvant treatment. HER2-positive status using archival paraffin-embedded tumor tissue will be confirmed in a central laboratory by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH).

A total of 800 patients will be randomized in a 1:1 ratio to one of two treatment arms:

Arm A:

- **pertuzumab placebo:** every 3 weeks until progressive disease or unacceptable toxicity
- **trastuzumab:** 8 mg/kg intravenous (IV) loading dose, followed by 6 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity
- **docetaxel:** 75 mg/m^2 IV every 3 weeks for at least 6 cycles until progressive disease or unacceptable toxicity (at the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, grade 4 neutropenia for > 5 days or absolute neutrophil count (ANC) < 100/µL for more than 1 day, or other non-hematological toxicities of grade > 2 [National Cancer Institute – Common Terminology Criteria for Adverse Events, NCI-CTCAE, version 3]).

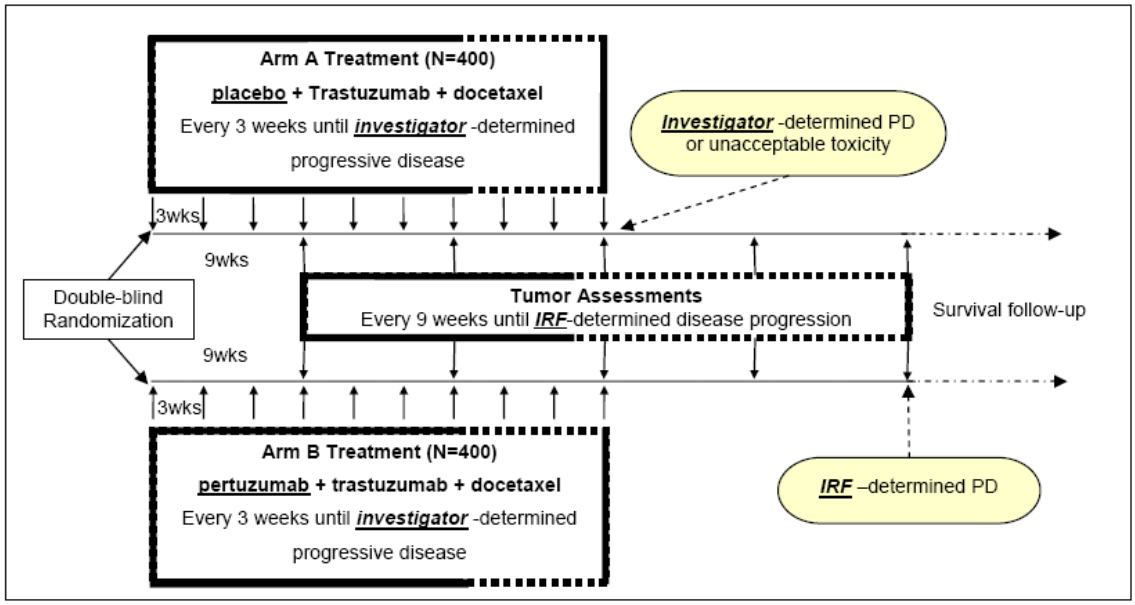
Arm B:

- **pertuzumab:** 840 mg IV loading dose, followed by 420 mg IV every 3 weeks until progressive disease or unacceptable toxicity
- **trastuzumab:** *as for Arm A*
- **docetaxel:** *as for Arm A*

Patients should remain in the treatment phase of the study until Investigator-assessed radiographic or clinical progressive disease (PD), unmanageable toxicity, or study termination by Genentech and Roche. Patients will not receive open-label pertuzumab after discontinuation of study treatment. For patients who discontinue study treatment for reasons other than death or IRF-determined progression, tumor assessments will continue after discontinuation of study treatment until IRF-assessed progression. In addition, patients will be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and Roche.

Tumor assessments will be conducted every 9 weeks from the date of randomization. Delays in treatment administration will not impact the timing of the tumor assessments. If a tumor assessment must be performed early/late, subsequent assessments will be conducted according to the original schedule of every 9 weeks from the date of randomization. Tumor assessments must be conducted until IRF-determined PD, even if study treatment has been discontinued due to an Investigator-determined PD or unacceptable toxicity, and even if a patient starts a new treatment for their breast cancer. (See Figure 1).

Figure 1 Study Design: Patient Treatment and Assessment



PD=progressive disease; IRF=Independent Review Facility.

A Data Monitoring Committee (DMC) will monitor patient safety. In addition to the DMC, an independent Cardiac Review Committee (CRC) will review cardiac data generated during the course of the study and report their findings to the DMC for review every 6 months beginning 9 months after the first patient is enrolled and at the safety interim analysis.

An IRF will evaluate progressive disease and overall tumor response through a periodic review of all radiographic (e.g. MRI, CT, bone scans, chest x-ray, etc.), as well as cytologic (e.g. relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available, generated from all patients.

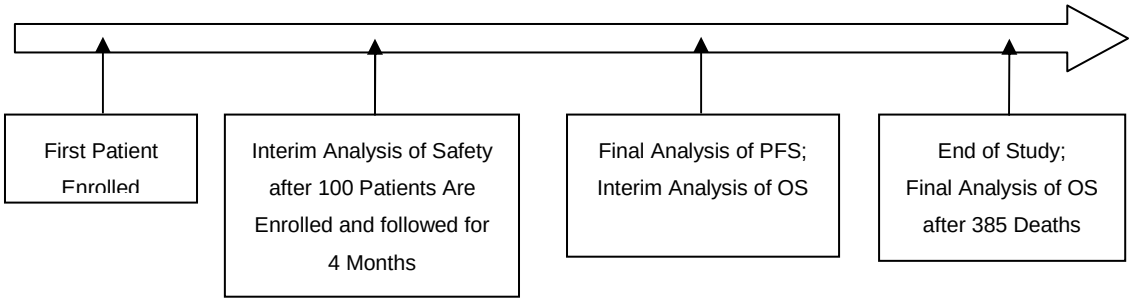
No interim analysis of the primary efficacy endpoint (IRF-determined PFS) is planned for this study. One safety-only interim analysis occurred after 100 patients had been enrolled and followed for at least 4 months, at which the DMC identified no safety concerns and recommended continuing the trial unchanged. The (final) primary efficacy analysis will take place when 381 IRF-assessed PFS events (corresponding to approximately 448 Investigator-assessed PFS events) have occurred. The primary efficacy analysis will be based on tumor assessments by the IRF.

At the time of the (final) primary PFS analysis, it is expected that 193 patients will have died. An interim analysis of OS will be conducted at the same time as the primary efficacy analysis of PFS. Patients who are still on study will continue to be followed for safety and survival. A final analysis of survival will be conducted when 385 deaths have been reported (unless the study is terminated early by the Sponsors).

1.3.1 End of Study

The trial will end when approximately 385 deaths have been reported or the trial is terminated by the Sponsors (see Figure 2).

Figure 2 Study Design: Analysis Timing



OS = overall survival; PFS = progression-free survival.

1.4 Sample Size and Power Calculations

A sample size of 800 patients was estimated to be needed to provide 80% power to detect a 33% improvement in OS (Hazard Ratio (HR) = 0.75) at the two-sided significance level of 5%. Since both PFS and OS analyses are event-driven, and to avoid prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial was designed to enroll sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of the final PFS analysis.

Assuming that the median OS in the control arm is 36 months and OS is exponentially distributed, one interim analysis at 50% of total required deaths, and a Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary, approximately 385 deaths would be required. Based on the protocol-assumed accrual rate of approximately 40 patients per month after a 9-month ramp-up period, it was estimated that 800 patients would need to be enrolled and followed for an additional 29.5 months to obtain 385 deaths. The estimates for the 9-month ramp-up period detailed in the protocol are as follows:

- Month 1 – one patient
- Month 2 – two patients
- Month 3 – four patients
- Month 4 – eight patients
- Month 5 – thirteen patients
- Month 6 – nineteen patients
- Month 7 – twenty-six patients

– Month 8 – thirty-four patients

– Month 9 – forty patients

Based on these protocol assumptions, the enrollment period was estimated to be 26.5 months, and 50% of the required deaths would be reached at around 33.5 months.

Following a review of the actual recruitment rate after 12 months of recruitment, the estimates were revised, assuming a peak accrual of 35 patients per month. The revised enrollment period was estimated to be 31.9 months with 50% of the required deaths reached after 36.4 months.

Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it was estimated that 381 IRF-assessed PFS events, corresponding to approximately 448 Investigator-assessed PFS events, will have occurred when 50% of the required deaths (193 deaths) is reached. It is currently estimated that 160 deaths will have occurred at the time of the primary analysis. Table 1 lists the power for final PFS analysis at the two-sided significance level of 5%, with 381 IRF-assessed PFS events. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.

Table 1 Statistical Power for Final PFS Analysis

Effect size	Power for log rank test of PFS
40% improvement in PFS	90%
33% improvement in PFS	80%

All sample size calculations were performed using East® Versions 4 and 5 (Cytel Inc., Cambridge, MA). The module used was "Survival Superiority Trials: Two-Sample Test – Log rank test: Drop outs, piecewise constant hazard variable accrual".

1.5 Blinding and Randomization

A total of approximately 800 patients (approximately 400 per arm) will be enrolled. Eligible patients will be randomized in a 1:1 ratio to one of two treatment arms by central randomization using an Interactive Voice Response System (IVRS).

A complete block randomization scheme will be applied to achieve balance in treatment assignment within each of the eight strata, as defined by the following stratification factors:

- prior treatment status:
  - de novo
  - adjuvant or neo-adjuvant therapy (includes chemotherapy and/or trastuzumab in the adjuvant or neo-adjuvant setting)
- region
  - Asia
  - Europe

- North America
- South America

Unblinding of treatment assignment will not be permitted during the study except for safety issues that may arise during study conduct. An approval from the Sponsor's medical monitor(s) must be obtained prior to any unblinding of treatment code.

Patients who enroll in this study are not permitted to be re-randomized to this study and enrolled for a second course of treatment.

2. EVALUATIONS PERFORMED BEFORE DATABASE CLOSURE

2.1 Program Development and Validation Activities

Since the study is blinded, no access to the treatment code is available during development of programs. Therefore, programs will be developed and validated before database closure using a dummy treatment code.

2.2 Formal Data Monitoring Committee (DMC) Activities

A DMC was convened to monitor patient safety at defined intervals. In addition to the DMC, an independent Cardiac Review Committee (CRC) will review all suspected cases of left ventricular systolic dysfunction (LVSD). This CRC will report their findings to the DMC on a regular basis and at the time of the safety interim analysis. Specific details of the schedule of DMC and CRC activities can be found in the DMC and CRC charters.

2.3 Interim Safety Analysis

In addition to the periodic safety monitoring by the DMC and CRC, one interim safety analysis with a formal stopping criterion was planned. This interim safety analysis took place after 100 patients had been enrolled and followed for at least 4 months. The data cut for the interim analysis took place 4 months after the date that the 100th patient was randomized. The 100th patient was randomized on 3rd November 2008 and therefore the date of the data cut was 3rd March 2009. The interim analysis data displays were based on all patients randomized and on the database at the time of the data cut. Selected summary table displays (including the CRC adjudicated data displays and the AEs of special interest) were also be produced based on the patients randomized up to and including the date that the 100th patient was randomized, i.e. those patients randomized at least 4 months prior to the data cut.

The stopping criterion was based on the incidence of cardiac events, as determined by the CRC, defined as symptomatic LVSD events (deaths or non-deaths), non-LVSD cardiac deaths and probable cardiac deaths.

Cardiac events potentially related to prolongation of QT were also included in the safety summaries for the interim analysis. These events were identified by selection of patients reporting any of the following adverse events, based on preferred term: Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope and convulsion.

The DMC reviewed all safety data from all patients enrolled and could recommend stopping the study if, among the patients randomized at least 4 months prior to the data cut, the incidence of cardiac events (symptomatic LVSD events (deaths or non-deaths), non-LVSD cardiac deaths and probable cardiac deaths) based upon the CRC assessment was at least 9.3% higher in the pertuzumab arm compared with the control arm. The DMC could also recommend stopping the study if, in their opinion, the incidence of other clinically significant toxicities, such as neutropenia, neutropenic sepsis, or severe pulmonary toxicity, was unacceptably high in the pertuzumab arm compared with the control arm.

Assuming that the cardiac event rate in the control arm was 5%, the stopping guidance for cardiac event rate was chosen so that the chance of falsely stopping the study at the interim analysis would have been be < 5% if there was no difference in event rate between two arms. If the event rate in the pertuzumab arm was 10%, the chance of stopping the trial at the interim analysis was approximately 19%. However, if the event rate in the pertuzumab arm was 15%, the chance of stopping the trial at the interim analysis would increase to approximately 47%.

The recommendation from the DMC following the safety interim analysis was to continue the study unchanged.

2.4 Blinding of DMC, CRC and Interim Analysis

All CRC data review activities will be based on blinded data. The DMC will review and discuss predefined unblinded data outputs relating to the safety of study participants at their periodic scheduled reviews and at the interim analysis. All unblinded outputs will be prepared by a Data Coordinating Centre (DCC) statistician for the DMC. All Sponsor and Study Management Team (SMT) personnel will remain blinded and will not be involved in DMC discussions and recommendations.

Full details are provided in the DMC and CRC charters.

3. ANALYSIS POPULATIONS

The following analysis populations are defined.

3.1 All Patients Population

All randomized patients will be included in the All Patients Population. All data listings will be based on this population. Where listings are separated by treatment arm, safety data listings will be grouped by actual study treatment received and all other listings will be grouped by treatment randomized. Given that only randomized patients are entered onto the study database, it is implicit that the All Patients Population will comprise all patients in the study database.

3.2 Intent-to-Treat (ITT) Population

All randomized patients will be included in the intent-to-treat (ITT) population. All efficacy analyses will be based on the treatment arm to which the patients were randomized. Given that only randomized patients are entered onto the study database, it is implicit that the ITT Population will comprise all patients in the study database. The

ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment.

3.3 Protocol Violations

A per protocol analysis population is not being defined for this study. The protocol violations will be documented according to predefined criteria (Appendix 1) to be used as information in the Clinical Study Report (CSR). The only major protocol violation defined for this study is no study medication taken, which will lead to exclusion from the Safety Analysis Population (SAP – see Section 3.4). Violations of protocol-defined inclusion/exclusion criteria and on-study protocol violations will be classified as minor violations, and will not lead to exclusion from any analysis population.

3.4 Safety Analysis Population

All patients randomized who have received any amount of study medication (i.e. pertuzumab/placebo dose > 0 or trastuzumab dose > 0 or docetaxel dose > 0) will be included in the Safety Analysis Population (SAP). By assumption patients who have received any amount of study medication are assumed to have had the opportunity to report adverse event safety data regardless of whether they have any post-baseline safety assessments recorded and will be included in the SAP. All safety analyses will be based on the treatment the patients actually received such that a patient who received any dose of pertuzumab will be included in the pertuzumab arm (regardless of whether this was intended and regardless of whether any chemotherapy or trastuzumab were given).

3.5 Other Analysis Populations

No additional analysis populations are defined. However, it should be noted that for certain outcomes, the analysis may be based on sub-sets of the ITT population, as the outcome may only be relevant for specific patients. For objective response rate and time to response, only patients with measurable disease at baseline will be included in the analysis (see Section 7.2.3.2 for a definition of measurable disease). For duration of response, only responders (i.e. patients with a best overall response of CR or PR) will be included in the analysis. For the time to symptom progression from the FACT-B questionnaire, only female patients will be included in the analysis. More details are provided under the individual sections detailing these analyses.

3.6 Outputs by Treatment Received

If any patients are randomized but not treated, listings produced for all patients by treatment received will include patients under the category ‘Trt Not Given’.

Data for all treated patients will be reported under the ‘Pertuzumab + trastuzumab + docetaxel arm or the ‘Placebo + trastuzumab + docetaxel’ arm (with allocation based on whether the patient received pertuzumab or placebo) irrespective of whether they received trastuzumab or docetaxel or not.

Patients who receive one or more administrations of pertuzumab at any time during the study will be reported under ‘Pertuzumab’ as opposed to ‘Placebo’ even if this administration was given in error (i.e. the patient was randomized to receive placebo but received one or more doses of pertuzumab).

4. DEFINITION AND DERIVATION OF KEY DATA POINTS

4.1 Study Day 1

Study Day 1 is defined as the date of the first administration of any component of the study treatment regimen received, after randomization. As study medication is administered in the order of pertuzumab/placebo followed by trastuzumab then docetaxel, Study Day 1 will usually be the date of the first pertuzumab/placebo administration. The first dose of trastuzumab and docetaxel are administered on the day after the pertuzumab/placebo administration in the first cycle. From cycle 2 onwards, all treatments are expected to be administered on the same day.

Study day calculations will be relative to the first dose of study medication. Study day will therefore be missing for patients who did not receive any study medication.

If the dates are partial, study day should be imputed using the rules specified in Section 4.5. If the event/assessment date is on or after the first dose of study medication then study day = (event/assessment date – date of 1st study drug administration) + 1. Otherwise study day = (event/assessment date – date of 1st study drug administration).

4.2 Baseline Values

Unless otherwise specified, the baseline value of an assessment is defined as the last valid value recorded during the pre-treatment period before or on study Day 1. (A measurement on study Day 1 is assumed to be prior to study medication administration, using the treatment cycles rule of whether we assign an assessment to before or after a cycle starts). If there is more than one value on the last baseline date then the unscheduled value will be taken (if there is both a scheduled and an unscheduled value) or the last value based on the repetition number (in this case we will use page number) of the assessment (if both are unscheduled values).

The protocol-specified window for the majority of screening assessments is 1 to 28 days prior to randomization, i.e. Day -28 to -1. The baseline LVEF may be taken up to 42 days prior to randomization. Any baseline assessments falling outside of the protocol-specified windows will still be included in the SAP and ITT populations, as long as they occur prior to the first dose of study treatment.

Unless otherwise stated the baseline value as defined above will be summarized in outputs (e.g. Demography), instead of the screening value (in most cases there will only be a screening value and so this will be the baseline value). In listings all values will be included and will be labeled using both the information from the eCRF page on which data are recorded and an identifier that the data are pre-treatment based on start date of study medication (see Section 4.11).

4.3 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. The cut-off shown for the overall study treatment period applies only to patients who have withdrawn from study treatment based on the database received. It will be assumed that patients who have not withdrawn study

treatment according to the database are still in the treatment period. The rules defined in Section 4.5.1.1 below will be applied to any partial/invalid start dates to determine if an event/treatment/assessment falls during the cutoff dates for the overall treatment period.

4.3.1 Pre-Study-Treatment Period

The pre-study-treatment (or "pre-treatment") period includes medical history, demographic data, screening assessments and any other evaluations undertaken prior to receiving first dose > 0 of study treatment. Adverse events occurring before the first dose > 0 of study treatment will be labeled as "Pre-Trt".

4.3.2 Overall Study Treatment Period

The overall study treatment period begins on Study Day 1, upon receiving the first dose > 0 of study treatment. The overall study treatment period ends 42 days after the last dose > 0 of study treatment.

4.3.3 Definition of Last Known Date

The last known date is the latest date that a patient is considered to have participated in the study based on complete and partial dates and is needed to determine the time to event and censoring for OS, end dates of events and the duration of follow up. The 'last known' date should be identified after the data cut has been applied, using the latest of:

- all complete dates left in the database
- all partial start dates using partial date imputation rules (in Section 4.5.1.1)
- all partial end dates, imputed as the earliest date possible - i.e. using the 1st of month or 1st January (depending on day missing or day and month missing). This is because to use the latest date possible would be over-conservative as end dates (such as for concomitant treatments) may be recorded as year only. In this case, assuming that the patient is still in study at 31st December would be over inclusive for the purpose of last known date.

Note that if last known date is defined by a partial date that uses the Data Management partial date rules, the partial date will be re-set using a conservative approach. For example, if a 'month and year' partial date is entered, and the DM rules assign to the 15th of the month, the partial date would be reset to the 1st of the month for the purposes of identifying the last known date.

Last known date is based on patient activity as opposed to an administrative date that did not involve the patient, for example the date of CRC adjudication.

The date of contact on the "Survival follow-up" DCS may be classified as either patient activity or an administrative date, depending on the patient's survival status. The date of contact will only be considered for the last known date if the survival status on the "Survival follow-up" DCS is 'alive'. If the survival status is 'dead', 'lost to follow up' or 'withdrew consent', the date of contact will be deemed an administrative date, and should not be considered for the last known date.

Sampling dates from the PCON GDM, for pharmacokinetic (PK) analysis, are excluded from the derivation of last known date, as these dates may not be a reliable indicator of patient activity in the study.

Time for last known date will be set as default to 23:59:59 to cover events occurring at any point in this day.

4.3.4 Definition of Last Known Date in the Treatment Period

The last known date in the treatment period is the latest date the patient is considered to have participated in the overall study treatment period based on complete and partial dates.

The last known date in the treatment period will be identified by taking the latest treatment start or end date and adding 42 days to this date, and then identifying the latest date that falls within the last treatment start or end date + 42 days from the following dates:

- all complete dates left in the database, excluding dates from the survival follow-up page
- all partial start dates using partial date imputation rules (in Section 4.5.1.1), excluding dates from the survival follow-up page
- all partial end dates, imputed as the earliest date possible - i.e. using the 1st of month or 1st January (depending on day missing or day and month missing). This is because to use latest date possible would be over-conservative as end dates (such as for concomitant treatments) may be recorded as year only. In this case, assuming that the patient is still in study at 31st December would be over inclusive for the purpose of the last known date in the treatment period.

Note that if the last known date in treatment period is defined by a partial date that uses the DM partial date rules, the partial date will be re-set using a conservative approach. For example, if a 'month and year' partial date is entered, and the DM rules assign to the 15th of the month, the partial date would be reset to the 1st of the month for the purposes of identifying the last known date.

Last known date in the treatment period is based on patient activity as opposed to an administrative date that did not involve the patient, for example the date of CRC adjudication.

Time for last known date in the treatment period will be set as default to 23:59:59 to cover events occurring at any point in this day.

Sampling dates from the PCON GDM, for PK analysis, are excluded from the derivation of last known date in treatment period, as these dates may not be a reliable indicator of patient activity in the study.

For patients still on treatment at the time of the datacut, the last known date in the treatment period will be the same as their last known date, defined in Section 4.3.3.

4.4 Missing Date Rules

For by visit data, apart from data coming from screening assessment pages, missing dates will be removed from the datacut. Any other missing dates follow the same rules of imputation as partial dates, as detailed in the following sections.

Note that it is not anticipated that missing dates will arise for by visit data since the eCRF requires a date to be entered. However, it is possible to receive data containing date=07/07/1977. This is a potential data cleaning issue and this date should be treated as a missing date.

4.5 Partial Date Rules

The electronic data capture (EDC) system allows some dates to be partially entered. For every partial date, our database also contains a date that has been imputed by the Data Management (DM) Clinical Programming group according to the rules below.

Table 2 Data Management Rules For Imputation of Partial Dates

Value	Imputation
Missing day; Month and year present	Day imputed to 15th of month.
Missing day and month; Year present	Day and month imputed as June 30th.
Missing year	Not imputed.

All partial dates will use the DM partial date rules, defined above, except for those described in the following sections.

4.5.1 Partial Start Dates

4.5.1.1 Adverse Events (Including LVSD, Cardiac Symptoms), Other Treatments, Withdrawals and Hospitalizations

The following rules will be applied in order to impute partial/invalid start dates for adverse events (including LVSD events and cardiac symptoms), withdrawal (only date of last contact field), previous and concurrent medications and hospitalization. These imputed dates can be used where it is necessary for an analysis to impute a partial/invalid start date, for example to determine an adverse event or hospitalization duration or to categorize a treatment as previous or previous-concomitant. These rules are conservative in that where it cannot be determined if the event/other treatment/hospitalization is before or after first study treatment, it will be assumed to be treatment emergent/concomitant/after start of treatment.

Note that invalid dates are any that have NK, ND, NA instead of a valid day, month or year.

Also, if a previous/concomitant medication page doesn't have start date recorded (i.e. the eCRF page does not include a field for start date), then we should not impute as we would expect missing day, month and year in this case.

Table 3 Imputation of Partial Start Dates

Value	Imputation
Missing/invalid day; Month and year present	If the patient's start date of the trial (defined as date of first infusion of study medication) occurs within this month, the imputed date will be set to 1 day after the start of trial (if the start of the trial is the last day of the month then it will be set to the same day as the start of the trial). Otherwise it will be set to 1st of month.
Missing/invalid day and month; Year present	If the patient's start date of the trial occurs within this year, the imputed date will be set to 1 day after the start of trial (if the start of the trial is the last day of the year then it will be set to the same day as the start of the trial). If no infusion occurred during this year, impute day and month as 1st January.
Missing/invalid day, month and year	The imputed date will be set to 1 day after the start of trial. NB: for missing date of last contact a date will not be imputed.
End dates	The imputed date in the above scenarios will also be checked against the associated end date, provided there is more information known for the end date than for the start date. This is to ensure that the start date is before the end date and that we are utilizing all available information from the end date. If not, the start date will be set to 1st of month of a month and year partial start date, and to the 1st January of a year only start date. If the original start date is missing, the start date will be set to the 1st of January of the end date year.

4.5.1.2 Deaths

A partial/invalid date of death will be imputed using the rules defined above in Section 4.5.1.1. One extra rule will be applied: The imputed date will be compared to all further dates within the database and if the imputed date occurs before any of these, then it will be adjusted to the last known date.

4.5.2 End Dates

4.5.2.1 Adverse Events (Including LVSD, Cardiac Symptoms), Other Treatments, and Hospitalizations

The following rules will be applied in order to impute partial/invalid end dates for adverse events (including LVSD events and cardiac symptoms), previous and concomitant medications and hospitalization. These imputed dates can be used where it is necessary for an analysis to impute a partial/invalid end date, for example to determine an adverse event or hospitalization duration or to categorize a treatment as previous or previous-concomitant. Partial end dates for previous chemotherapy for breast cancer (recorded on the "Other previous chemotherapy" DCS) will also be imputed using these rules, to allow the calculation of the patients' disease free interval and time from last trastuzumab to diagnosis of metastatic disease. However, if the end date of the previous chemotherapy for breast cancer is missing/invalid, the date will not be imputed. The rules are conservative as they assume the maximum duration possible for any on treatment events.

Also, if a previous/concomitant medication page doesn't have end date recorded (i.e. the eCRF page does not include a field for end date), then we should not impute as we would expect missing day, month and year in this case.

Table 4 Imputation of Partial End Dates

Value	Imputation
Missing/invalid day; Month and year present	Replace by earliest of last day of the month and last known date
Missing/invalid day and month; Year present	Replace by earliest of 31st December and last known date
Missing/invalid day, month and year	Replace by last known date. NB. For missing end date of previous chemotherapy for breast cancer, a date will not be imputed
Start dates	The imputed date in the above scenarios will also be checked against the associated start date of an event (including imputed start dates) to ensure that the end date is after the start date and if not the end date will be set to the start date.

4.6 Partial Dates in Outputs and Derivations

Dates as recorded on the eCRF (even if missing or partial or invalid) will be shown in data listings, in order that listed data accurately reflects the study database. Similarly the study day and duration of an event will not be calculated for listings using imputed dates other than where noted for certain Special Safety listings.

Summaries and derivations will use the imputed dates as defined above unless further explained in the derivation rules in later sections of this document for specific assessments.

4.7 Worst Value

Where it is specified to report the 'worst' value for a summary table of by visit data relating to when within a treatment cycle a repeat assessment has been performed, these are defined as follows:

AEs – highest NCI CTCAE grade

LVEF - lowest value

ECOG status – highest value

Laboratory parameters - see Appendix 2)

FACT-B TOI-PFB score – lowest value

Vital signs – not applicable (it will not be possible for this situation to arise since unscheduled values will not be included in summary tables).

4.8 Treatment Cycles

4.8.1 Definition

Treatment cycles will be remapped to actual cycle number using a patient's valid treatment infusion dates to determine the remapped cycle number, rather than using the planned/scheduled treatment cycle identifier as displayed in the eCRF (although the latter information will also be included in listings). A treatment infusion is defined as valid if the dose received is greater than zero. Consequently, differences may occur between the actual treatment cycle and planned treatment cycle shown in the eCRF, for example if a patient misses a treatment cycle.

Treatment cycles will be labeled sequentially Cycle 1, Cycle 2 etc.

The date on which each treatment cycle starts is defined as the first date in an eCRF module on which a patient received a "new" (see definition below) infusion of any of the 3 treatments (pertuzumab/placebo, trastuzumab, docetaxel).

For example, if a patient having already received one cycle of pertuzumab, trastuzumab and docetaxel misses pertuzumab at the scheduled Cycle 2, but has a valid infusion of trastuzumab and docetaxel (i.e. if there is no valid pertuzumab infusion but there are valid trastuzumab and docetaxel ones in the same eCRF module), then the remapped treatment Cycle 2 is defined as starting on the earliest date that the infusion of trastuzumab or docetaxel started. See possible example of this scenario below.

Scheduled Visit	Drug	Dose	Start Date	Treatment Cycle	Cycle Start Date
Cycle 1	PERTUZUMAB	100	01JAN2008	Cycle 1	01JAN2008
Cycle 1	TRASTUZUMAB	100	02JAN2008	Cycle 1	01JAN2008
Cycle 1	DOCETAXEL	100	02JAN2008	Cycle 1	01JAN2008
Cycle 2	PERTUZUMAB	0	21JAN2008	*Cycle 1*	*01JAN2008*
Cycle 2	TRASTUZUMAB	100	22JAN2008	Cycle 2	22JAN2008
Cycle 2	DOCETAXEL	100	22JAN2008	Cycle 2	22JAN2008

This treatment cycle then ends immediately before the start of the next valid infusion of any of the 3 treatments in a different eCRF module.

Also if a patient misses all three treatments at Cycle 2, then the next time the patient receives pertuzumab, trastuzumab or docetaxel will be considered as the remapped Cycle 2. See possible example below:-

Scheduled Visit	Drug	Dose	Start Date	Treatment Cycle	Cycle Start Date
Cycle 1	PERTUZUMAB	100	01JAN2008	Cycle 1	01JAN2008
Cycle 1	TRASTUZUMAB	100	02JAN2008	Cycle 1	01JAN2008
Cycle 1	DOCETAXEL	100	02JAN2008	Cycle 1	01JAN2008

Scheduled Visit	Drug	Dose	Start Date	Treatment Cycle	Cycle Start Date
Cycle 2	PERTUZUMAB	0	21JAN2008	*Cycle 1*	*01JAN2008*
Cycle 2	TRASTUZUMAB	0	22JAN2008	*Cycle 1*	*01JAN2008*
Cycle 2	DOCETAXEL	0	22JAN2008	*Cycle 1*	*01JAN2008*
Cycle 3	PERTUZUMAB	100	15FEB2008	Cycle 2	15FEB2008
Cycle 3	TRASTUZUMAB	100	16FEB2008	Cycle 2	15FEB2008
Cycle 3	DOCETAXEL	100	16FEB2008	Cycle 2	15FEB2008

The original scheduled visit will be considered in defining a "new" infusion. This will enable us to determine that a treatment cycle is new in the case where a patient may have missed certain treatments within each scheduled visit. See possible example below:-

Scheduled Visit	Drug	Dose	Treatment Cycle
Cycle 1	PERTUZUMAB	100	Cycle 1
Cycle 1	TRASTUZUMAB	0	*Cycle 1*
Cycle 1	DOCETAXEL	0	*Cycle 1*
Cycle 2	PERTUZUMAB	0	*Cycle 1*
Cycle 2	TRASTUZUMAB	100	Cycle 2
Cycle 2	DOCETAXEL	100	Cycle 2

In this example, although the bottom 2 records are the 1st valid doses for trastuzumab and docetaxel, and a 2nd infusion of pertuzumab has not started, Cycle 2 is attributed to the bottom two records using the fact that the scheduled visit has changed (i.e. a different eCRF module has been used).

Within the treatment period, each treatment cycle ends on the day the next cycle starts. If no further treatment cycles occur then the last treatment cycle (or lab window) will end the day before the "treatment discontinuation" visit, as defined in Section 4.9, (if this has taken place within the treatment period, i.e. a maximum of 42 days after last infusion) or at the end of the treatment period, i.e 42 days after the last dose > 0 (if it has not taken place within the treatment period). This definition is not applicable for AEs, where the last treatment cycle ends 42 days after the last dose > 0 of study medication.

4.8.2 Rules for Assigning Data to Treatment Cycle

All assessments at both scheduled and unscheduled visits within the study treatment period will be remapped to actual treatment cycle (as defined above), or to the treatment discontinuation visit.

In order to ensure that data when reported are attributed to the actual treatment cycle at which it is collected, data will be remapped to actual treatment cycle using the following rules:

- For the reporting of AEs by overall treatment cycle and of pertuzumab infusion-associated AEs: AEs reported with a date of onset equal to the date of the start of a treatment cycle will be assigned to that treatment cycle. (Note for summaries of pertuzumab infusion-related AEs, remapped treatment cycle will be shown, rather than the pertuzumab infusion number – these may not fully correspond for a minority of patients e.g. any who miss an infusion of pertuzumab at a cycle but receive the other components). AEs reported from the date of the last infusion of any study treatment up to 42 days after the last dose of study medication will be assigned to the last treatment cycle.
- Physical examinations, ECGs, assessments of LVEF, ECOG, weight, height, cardiac questionnaire and cardiac symptoms, HAHA, FACT-B (quality of life), cytology and tumor, radiological and clinical examinations (and any other assessments where time is not collected) occurring on the same day as the start of a treatment cycle will be assigned to the previous treatment cycle. i.e. it is assumed that the assessments were taken prior to the treatment infusion in order to eliminate any safety concerns and allow study treatment to proceed. (It is possible that an assessment may be repeated on the same day but post-infusion e.g. as a result of an adverse event during an infusion, however, since assessment time is not collected this will be identified for the CSR by review of safety listings).Labs will be remapped to treatment cycles based on infusion dates and within treatment cycle, will further be assigned to a window for reporting purposes:

– Labs assessments performed before the start of the first cycle of study medication will be handled as baseline values (see Section 4.2).

– For each treatment cycle **after** Cycle 1, a pre-infusion assessment will be defined as any assessment taken no more than 3 days before or taken on the day the next treatment cycle starts. Values remapped to this window will be labeled CYC X D1 in listings (see Appendix 3).

– To reflect the post-infusion status at a specific time point, a day 8 assessment will be defined as any assessment taken during day 7 to day 9 (inclusive) of the cycle. Values remapped to this window will be labeled CYC X D8 in listings (see Appendix 3).

– To take into account the post-infusion status at any time during a cycle up until the next pre-infusion assessment window, for each treatment cycle **including** Cycle 1, a post-infusion assessment will be defined as any assessment taken during day 2 of the cycle and up to and including 4 days before the start of the next cycle. Values remapped to this window will be labeled CYC X or CYC X D8 if they also fall into the day 8 assessment window defined above (see Appendix 3).

– In the event of the above yielding overlapping windows (for example if consecutive infusions are 12 or less days apart, then consecutive pre-infusion windows or a pre-infusion and a day 8 window could overlap) the order of priority will be: 1) baseline/pre-trt or trt end; 2) post-baseline pre-infusion windows; 3) day 8/post-infusion

- Scheduled cycle assessments of vital signs will be remapped to a treatment cycle by checking the CRF book (clinical planned event) that they are recorded on, and then mapping these to the same re-mapped cycle as the trial medication that was recorded on that CRF book. These will not be mapped using the dates recorded on the CRF pages as these are the visit dates and not the assessment dates.. Since vital signs are measured pre- and post-infusion, the assumption that a scheduled dosing vital sign assessment belongs to the same cycle as a trial medication cycle is fair as these should be carried out on the same date. Within the cycle, data are then summarized by scheduled time relative to infusion as recorded on the eCRF (e.g. 'pre' or 'post'). For unscheduled assessments of vital signs or any other scheduled assessments (e.g. screening, follow up or treatment end) we will re-map based on visit dates. Any of these assessments on the day of an infusion will be mapped to the treatment cycle to which the infusion belongs, rather than the previous one. Note that because time relative to infusion is not recorded for all other visits (including unscheduled, screening, follow up and treatment end), these will not be included in summary tables.
- Scheduled assessments of ECOG, physical examination and the cardiac questionnaire, which do not have an assessment date recorded, are remapped based on the visit date, and as such will be re-mapped to the previous cycle, as the visit date (being the earliest date of any assessment within the cycle) is expected to be pre-infusion. There is a small acceptable risk with this rule that if the visit date is before the actual assessment date, the assessments will be remapped to the previous cycle when they could in fact belong to the next cycle.
- Pre-medications will be assigned to the same cycle, if taken within 2 days prior to the start of the treatment cycle.
- Other Treatments and treatments received for AEs with a date of onset equal to the date of the start of a treatment cycle will be assigned to that treatment cycle.
- Trial medications administered on the same day as the cycle start date will be assigned to that new cycle, regardless of any time information collected. For example, if a patient has a zero dose for a drug on cycle 2, where the actual time is not collected (hence, time is 00:00:00) but has other medication with dose > 0 on the same day and with same cpe label, then drug with dose =0 will be assigned to cycle 2.

Assessments occurring after the last treatment infusion are addressed in Sections 4.9 and 4.10 below.

Where multiple assessments or AEs occur within a treatment cycle or lab window, the worst value will be reported in summary tables of by-treatment-cycle data. For AEs, worst is defined as the highest onset NCI-CTCAE grade (summaries by grade) or a related event (summaries by relationship to study medication). Refer to Section 4.7 for the definition of worst value for all other applicable assessments.

All data will be included in listings. Listings will display both the actual treatment cycle (and also lab window if applicable) and the scheduled or unscheduled visit as displayed in the eCRF (see Section 4.11).

In summary tables presented by scheduled visit, unscheduled assessments will only appear in the table if the data fulfills the definition of either the 'Final treatment value' or 'Worst treatment value', if occurring within 42 days post last infusion.

4.8.3 Handling of Partial or Missing Dates for Treatment Cycles

The following procedures will be followed to handle partial/invalid dates when reporting data by treatment cycle.

If the date of a visit-based data point is 'NK', then the cycle will appear as 'Unknown' in listings. Additionally, non-visit based data and screening assessments for visit based data where the original (unimputed) date is missing or reported as 'NK' will be included in the data cut and listed as 'Unknown' cycle.

If a partial/invalid date has been entered for an assessment/AE/medication, a date will not be imputed to remap the data to a cycle, as there is a risk that the assessment will be remapped to the incorrect treatment cycle. For example, if treatment Cycle 2 started on August 5th 2008 and treatment Cycle 3 started on August 25th 2008, and an assessment date was reported as 'August 2008', it cannot be determined whether this assessment falls within Cycle 1, 2 or 3. If the rules in Section 4.5 are applied, this date would be imputed as 1st August 2008. The date would then be mapped to Cycle 1, but this may not be correct. In this situation, the cycle will appear as 'Unknown' in listings and the data will not be included in a summary presenting data by cycle.

As all pre-medications within 2 days before treatment begins are mapped to the same cycle as treatment, when assigning pre-medication to the correct treatment cycle the partial dates should be compared to cycle start day -2. For example, if a patient's pre-medication is dated as JUL2009 and the CYCLE 1 started on the 02AUG2009 then this CPE should be set as UNKNOWN. Whereas if the pre-medication date is AUG2009 this can be set as CYCLE 1 as earliest it could have occurred is 01AUG2009 which is within 2 days of cycle start.

There may be certain scenarios where a cycle can and therefore will be assigned based on a partial date, although this will be restricted to where a treatment cycle lasts throughout a calendar month (e.g. Cycle 4 starts 28th February 2008, Cycle 5 starts 1 April 2008), for pre-treatment AEs/medications (e.g. date of onset = March 08, date of Cycle 1 = 1st April 08, map to 'Pre-Trt') or assessments during the follow-up period (date of last dose = 2nd October 2008, date of assessment = Feb 09 (i.e. > 42 days after last dose), map to 'Post-Trt'). In this case the derived cycle will be shown in the listing.

4.9 Treatment Discontinuation Visit

A 'treatment discontinuation' visit is scheduled to take place 28-42 days after the date of the patient's last dose of study treatment. For reporting, the label used to identify data from this assessment will be "Trt End" in listings (based on the label of "Treatment End" that has been used in the GDMs) and "Treatment End" in summary tables. In the event that treatment discontinuation assessments have been performed on more than one date, the earliest date will be used to define the visit date.

- The end of the overall study treatment period occurs 42 days after the last dose > 0 of study treatment, as defined in Section 4.3.2.
- If the treatment discontinuation visit occurred during the day after the last study treatment dose > 0 through to the end of the overall study treatment period: data collected at assessments falling during or after the last dose > 0 and before the treatment discontinuation visit will be mapped to the last treatment cycle; data collected at assessments at or after the treatment discontinuation visit up to the end of the overall study treatment period will be mapped to the treatment discontinuation visit.
- If there is no treatment discontinuation visit during this period: data collected at assessments falling during or after the last dose > 0 up to the end of the overall study treatment period will be mapped to the last treatment cycle, and any data from a treatment discontinuation visit will not be mapped.
- If there is a treatment discontinuation visit after the end of the overall study treatment period, the assessments made will be listed only.
- By visit data will be remapped to the treatment discontinuation visit if appropriate based on dates and will be shown under this visit in summary tables and listings. The main types of by visit data usually collected at the treatment discontinuation visit include LVEF, ECOG, labs and vital signs. Note that other types of by visit data not scheduled to be collected at this visit will be remapped to the treatment discontinuation visit for reporting purposes if they occur at an unscheduled visit during the period between the treatment discontinuation visit and the end of the treatment period.
- For LVEF/ECOG specifically, the last assessment up to the end of the overall study treatment period will also be reported under the "Final Treatment Value" label in summary tables (in addition to being included either under the treatment cycle corresponding to the patient's last study treatment or the treatment discontinuation category as appropriate). Also the worst value during the overall treatment period will be reported under "Worst Treatment Value" label.

4.10 Post-Treatment Treatment Period

Any assessments occurring after the end of the overall study treatment period (i.e. 42 days after the last dose > 0 of study treatment) will not be remapped to a scheduled visit or time point for reporting. Listings will show both the scheduled or unscheduled assessment (eCRF page) at which the data have been collected and an identifier that data are collected post-treatment (see Section 4.11).

4.11 Reporting and Labeling of Data By Remapped Treatment Cycle vs. Scheduled Visit

Remapped data will either be presented only by scheduled visit, only by actual (remapped) treatment cycle or in both ways. This will depend on the datatype. Data collection in this study is both linked to treatment infusions (e.g. LVEF) and at scheduled times relative to randomization (e.g. tumor assessments). Consequently, data will be presented in the following ways:

- By remapped treatment cycle only: labs, vital signs, AEs by cycle, ECOG, pregnancy test, HAHA data, cytology, cardiac questionnaire
- Separately by both remapped treatment cycle and scheduled visit: LVEF, FACT-B.
- By scheduled visit only: tumor assessments

Where data are summarized by scheduled visit, data will be reported using the CPE label from the eCRF (e.g. 'Week 9' – LVEF assessment). Where data are summarized by remapped treatment cycle, the remapped treatment cycle number will be shown (e.g. 'Cycle 1').

Summary tables will only include data falling during the overall treatment period (as defined in Section 4.3.2), whereas listings will include all data.

Both the scheduled visit and remapped treatment cycle will be presented in listings. Where the corresponding summary table presents data by scheduled visit only (i.e. tumor assessments) this will be in the format 'Week XX (Cycle XX)' for data from the treatment period collected at a scheduled visit or 'Unsched (Cycle XX)' for data from the treatment period collected at an unscheduled visit (sometimes referred to as coming from a 'back of book' eCRF page). For all other data types this will be in the format 'Cycle XX (Week XX)' or 'Cycle XX (Unsched)', i.e. showing the derived label first, then the CPE in brackets. For labs, where additional windows are applied, this information will also be included in the label (see Appendix 3). Similarly, for listing pre-treatment data, 'Pre-Trt' Will be shown as well as the CPE from the eCRF. For listing data after the end of the study treatment period, 'Post-Trt' will be shown in the treatment label as well as the CPE label from the eCRF. Data remapped to, or collected at the treatment discontinuation visit will be labeled 'Trt End'.

The remapped treatment cycle labels that will be used and examples of how the CPE will be shown are included in Appendix 3.

4.12 Reporting of Adverse Event Data

Adverse events occurring during the treatment period are scheduled to be collected from study Day 1 (defined as the first day any component of the study treatment regimen received) until the treatment discontinuation visit (scheduled visit 28-42 days after the last date the patient received any component of the study treatment regimen). For reporting purposes, primary AE summary tables will include all adverse events from 1st infusion of any study medication (study Day 1) to the last infusion plus 42 days. Primary AE listings will include all AEs, including any AEs occurring pre-treatment and any occurring during the post-treatment period. In listings that require AEs to be reported by cycle, AEs occurring before study Day 1 will be labeled as "Pre-Trt". A separate

listing of SAEs reported prior to study Day 1 will be produced. Selected AE summary tables will be produced for AEs reported during the follow-up period, including all AEs with a date of onset more than 42 days after the last date of study treatment. AEs that are expected to be reported during this period are cardiac events and treatment-related SAEs. Further details are provided in Section 9.2. If an AE is reported with a partial date, the partial date rules defined in Section 4.5.1.1 will be applied.

5. PATIENT DISPOSITION

The reason for patient stopping study treatment, which is given on the "Treatment Period Completion" of the data collection specification (DCS), will be summarized by treatment arm using MARS template EX11.

The withdrawal date for a patient will be defined as the latest of the following dates:

1. The "date of last contact with patient during treatment period" or "date of last infusion" obtained from the "Treatment Period Completion" DCS. Note that the "date of last contact with patient during treatment period" represents the date entered by the Investigator on this DCS page, and may differ from the derived 'last known date in the treatment period' defined in Section 4.3.4).
2. If the patient died while on study treatment, the "date of death", as obtained from the "In the case of patient's death" DCS. Note: the date of death recorded on the "Survival follow-up" DCS will not be used as a substitute for the withdrawal date, as this date will occur during the follow-up period.

Note that the withdrawal date derivation should use any partial date imputations that have been applied to "date of last contact" or "date of death", but if the derived withdrawal date comes from one of these imputed dates then withdrawal date should be considered to be a partial date (therefore rules for displaying partial dates and associated study days/durations in outputs (Section 4.6) still apply).

The MARS template EX03 will be used to list the Treatment Withdrawals by Trial Treatment and CRTN/Patient Number with Actually Received Treatment. Derived variables included in this listing are:

- Day of withdrawal, calculated as (date of withdrawal – date of first study medication) + 1
- Days on trial treatment: for each administration, calculate (treatment end date – treatment start date) + 1, and sum over all administrations
- Time of withdrawal after last dose in days, calculated as (date of withdrawal – date of last dose of any study medication)

If the date of last dose is the same as the date of withdrawal, time after last dose will be presented in the listing as '<1'.

The MARS listing EC01 will list Analysis Populations and Protocol Violations by Trial Treatment and CRTN/Patient Number. Protocol violations will be classified as either inclusion, exclusion or on-study. All protocol violations are considered minor and will not lead to exclusion from any analysis population with the exception of patients

receiving no study medication. This violation is deemed major and will lead to exclusion from the Safety Analysis Population. All randomized patients are included in the ITT population, and therefore ITT exclusions are not applicable.

A summary of Analysis Populations will be provided for all patients by Trial Treatment in T_FAPOP. The table will include the number of patients randomized (and included in the ITT population), and of these the number (%) receiving the randomized treatment, a non-randomized treatment (i.e. the patient was mis-randomized) and no randomized treatment. A summary will also be provided, by actual treatment received, or the number (%) receiving study treatment (and thus included in the SAP), receiving the randomized treatment and receiving a non-randomized treatment. A summary of protocol violations will be provided in T_FECPV, including the number (%) of patients with at least 1 inclusion violation, at least 1 exclusion violation and an on-study violation. The individual violations within these categories will also be summarized.

A summary (median and range) of the duration of time in weeks on treatment and on study will be provided in Table T_UFUP. Time on treatment will be calculated as:

((last known date in study treatment period – date of first dose) + 1) / 7

See Section 4.3.4 for the definition of the derived last known date in study treatment period.

Time on study, which includes the post-treatment follow-up period, will be calculated as:

((last known date – date of randomization) + 1) / 7

See Section 4.3.3 for the definiton of the last known date.

Two tables will be produced to reflect the Summary of Demographic Data by Trial Treatment and Withdrawal from Trial Treatment, in order to explore whether any demographic or baseline factors are potentially associated with a higher likelihood if early study termination.

In the first table, the ‘Withdrawal from Treatment Yes’column will include all patients who have stopped study treatment, irrespective of the reason. In the second table, patients who withdrew from study treatment due to insufficient therapeutic response (which is expected to be those patients who withdrew from treatment due to disease progression) will be counted in the ‘Withdrawal from Treatment No’column, to ensure that differences between the arms are not hidden by larger differences in the number of patients with disease progression.

Table 5 Outputs for Patient Disposition and Withdrawals

Output Title	Output reference*	Population
Listing of Treatment Withdrawals by Trial Treatment and CRTN/Patient Number with Actually Received Treatment	L_EX03	All Patients (By Treatment Received)
Summary of Patient Withdrawals from Trial Treatment by Trial Treatment	T_EX11	Safety
Listing of Protocol Violations by Trial Treatment and CRTN/ Patient Number	L_EC01	All Patients (By Treatment Randomized)
Summary of Analysis Populations by Trial Treatment	T_FAPOP	All Patients
Summary of Protocol Violations by Trial Treatment	T_FECPV	All Patients (By Treatment Randomized)
Summary of Duration (Weeks) of Patient Time on Treatment and on Study by Trial Treatment	T_UFUP	Safety
Summary of Demographic Data by Trial Treatment and Withdrawal from Trial Treatment	T_DEMWD_WDTT	Safety
Summary of Demographic Data by Trial Treatment and Withdrawal from Trial Treatment Due to Reasons Excluding Insufficient Therapeutic Response	T_DEMWD_WDNIR	Safety

* The output reference, used throughout this document, provides a unique reference to the output template presented in the DRAM Part 2

6. BASELINE CHARACTERISTICS

6.1 Demographic Variables

The following baseline variables will be listed for all patients and summarized by treatment arm for the ITT and Safety populations. Continuous variables will be summarized using descriptive statistics (mean, standard deviation, standard error of mean, median, minimum and maximum) and categorical variables using frequency summaries.

- Age (years): age will be presented using the GDM derivation (trunc(months_between(date of birth, consent date)/12)). If the date of birth is a partial date, it will be imputed using standard rules for imputing partial dates (see Section 4.5, Table 2).
- Age groups: Frequency summaries for the following age groups will also be provided: < 65 and ≥ 65 years; < 75 and ≥ 75 years
- Sex.
- Female reproductive status.
- Race. Categories are as defined on the eCRF:

– White

– Black

– Asian

– American Indian or Alaska native

– Native Hawaiian or other Pacific Islander

– Other. If race is recorded as 'Other', the actual text specified will appear in the summary table and listing.

- Ethnicity: Hispanic/non-Hispanic
- Smoking status: never smoked/current smoker/past smoker

Data for the above characteristics are to be taken from the "Randomization" DCS and the "Personal Data" DCS.

- Prior treatment status: de novo versus prior adjuvant or neo-adjuvant therapy. If the question concerning any previous chemotherapy or biological therapy (including trastuzumab) for breast cancer is answered yes on the "Other previous chemotherapy" DCS then the patient's prior treatment status will be classified as "adjuvant or neo-adjuvant therapy ". Otherwise the patient's status will be classified as "de novo".
- Region: the number and percentage of patients in each stratification region (North America, South America, Europe and Asia)
- Weight (kg) at baseline.
- Height (cm) at screening.
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline: the number and percentage of patients with ECOG scores 0-4.

Weight and ECOG status at baseline will be taken from the "Vitals (screen)" DCS, unless an additional baseline assessment has been taken prior to the start of study treatment. Height will be taken from the "Vitals (screen)" DCS.

- Baseline LVEF (taken from the "LVEF" DCS).
- Chest X-ray result at baseline (abnormal (yes/no)) taken from the "Chest X-ray" DCS.
- Visceral vs non-visceral disease at screening, derived from the "Target lesions (screening)" and "Non-target lesions (screening) DCS pages. Refer to section 7.1.6 for a definition of visceral and non-visceral disease.
- Disease status (measurable or non-measurable disease) at screening, derived from the "Target lesions (screening)" and "Non-target lesions (screening) DCS pages. See Section 7.2.3.2 for a definition of measurable and non-measurable disease.

The MARS template DM01 will be used to produce listings of patient demographic data by trial treatment and CRTN/patient number. Two listings will be produced in order to accommodate the number of characteristics. The MARS template DM03 will be used to produce a randomization list by CRTN/Patient number. The MARS template DM04 will be used to generate a summary of Enrolment by Trial Treatment, listing the Investigators, centers and number of patients enrolled in this study.

The MARS template DM11 will be used to produce the following summary tables which include summaries by stratification factor:

- Summary of demographic data by trial treatment
- Summary of demographic data by trial treatment and region
- Summary of demographic data by trial treatment and prior treatment status

Each demographic summary table will include separate columns for each treatment group and a total column, summarizing the data across both treatment groups (within strata if applicable).

Table 6 Outputs for Baseline Characteristics

Output Title	Output reference	Population
Listing of Demographic Data and Baseline Characteristics by Trial Treatment and CRTN/Patient Number (1)	L_DM01_1	All Patients (By Treatment Randomized)
Listing of Demographic Data and Baseline Characteristics by Trial Treatment and CRTN/Patient Number (2)	L_DM01_2	All Patients (By Treatment Randomized)
Randomization List by CRTN/Patient Number	L_DM03	All Patients (By Treatment Randomized)
Listing of Investigators, Centers and Number of Patients Randomized	L_DM04	All Patients
Summary of Demographic Data by Trial	T_DM11_I	ITT (By

Output Title	Output reference	Population
Treatment		Treatment Randomized)
Summary of Demographic Data by Trial Treatment	T_DM11_S	Safety
Summary of Demographic Data by Trial Treatment and Region	T_DM11_REG	ITT (By Treatment Randomized)
Summary of Demographic Data by Trial Treatment and Prior Treatment Status	T_DM11_PTS	ITT (By Treatment Randomized)

6.2 History of Breast Cancer

History of breast cancer will be taken from the "History of breast cancer" DCS. Listings will present all patients by treatment randomized and tables will present the ITT population.

Listing L_DM01_DBASE_01 will present the date of first histological diagnosis, breast cancer subtype, primary tumor histological grade, estrogen and progesterone receptor status by trial treatment and CRTN/patient number. Listing L_DM01_DBASE_02 will present the date of locally recurrent disease, date of metastatic disease, end date of the last systemic treatment (i.e. chemotherapy or biological therapy) and disease-free interval (months). The disease-free interval (months) is calculated as the time in months (12*number of days/365.25) from the date of the last chemotherapy or biologic therapy ("Other previous chemotherapy" DCS) to the date of metastatic disease ("History of breast cancer" DCS). If either the date of last systemic treatment or the date of metastatic disease are partial dates, the following partial date rules will be applied in order to calculate the disease-free interval: the date of last systemic treatment will be imputed using the partial end date rules outlined in section 4.5.2, and the date of metastatic disease will be imputed using the DM partial date rules (see Table 2). If either date is missing, no derivation will be applied to the date, and the disease-free interval will be set to 'NK' in the listing. If the calculated value is negative (i.e. if the patient stopped chemotherapy/biologic therapy after the date of metastatic disease, the disease-free interval will be set to zero. For de-novo patients, who have not previously received chemotherapy or biological therapy, the disease-free interval will be set to 'N/A' in the listing.

Listing L_DM01_HER2 will present the HER2 status, with both the IHC result and FISH result presented. Also included in this listing with be the biopsy date and corresponding biopsy study day and details of the specimen tested (primary cancer or metastatic site). All data for this listing will be taken from the "HER2 test" DCS.

Table T_DM11_DB_01 summarizes the history of breast cancer and HER2 status by trial treatment. The 'Metastatis/Recurrence' variable will be derived from the date of locally recurrent disease and the date of metastatic disease, recorded on the "History of breast

cancer" DCS. Patients will be categorized as 'Metastatic disease' if the date of metastatic disease is not missing. Similarly, patients will be categorized as 'Locally recurrent disease' if the date of locally recurrent disease is not missing. If both dates are non-missing, a worst case approach will be taken and the patient will be categorized as 'Metastatic disease'. For HER2 status, the IHC result (0, 1+, 2+, 3+) and FISH result (negative, positive) at screening are taken from the "HER2 test" DCS. The IHC results are recorded as 0, +, ++ and +++ on the DCS and will be presented in the summary table as 0, 1+, 2+ and 3+, respectively. Breast cancer subtype, recorded on the "History of breast cancer" DCS, will be summarized separately in T_FDBASE01, as the patient may report multiple responses to this question.

In addition, it is of interest to investigate the concordance between IHC and FISH results where both are available. A summary presenting the number and percentage of patients with each possible combination of IHC and FISH results (as shown in the table below) will be presented by treatment arm in Table T_DM11_HER2X. To be eligible to enter the study, patients are expected to be HER2 positive. The table cells marked with 'x' indicate the combinations that would be interpreted as HER2 positive.

	FISH -	FISH +
IHC 0		x
IHC 1+		x
IHC 2+		x
IHC 3+	x	x

Table T_UFMETS summarizes the locally recurrent (breast) and metastatic sites at baseline by trial treatment. The locally recurrent and metastatic sites at screening are taken from "Target lesions (screening)" and "Non-target lesions (screening)" DCS pages.

Table 7 Outputs for History of Breast Cancer

Output Title	Output reference	Population
Listing of History of Breast Cancer (1) by Trial Treatment and CRTN/Patient Number	L_DM01_DBASE_01	All Patients (By Treatment Randomized)
Listing of History of Breast Cancer (2) by Trial Treatment and CRTN/Patient Number	L_DM01_DBASE_02	All Patients (By Treatment Randomized)
Listing of HER2 Expression from Tissue Sample by Trial Treatment and CRTN/Patient Number	L_DM01_HER2	All Patients (By Treatment Randomized)
Summary of History of Breast Cancer and HER2 Status by Trial Treatment	T_DM11_DB_01	ITT (By Treatment Randomized)
Summary of History of Breast Cancer on Breast Cancer Subtype by Trial Treatment	T_FDBASE01	ITT (By Treatment Randomized)
Summary of Locally Recurrent (Breast) and Metastatic Sites at Baseline by Trial Treatment	T_UFMETS	ITT (By Treatment Randomized)
Cross Comparison of HER2 Results from IHC and FISH Testing	T_DM11_HER2X	ITT (By Treatment Randomized)

6.3 Previous and Concomitant Treatments

Previous, previous-concomitant and concomitant treatment during the study will be listed and summarized descriptively as described in Sections 6.3.1 to 6.3.5.

Apart from 'previous and concomitant treatments other than for breast cancer' where the rules in Section 6.3.2 will be applied to report treatments as previous or previous-concomitant/concomitant, treatments will be reported based on the eCRF page they are recorded on (without reference to the actual or imputed treatment date relative to that of study treatment infusions).

6.3.1 Previous Treatments for Breast Cancer

Previous treatments for breast cancer are taken from the "Previous surgery" DCS, the "Previous radiotherapy" DCS, the "Previous hormone therapy" DCS, and the "Other previous chemotherapy" DCS.

The MARS template TR01 will be used to produce listings of previous radiotherapy, hormone therapy, chemotherapy or biological therapy for breast cancer and previous surgery for breast cancer by trial treatment and CRTN/patient number. Table T_UHIST1 will summarize all previous treatments above for breast cancer by trial treatment.

In addition, the number and percentage of patients with prior trastuzumab and time (months) from last trastuzumab treatment to diagnosis of metastatic disease by treatment arm will be included in this summary. Patients will be classified as having prior trastuzumab treatment if a record of trastuzumab treatment is recorded on the "Other previous chemotherapy" DCS, defined as any treatment preferred term containing the text 'TRASTUZUMAB'. For patients with prior trastuzumab treatment, the time (months) from last trastuzumab treatment to diagnosis of metastatic disease will be derived as the time in months (number of days/365.25*12) from the treatment end date associated with the latest trastuzumab treatment (from "Other previous chemotherapy" DCS) to the date of metastatic disease (from "History of breast cancer" DCS). If either the date of last trastuzumab treatment or the date of metastatic disease are partial dates, the following partial date rules will be applied in order to calculate the interval: the date of last trastuzumab treatment will be imputed using the partial end date rules outlined in section 4.5.2, and the date of metastatic disease will be imputed using the DM partial date rules (see Table 2). If the derived time from last trastuzumab treatment is negative, i.e. if the patient stopped trastuzumab after the date of metastatic disease, the time since last trastuzumab will be set to zero.

Table 8 Outputs for Previous Treatments for Breast Cancer

Output Title	Output reference	Population
Listing of Previous Radiotherapy for Breast Cancer by Trial Treatment and CRTN/Patient Number	L_TR01_PRBC	All Patients (By Treatment Randomized)
Listing of Previous Hormone Therapy for Breast Cancer by Trial Treatment and CRTN/Patient Number	L_TR01_HOR	All Patients (By Treatment Randomized)
Listing of History of Previous Surgery for Breast Cancer by Trial Treatment and CRTN/Patient Number	L_TR01_SUR	All Patients (By Treatment Randomized)
Listing of Previous Chemotherapy or Biological Therapy for Breast Cancer by Trial Treatment and CRTN/Patient Number	L_TR01_CHE	All Patients (By Treatment Randomized)
Summary of Previous Radiotherapy, Previous Hormone Therapy, Previous Surgery and Previous Chemotherapy or Biological Therapy for Breast Cancer by Trial Treatment	T_UHIST1	ITT (By Treatment Randomized)

6.3.2 Previous and Concomitant Treatments Other than for Breast Cancer

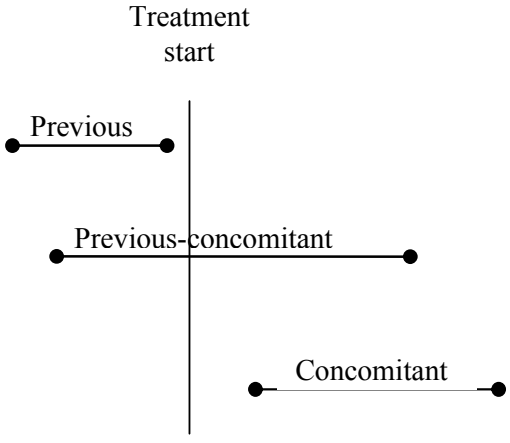
Previous, Previous-Concomitant and concomitant treatment not associated with breast cancer, (hereafter referred to as 'other') will be differentiated using dates and the 'previous' tick box on the "Prev. and concomitant treatments" DCS. The 'previous' tick box identifies those treatments which started before study treatment start. For these records, the Investigator is not required to enter a start date.

The following rules are not applicable to pre-medication. Previous and concomitant treatments collected on other eCRF pages (e.g Radiotherapy) will not have the following rules applied.

- Previous treatments are defined as all treatments with an end date occurring before date of first study treatment (regardless of whether the 'previous' tick box is checked) or if no end date entered, where 'previous' is ticked and the 'ongoing at final contact' tick box is not ticked.
- Previous-Concomitant treatments are any medication started before study treatment start (based on date or the 'previous' tick box) and ending after the start of study treatment, or ongoing at the final contact as indicated by the 'Ongoing at final contact' tick box.
- Concomitant treatments are defined as any medication starting on or after the first day of study treatment where previous tick box is not checked.
- Any medications for those patients who do not receive study treatment will be considered to be previous medication irrespective of whether 'previous' or 'ongoing at final contact' on the "Prev. and concomitant treatments" DCS is ticked.

This is displayed in Figure 3 below.

Figure 3 Definition of Previous, Previous-Concomitant and Concomitant Treatments Relative to Treatment Start



Rules for dealing with partial/invalid dates are as defined in Section 4.5.1.1 and 4.5.2.1.

The 'pre-medication' tick box identifies those treatments that are prescribed to minimize infusion related reactions and or adverse events typically associated with the study

medication. In some cases the pre-medication may be started before study treatment start. A listing and summary table will be produced for all treatments identified as 'pre-medication'.

A listing of all previous, previous-concomitant and concomitant treatments will be produced with onset and duration by trial treatment and CRTN/Patient Number using MARS template TR01. Medications identified as 'pre-medication' will be excluded from this listing.

The MARS template TR11 will be used to produce a summary by trial treatment and class of Previous Treatments, as defined above.

The MARS template TR11 will be used to produce a summary by trial treatment and class of Previous-Concomitant and Concomitant treatments, as defined above. The summary tables of previous treatments and previous-concomitant and concomitant treatments will exclude any medications identified as 'pre-medication'.

Treatment or medical procedures used for adverse events will be taken from the "Adverse event" DCS. Treatment or medical procedure used for a symptomatic left ventricular systolic dysfunction (LVSD) event will be taken from the "LVSD event" DCS.

The MARS template TR11 will be used to produce corresponding summaries by trial treatment and class.

The MARS template TR02 will be used to produce a listing of Treatments (incl. medical procedures) for Adverse Events and also for Symptomatic LVSD Events by Trial Treatment and CRTN/Patient Number and TR11 will be used to produce a summary for each.

The MARS template TR09 presents a Glossary of Superclass Terms, Preferred Terms and Verbatim Terms for Medications and Procedures.

Table 9 Outputs for Previous and Concomitant Treatments Other than for Breast Cancer

Output Title	Output reference	Population
Listing of Other Previous, Previous-Concomitant and Concomitant Treatments with Onset and Duration by Trial Treatment and CRTN/Patient Number	L_TR01_MED	All Patients (By Treatment Randomized)
Listing of Pre-medication Treatments by Trial Treatment and CRTN/Patient Number	L_TR01_PM	All Patients (By Treatment Randomized)
Summary of Other Previous Treatments by Trial Treatment and Class	T_TR11_PREV	ITT (By Treatment Randomized)

Output Title	Output reference	Population
Summary of Pre-medication Treatments by Trial Treatment and Class	T_TR11_PM	ITT (By Treatment Randomized)
Summary of Other Previous-Concomitant and Concomitant Treatments by Trial Treatment and Class	T_TR11_CN	ITT (By Treatment Randomized)
Listing of Other Concomitant Treatments (Incl. Medical Procedures) for Adverse Events by Trial Treatment and CRTN/Patient Number	L_TR02_AE	All Patients (By Treatment Randomized)
Listing of Other Concomitant Treatments (Incl. Medical Procedures) for Symptomatic LVSD Events by Trial Treatment and CRTN/Patient Number	L_TR02_LVSD	All Patients (By Treatment Randomized)
Summary of Other Concomitant Treatments (Incl. Medical Procedures) for Adverse Events by Trial Treatment	T_TR11_AE	ITT (By Treatment Randomized)
Summary of Other Concomitant Treatments (Incl. Medical Procedures) for Symptomatic LVSD Events by Trial Treatment	T_TR11_LVSD	ITT (By Treatment Randomized)
Glossary of Superclass Terms, Preferred Terms, and Verbatim Terms for Medications and Procedures	L_TR09	

6.3.3 Medical/Surgical Procedures

Medical/surgical procedures that occurred during the study treatment phase, including any for breast cancer, are recorded on the "Surgical procedures" DCS.

The MARS template TR01 will be used to produce a listing of Medical/Surgical Procedures During the Study Treatment Phase by Trial Treatment and CRTN/Patient Number. The MARS template TR11 will be used to produce a summary of Medical/Surgical Procedures During the Study Treatment Phase by trial treatment.

Table 10 Outputs for Medical/Surgical Procedures During the Study Treatment Phase

Output Title	Output reference	Population
Listing of Medical/Surgical Procedures During the Study Treatment Phase by Trial Treatment and CRTN/Patient Number	L_TR01_PROC	All Patients (By Treatment Randomized)
Summary of Medical/Surgical Procedures During the Study Treatment Phase by Trial Treatment	T_TR11_PROC	ITT (By Treatment Randomized)

6.3.4 Concomitant Radiotherapy for Breast Cancer

Concomitant radiotherapy for breast cancer is taken from the "Concomitant radiotherapy" DCS.

The MARS template TR01 will be used to produce a listing of concomitant radiotherapy by trial treatment and CRTN/patient number. The MARS template TR11 will be used to produce a summary of concomitant radiotherapy by trial treatment.

Table 11 Outputs for Concomitant Radiotherapy or Medical/Surgical Procedures for Breast Cancer

Output Title	Output reference	Population
Listing of Concomitant Radiotherapy for Breast Cancer by Trial Treatment and CRTN/Patient Number	L_TR01_CRBC	All Patients (By Treatment Randomized)
Summary of Concomitant Radiotherapy for Breast Cancer by Trial Treatment	T_TR11_CRBC	ITT (By Treatment Randomized)

6.3.5 New Therapy or Medical/Surgical Procedures for Breast Cancer (After Coming Off Study Treatment)

New medical procedures for breast cancer after coming off study treatment is taken from the "Subsequent anticancer procedure" DCS. New therapy for breast cancer after coming off study treatment is taken from the "Subsequent anticancer treatment" DCS.

New therapy and medical/surgical procedures for breast cancer after coming off study treatment will be listed using MARS template TR01. New therapy and medical/surgical procedures for breast cancer after coming off study treatment will be summarized using MARS template TR11.

Table 12 Outputs for New Therapy or Medical/Surgical Procedures for Breast Cancer (After Coming Off Study Treatment)

Output Title	Output reference	Population
Listing of New Therapy and Medical/Surgical Procedures for Breast Cancer After Coming Off Study Treatment by Trial Treatment and CRTN/Patient Number	L_TR01_NEW	All Patients (By Treatment Randomized)
Summary of New Therapy and Medical/Surgical Procedures for Breast Cancer After Coming Off Study Treatment by Trial Treatment	T_TR11_NEW	ITT (By Treatment Randomized)

6.4 Previous or Current Diseases other than Breast Cancer

Previous or current diseases at baseline are taken from the "Diseases other than breast cancer" DCS. Previous diseases are defined as all diseases where the status is recorded as 'Not active'. Current diseases are defined as all diseases where the status is recorded as either 'Active with treatment' or 'Active without treatment'.

The MARS template DG01 will be used to produce a listing of Patients with Previous or Current Diseases Other than Breast Cancer by Trial Treatment and CRTN/Patient Number. The MARS template DG11 will be used to produce a summary of Previous Diseases at Baseline Other than Breast Cancer by Body System and Trial Treatment, and a summary of Current Diseases at Baseline Other than Breast Cancer by Body System and Trial Treatment.

The MARS template DG09 presents a Glossary of Superclass Terms, Preferred Terms and Verbatim Terms for Diseases.

Table 13 Outputs for Previous and Current Diseases (other than Breast Cancer)

Output Title	Output reference	Population
Listing of Patients with Previous or Current Diseases Other than Breast Cancer by Trial Treatment and CRTN/Patient Number	L_DG01	All Patients (By Treatment Randomized)
Summary of Previous Diseases Other than Breast Cancer at Baseline by Body System and Trial Treatment	T_DG11_PREV	ITT (By Treatment Randomized)
Summary of Current Diseases Other than Breast Cancer at Baseline by Body System and Trial Treatment	T_DG11_CN	ITT (By Treatment Randomized)
Glossary of Superclass Terms, Preferred Terms and Verbatim Terms for Diseases	L_DG09	

7. EFFICACY ANALYSIS

7.1 Primary Variable

The primary efficacy endpoint is PFS based on IRF evaluations. Assessment of PFS by the IRF will be based on the combined radiological/clinical review.

7.1.1 Definition

The primary PFS endpoint is defined as the time (months) from randomization to the first documented radiographical progressive disease (PD), as determined by the IRF using RECIST (Therasse et al. 2000 [1]) criteria version 1.0, or death from any cause, whichever occurs first. Radiographic tumor assessments include MRI, CT, bone scans (the same technique is to be used for all tumor assessments), and chest x-ray. In addition, bone scans are to be performed at the treatment discontinuation visit and as clinically indicated after this visit if the patient does not have disease progression. Cytologic (e.g. relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available, will also be used by the IRF to assess disease progression, if available.

The date of progression is assigned by the IRF as the earliest date of a scan where an overall disease status of PD is determined. If, for a given visit where a PD event is determined a patient has more than one method of imaging on varying dates, then the IRF will assign the endpoint date as first date associated with that visit

Full details of the IRF assessments of tumor scans and assignment of dates are documented in the IRF Charter. Link to IRF Charter.

Patients who do not have documented IRF-determined PD at the time of the data cut-off for the primary efficacy analysis, or patients who have not died within 18 weeks of the last tumor assessment at which the IRF determined they were progression-free, will be

censored at the date of the last IRF-reviewed, evaluable tumor assessment (since surrogating death at anytime as an event can artificially prolong PFS time due to the much longer life expectancy in this patient population compared with PFS). Patients who have died within 18 weeks of the last tumor assessments and who have no documented IRF-determined PD will be included as having an event, with the event date for PFS as the date of death, taken from either the "In the case of patient's death" DCS or the "Survival follow-up" DCS. This includes patients who have died within 18 weeks of the baseline tumor assessment, who have no post-baseline tumor assessment. If no tumor assessments are performed after the baseline visit, and the patient has not died within 18 weeks of the baseline tumor assessment, the patient will be censored at 1 day.

An adequate/evaluable PFS evaluation is defined as an IRF assessment which results in a valid (non-missing) evaluation or target lesions, a valid (non-missing) evaluation of non-target lesions or a non-missing and evaluable tumor response, i.e., a complete response (CR), partial response (PR), stable disease (SD), or PD.

Refer to the IRF Charter for full details of the IRF read procedures: Link to IRF Charter.

The analyzed IRF endpoint data will be listed.

7.1.2 Hypothesis and Analysis Methods for Primary Analysis of IRF PFS

The analysis of IRF-assessed PFS will be based on the ITT analysis population. The difference in IRF-assessed PFS between the two treatment arms will be compared using the log-rank test at a two-sided 5% significance level, stratified by prior treatment status and region. The null hypothesis ($\mathbf{H_0}$) is that the survival distributions of PFS in the two treatment arms (denoted as $\mathbf{S_{<pertuzumab>}}$ or $\mathbf{S_{<placebo>}}$) are the same. The alternative hypothesis ($\mathbf{H_1}$) is that the survival distribution of PFS in the treatment arm and the control arm are different:

$$\mathbf{H_0:\ S_{<pertuzumab>} = S_{<placebo>}} \quad \textbf{vs.} \quad \mathbf{H_1: S_{<pertuzumab>} \neq S_{<placebo>}}$$

The log rank test will be used to compare PFS distributions between treatment arms. The Kaplan-Meier approach will be used to estimate the median PFS for each treatment arm and the corresponding two-sided $(1-\alpha)$% CI, together with the mean, the estimates for the other quartiles and the range (minimum, maximum). The range will be determined including censored observations. The Cox proportional hazard model, stratified by prior treatment status and region, will be used to estimate the hazard ratio (HR) between the two treatment arms and its 95% confidence interval (CI). An unstratified analysis will also be performed.

A summary table with estimated event rates over time by treatment group will be presented. The table will present the following pieces of information for each pre-specified time point: number of patients at risk, number of events, number of censored cases, Kaplan-Meier estimate of the event-free rate at that timepoint, $(1-\alpha)$% confidence interval for the estimated event-free rate. Additionally at the time of the primary analysis, the final number of events (IRF PD, deaths within 18 weeks of the last IRF tumor assessment) and censored patients (censored at 1 day due to no follow-up, death more

than 18 weeks after last IRF tumor assessment, other censored patients) will be summarized.

All time-to-event endpoints will be listed. Both the IRF-assessed and Investigator-assessed assessments of PFS, time to response and duration of response will be included in the listing, as well as overall survival.

Table 14 Primary PFS Outputs

Output Title	Output reference	Population
Patient Listing of PFS (IRF and Investigator-Assessed), Time to Response (IRF and Investigator-Assessed), Duration of Response (IRF and Investigator-Assessed), and Overall Survival by Trial Treatment and CRTN/Patient Number	L_TTEV	All Patients (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Primary Analysis	T_TTEV_IRF_STR_PFS	ITT (By Treatment Randomized)
Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival Time (months) by Trial Treatment	F_TTEV1_IRF_PFS	ITT (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Unstratified Analysis	T_TTEV_IRF_PFS	ITT (By Treatment Randomized)
Summary of Event Rates for IRF-Assessed Progression-Free Survival over Time by Trial Treatment	T_EVRATE_IRF_PFS	ITT (By Treatment Randomized)
Summary of Number of Patients with Events for IRF-Assessed PFS by Trial Treatment.	T_FRATEPDIRF	ITT (By Treatment Randomized)

7.1.3 Stratified Analyses and Identification of Stratification Factors

As the primary analysis and the sensitivity analyses of the primary endpoint will include the stratification factors (prior treatment status and region), an unadjusted (non-stratified) Cox regression analysis will also be performed to test the robustness of the primary analysis. The results of both the stratified and non-stratified analyses will be summarized (T_UNSTRPFS_IRF).

For stratified analyses, the stratification factors will be determined using eCRF data rather than the Interactive Voice Response System (IVRS). However, data from the IVRS is checked against the clinical database on an ongoing basis and will be uploaded to the

database in order that a cross tabulation of stratification factors according to the IVRS against those on the database can be produced (T_FSTR).

Table 15 Outputs for Stratification Factors

Output Title	Output reference	Population
Summary of Stratified Versus Non-Stratified Log-Rank Test and Cox Regression for IRF-Assessed PFS Time	T_HRLR_IRF_PFS	ITT (By Treatment Randomized)
Summary of Stratification Factors, Clinical Database versus IVRS	T_FSTR	ITT (By Treatment Randomized)

7.1.4 Sensitivity Analyses

PFS based on Investigator assessment is planned as a secondary endpoint of the study. In addition to this, the robustness of the primary analysis will be evaluated through sensitivity analyses. Six sensitivity analyses are proposed to account for potential impact of the following factors on PFS calculations:

1. Possible differences between Investigator and IRF tumor assessments
2. Censoring at the time of Next Anti-Cancer Therapy (NACT)
3. IRF PFS on treatment
4. Potential bias introduced by varied tumor assessment intervals as a result of missing visit(s)
5. Timing of death – including all deaths as an event
6. Patients stopping treatment early due to toxicity

Sensitivity analyses 1 to 3 and 5 to 6 will be performed as planned. The data associated with sensitivity analysis 4 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 by the IRF at a tumor assessment immediately following a missing tumor assessment (sensitivity analysis 4)

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

Details of the secondary endpoint of PFS based on Investigator assessments and each of the proposed sensitivity analyses are provided in the following sections.

7.1.4.1 PFS Based on Investigator Assessments

The secondary endpoint of PFS based on Investigator assessment is defined as the time (months) from randomization to the first documented radiographic progressive disease, as determined by the Investigator using RECIST criteria version 1.0 (Therasse et al. 2000 [1]), or death from any cause within 18 weeks of the last tumor assessment, whichever comes first. Cytologic (eg. relevant cytology reports documenting malignant pleural

effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available, will also be used by the Investigator to assess disease progression, if applicable.

Evidence of Investigator-assessed PD is taken from the "New lesions - Response" DCS where the "overall response" of "progressive disease" is ticked and the "yes" box for "symptomatic deterioration, i.e. without confirmation by imaging methods" is blank (since tumor assessments in this study must be based on radiographic evidence). The date of PD will be defined as the 'Date of assessment' taken from the associated "Target lesions" DCS (note that the date of assessment is entered only once, and covers target, non-target and new lesions). In addition, PD may also be defined based on the 'date of death' recorded on either the "In the case of patient's death" DCS or the "Survival follow-up" DCS, provided the date of death is no more than 18 weeks after the 'Date of assessment' recorded on the last "Target lesions" DCS. This includes patients who have died within 18 weeks of the baseline tumor assessment, and did not progress before. The earliest PD date is used in the calculation of PFS based on Investigator assessments.

An adequate/evaluable PFS evaluation is defined as an Investigator's tumor assessment which results in a valid (non-missing) evaluation or target lesions, a valid (non-missing) evaluation of non-target lesions or a non-missing and evaluable tumor response, i.e., a complete response (CR), partial response (PR), stable disease (SD), or PD.

Analysis methods and censoring are the same as those described for the primary efficacy endpoint, with patients without an event censored at their last Investigator tumor assessment. Analysis of Investigator-assessed PFS will be based on the ITT analysis population.

The number of patients considered to have PD on the basis of "symptomatic deterioration" will be evaluated, and if this incidence is sufficiently large (e.g. > 2%) an additional analysis of Investigator-assessed PFS will be performed in which patients with PD assessed by symptomatic deterioration will be counted as having experienced the event (Investigator-assessed PD), in addition to the patients already defined as having an event in the main analysis of Investigator-assessed PFS. In this case, the date of PD will be taken as the first tumor assessment date at which the Investigator indicated the patient had a PD due to symptomatic deterioration.

7.1.4.2 Possible Differences between Investigator and IRF Tumor Assessments – Sensitivity Analysis 1

A sensitivity analysis will be performed using the earliest PD date as assessed by **either** the IRF or Investigator as the date of event. At the date of clinical cut off for database closure if no PD or death within 18 weeks of last tumor assessment has been documented, then the censoring date will be the latest date out of the IRF and Investigator evaluable tumor assessments. If no post baseline tumor assessment is available, and the patient has not died within 18 weeks of the baseline tumor assessment, then the patient will be censored at 1 day.

The date of the Investigator-assessed PD is defined as described in Section 7.1.4.1.

In addition, the agreement or disagreement between IRF-determined PFS (PFS_{IRF}) and Investigator-determined PFS (PFS_{INV}) will be summarized by treatment arm. Among patients who experience a PFS event as determined either by the IRF or site Investigator, PFS_{IRF} and PFS_{INV} will be considered in agreement if the absolute difference between PFS_{IRF} and PFS_{INV} is $\leq$ 30 days and both Investigator and IRF assessments agree on whether a PFS event has occurred. Overall concordance will include those events deemed to be in agreement, as described above, as well as patients deemed by have no event by both the IRF and the Investigator.

7.1.4.3 Timing of Next-Line Anti-Cancer Therapy (NACT) – Sensitivity Analysis 2

To investigate the potential effect of Investigator decisions to introduce new cancer therapy prior to meeting the primary endpoint, a sensitivity analysis will be performed censoring patients who start NACT prior to IRF-assessed PD, death (within 18 weeks of last tumor assessment) or last IRF tumor assessment, with the censoring occurring at the date of the last IRF-assessed tumor assessment prior to the start of NACT. Time to progression or death before start of NACT is defined as the time between randomization and the date of first documented IRF-assessed PD or death, whichever comes first and only if it occurs before the start of NACT. The start date of the NACT is taken as the earliest start date of treatment from the "Subsequent anticancer treatment" DCS.

Patients who never start NACT, without IRF-assessed PD or death (within 18 weeks of last tumor assessment) are censored at their date of last IRF-assessed tumor assessment. If no post baseline IRF tumor assessment is available, and the patient has not died within 18 weeks of their baseline tumor assessment, then the patient will be censored at 1 day.

If a treatment has been recorded in the "Subsequent anticancer treatment" DCS (treatment text is not missing) and the start date of NACT is missing, the NACT start date will be imputed as 1 day after the last known date in the treatment period. If the NACT start date is partial (year only or month and year), the following rules will apply:

- For month and year partial dates, if the partial date falls within the same month as the last known date in treatment period, set to last known date in treatment period +1. Otherwise set to the latest of the 1st of the month and the first treatment administration date+1
- For year only partial dates, if the partial date is in the same year as the last known date in treatment period, set to last known date in treatment period+1. Otherwise set to the latest of 1st January and first treatment administration date+1

7.1.4.4 IRF PFS on Treatment – Sensitivity Analysis 3

The primary endpoint will be repeated looking at IRF PFS on treatment (time to progression or death on-treatment) defined as time between randomization and date of first documented IRF assessed disease progression or death, whichever occurs first and only if it occurs no later than 42 days after the last confirmed intake of any study medication.

Patients who neither progressed nor died in this interval, or who are lost to follow-up are censored at the date of last tumor assessment within this time window. Patients for whom no post-baseline tumor assessments are available, and the patient has not died on treatment within 18 weeks of their baseline tumor assessment, are censored at 1 day.

7.1.4.5 Potential Bias Introduced by Varied Tumor Assessment Intervals as a Result of Missed Visit(s) – Sensitivity Analysis 4

A summary table will be produced showing patients with PD based on IRF evaluations whose PD was identified at a tumor assessment preceded by a missed assessment. If there are grounds for concern over the impact of missed assessments on the primary PFS analysis (refer to Section 7.1.4), a sensitivity analysis will be performed investigating the effect of missing tumor assessments followed by an IRF assessment of PD or prior to death within 18 weeks of last tumor assessment (without previous PD). In this analysis the missing assessment (or earliest missing assessment if more than one is missed) will be replaced by an assessment of PD, and the time to event will be set as expected day of the missing scheduled visit, i.e 63 days (9 weeks), 126 days (18 weeks) etc. If no assessment is missed then the first PD date as assessed by the IRF will be used as the date of event. In the case of death without prior PD within 18 weeks of the last tumor assessment, where death was preceded by a missing tumor assessment, the missing assessment will be replaced by an assessment of PD, for the purposes of this sensitivity analysis. This rule is only applicable for deaths within 18 weeks of the last IRF-assessed tumor assessment.

Missed tumor assessments will be identified based on the date of the assessment and the expected time windows for tumor assessments. Tumor assessments are scheduled to take place every 9 weeks from the date of randomization until IRF-confirmed PD. If an assessment has not taken place at 9 weeks (+/- 3 days) after the date of randomization, then this assessment will be considered as missed, provided the patient has a further tumor assessment after this point. Missed assessments at 18 weeks (+/- 3 days), 27 weeks (+/- 3 days) etc. will be determined in the same way. Note that this analysis, which assesses the potential to identify PD at an earlier timepoint, uses the protocol-defined window of +/- 3 days, such that PDs identified out of window will be reset for analysis purposes to the standard time of 9 weeks, 18 weeks etc. In contrast, for the summary of the timing of tumor assessments described in Section 7.1.5, it is recognized that minor factors outside of the patient's control, such as Bank Holidays, could affect the timing of a patient's next Tumor Assessment, and therefore for compliance purposes a wider window of +/- 7 days is deemed appropriate.

If no IRF-assessed PD or death has been documented for a patient then the censoring date for that patient will be the last date of the IRF evaluable tumor assessment date. If no post baseline tumor assessment is available, and the patient has not died within 18 weeks of their baseline tumor assessment, then the patient is censored at 1 day.

7.1.4.6 Timing of Death – Sensitivity Analysis 5

A sensitivity analysis will be performed whereby deaths occurring due to any cause more than 18 weeks after the last IRF tumor assessment will be included as events for patients that have not previously had an event (IRF-assessed PD or death within 18 weeks of last tumor assessment). If no IRF-assessed PD or death has been documented for a patient

then the censoring date for that patient will be the last date of the IRF evaluable tumor assessment date.

The date of death is taken from the "In the case of patient's death" DCS, or the "Survival follow-up" DCS.

If no post baseline tumor assessment is available, and the patient has not died, then the patient is censored at 1 day.

These sensitivity analyses are listed in Table 16 in addition to the PFS calculation as defined for the primary analysis. All sensitivity analyses will be stratified by prior treatment status and region, and based on the ITT population.

7.1.4.7 Impact of Discontinuation from Study Treatment Due to Toxicity – Sensitivity Analysis 6

An additional sensitivity analysis will be performed to assess the impact of discontinuation of study treatment due to toxicity on IRF-PFS, as recommended by the FDA.

Patients who have discontinued all study treatment due to toxicity are defined as those patients for whom the reason for stopping treatment is reported as 'AE/Intercurrent Illness' on the Treatment Completion DCS. Patients who have discontinued all study treatment due to toxicity will be censored at their last IRF-assessed tumor assessment on or before their treatment discontinuation date. Patients with no post-baseline IRF-assessed tumor assessment prior to discontinuation of study treatment will be censored at 1 day.

For all other patients in the ITT population, the time to PFS will be defined according to the rules described for the Primary Analysis (see Section 7.1.1).

Table 16 Sensitivity Analyses for Various Scenarios of Censoring in PFS Calculation

Scenario Evaluated	Primary Analysis	Sensitivity Analysis (SA)				
		SA1 PD date per either IRF- or Investigator-assessment	SA2 Censoring for next-line anti-cancer therapy (NACT)	SA3 IRF PFS on treatment	SA4 Correcting for potential bias in follow-up schedules	SA5 Including all deaths as an event
PD documented without missing any scheduled tumor assessment	Progressed on the first IRF-assessed PD date	Progressed on the first IRF- or Investigator-assessed PD date	Progressed on the first IRF-assessed PD date prior to the NACT. If no PD or death before the NACT, censored on date of last tumor assessment prior to NACT.	Progressed on the first IRF-assessed PD date within the treatment period (date of last study treatment + 42 days). If no PD within the treatment period, censored on date of last IRF-assessed tumor assessment within the treatment period	Progressed on the first IRF-assessed PD date	Progressed on the first IRF-assessed PD date
PD documented after missing scheduled tumor assessment(s)					Progressed on the earliest missed assessment since last IRF assessment	
No PD or death documented at time of data cutoff	Censored on the last IRF-evaluable tumor assessment date *	Censored on the last IRF- or Investigator-evaluable tumor assessment date *	Censored on date of last tumor assessment prior to NACT	Censored on date of last IRF-assessed tumor assessment within the treatment period	Censored on the last IRF-evaluable tumor assessment date *	Censored on the last IRF-evaluable tumor assessment date *

<table>
<tr><td rowspan="2">Scenario Evaluated</td><td rowspan="2">Primary Analysis</td><td colspan="5">Sensitivity Analysis (SA)</td></tr>
<tr><td>SA1
PD date per either IRF- or Investigator-assessment</td><td>SA2
Censoring for next-line anti-cancer therapy (NACT)</td><td>SA3
IRF PFS on treatment</td><td>SA4
Correcting for potential bias in follow-up schedules</td><td>SA5
Including all deaths as an event</td></tr>
<tr><td>No PD. Death within 18 weeks of the last IRF evaluable tumor assessment and before the NACT</td><td colspan="2">PFS event on the date of death</td><td rowspan="3">If death occurs within the treatment period (date of last study treatment + 42 days), event on the date of death. If death after the treatment period, censored on date of last IRF-assessed tumor assessment within the treatment period</td><td colspan="2">PFS event on the date of death</td></tr>
<tr><td>No PD. Death within 18 weeks of the last IRF evaluable tumor assessment and after the NACT</td><td colspan="2">PFS event on the date of death</td><td>Censored on date of last tumor assessment prior to NACT</td><td colspan="2">PFS event on the date of death</td></tr>
<tr><td>No PD. Death more than 18 weeks after the last IRF evaluable tumor assessment</td><td>Censored on the last IRF-evaluable tumor assessment</td><td>Censored on the last IRF- or Investigator-evaluable tumor assessment</td><td>Censored on date of last tumor assessment prior to NACT</td><td>Censored on the last IRF-evaluable tumor assessment</td><td>PFS event on the date of death</td></tr>
<tr><td>No post baseline tumor assessment</td><td colspan="5">Censored on date of randomization+1 day</td></tr>
</table>

NACT= next-line anti-cancer therapy, * A tumor assessment is evaluable if the tumor response is neither missing nor unable to evaluate.

Table 17 Sensitivity Analyses PFS Outputs

Output Title	Output reference	Population
Summary of Investigator-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region	T_TTEV_INV_STR_PFS	ITT (By Treatment Randomized)
Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival Time (months) by Trial Treatment	F_TTEV1_INV_PFS	ITT (By Treatment Randomized)
Summary of Number of Patients with PD due Solely to Symptomatic Deterioration by Trial Treatment	T_FPDSYMP	ITT (By Treatment Randomized)
Summary of Investigator-Assessed Progression-Free Survival (months), Including Symptomatic Deterioration, by Trial Treatment, Stratified by Prior Treatment Status and Region	T_TTEV_INV_STR_SYMP_PFS	ITT (By Treatment Randomized)
Summary of Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 1	T_TTEV_IRF_SENS1_STR_PFS	ITT (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 2	T_TTEV_IRF_SENS2_STR_PFS	ITT (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 3	T_TTEV_IRF_SENS3_STR_PFS	ITT (By Treatment Randomized)
Summary of Incidence of IRF-Assessed PD Identified at a Tumor Assessment Immediately Following a Missed Tumor Assessment by Trial Treatment	T_FPDMISS	ITT (By Treatment Randomized)

Output Title	Output reference	Population
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 5	T_TTEV_IRF_SENS4_STR_PFS	ITT (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 5	T_TTEV_IRF_SENS5_STR_PFS	ITT (By Treatment Randomized)
Summary of IRF-Assessed Progression-Free Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Sensitivity Analysis 6	T_TTEV_IRF_SENS6_STR_PFS	ITT (By Treatment Randomized)
Concordance of IRF and Investigator Assessment of PFS by Trial Treatment	T_FCONPFS	ITT (By Treatment Randomized)

7.1.5 Investigation of Follow-Up Duration and Assessment Dates

When comparing time-to-event endpoints between treatment groups, it is important to assess whether there are systematic differences in the completeness and duration of follow-up or in the time windows during which the tumor assessments took place. In a blinded placebo-controlled study, the existence of such differences may be an indicator of differences in safety or efficacy between treatment arms. Alternatively, such differences may indicate suboptimal data quality, which could potentially affect the conclusions regarding treatment effect drawn from the study. Ideally, follow-up should be complete in all patients, i.e. if at all possible, none of the patients enrolled should be lost to follow-up or have missing assessments (although this is rarely possible in large studies of patients with advanced cancer such as this study).

For the comparison of the timing of assessments a check will be made for each treatment group on how many of the patients had their tumor assessment within ± 7 days around the scheduled visit date (assessments scheduled every 9 weeks).

The reasons for deviation from scheduled tumor assessments or for unscheduled tumor assessments taking place before IRF-assessed PD, will be listed by treatment arm.

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 (i.e. an IRF-determined event or death) are censored at the date of their event and patients without an event are regarded as having had an event at the censoring date.

Table 18 Outputs for Investigation of Follow-Up/Assessment Dates

Output Title	Output reference	Population
Listing of Deviations from Scheduled Tumor Assessments by Trial Treatment and CRTN/Patient Number	L_TUM_DEV	All Patients (By Treatment Randomized)
Listing of Reasons for Unscheduled Tumor Assessments by Trial Treatment and CRTN/Patient Number	L_TUM_UNS	All Patients (By Treatment Randomized)
Summary of Time to Censoring for IRF-Assessed PFS by Trial Treatment	T_TTEV_IRF_TTC_PFS	ITT (By Treatment Randomized)
Kaplan-Meier Curve of Time to Censoring for IRF-Assessed PFS by Trial Treatment	F_TTEV1_IRF_TTC_PFS	ITT (By Treatment Randomized)
Summary of Timing of On-Study Tumor Assessments	T_FTIM	ITT (By Treatment Randomized)

7.1.6 Cox Regression Models for the Primary Endpoint

Multiple Cox regression will be performed, including in the model pre-defined stratification and baseline prognostic factors (treatment–covariate interaction terms are not included), selected from the baseline characteristics listed in Section 6.1 and the history of breast cancer characteristics detailed in Section 6.2. The selected list if covariates to include in the full model is specified below:

- Prior Treatment Status (stratification factor)
- Region (stratification factor)
- Age-group (< 65, ≥ 65 years)
- Age-group (< 75, ≥ 75 years)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Visceral disease vs non-visceral disease
- IHC HER2 Status (0/1+, 2+, 3+)
- Estrogen Receptor (ER)/ Progesterone Receptor (PgR) Status (ER and PgR negative vs ER and/or PgR positive)

Due to small sub-group sizes, race will be limited to 4 categories for the analysis: White, Black, Asian and Other, where 'Other' will include the combined patients in the 'American Indian or Alaska native', 'native Hawaiian or other Pacific Islander' and 'Other' categories.

Non-visceral disease will include tumors located in the breast, bone, bone marrow, lymph nodes, skin and soft tissue. All other locations will be classed as visceral disease. Patients

with tumors in multiple locations that cover both visceral and non-visceral disease (eg. a patient with a tumor in the liver and bone lesions) will be classed as having 'visceral disease' for the purposes of the analysis.

Covariates with x levels will be recoded into (x-1) Boolean variables, for inclusion in the cox regression models. Comparisons will be made between the following levels of each covariate within the model:

Randomized treatment: pertuzumab + trastuzumab + docetaxel vs placebo + trastuzumab + docetaxel

Prior Treatment Status: Neoadjuvant or adjuvant vs de-novo

Region: Asia vs Europe; North America vs Europe; South America vs Europe

Age-group: ≥65 years vs <65 years

Age-group: ≥75 years vs <75 years

Race: Black vs White: Asian vs White: Other vs White

Disease type: Visceral disease vs non-visceral disease

IHC HER2 Status: 0/1+ vs 3+, 2+ vs 3+

ER/PgR status: ER and PgR negative vs ER and/or PgR positive

The HR for treatment (compared to the reference group) when adjusting for all covariates, together with $(1-\alpha)$% CI and the p-value of the Wald test, testing the null hypothesis that treatment has no impact on the PFS endpoint when adjusting for all covariates will be presented in a summary table. For each covariate, the HR when adjusting for all other covariates and treatment and the corresponding $(1-\alpha)$% CI will also be presented. The p-value of the Wald test, testing the null hypothesis that the covariate has no influence on the PFS endpoint when adjusting for the remaining covariates and treatment, will also be presented.

A univariate analysis will be conducted by including only one covariate, with and without treatment, in the regression model. The number of patients included in the analysis, the HR for treatment compared to the reference group, the corresponding $(1-\alpha)$% CI and the p-values (Wald test) for the covariate as well as for the treatment effect adjusted for that covariate will be presented in a summary table. In the model that contains only the covariate, the null hypothesis of the Wald test is that the covariate has no influence on the time-to-event endpoint. In the model including both, covariate and treatment, the null hypothesis of the Wald test is that treatment adjusted for the covariate has no influence on the PFS endpoint.

Further exploratory analysis will be performed where all covariates which are significant at the 0.15 level in the univariate analysis will then be included in a multivariate analysis, and backwards selection at the 5% level will be performed to obtain a final model. Summaries of both the full model and the final model will be produced. Additionally, as there are two separate covariates for age-group, each with a different cut-off (65 years

and 75 years), two separate full models will be produced, each one containing just one of the age-group covariates, and allowance is also made for the possibility of producing two final model summaries, if both age-group covariates are significant.

Table 19 Outputs for Cox Regression Models

Output Title	Output reference	Population
Summary of Multiple Cox Regression for IRF-Assessed Progression-Free Survival (months) without Interactions – Full Model (1)	T_HRMCOX_FULLM_AGE65_IRF_PFS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for IRF-Assessed Progression-Free Survival (months) without Interactions – Full Model (2)	T_HRMCOX_FULLM_AGE75_IRF_PFS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for IRF-Assessed Progression-Free Survival (months) without Interactions – Final Model (1)	T_HRMCOX_FINM_AGE65_IRF_PFS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for IRF-Assessed Progression-Free Survival (months) without Interactions – Final Model (2)	T_HRMCOX_FINM_AGE75_IRF_PFS	ITT (By Treatment Randomized)
Summary of Cox Regression for IRF-Assessed Progression-Free Survival (One Covariate without/with Treatment)	T_HRCCOX_IRF_PFS	ITT (By Treatment Randomized)

7.1.7 Proportional Hazards Assumption

The proportional hazards assumption is that the hazard (i.e. instantaneous risk of an event) for any individual is a fixed proportion of the hazard for any other individual and is therefore constant across time. The proportional hazards assumption will be checked for the two treatment groups, by plotting the log (-log) of the estimated survivor function against log time. If the proportional hazard assumption holds, the 2 curves should be approximately parallel straight lines. Intersecting survivor functions are an indication for the violation of the proportional hazards assumption. Consideration will also be made over the consistency of the log-rank test and HR from the Cox model. If the assumption is violated, further discussions with Clinical Science and investigation into any change in hazard ratio over time and interactions with treatment will take place.

7.1.8 Subgroup Analyses

Subgroup analyses for IRF-determined PFS will be performed for pre-defined categorical covariates:

- Prior Treatment Status (stratification factor)

- Region (stratification factor)
- Age-group (< 65, ≥ 65 years)
- Age-group (<75, ≥ 75 years)
- Race (White, Black, Asian, Other)
- Disease type (Visceral disease vs non-visceral disease)
- IHC HER2 Status (3+)
- FISH (positive)
- ER/PgR Status (ER and PgR negative vs ER and/or PgR positive)

For the purposes of the subgroup analysis, race has been restricted to 4 categories, with 'Other' comprising patients of the following races: 'American Indian or Alaska native', 'native Hawaiian or other Pacific Islander', 'Other'.

For the HER2 parameters, the majority of patients are expected to be IHC 3+ and FISH positive, based on draft blinded baseline data (at least 90%). Given the low number of patients expected to have statuses other than IHC 3+/FISH+, and resultant low sensitivity for analyses of these smaller groups, the subgroup analyses will be limited to only IHC 3+ and FISH+ patients.

Non-visceral disease will include tumors located in the breast, bone, bone marrow, lymph nodes, skin and soft tissue. All other locations will be classed as visceral disease. Patients with tumors in multiple locations that cover both visceral and non-visceral disease (e.g. a patient with a tumor in the liver and bone lesions) will be included in the 'visceral disease' subgroup.

For each of the subgroups defined by the covariate factor levels, the summary tables will present the number of patients and the number and proportion of events by treatment group. The estimated HR for pertuzumab group compared to placebo, resulting from the Cox regression models including only treatment as factor, will be presented for each subgroup level together with the corresponding two-sided (1-α)% CI.

Forest plots of the HR and corresponding (1-α)% CI will be produced for all subgroups. If the Forest plot suggests there are differences in the HRs between levels of a subgroup, then Kaplan Meier plots will be produced and further investigation of potential interaction with treatment carried out.

Table 20 Outputs for Subgroup Analyses of PFS

Output Title	Output reference	Population
Summary of Hazard Ratios and 95% Confidence Intervals for IRF-Assessed Progression-Free Survival by Subgroup	T_HRSCOX_IRF_PFS	ITT (By Treatment Randomized)
Forest Plot of Hazard Ratios and 95% Confidence Intervals for IRF-Assessed Progression-Free Survival by Subgroup	F_HRSCOX_IRF_PFS	ITT (By Treatment Randomized)

7.2 Secondary Variables

The secondary efficacy variables are as follows:

1. Overall survival (key secondary variable)
2. PFS based on Investigator assessment
3. Objective response
4. Duration of objective response
5. Time to symptom progression (as assessed by FACT-B)
6. Biomarkers analysis

The fixed-sequence testing procedure (Westfall and Krishen 2001 [2]) will be used to adjust for multiple statistical testing of IRF-assessed PFS, OS, and objective response rate at the final PFS analysis, for the purposes of confirmatory statistical testing. The testing procedure will follow the steps below:

1. Test the primary endpoint, PFS based on IRF assessments, at a two-sided 5% significance level. If positive, continue to step 2; otherwise, stop.
2. Test OS at an overall two-sided 5% significance level. If positive, continue to step 3; otherwise, stop.
3. Test objective response rate at a two-sided 5% significance level.

In the event that the confirmatory-fixed testing sequence leads to stopping at either step 1 or step 2, the remaining endpoints would still be tested for significance, but the results would be deemed to be exploratory.

An overview of efficacy will be included, incorporating the key summary statistics from the primary analysis and the secondary endpoints.

7.2.1 Overall Survival (OS)

7.2.1.1 Definition

OS is defined as the time (months) from the date of randomization to the date of death from any cause.

The date of death is taken from the “In the case of patient’s death” DCS, or the “Survival follow-up” DCS.

If a patient has completed more than 1 survival follow-up form, the patient’s status will be derived from their most recent form. Patients who are alive (survival status = alive), lost to follow up at the time of the analysis (survival status = lost to follow-up) or who withdraw consent for survival follow-up (survival status = withdrew consent) will be censored at the last known date (see Section 4.3.3 for definition). If the patient has not completed any survival follow-up forms (for example, if the patient is still on treatment at the time of analysis and the patient has not died, patients will be also censored at the last known date (see Section 4.3.3). Patients with no post-baseline information will be censored at 1 day.

In the unlikely event of a partial date of death, the rules for partial dates defined in Section 4.5.1.2 will be applied.

An OS analysis will take place at the time of the primary clinical data cut for PFS (interim survival analysis) and again after 385 deaths (final overall survival analysis) or at the end of study if it is terminated before this. Further details are given in the following section.

7.2.1.2 Hypothesis and Analysis Methods

Analysis methods are the same as those described for the primary efficacy endpoint. OS analysis will be based on the ITT analysis population.

To minimize the chance of a biased OS estimate resulting from prolonged interval between survival follow-ups (intervals scheduled at every 18 weeks), immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient who is on study to confirm current survival status. (The study Sponsors will notify all Investigators of the timing of this survival data sweep.)

The two-sided significance level of 5% will be split over the two OS analyses. The first analysis of OS will occur at the time of the primary (final) PFS analysis, when 50% of the deaths are anticipated to have occurred. The final analysis of OS will occur when all 385 required deaths have occurred. A Lan-DeMets alpha spending function with the O'Brien-Fleming stopping boundary will be used to determine the significance level at the first and final analysis of OS. Assuming 50% of the total 385 required deaths (193 deaths) have occurred at the time of (final) primary analysis of PFS, the alpha level for the first OS analysis will be 0.0031, and that for the final OS analysis will be 0.049.

Table 21 Outputs for Overview of Efficacy and Overall Survival

Output Title	Output reference	Population
Overview of Efficacy by Trial Treatment	T_OVEFF	ITT (By Treatment Randomized)
Summary of Overall Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region	T_TTEV_STR_OS	ITT (By Treatment Randomized)
Kaplan-Meier Curve of Overall Survival (months) by Trial Treatment	F_TTEV1_OS	ITT (By Treatment Randomized)
Summary of Overall Survival (months) by Trial Treatment, Unstratified Analysis	T_TTEV_OS	ITT (By Treatment Randomized)

7.2.1.3 Sensitivity and Robustness Checks

The time to censoring for overall survival will be investigated to identify whether there are differences in follow-up time between the two treatment arms. A summary table and Kaplan-Meier plot of the time to censoring for OS in the two treatment arms will be produced. In this analysis, patients who had events in the overall survival analysis (i.e. a death from any cause) are censored at the date of their event and patients without an event are regarded as having had an event at the censoring date.

Note that the time to censoring is equivalent to the duration of follow-up for safety, as described in Section 9.5.

Overall survival will also be compared between treatment groups using the Wilcoxon Test, stratified by prior treatment status and region, to assess the sensitivity of the log-rank test results. The Wilcoxon test places more weight on the early events.

A 2-year landmark analysis will be performed, in the form of a truncated overall survival (tOS) analysis at 2 years. A cutpoint of 2 years has been chosen primarily as a conservative measure for reflecting clinical benefit. A truncated survival endpoint at two years is considered a robust and clinically highly relevant endpoint for capturing clinical benefit of a new therapy.

The tOS analysis will be stratified by prior treatment status and region, and the survival times compared by the Wilcoxon test, which places more weight on the early differences. Overall survival will be calculated in the same way as described in Section 7.2.1.2 for the main analysis of OS, with the following 2 exceptions:

- Patients with an event beyond 2 years will be censored at 2 years
- Patients with a censoring date beyond 2 years will be censored at 2 years

Table 22 Outputs for Investigation of Follow-up for OS

Output Title	Output reference	Population
Summary of Time to Censoring for Overall Survival by Trial Treatment	T_TTEV_TTC_OS	ITT (By Treatment Randomized)
Kaplan-Meier Curve of Time to Censoring for Overall Survival (months) by Trial Treatment	F_TTEV1_TTC_OS	ITT (By Treatment Randomized)
Summary of Overall Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region – Wilcoxon Test	T_TTEV_ WIL_STR_OS	ITT (By Treatment Randomized)
Truncated Overall Survival (tOS) at 2 Years by Trial Treatment, Stratified by Prior Treatment Status and Region	T_TTEV_ LMK_STR_OS	ITT (By Treatment Randomized)

7.2.1.4 Additional Exploratory Analyses

Cox regression multivariate and univariate modeling strategy specified for the primary variable will also be carried out for OS (see Section 7.1.6). Similarly, a subgroup analysis of OS will be performed, using the same subgroup variables as defined for PFS (see Section 7.1.8). These analyses are planned only to take place at the time of the final OS (and not at the time of the primary clinical cut).

Table 23 Outputs for Cox Regression Models for Overall Survival

Output Title	Output reference	Population
Summary of Multiple Cox Regression for Overall Survival (months) without Interactions – Final Analysis, Full Model (1)	T_HRMCOX_FULLM_AGE65_OS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for Overall Survival (months) without Interactions – Final Analysis, Full Model (2)	T_HRMCOX_FULLM_AGE75_OS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for Overall Survival (months) without Interactions – Final Analysis, Final Model (1)	T_HRMCOX_FINM_AGE65_OS	ITT (By Treatment Randomized)
Summary of Multiple Cox Regression for Overall Survival (months) without Interactions – Final Analysis, Final Model (2)	T_HRMCOX_FINM_AGE75_OS	ITT (By Treatment Randomized)
Summary of Cox Regression for Overall Survival (months) (One Covariate without/with Treatment) – Final Analysis	T_HRCCOX_OS	ITT (By Treatment Randomized)
Summary of Hazard Ratios and 95% Confidence Intervals for Overall Survival by Subgroup	T_HRSCOX_OS	ITT (By Treatment Randomized)
Forest Plot of Hazard Ratios and 95% Confidence Intervals for Overall Survival (months) by Subgroup	F_HRSCOX_OS	ITT (By Treatment Randomized)

7.2.2 PFS Based on Investigator Assessments

See Section 7.1.4.1.

7.2.3 Objective Response

7.2.3.1 Definition

Objective response (OR) is defined as confirmed CR or PR determined by the IRF using RECIST criteria version 1.0 (Therasse et al. 2000 [1]) on two consecutive occasions ≥ 4 weeks (≥ 28 days) apart. For the definition of tumor response, and more detailed rules on the confirmation requirements, including cases where the assessments do not need to be consecutive, see Appendix 4. Algorithms for response for target lesions according to RECIST are presented in Appendix 5.

7.2.3.2 Hypothesis and Analysis Methods

Only patients from the ITT analysis population with measurable disease according to the IRF at baseline will be included in the analysis of the OR. A patient is deemed to have measurable disease if they have at least 1 target lesion at screening. Any patients with non-target lesions only will be deemed to have non-measurable disease. Objective response will be based on the best overall response recorded from the start of trial treatment until IRF-assessed PD, death or first administration of NACT, whichever occurs first. Refer to Section 7.1.4.3 for imputation rules applied to missing and partial NACT start dates. Patients without a post-baseline tumor assessment will be considered to be non-responders. Patients with a best overall response (BOR) of CR or PR, confirmed at least 4 weeks apart, will be classified as responders. All other patients will be classified as non-responders. Patients with disease localized only to the bone will not be included in the analysis of OR. The main analysis of OR will be based on the IRF assessments. The analysis of IRF-assessed objective response forms part of the formal confirmatory testing hierarchy (see Section 7.2 for further details). The objective response rate based on the Investigator assessments will also be summarized.

An estimate of the OR rate and 95% CI using Pearson-Clopper method will be calculated for each treatment arm. The difference in OR rate will also be provided with 95% CIs (using Hauck-Anderson method). The Mantel-Haenszel χ^2 test stratified by prior treatment status and region will be used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test will also be performed. In addition the rates and the corresponding 95% Pearson-Clopper CIs for each of the best overall response categories (CR, PR, SD, PD, UA) by treatment group will be presented, along with the number missing (no response assessment) in each group.

The order of precedence when deriving the patient's best overall response is as follows:

1. Confirmed CR
2. Confirmed PR
3. SD (maintained for at least 6 weeks, i.e. the patient has at least one assessment of SD a minimum of 6 weeks after baseline)
4. UA (if overall response is UA)
5. PD
6. UA (if SD is not documented for at least 6 weeks without PD)

7.2.3.3 Sensitivity and Robustness Checks

The analysis of OR will be repeated based on the Investigator assessments of response. This analysis will be performed on patients from the ITT population with measurable disease according to the Investigator, defined as the presence of at least 1 target lesion at screening. Objective response will be based on the best overall response recorded from the start of trial treatment until Investigator-assessed PD, death or first administration of NACT, whichever occurs first. Refer to Section 7.1.4.3 for imputation rules applied to missing and partial NACT start dates.

7.2.3.4 Additional Exploratory Analyses

No additional exploratory analyses are planned.

Table 24 Outputs for Tumor Response

Output Title	Output reference	Population
Patient Listing of Investigator-Assessed Target Lesions by Trial Treatment and CRTN/Patient Number	L_TAR_INV	All Patients (By Treatment Randomized)
Patient Listing of Investigator-Assessed Non-Target Lesions by Trial Treatment and CRTN/Patient Number	L_NTAR_INV	All Patients (By Treatment Randomized)
Patient Listing of Investigator-Assessed New Lesions by Trial Treatment and CRTN/Patient Number	L_NEWL_INV	All Patients (By Treatment Randomized)
Patient Listing of IRF Tumor and Response Assessments by Trial Treatment, CRTN/Patient Number and Scheduled Visit	L_TUMIRFOVR	All Patients (By Treatment Randomized)
Patient Listing of Investigator Tumor and Response Assessments by Trial Treatment, CRTN/Patient Number and Scheduled Visit	L_TUMINV	All Patients (By Treatment Randomized)
Patient Listing of Investigator Tumor Assessment Comments by Trial Treatment, CRTN/Patient Number and Scheduled Visit	L_TUMINVCOM	All Patients (By Treatment Randomized)
Summary of IRF Best Overall Response (RECIST) for Objective Response (OR) by Trial Treatment, Stratified by Prior Treatment Status and Region, Patients with IRF-Determined Measurable Disease at Baseline	T_RR_IRF_STR_OR	ITT (By Treatment Randomized)

Output Title	Output reference	Population
Summary of IRF Best Overall Response (RECIST) for Objective Response (OR) by Trial Treatment, Unstratified Analysis, Patients with IRF-Determined Measurable Disease at Baseline	T_RR_IRF_OR	ITT (By Treatment Randomized)
Summary of Investigator-Assessed Best Overall Response (RECIST) for Objective Response (OR) by Trial Treatment, Stratified by Prior Treatment Status and Region, Patients with Investigator-Determined Measurable Disease at Baseline	T_RR_INV_STR_OR	ITT (By Treatment Randomized)
Summary of Investigator-Assessed Best Overall Response (RECIST) for Objective Response (OR) by Trial Treatment, Unstratified Analysis, Patients with Investigator-Determined Measurable Disease at Baseline	T_RR_INV_OR	ITT (By Treatment Randomized)
Listing of Cytology Results by Trial Treatment and CRTN/Patient Number	L_CYTOL	All Patients (By Treatment Randomized)
Summary of Cytology Results by Treatment Cycle and Trial Treatment	T_FCYTOL	ITT (By Treatment Randomized)
Listing of Bone Scan Clinically Significant Abnormalities by Trial Treatment and CRTN/Patient Number	L_VS03_BONE	All Patients (By Treatment Randomized)

In the event that a patient has multiple cytology assessments attributed to the same treatment cycle, the following rules will apply when summarizing the cytology results:

- Disease status assessed by cytology: count worst response, where 'Yes' is deemed worse than 'No'
- Malignant cells status: count worst response, where 'Positive' is deemed worse than 'Negative'
- Type of sample: count all unique values

7.2.4 Duration of Objective Response

7.2.4.1 Definition

Duration of response (weeks) is defined as the period from the date of initial confirmed PR or CR (defined as the date of tumor assessment at which the PR/CR was first detected

by the IRF) until the date of IRF-determined progressive disease or death within 18 weeks of the last tumor assessment from any cause. Tumor responses will be based on the IRF evaluations using RECIST criteria version 1.0 (Therasse et al. 2000 [1]). If the visit when the initial PR or CR is observed spans multiple dates, the latest date will be used for the calculation of response duration.

7.2.4.2 Hypothesis and Analysis Methods

Only patients in the ITT analysis population with an IRF-determined objective response (CR or PR), observed prior to IRF-assessed PD, death or NACT, will be included in the analysis of duration of objective response. Duration of response will be based on all IRF-assessed tumor assessments recorded from the date of initial response (CR or PR) until IRF-assessed PD, death or first administration of NACT, whichever occurs first. Patients who do not progress or die after they have had a confirmed response are censored at the date of their last IRF-evaluable tumor measurement. The duration of response (weeks) will be derived as:

((date of progression/death/censoring – date of initial CR or PR) +1)/7

Since this subgroup is not a randomized subset, formal hypothesis testing will not be performed. Duration of objective response will be estimated using the Kaplan-Meier approach. Estimation of the HR between the two treatment arms using Cox regression will be made.

7.2.4.3 Sensitivity and Robustness Checks

The analysis of duration of response will be repeated based on Investigator assessments, to assess the robustness of the IRF-based analysis. Patients with OR (CR or PR) as determined by the Investigator, prior to Investigator-assessed PD, death or NACT, will be included in the analysis. Duration of response will be based on all investigator-assessed tumor assessments recorded from the date of initial response (CR or PR) until IRF-assessed PD, death or first administration of NACT, whichever occurs first. The duration of response is defined as the period (weeks) from the date of the initial confirmed PR or CR (defined as the date of tumor assessment at which the Investigator first detected a PR/CR) until the date of Investigator-determined PD or death from any cause within 18 weeks of the last Investigator tumor assessment. Patients who do not progress or die after a confirmed response are censored at the date of their last Investigator tumor assessment. Specifically, the duration of response (weeks) will be derived as:

((date of progression/death/censoring – date of initial CR or PR)+1)/7

The analysis of Investigator-assessed duration of response is deemed exploratory.

7.2.4.4 Additional Exploratory Analyses

No additional exploratory analyses are planned.

Table 25 Outputs for Duration of Tumor Response

Output Title	Output reference	Population
Summary of Kaplan-Meier Analysis of Duration (weeks) of IRF-Assessed Objective Response for Patients who Responded by Trial Treatment	T_TTEV_IRF_ORS	All Patients (By Treatment Randomized)
Kaplan Meier Curve of Duration (weeks) of IRF-Assessed Objective Response for Patients who Responded by Trial Treatment	F_TTEV1_IRF_ORS	ITT (By Treatment Randomized)
Summary of Kaplan-Meier Analysis of Duration (weeks) of Investigator-Assessed Objective Response for Patients who Responded by Trial Treatment	T_TTEV_INV_ORS	All Patients (By Treatment Randomized)
Kaplan Meier Curve of Duration (weeks) of Investigator-Assessed Objective Response for Patients who Responded by Trial Treatment	F_TTEV1_INV_ORS	ITT (By Treatment Randomized)

7.2.5 Time to Symptom Progression

7.2.5.1 Definition

This is defined as the time (weeks) from randomization to the first symptom progression as evaluated from the Functional Assessment of Cancer Therapy-for patients with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical Functional Breast (TOI-PFB) subscale. Female patients are to complete this paper questionnaire at baseline and within 3 days prior to each tumor assessment (every 9 weeks from the date of randomization) until IRF-determined progressive disease. Male patients are excluded because the questionnaire is designed specifically for women.

All items in the questionnaire are to be rated on a five-point scale ranging from “not at all” (0) to “very much” (4). The TOI-PFB is a 24-item subscale, generated using the three subsections from the FACT-B questionnaire: Physical Well-being, Functional Well-being and Additional Concerns. The TOI-PFB score can range from 0 to 96. The higher the score, the better the perceived quality of life. A decrease of five points or more in the TOI-PFB score from baseline is considered clinically significant (i.e. symptom progression). However, it is important to note that symptom progression according to the TOI-PFB score does not necessarily indicate disease progression – a patient’s TOI-PFB score might deteriorate due to treatment-related toxicity for example, or for other reasons.

7.2.5.2 Hypothesis and Analysis Methods

Analysis methods are the same as those described for the primary efficacy endpoint. Analysis of time to symptom progression is deemed exploratory. Analysis of time (weeks) to symptom progression (analysis including baseline score and stratified by prior treatment status and region, and unstratified analysis) will be based on female patients only in the ITT analysis population.

Within the FACT-B, the majority of questions are phrased positively, such that a response of 'very much' (and consequently a score of 4) indicates the highest level of quality of life. For example, question GS1: "I feel close to my friends". However, some questions are phrased contra-positively, such that a response of 'very much' would indicate the lowest level of quality of life. For example, question GP1: "I have a lack of energy". Consequently, prior to deriving any scores associated with the FACT-B, all contra-positively phrased questions are recoded according to the following formula to ensure a score of 4 will represent the highest quality of life.

Derived score = 4 – raw score

where the raw score is the score as circled on the CRF, and subsequently entered on the database.

The full list of the negatively-phrased questions within the FACT-B, and their corresponding subsection, is as follows:

- Physical Well-being: GP1, GP2, GP3, GP4, GP5, GP6, GP7
- Emotional Well-being: GE1, GE3, GE4, GE5, GE6
- Additional concerns: B1, B2, B3, B5, B6, B7, B8, P2

To derive the TOI-PFB score, the contra-positive questions are first recoded, as described above. The TOI-PFB is then derived by summing the item scores within the relevant subsections. If less than 50% of items within a subsection or less than 80% of all 24 items in TOI-PFB are completed then the subscales and total scores are considered unreliable indicators of patient's perceived health status and will not be calculated, and this assessment will not contribute to the analysis of the time to symptom progression. If the TOI-PFB score cannot be calculated at all post-baseline assessments, the time to symptom progression will be censored at the date of randomization + 1 day.

Provided at least 50% of the items within a subsection have been answered, or at least 80% of the items within the TOI-PFB have been answered, then the score (subsection or TOI-PFB as applicable) is computed as follows:

$$Subsection\ Score = \left(\sum items\right) * (n\_subsection) \div (n\_items),$$

where n_subsection equals the expected number of items in the subsection (i.e. 24 for the TOI-PFB) and n_items equals the number of items answered in each subsection.

If either the physical, functional or additional concerns subsections scores are set to missing, the TOI-PFB will also be set to missing.

Data for patients who do not have an observed symptom progression at time of data cutoff will be censored at the last observed TOI-PFB assessment date at which a valid TOI-PFB score has been calculated.

If baseline TOI-PFB assessment is unavailable/not calculated for reason above, or if there is no post-baseline TOI-PFB assessments performed, data will be censored at the time of randomization plus 1 day. In addition to the summary table of time to symptom progression, the corresponding Kaplan-Meier curve will also be produced.

All data from the FACT-B questionnaire will be listed, including the derived variables for the analysis of symptom progression. Due to the volume of questions, the data will be split across 4 separate listings as follows:

1. Physical wellbeing (GP1-GP7) and Social/Family well-being (GS1-GS7) questions
2. Emotional wellbeing (GE1-GE6) and Functional wellbeing (GF1-GF7) questions
3. Additional concerns (B1-B9 & P2) questions
4. TOI-PFB score, change from baseline, symptom progression (Yes/No) and time to symptom progression

The listings will reference the FACT-B questions only by their identifier, eg. GP1, GP2 etc, due to space limitations. A separate listing will therefore be provided of the question text associated with each question identifier.

The TOI-PFB total scores and change from baseline over time will be summarized over time by trial treatment using descriptive statistics. Separate tables will be produced summarizing the data by scheduled visit and by actual treatment cycle.

For the output by treatment cycle, if a patient has multiple assessments attributed to the same treatment cycle the worst TOI-PFB score should be presented in the summary table, where worst is defined as the lowest TOI-PFB score. The worst TOI-PFB assessment is identified after derivation of the TOI-PFB score, rather than at the individual question level. Thus, calculate the TOI-PFB score by date across the Physical, Functional and Additional Concerns domains, and select the lowest TOI-PFB score within the cycle.

Compliance with the completion of the FACT-B questionnaire will be assessed by deriving at each scheduled visit at which the questionnaire is expected to be completed (every 9 weeks) the number and percentage of patients with a valid questionnaire. Eligible patients at each timepoint are defined as patients who do not have IRF-confirmed PD or have not died prior to the lower limit of the window of -7 days before the scheduled visit date (week 9, week 18 etc). Patients with a valid questionnaire are defined as eligible patients with a non-missing response to at least 1 question of the FACT-B questionnaire within the window of +/- 7 days around the scheduled visit date (9 weeks, 18 weeks etc.).

Table 26 Outputs for FACT-B Questionnaire

Output Title	Output reference	Population
Patient Listing of FACT-B Questionnaire by Trial Treatment and CRTN/Patient Number (1)	L_FACT_FEM_L1	All Patients (By Treatment Randomized)
Patient Listing of FACT-B Questionnaire by Trial Treatment and CRTN/Patient Number (2)	L_FACT_FEM_L2	All Patients (By Treatment Randomized)

Output Title	Output reference	Population
Patient Listing of FACT-B Questionnaire by Trial Treatment and CRTN/Patient Number (3)	L_FACT_FEM_L3	All Patients (By Treatment Randomized)
Patient Listing of FACT-B Questionnaire by Trial Treatment and CRTN/Patient Number (4)	L_TFACT_FEM	All Patients (By Treatment Randomized)
Listing of FACT-B Questionnaire Text	L_FACTQU	N/A
Summary of Time (weeks) to Symptom Progression from FACT-B Questionnaire by Trial Treatment, Stratified by Prior Treatment Status and Region	T_TTEV_STR_SYM_FEM	ITT (By Treatment Randomized)
Kaplan-Meier Curve of Time to Symptom Progression from FACT-B Questionnaire (weeks) by Trial Treatment	F_TTEV1_SYM_FEM	ITT (By Treatment Randomized)
Summary of Time (weeks) to Symptom Progression from FACT-B Questionnaire by Trial Treatment, Unstratified Analysis	T_TTEV_SYM_FEM	ITT (By Treatment Randomized)
Summary of TOI-PFB Total Scores and Change from Baseline over Time by Scheduled Visit and Trial Treatment	T_UFACT_FEM_SV	ITT (By Treatment Randomized)
Summary of TOI-PFB Total Scores and Change from Baseline over Time by Treatment Cycle and Trial Treatment	T_UFACT_FEM_CY	ITT (By Treatment Randomized)
Summary of Compliance with FACT-B Questionnaire	T_FCOMPFACT	ITT (By Treatment Randomized)

7.2.5.3 Sensitivity and Robustness Checks

No sensitivity analysis is planned.

7.2.5.4 Additional Exploratory Analyses

No additional exploratory analysis is planned.

7.2.6 Biomarkers Analysis

The objective of the further statistical analyses of biomarkers in this study is the identification of those markers or combinations of markers which show best association

with positive or negative clinical outcome of pertuzumab treatment. Special emphasis will be on the identification of markers that discriminate between patients (subgroups) that specifically benefit from the treatment. Based on prior biomarker analyses performed in phase II studies in HER2+ breast cancer (BO17929 and WO20697) to investigate correlation of markers with treatment response, no hypotheses of markers predictive of treatment response have been identified to be tested in this study, therefore, biomarker analyses are considered exploratory.

Please refer to the Protocol TOC4129g/WO20698, Section 5.4.7 for further details of biomarker sampling performed in this study. The following table shows the proposed pre-defined biomarker panel for analysis.

Table 27 Pre-defined Biomarker Panel for Analysis

Sample type	Biomarker	Testing method	Central lab
Tumor tissue (FFPE) HER2 screening by Dako HER2 IHC/FISH	HER2, HER3, EGFR, Amphiregulin, Betacellulin mRNA expression levels	qRT-PCR	TARGOS Molecular Pathology GmbH
	ER/PgR, HER3, IGF-1R, PTEN, pAKT protein expression levels	IHC	
	c-myc gene amplification	FISH	
	PIK3CA mutation	RMD Taqman PI3K mutation assay (8 hot spot mutations)	Roche TRS DNA lab
Serum	HER2/ECD level HER ligands: EGF, TGFα, Amphiregulin levels	ELISA (SIEMENS assay) ELISA (IMPACT)	Covance and Roche TRS protein lab
Whole blood sample	Fcγ-Receptor polymorphism	DNA polymorphism analyses (pCR based)	Roche TRS DNA lab

For the above biomarker panel, the association of marker expression with treatment benefit for the primary endpoint of IRF-assessed PFS will be investigated. For each marker and treatment arm, patients will be divided according to median expression into low and high-expression subgroups and the HR will be used to assess treatment benefit by comparing treatment arms for the low and high-expression subgroups. For the CSR, it is proposed that these analyses will be presented in the form of a Forest Plot. Since these analyses are considered exploratory, no formal adjustment to the type1 error level will be applied to account for multiple testing. As an additional analysis to identify markers that are prognostic for treatment outcome, differences in efficacy between low and high-expression subgroups will be investigated for IRF PFS for both treatment arms.

Based on these analyses and on the strength of the findings, the prognostic and/or predictive value of the biomarkers tested will be assessed. This assessment will take into account statistical and clinical considerations, including likelihood of false-positive results, distribution of marker expression between arms and strength of any interaction

between treatment and marker subgroup. Further exploratory analyses will be performed if any signals are felt to be of sufficient magnitude and plausibility to warrant this. This may include exploring whether the association is also consistent for the interim overall survival data. Otherwise, the scope of analyses for the CSR will be limited to the above.

7.3 Exploratory Variables

The following endpoints, which were not specified as planned endpoints within the Study Protocol, will be evaluated as exploratory analyses:

1. Time to Response (IRF and Investigator assessed)
2. Clinical Benefit Response (IRF and Investigator assessed)

Details of each analysis are described in the following sections:

7.3.1 Time to Response

7.3.1.1 Definition

Time to response will be summarized based on both the IRF and Investigator tumor assessments. Time to response is defined as the period (weeks) from randomization to the date of initial confirmed PR or CR (defined as the date of tumor assessment at which the PR/CR was first detected by the IRF/Investigator). Time to response will be based on tumor assessments up to IRF/Investigator-assessed PD (as appropriate to the endpoint), death or NACT, whichever occurs earlier. Refer to Section 7.1.4.3 for imputation rules applied to missing and partial NACT start dates.

7.3.1.2 Hypothesis and Analysis Methods

Patients in the ITT population with measurable disease at baseline (according to the IRF or Investigator, as appropriate) will be included in the analysis of time to response. See Section 7.2.3.2 for the definition of measurable disease. Patients who do not respond and do not experience disease progression or death (within 18 weeks of last tumor assessment) will be censored at the date of their last tumor assessment (IRF-assessed or Investigator-assessed as appropriate). Patients who do not respond and who experience disease progression or death (within 18 weeks of the last tumor assessment) or start NACT will be censored at their date of PD (IRF or Investigator assessed, as appropriate) date of death, or the last TA prior to onset of NACT, whichever is earlier. Patients with no tumor assessments after baseline will be censored at 1 day.

No hypothesis testing will be performed on this endpoint as the analysis is considered to be exploratory.

7.3.1.3 Sensitivity and Robustness Checks

Not applicable.

7.3.1.4 Additional Exploratory Analyses

Not applicable.

Table 28 Outputs for Time to Tumor Response

Output Title	Output reference	Population
Summary of Kaplan-Meier Analysis of IRF-Assessed Time to Response (weeks) by Trial Treatment, Patients with IRF-Determined Measurable Disease at Baseline	T_TTEV_IRF_TTR	All Patients (By Treatment Randomized)
Kaplan Meier Curve of IRF-Assessed Time to Response (weeks) by Trial Treatment, Patients with IRF-Determined Measurable Disease at Baseline	F_TTEV1_IRF_TTR	ITT (By Treatment Randomized)
Summary of Kaplan-Meier Analysis of Investigator-Assessed Time to Response (weeks) by Trial Treatment, Patients with Investigator-Determined Measurable Disease at Baseline	T_TTEV_INV_TTR	All Patients (By Treatment Randomized)
Kaplan Meier Curve of Investigator-Assessed Time to Response (weeks) by Trial Treatment, Patients with Investigator-Determined Measurable Disease at Baseline	F_TTEV1_INV_TTR	ITT (By Treatment Randomized)

7.3.2 Clinical Benefit Response

7.3.2.1 Definition

Clinical Benefit Response (CBR) will be evaluated based on both the IRF and Investigator tumor assessments. CBR will be based on tumor assessments up to IRF/Investigator-assessed PD (as appropriate to the endpoint), death or NACT, whichever occurs earlier. Refer to Section 7.1.4.3 for imputation rules applied to missing and partial NACT start dates. Patients are defined as showing clinical benefit if they have an objective response (CR or PR subsequently confirmed a minimum of 4 weeks later), or stable disease (SD) that is maintained for at least 180 days.

7.3.2.2 Hypothesis and Analysis Methods

The analysis of the CBR will be based on the ITT population. It is not necessary to restrict the analysis of CBR to patients with measurable disease, as done for the analysis of ORR, because it is possible to observe clinical benefit in patients with non-measurable disease, in the form of stable disease. Patients with a best overall response (BOR) of CR or PR, confirmed at least 4 weeks apart, or with SD maintained for at least 180 days will be classified as demonstrating clinical benefit. All other patients, including patients with no post-baseline tumor assessments, will be classified as non-responders with respect to clinical benefit.

The analysis will be descriptive, with no hypothesis testing performed, as this is an exploratory endpoint. An estimate of the CBR and 95% CI using the Pearson-Clopper method will be calculated for each treatment arm.

7.3.2.3 Sensitivity and Robustness Checks

Not Applicable.

7.3.2.4 Additional Exploratory Analyses

Not applicable.

Table 29 Outputs for Clinical Benefit Response

Output Title	Output reference	Population
Summary of IRF-Assessed Clinical Benefit Response (CBR) by Trial Treatment	T_RR_IRF _CBR	ITT (By Treatment Randomized)
Summary of Investigator-Assessed Clinical Benefit Response (CBR) by Trial Treatment	T_RR_INV_CBR	ITT (By Treatment Randomized)

8. PHARMACOECONOMIC ANALYSIS

Analysis will be performed on the Safety analysis population.

Details of hospitalization are recorded on the "MRU (Hospitalization)" DCS, and are collected during the period when the patient is on study treatment.

The number of hospital visits, number of days admitted, admissions to ICU/CCU, including duration, and the principal reason for hospitalization will be summarized by treatment arm. To account for the possibility that an individual patient may experience more than 1 hospitalization during the study, summaries will be provided for both the total duration of hospital stay and the longest duration of hospital stay. Similar summaries will be provided for patients who are admitted to ICU/CCU more than once during the study. If the patient had been hospitalized on more than 1 occasion, the principle reason for hospitalization will count all unique responses for each patient (adverse event or other).

In the event of a partial date for the date of hospital discharge (including missing dates for patients not yet discharged), the rules for partial dates described in Section 4.5.2.1 will be applied in order to calculate total duration of hospital stay and, if applicable, longest duration of hospital stay. If the patient is still in ICU/CCU at the time of the datacut, the number of days in ICU/CCU will be set to missing for that admission, as the date of admission to ICU/CCU is unknown.

Table 30 Outputs for Hospitalization

Output Title	Output reference	Population
Listing of Hospitalization by Trial Treatment and CRTN/Patient Number	L_HOSP	All Patients (By Treatment Received)
Summary of Hospitalization by Trial Treatment	T_UFHOSP	Safety

9. SAFETY ANALYSIS

Safety of study treatment will be evaluated as follows:

– Incidence and severity of adverse events and serious adverse events (SAEs)

– Incidence of symptomatic LVSD (CHF, NCI CTCAE grades 3 to 5) and asymptomatic LVSD (NCI CTCAE grades 1 and 2) events

– LVEF measurements over the course of the study

– Laboratory test abnormalities

9.1 Exposure to Study Medication

All exposure to study medication analyses will be based on the Safety analysis population.

9.1.1 Pertuzumab/Placebo

The administration of pertuzumab/placebo is taken from the "Pertuzumab – Placebo admin" DCS.

If a patient takes the incorrect randomized treatment at any time during the study, and consequently has cycles for both placebo and pertuzumab, all cycles will be assumed to be pertuzumab for the purposes of deriving the summary outcomes variables below.

1. The total number of cycles with pertuzumab/placebo administered will be summarized as number and percentage by treatment arm. The total amount of pertuzumab/placebo received will be summarized by treatment arm using descriptive statistics: patient frequency, mean, standard deviation, median, minimum and maximum. In addition, the number of cycles where an infusion is delayed, slowed down, interrupted or discontinued will be summarized by treatment arm, both overall and also where the dosing change is due to an adverse event. For the cycles where infusion is delayed, the number of days delayed is summarized as ≤ 3 days, > 3 to < 7 days, 7 to 14 days, > 14 to 24 days and > 24 days. If a delay has been indicated on the eCRF, and the delay occurs in Cycle 1, the length of delay will be derived as (date of infusion – date of study Day 1). Otherwise, for delays in all other cycles, the length of delay will be derived as ((date of infusion – date of previous infusion) – 21). Note that a delayed cycle must have a valid (>0) dose. A cycle with a dose of zero or missing with 'delay' indicated is deemed either a missed or incomplete cycle, dependent on

whether the patient received any component of the treatment regimen. For the infusion interruption, the number of patients with at least 1 infusion interrupted is summarized. This is further categorized as number of patients with 1 interruption, 2 or 3 interruptions etc. across all cycles. Infusions that were slowed down will be summarized in a similar manner. The cycles where pertuzumab/placebo is discontinued will be summarized by treatment arm. The number of patients with an incomplete cycle of pertuzumab/placebo will also be summarized. Patients are defined as having an incomplete cycle of pertuzumab/placebo if the patient has a valid trastuzumab and/or docetaxel record (dose > 0), but pertuzumab/placebo is missed (dose = 0)

9.1.2 Trastuzumab

The administration of trastuzumab is taken from the "Trastuzumab admin" DCS. The data will be summarized in the same way as for pertuzumab/placebo.

If trastuzumab is delayed in any cycle, and a valid (>0) dose has been entered for trastuzumab, the length of delay will be derived as follows, accounting for the fact that trastuzumab is scheduled to be administered on Day 2 of Cycle 1 and Day 1 of each subsequent cycle:

Cycle 1: (date of infusion – date of study Day 2)

Cycle 2: ((date of infusion – date of previous infusion) – 20)

All other cycles: ((date of infusion – date of previous infusion) – 21)

An incomplete cycle of trastuzumab is defined as a cycle where a patient has a valid pertuzumab/placebo and/or docetaxel record (dose > 0), but trastuzumab is missed (dose = 0).

9.1.3 Docetaxel

The administration of docetaxel is taken from the "Docetaxel first admin" DCS and the "Docetaxel admin" DCS. The data will be summarized in the same way as for pertuzumab/placebo.

If docetaxel is delayed in any cycle, and a valid (>0) dose has been entered for docetaxel, the length of delay will be derived in the same manner as the length of trastuzumab delay, given that docetaxel is scheduled to be administered on Day 2 of Cycle 1 and Day 1 of each subsequent cycle.

An incomplete cycle of docetaxel is defined as a cycle where a patient has a valid pertuzumab/placebo and/or trastuzumab record (dose > 0), but docetaxel is missed (dose = 0).

The first administration of docetaxel is 75 mg/m^2 for all patients. At the Investigator's discretion, docetaxel may be increased to 100 mg/m^2 if patients tolerate at least 1 cycle of docetaxel at 75 mg/m^2 without any toxicities (eg, febrile neutropenia, grade 4 neutropenia for >5 days, ANC <100/μL or grade >2 non-hematological toxicities). The number and percentage of patients with or without a change in dose (from 75 mg/m^2 to 100 mg/m^2)

and the reasons for not changing the dose will be summarized by treatment arm and by cycle.

A separate table will be produced which will summarize the number (%) of patients who permanently discontinued docetaxel, while remaining on pertuzumab/placebo and trastuzumab, and the reasons for the discontinuation. As Investigators may stop docetaxel after approximately 6-8 cycles, based on normal clinical practice, a summary will be provided of the cycle at which docetaxel was permanently discontinued (where a valid treatment cycle is defined as a cycle with any treatment (pertuzumab, trastuzumab or docetaxel) with a dose >0), and the number (%) of patients receiving at least 6 cycles of docetaxel (docetaxel cycle defined as a cycle with docetaxel dose >0). A corresponding listing of docetaxel discontinuation will also be provided.

A listing of all study medication administration and any dose adjustment will be presented by trial treatment and CRTN/patient number. The listing will include the derived variable 'duration', representing the total time (calculated in minutes) between the infusion start time and the infusion end time.

Output T_FMEDT2 will be used to summarize the disposition of patients cumulatively, with respect to remapped cycles initiated (dose>0) during the overall treatment period.

Table 31 Outputs for Study Medication

Output Title	Output reference	Population
Listing of Study Medications by Trial Treatment and CRTN/Patient Number	L_MEDT	All Patients (By Treatment Received)
Summary of Treatment Cycles by Trial Treatment	T_FMEDT2	Safety
Summary of Number of Pertuzumab/Placebo Infusions Administered, Delayed, Slowed Down, Interrupted, or Discontinued by Trial Treatment	T_FMEDT4_PZP	Safety
Summary of Number of Trastuzumab Infusions Administered, Delayed, Slowed Down, Interrupted, or Discontinued by Trial Treatment	T_FMEDT4_TRA	Safety
Summary of Number of Docetaxel Infusions Administered, Delayed, Slowed Down, Interrupted, or Discontinued by Trial Treatment	T_FMEDT4_DOC	Safety
Summary of Total Dose of Pertuzumab/Placebo Received by Trial Treatment	T_UMEDT1_PZP	Safety
Summary of Total Dose of Trastuzumab Received by Trial Treatment	T_UMEDT1_TRA	Safety

Output Title	Output reference	Population
Summary of Total Dose of Docetaxel Received by Trial Treatment	T_UMEDT1_DOC	Safety
Summary of Docetaxel Dose Escalation and Reasons for Not Escalating Docetaxel Dose by Treatment Cycle and Trial Treatment	T_UMEDT2ESC	Safety
Summary of Discontinuation of Docetaxel by Trial Treatment	T_FMEDTDIS	Safety
Listing of Reasons for Discontinuation of Docetaxel by Trial Treatment and CRTN/Patient Number	L_EXITDISD	All Patients (By Treatment Received)
Listing of Docetaxel Dose Escalation and Reasons for Not Escalating Docetaxel Dose by Trial Treatment and CRTN/Patient Number	L_MEDT2_DOC	All Patients (By Treatment Received)

9.2 Adverse Events

All adverse event (AE) analyses will be performed on the Safety analysis population.

Adverse events will be taken from the "Adverse event" DCS.

Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE, Version 3.0. All AEs are listed, including those occurring prior to the date of first study treatment and those occurring during the post-treatment period, but only AEs that occur on or after study Day 1 (i.e. after the first dose of any study treatment) and up to up to 42 days after the last dose > 0 of study treatment (as per the definition of the overall treatment period – see Section 4.3.2) will be presented in summary tables. The severity of an event is recorded on the DCS as NCI CTCAE grades 1 to 4. NCI CTCAE grade 5 will be imputed for outcome of an event ticked as "death". All adverse events, including serious adverse events, will be summarized by treatment arm, body system and NCI CTCAE grade. In addition, adverse events leading to discontinuation of any study medication (pertuzumab/placebo, trastuzumab or docetaxel) or adverse events resulting in a dose modified, interrupted or discontinued will be summarized by treatment arm. For each patient's adverse events, the maximum severity recorded as NCI CTCAE grade for an event will be summarized. For the relationship to study medication, a response to the question on the "Adverse event" DCS "Is there a reasonable suspected causal relationship to study medication?" of "yes" will be reported as "possible" relationship to study medication and a response of "no" will be reported as "unrelated" to the study medication.

The following listings will be produced using the MARS template AE01:

- Listing of Adverse Events by Trial Treatment and CRTN/Patient Number
- Listing of Serious Adverse Events by Trial Treatment and CRTN/Patient Number
- Listing of NCI CTCAE Grades 3, 4 and 5 Adverse Events by Trial Treatment and CRTN/Patient Number

The MARS template AE02 will be used to produce a listing of Patients with Adverse Events by Trial Treatment and CRTN/Patient Number with Cumulative Dose. The cumulative dose of all 3 study treatments (pertuzumab/placebo, trastuzumab and docetaxel) up to the time of onset of the AE will be presented in this listing.

The MARS template AE05 will be used to produce a listing of Adverse Events by Trial Treatment and CRTN/Patient Number with Actually Received Treatment.

The MARS template AE03 will be used to produce a listing of Adverse Events by Trial Treatment and Body System.

The MARS template AE09 will be used to produce a glossary of Preferred Terms for Adverse Events.

The MARS template AE01 will be used to produce a listing of Adverse Events with Intensity, Outcome and Concomitant Treatment given for the AE by Trial Treatment, CRTN/Patient Number and Cycle. Multiple treatments given for the same AE will be listed on one line, separated by commas.

9.2.1 Overview of Adverse Event Experience

An overview of adverse events reported during the treatment period (date of last study medication + 42 days) will be produced, in which the following derived outcomes will be presented. For all AE types listed below, multiple occurrences of the same adverse event in one individual are counted only once. For summaries by grade or relationship to study medication, the worst event (highest grade or related event) is counted when there are multiple occurrences of the same adverse event in one individual:

- The incidence of any AE.
- The incidence of NCI CTCAE grade 3, 4 or 5 AEs.
- The incidence of serious AEs.
- The incidence of related AEs.
- The incidence of AEs leading to discontinuation of study medication.
- The incidence of AEs leading to dose interruption/modification.
- The incidence of AEs leading to death.
- The incidence of AEs during pertuzumab infusion (all grades and grade ≥ 3)
- The incidence of the following Events to Monitor:
  - Symptomatic LVSD adjudicated by the CRC (all grades and NYHA Class III/IV)
  - Symptomatic LVSD assessed by the Investigator (all grades and NYHA Class III/IV)
  - Left Ventricular Dysfunction (all grades and grade ≥ 3)

- Diarrhoea (all grades and grade ≥ 3)
- Rash (all grades and grade ≥ 3)
- Leukopenia (all grades and grade ≥ 3)
- Leukopenic Infection (all grades and grade ≥ 3)
- Febrile neutropenic Infection (all grades and grade ≥ 3) [subgroup of "Leukopenic infection", i.e. AEs are also counted under "Leukopenic infection"
- Interstitial Lung Disease (all grades and grade ≥ 3)
- Hypersensitivity/anaphylaxis (all grades and grade ≥ 3)
- Serious Cardiac Failure (all grades and grade ≥ 3)
- QT prolongation events (all grades and grade ≥ 3)
- Mucositis (all grades and grade ≥ 3)

The Events to Monitor are described in more detail Section 9.6.2. Refer to Section 9.6.2.1 for details of the SMQs or the adverse event group terms (AEGTs) defined for each of these Events to Monitor.

The following summaries will be presented using the MARS template AE11:

- Summary of Adverse Events by Body System and Trial Treatment
- Summary of Serious Adverse Events by Body System and Trial Treatment
- Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System and Trial Treatment

The following summary will be presented using the MARS template AE15:

- Summary of adverse events by body system, Trial Treatment and intensity (by NCI-CTCAE Grade 1-5)

The Grade 5 column will be displayed in the above output even if there are no Grade 5 AEs.

The following summary will be presented using the MARS template AE21:

- Summary of Adverse Events by Trial Treatment, Body System and Relation to Trial Treatment

The following summary will be presented using the MARS template AE13:

- Summary of Adverse Events with an Incidence Rate of at least 5% by Trial Treatment

Further outputs of related adverse events will be produced, as follows:

- Summary of Related Adverse Events by Body System and Trial Treatment
- Summary of Related Serious Adverse Events by Body System and Trial Treatment

- Summary of Related NCI-CTCAE Adverse Events by Body System and Trial Treatment
- Summary of Related Adverse Events Leading to Discontinuation of Docetaxel Only by Body System and Trial Treatment
- Summary of Related Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to Discontinuation of Docetaxel Only, by Body System and Trial Treatment
- Summary of Related Adverse Events that Resulted in Death by Body System and Trial Treatment

9.2.2 Discontinuation or Dosage Modification of Study Medication due to an AE

On the "Adverse event" DCS, if "pertuzumab/placebo adjustment" or "trastuzumab adjustment" or "docetaxel adjustment" is ticked as "discontinued", one of the study medications must have been permanently discontinued. The study drug must have been stopped during the same cycle in which the AE was recorded in order to be linked to the AE, i.e. there is no further infusion of this treatment after the AE start date. Patient listings will list all AEs that resulted in permanent discontinuation of one or more study medications and the study medication(s) that was stopped on or near the date that the AE occurred. Two separate listings will be produced, to account for the fact that docetaxel may be discontinued while the patient continues in the study receiving pertuzumab/placebo and trastuzumab. One listing will include AEs that lead to the discontinuation of docetaxel only, and the second listing will include AEs that led to the discontinuation of all study treatment (i.e it will exclude any events leading to the discontinuation of docetaxel only). Two separate summary tables will also be produced.

The following listings will be presented using the MARS template AE01:

- Listing of Adverse Events Leading to Discontinuation of Docetaxel only by Trial Treatment and CRTN/Patient Number
- Listing of Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to the Discontinuation of Docetaxel only, by Trial Treatment and CRTN/Patient Number

The following listing will be presented using the MARS template AE04 to show all AEs for patients withdrawn due to AE:

- Listing of Patients Withdrawn for Adverse Events by Trial Treatment and CRTN/Patient Number

The following summary will be presented using the MARS template AE11:

- Summary of Adverse Events Leading to Discontinuation of Docetaxel only by Body System and Trial Treatment
- Summary of Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to the Discontinuation of Docetaxel only, by Body System and Trial Treatment

The adverse events that lead to dose modification or interruption of study drug will be determined by selecting each patient who had "pertuzumab/placebo adjustment" or "trastuzumab adjustment" or "docetaxel adjustment" ticked as "dosage modified/interrupted" on the "Adverse event" DCS. For pertuzumab/placebo and trastuzumab, the label will appear as "interrupted" in the listings (since no dosage modification is allowed for these study medications in this study). For docetaxel, the label will appear as "dosage modified" in the listings. For each treatment adjustment, the combination of all study medications will be shown on one line in the listing, separated by a space and abbreviated with footnotes to explain. For example, "P=NONE T=NONE D=DOSAGE MODIFIED" denotes no adjustments to pertuzumab/placebo and trastuzumab but the dose of docetaxel was modified.

The following listing will be presented using the MARS template AE01:

- Listing of Adverse Events that Resulted in Interruption/Modification of Study Medication by Trial Treatment and CRTN/Patient Number

The following summary will be presented using the MARS template AE11:

- Summary of Adverse Events that Resulted in Interruption/Modification of Study Medication by Body System and Trial Treatment

9.2.3 Death due to an AE

The AEs that resulted in death will be determined by selecting for each patient who had the "outcome" ticked as "death" on the "Adverse event" DCS.

The following listing will be presented using the MARS template AE01:

- Listing of Adverse Events that Resulted in Death by Trial Treatment and CRTN/Patient Number

The following summary will be presented using the MARS template AE11:

- Summary of Adverse Events that Resulted in Death by Body System and Trial Treatment

9.2.4 Infusion-Associated Adverse Events

Adverse events that started during a pertuzumab infusion will be identified by the response to the question on the "Adverse event" eCRF page 'Did this event start during the pertuzumab infusion?'. Additional adverse events that started on the day of a pertuzumab/placebo infusion (but not during an infusion) or the day after a pertuzumab/placebo infusion will be identified by comparing the AE start date with the pertuzumab/placebo infusion dates. Imputed adverse event dates will not be used here (therefore a partial/invalid date could never be considered as occurring on the same day as or the day after a pertuzumab/placebo infusion).

The following listing will be presented using the MARS template AE01:

- Listing of Adverse Events that started During, on the day of or the day after a Pertuzumab/Placebo infusion by Trial Treatment and CRTN/Patient Number

The following summaries will be presented for infusion-related AEs:

- Summary of Adverse Events that started During a Pertuzumab/Placebo infusion by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade
- Summary of Adverse Events that started on the Day of a Pertuzumab/Placebo infusion, including During Infusion, by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade
- Summary of Adverse Events that started on the day of a Pertuzumab/Placebo infusion or the day after but Not During Infusion by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade
- Summary of Adverse Events that started During or on the day of a Pertuzumab/Placebo infusion or the day after by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade

9.2.5 Adverse Events During and After Discontinuation of Docetaxel

Separate summaries of adverse events will be produced for the period when the patient is receiving docetaxel and also for the period following discontinuation of docetaxel. The cutoff for the period following discontinuation of docetaxel will be 42 days after the last dose > 0 of any study treatment.

The treatment period of docetaxel will be defined as starting on the day of the first docetaxel dose >0. The timing of the end of the docetaxel treatment period will depend on whether the patient discontinued docetaxel only or discontinued all treatments at the same cycle, as defined below.

If docetaxel is discontinued, but pertuzumab and/or trastuzumab continues (as indicated by a non-missing ‘date of last docetaxel infusion’ on the “Docetaxel discontinuation” DCS), the summary of AEs during docetaxel treatment will include all AEs that start prior to the date of the next infusion of pertuzumab/trastuzumab. The summary of AEs after discontinuation of docetaxel will include AEs that start between the date of the next infusion of pertuzumab/trastuzumab in the next cycle, and 42 days (inclusive) after the last dose > 0 of any study treatment (if all treatments are discontinued prior to the datacut, otherwise include all AEs up to the date of the datacut).

If all study treatments are discontinued at the same cycle (as indicated by a non-missing ‘date of last infusion’ on the “Treatment period completion” DCS and a blank ‘Date of last docetaxel infusion’ on the “Docetexal discontinuation” DCS), the summary of AEs during docetaxel treatment will include all AEs that start up to 42 days (inclusive) after the last dose > 0 of docetaxel. As this cutoff also defines the end of the treatment period, no AEs will be assigned to the listing/summary of AEs after discontinuation of docetaxel for this group of patients.

For patients who are still receiving docetaxel at the time of the data cut, the docetaxel treatment period will end on the date of the data cut, such that all AEs that start on or before the data cut are included in the summary of AEs during docetaxel treatment.

If an AE is reported with a partial start date, the rules defined in 4.5.1.1 will be applied to determine if the event started during the docetaxel treatment period.

Separate listings of all AEs in each period will be provided using MARS template AE01, as well as an overall summary (MARS template AE11) and summaries by NCI-CTCAE grade (MARS template AE15) and relationship to study medication (MARS template AE21). Specifically, the following outputs will be produced.

- Summary of Adverse Events that Started During Docetaxel Treatment by Body System and Trial Treatment
- Summary of Adverse Events that Started During Docetaxel Treatment by Body System, Trial Treatment and Intensity (by NCI-CTCAE Grade 1-5)
- Summary of Adverse Events that Started During Docetaxel Treatment by Trial Treatment, Body System and Relation to Trial Treatment
- Listing of Adverse Events that Started During Docetaxel Treatment by Trial Treatment and CRTN/Patient Number
- Summary of Adverse Events that Started After Discontinuation of Docetaxel by Body System and Trial Treatment
- Summary of Adverse Events that Started After Discontinuation of Docetaxel by Body System, Trial Treatment and Intensity (by NCI-CTCAE Grade 1-5)
- Summary of Adverse Events that Started After Discontinuation of Docetaxel by Trial Treatment, Body System and Relation to Trial Treatment
- Listing of Adverse Events that Started After Discontinuation of Docetaxel by Trial Treatment and CRTN/Patient Number

9.2.6 Adverse Events Reported During the Post-Treatment Period

The post-treatment period is defined as the period following the treatment discontinuation visit, which is scheduled to take place 28-42 days after the date of the last dose of any study medication. During the post-treatment period, new AEs will be reported if they fulfill the following criteria:

1. Treatment-related SAE
2. Congestive heart failure (CHF)

SAEs suggestive of CHF will be identified from the SMQ (wide) “Cardiac Failure”. For reporting purposes, outputs for the post-treatment period will include all AEs which started more than 42 days after the last dose of study treatment. The following summary tables will be produced of AEs reported during the post-treatment period using MARS template AE11:

- Summary of Adverse Events Reported During the Post-Treatment Period by Body System and Trial Treatment

- Summary of SAEs suggestive of CHF (SMQ wide "Cardiac Failure")reported During the Post-Treatment Period by Body System and Trial Treatment
- Summary of Serious Related Adverse Events reported During the Post-Treatment Period by Body System and Trial Treatment

9.2.7 Adverse Events by Subgroups

Adverse events and NCI-CTCAE Grade 3, 4 or 5 adverse events will be evaluated within the following subgroups:

- Age-group (<65 years, ≥ 65 years)
- Age-group (<75 years, ≥ 75 years)
- Race (White, Black, Asian, Other)
- Region (Europe, North America, South America, Asia)

For the purposes of the sub-group analysis, race has been restricted to 4 categories, with 'Other' comprising patients who have selected the following race categories on the eCRF: 'American Indian or Alaska native', 'native Hawaiian or other Pacific Islander', 'Other'

Full summary tables of all AEs by subgroup and all NCI-CTCAE Grade 3, 4 or 5 AEs will be produced. Further tables will then be produced of AEs by subgroup restricted to those events where the difference in incidence between the treatment arms is ≥ 5% within any subgroup category, and NCI-CTCAE Grade 3, 4 or 5 AEs by subgroup, restricted to those events where the difference in incidence between the treatment arms is ≥ 2% within any subgroup category.

Table 32 Outputs for Adverse Events

Output Title	Output reference	Population
Listing of Adverse Events by Trial Treatment and CRTN/Patient Number	L_AE01	All Patients (By Treatment Received)
Listing of Adverse Events by Trial Treatment and CRTN/Patient Number with Actually Received Treatment	L_AE05	All Patients (By Treatment Received)
Listing of Serious Adverse Events by Trial Treatment and CRTN/Patient Number	L_AE01_S	All Patients (By Treatment Received)
Listing of NCI-CTCAE Grade 3, 4 or 5 Adverse	L_AE01_345	All Patients

Output Title	Output reference	Population
Events by Trial Treatment and CRTN/Patient Number		(By Treatment Received)
Listing of Patients with Adverse Events by Trial Treatment and CRTN/Patient Number with Cumulative Dose	L_AE02	All Patients (By Treatment Received)
Listing of Patients with Adverse Events by Trial Treatment and Body System	L_AE03	All Patients (By Treatment Received)
Glossary of Preferred Terms for Adverse Events	L_AE09	
Listing of Adverse Events with Intensity, Outcome and Concomitant Treatment Given for the AE by Trial Treatment, CRTN/Patient Number and Treatment Cycle	L_AE01_IOC	All Patients (By Treatment Received)
Listing of Patients Withdrawn from all Study Treatment for Adverse Events by Trial Treatment and CRTN/Patient Number	L_AE04	All Patients (By Treatment Received)
Summary of Adverse Events by Body System and Trial Treatment	T_AE11	Safety
Summary of Serious Adverse Events by Body System and Trial Treatment	T_AE11_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System and Trial Treatment	T_AE11_345	Safety
Summary of Adverse Events by Trial Treatment, Body System and Relation to Trial Treatment	T_AE21	Safety

Output Title	Output reference	Population
Summary of Adverse Events with an Incidence Rate of at Least 5% by Trial Treatment	T_AE13	Safety
Summary of Adverse Events by Body System, Trial Treatment and Intensity (by NCI-CTCAE Grade 1-5)	T_AE15	Safety
Listing of Adverse Events Leading to Discontinuation of Docetaxel only by Trial Treatment and CRTN/Patient Number	L_AE01_DISD	All Patients (By Treatment Received)
Listing of Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to the Discontinuation of Docetaxel only, by Trial Treatment and CRTN/Patient Number	L_AE01_DIS	All Patients (By Treatment Received)
Summary of Adverse Events Leading to Discontinuation of Docetaxel only by Body System and Trial Treatment	T_AE11_DISD	Safety
Summary of Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to the Discontinuation of Docetaxel only, by Body System and Trial Treatment	T_AE11_DIS	Safety
Listing of Adverse Events that Resulted in Interruption/Modification of Study Medication by Trial Treatment and CRTN/Patient Number	L_AE01_INT	All Patients (By Treatment Received)
Summary of Adverse Events that Resulted in Interruption/Modification of Study Medication by Body	T_AE11_INT	Safety

Output Title	Output reference	Population
System and Trial Treatment		
Listing of Adverse Events that Resulted in Death by Trial Treatment and CRTN/Patient Number	L_AE01_DEA	All Patients (By Treatment Received)
Summary of Adverse Events that Resulted in Death by Body System and Trial Treatment	T_AE11_DEA	Safety
Listing of Adverse Events that Started During, on the Day of or the Day After a Pertuzumab/Placebo Infusion by Trial Treatment and CRTN/Patient Number	L_AE01_INF	All Patients (By Treatment Received)
Summary of Adverse Events that Started During a Pertuzumab/Placebo Infusion by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade	T_FAE1_HDU	Safety
Summary of Adverse Events that Started on the Day of a Pertuzumab/Placebo Infusion, Including During Infusion, by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade	T_ FAE1_HDAY	Safety
Summary of Adverse Events that Started on the Day of a Pertuzumab/Placebo Infusion or the Day After but Not During Infusion by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade	T_ FAE1_HDA	Safety

Output Title	Output reference	Population
Summary of Adverse Events that Started During or on the Day of a Pertuzumab/Placebo Infusion or the Day After by Trial Treatment, Treatment Cycle and NCI-CTCAE Grade	T_ FAE1_HDAA	Safety
Summary of Adverse Events that Started During Docetaxel Treatment by Body System and Trial Treatment	T_AE11_DDX	Safety
Summary of Adverse Events that Started During Docetaxel Treatment by Body System, Trial Treatment and Intensity (by NCI-CTCAE Grade 1-5)	T_AE15_DDX	Safety
Summary of Adverse Events that Started During Docetaxel Treatment by Trial Treatment, Body System and Relation to Trial Treatment	T_AE21_DDX	Safety
Listing of Adverse Events that Started During Docetaxel Treatment by Trial Treatment and CRTN/Patient Number	L_AE01_DDX	All Patients (By Treatment Received)
Summary of Adverse Events that Started After Discontinuation of Docetaxel by Body System and Trial Treatment	T_AE11_ADX	Safety
Summary of Adverse Events that Started After Discontinuation of Docetaxel by Body System, Trial Treatment and Intensity (by NCI-CTCAE Grade 1-5)	T_AE15_ADX	Safety

Output Title	Output reference	Population
Summary of Adverse Events that Started After Discontinuation of Docetaxel by Trial Treatment, Body System and Relation to Trial Treatment	T_AE21_ADX	Safety
Listing of Adverse Events that Started After Discontinuation of Docetaxel by Trial Treatment and CRTN/Patient Number	L_AE01_ADX	All Patients (By Treatment Received)
Summary of Related Adverse Events by Body System and Trial Treatment	T_AE11_REL_AE	Safety
Summary of Related Serious Adverse Events by Body System and Trial Treatment	T_AE11_REL_SAE	Safety
Summary of Related NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System and Trial Treatment	T_AE11_REL_345	Safety
Summary of Related Adverse Events Leading to Discontinuation of Docetaxel Only by Body System and Trial Treatment	T_AE11_REL_DISD	Safety
Summary of Related Adverse Events Leading to Discontinuation of Study Medication, Excluding Events Leading to Discontinuation of Docetaxel Only, by Body System and Trial Treatment	T_AE11_REL_DISA	Safety
Summary of Related Adverse Events Resulting in Death by Body System and Trial Treatment	T_AE11_REL_DTH	Safety
Overview of Adverse Events During the Overall Study Treatment Period by Trial	T_FAE2_TP	Safety

Output Title	Output reference	Population
Treatment		
Summary of Adverse Events Reported During the Post-Treatment Period by Body System and Trial Treatment	T_AE11_FU	Safety
Summary of SAEs Suggestive of CHF (SMQ Wide "Cardiac Failure") Reported During the Post-Treatment Period by Body System and Trial Treatment	T_AE11_SC_FU	Safety
Summary of Serious Related Adverse Events Reported During the Post-Treatment Period by Body System and Trial Treatment	T_AE11_SR_FU	Safety
Summary of Adverse Events by Body System, Trial Treatment and Age Group (<65, >=65 Years)	T_FAE3A_AGE65_TP_S	Safety
Summary of Adverse Events with Incidence Differing by >=5% Between Treatment Arms Within Age group (<65, >=65 Years) by Body System, Trial Treatment and Age group	T_FAE3B_AGE65_PER5_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System, Trial Treatment and Age Group (<65, >=65 Years)	T_FAE3A_CTC345_AGE65_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events with Incidence Differing by >=2% Between Treatment Arms Within Age group (<65, >=65 Years) by Body System, Trial Treatment and Agegroup	T_FAE3B_CTC345_AGE65_PER2_TP_S	Safety

Output Title	Output reference	Population
Summary of Adverse Events by Body System, Trial Treatment and Age Group (<75, >=75 Years)	T_FAE3A_AGE75_TP_S	Safety
Summary of Adverse Events with Incidence Differing by >=5% Between Treatment Arms Within Age group (<75, >=75 Years) by Body System, Trial Treatment and Age group	T_FAE3B_AGE75_PER5_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System, Trial Treatment and Age Group (<75, >=75 Years)	T_FAE3A_CTC345_AGE75_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events with Incidence Differing by >=2% Between Treatment Arms Within Age group (<75, >=75 Years) by Body System, Trial Treatment and Agegroup	T_FAE3B_CTC345_AGE75_PER2_TP_S	Safety
Summary of Adverse Events by Body System, Trial Treatment and Race	T_FAE3A_RACE_TP_S	Safety
Summary of Adverse Events with Incidence Differing by >=5% Between Treatment Arms Within Race by Body System, Trial Treatment and Race	T_FAE3B_RACE_PER5_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System, Trial Treatment and Region	T_FAE3A_CTC345_REGION_TP_S	Safety

Output Title	Output reference	Population
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events with Incidence Differing by >=2% Between Treatment Arms Within Race by Body System, Trial Treatment and Race	T_FAE3B_CTC345_RACE_PER2_TP_S	Safety
Summary of Adverse Events by Body System, Trial Treatment and Region	T_FAE3A_REGION_TP_S	Safety
Summary of Adverse Events with Incidence Differing by >=5% Between Treatment Arms Within Region by Body System, Trial Treatment and Region	T_FAE3B_REGION_PER5_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System, Trial Treatment and Region	T_FAE3A_CTC345_REGION_TP_S	Safety
Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events with Incidence Differing by >=2% Between Treatment Arms Within Region by Body System, Trial Treatment and Region	T_FAE3B_CTC345_REGION_PER2_TP_S	Safety

9.3 Deaths

Details of deaths are taken from the "In the case of patient's death" DCS and the "Survival follow-up" DCS.

The MARS template DD01 will be used to produce a listing of all patient deaths by trial treatment and CRTN/patient number. The MARS template DD11 will be used to produce a summary of deaths occurring after study Day 1 by trial treatment.

Table 33 Outputs for Deaths

Output Title	Output reference	Population
Listing of Patient Deaths by Trial Treatment and CRTN/Patient Number	L_DD01	All Patients (By Treatment Received)
Summary of Deaths by Trial Treatment	T_DD11	Safety

9.4 Laboratory Parameters

All laboratory analyses will be performed on the Safety analysis population. Clinical laboratory tests will be performed at local laboratories. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTC grades, Version 3.0. Selected laboratory abnormalities will be summarized by treatment arm.

Laboratory data are taken from the "Hematology", "Hematology (final visit) and "Blood chemistry" DCS pages.

Laboratory data will be summarized by treatment cycle and by study day windows defined in Section 4.8.2. Values from the post-infusion window will be shown in a summary table separate from the summary table showing values from the Day 8 window. If multiple values of a laboratory parameter fall within a treatment cycle or study day window, the worst assessment done within the treatment cycle will be used in the summaries. The worst value is also taken when calculating change from baseline. Any other occurrences will be listed only. Baseline laboratory data are defined as the last valid data reported on or before study Day 1.

Details of whether a low or high value of each parameter is deemed 'worst' for the purposes of the summary tables, is provided in Appendix 2. Refer to this appendix also for rules to apply when both a low (HYPO) or a high (HYPER) value could be deemed the worst value.

All Clinical Operations Guidelines (COG) laboratory data will be converted to the System International (SI) units.

The following summaries will be produced using MARS templates, including laboratory assessments from baseline up to the end of the overall treatment period:

1. A summary of the absolute values and change from baseline values of the laboratory assessments will be produced by treatment group and treatment cycle (LB10e).
2. A shift table of the number of laboratory values from the NCI-CTC grade of the laboratory value closest to, but not beyond, baseline to the worst case NCI-CTC grade laboratory value experienced from baseline to the end of the treatment period will be produced. The listing of shifts will be attached to the shift table (LB22).
3. A summary of the number and percentage of patients with each NCI-CTC grade per laboratory parameter will be produced by treatment group (LB23).

4. A summary of marked laboratory abnormalities, for parameters with no CTC grade defined (LB10c)

For each laboratory test, individual patient values will be listed and values outside the CTC range will be flagged. Standard Investigator range abnormalities (for values that are not CTC grade abnormal nor a marked abnormality) will also be flagged. The following listing will be produced using the MARS template LB02:

1. Listing of Laboratory Data by Trial Treatment and CRTN/Patient Number with Scheduled Visit.

The above listing will be repeated for all patients using Investigator unit (as opposed to SI units) to cover any rare case where an Investigator unit cannot be converted to the SI unit (although note that these values will not contribute to the summary tables). This listing will only show Investigator abnormality flags, not CTC grades (as this is dependent on SI units).

The serum and urine pregnancy test results recorded on the "Pregnancy test (serum)" and "Pregnancy test (urine)" DCS pages will be listed using the MARS template VS03, and summarized by treatment arm for female patients with child bearing potential (T_PREG). If a patient has multiple pregnancy tests of the same type (serum or urine) within a treatment cycle, the 'worst' test result will be included in the summary table, whereby a 'positive' test result is deemed worse than a 'negative' test result. All test results will appear in the listing.

Table 34 Outputs for Laboratory Parameters

Output Title	Output reference	Population
Listing of Laboratory Data by Trial Treatment and CRTN/Patient Number with Scheduled Visit	L_LB02	All Patients (By Treatment Received)
Listing of Laboratory Data by Trial Treatment and CRTN/Patient Number with Scheduled Visit (Investigator Units)	L_LB02_INV	All Patients (By Treatment Received)
Summary of Laboratory Data (Day 8 Values) by Treatment Cycle and Trial Treatment	T_LB10e_D8	Safety
Summary of Laboratory Data (Post Infusion Nadir) by Treatment Cycle and Trial Treatment	T_LB10e_ND	Safety
Shift Table for Laboratory Data by Trial Treatment and NCI-CTC Grade with Attached Listing of Shifts	T_LB22_WI	Safety

Output Title	Output reference	Population
Shift Table for Laboratory Data by Trial Treatment and NCI-CTC Grade without Attached Listing of Shifts	T_LB22_WO	Safety
Summary of Laboratory Data by Trial Treatment and NCI-CTC Grade	T_LB23	Safety
Summary of Marked Laboratory Abnormalities (For Parameters with no CTC Grade Defined) by Trial Treatment	T_LB10c	Safety
Listing of Pregnancy Test Results by Trial Treatment and CRTN/Patient Number	L_VS03_PREG	All Patients (By Treatment Received)
Summary of Pregnancy Test Results by Treatment Cycle and Trial Treatment	T_FPREG	Safety

9.4.1 Hepatic Dysfunction

Potential hepatic dysfunction will be investigated by evaluation of the laboratory data, with specific reference to the assessments of ASAT, ALAT, Total Bilirubin and Alkaline Phosphatase.

The number (%) of patients with raised liver function tests will be summarized by treatment arm. Data will be presented for both baseline and the overall study treatment period. The following categories of raised LFTs will be included in the summary table:

- ASAT ≥ 5xULN
- ASAT ≥ 10xULN
- ALAT ≥ 5xULN
- ALAT ≥ 10xULN
- ASAT ≥ 5xULN or ALAT ≥ 5xULN
- ASAT ≥ 10xULN or ALAT ≥ 10xULN
- ASAT ≥ 5xULN and ALAT ≥ 5xULN
- ASAT ≥ 10xULN and ALAT ≥ 10xULN
- Total Bilirubin ≥ 2xULN

The time to first raised LFT will be evaluated. The data will be presented by treatment arm in a summary table, and the associated Kaplan-Meier curve will also be produced. Raised LFTs are defined as any of the following:

- ASAT ≥ 5xULN
- ALAT ≥ 5xULN
- Total Bilirubin ≥ 2xULN

A listing of patients who meet any of the above criteria will also be provided.

Potential cases of pure hepatocellular injury sufficient to cause hyperbilirubinemia (Hy's Law) will be listed, by identifying any patient who meets the following criteria during the overall study treatment period:

- ASAT and/or ALAT >3xULN and Total Bilirubin ≥ 2xULN and Alkaline Phosphatase <2xULN

Based on Clinical Expert advice, a listing will also be provided of the patients who meet the criteria below at any point during the overall study treatment period:

- ASAT and/or ALAT >3xULN and Total Bilirubin ≥ 2xULN and Alkaline Phosphatase <5xULN

Finally, scatterplots will be produced of total bilirubin vs ASAT and total bilirubin vs ALAT. The data presented in the scatterplot will represent each patient's worst (highest) total bilirubin and their worst (highest) ASAT/ALAT.

Table 35 Outputs for Hepatotoxicity

Output Title	Output reference	Population
Summary of ASAT and/or ALAT >=5xULN or >=10xULN or Total Bilirubin >=2xULN by Trial Treatment	T_FLABHEP	Safety
Listing of Patients with ASAT and/or ALAT>=5xULN or >=10xULN or Total Bilirubin >=2xULN by Trial Treatment and CRTN/Patient Number	L_LB02_HEP	All Patients (By Treatment Received)
Listing of Laboratory Defined Cases of Raised Transaminases Assoc wth Hyperbilirubinemia (Hys Law: ASAT and/or ALAT>3xULN, Total Bilirubin >=2xULN & Alkaline Phosphatase <2xULN) by Trial Treatment and CRTN/Patient Number	L_LB02_HYS	All Patients (By Treatment Received)
Listing of Patients with ASAT and/or ALAT>3xULN, Total Bilirubin >=2xULN and Alkaline Phosphatase <5xULN by Trial Treatment and CRTN/Patient Number	L_LB02_LSEG	All Patients (By Treatment Received)
Scatterplot of Total Bilirubin vs ASAT	F_LABWORST_BILAS	Safety
Scatterplot of Total Bilirubin vs ALAT	F_LABWORST_BILAL	Safety

Output Title	Output reference	Population
Summary of Time to First Increase in LFTs (weeks) by Trial Treatment	T_TTLFT	Safety
Kaplan-Meier Curve of Time to First Increase in LFTs by Trial Treatment	F_TTEV1LFT	Safety

9.5 Duration of Safety Follow-up

The duration of follow-up for safety and survival will be compared between treatment arms, in order to establish whether there are systematic differences in the completeness and duration of follow-up. In a blinded placebo-controlled study, the existence of such differences may be an indicator of differences in safety or efficacy between treatment arms. Alternatively, such differences may indicate suboptimal data quality, which could potentially affect the conclusions regarding treatment effect drawn from the study.

A summary of the cumulative disposition of patients with respect to their duration of follow-up for safety and survival (months) will be provided for all patients in the ITT population. The date of last follow-up for safety will be defined by the 'last known date' (defined in Section 4.3.3) or the date of randomization + 1 day, if no post-baseline data are available. Duration of follow-up in months is defined as the ((date of last follow-up – date of randomization) + 1) / 7/4.3.

Table 36 Outputs for Investigation of Safety Follow-Up

Output Title	Output reference	Population
Summary of Time on Study from Randomization to End of Follow-up for Safety and Survival by Trial Treatment	T_FFU	ITT (By Treatment Randomized)

9.6 Events to Monitor

The following clinical diagnoses were selected as Events to Monitor based on clinical and nonclinical data for pertuzumab as well as the safety profile established for trastuzumab, monoclonal antibodies in general and potential effects associated with HER receptor inhibition.

Analysis of Events to Monitor will be performed on the Safety analysis population. All summary tables will be based on the incidence of events occurring during the study treatment period unless otherwise stated. Search strategies were defined by aggregate MedDRA preferred terms (PTs) where possible or if not available based on Roche AE Group Terms (AEGTs).

For Safety summaries that include analyses of time to first event and duration (e.g. episode(s) of diarrhoea), events will be included based on partial/invalid start and end dates. This is because these analyses focus on Events to Monitor with pertuzumab treatment for which the incidence and duration may be increased and, although the

occurrence of partial/invalid dates is anticipated to be low, it is felt appropriate to include events based on conservative imputation rules. However the incidence of partial dates will be reviewed based on listings in order that the potential effect of including imputed dates in these analyses can be considered.

The rules defined in Section 4.5.1.1 will be followed for imputing partial/invalid start dates. Partial/invalid end dates, or an end date in the case of an unresolved event (for the purposes of calculating the duration) will be imputed using the rules defined in Section 4.5.2.1.

9.6.1 Cardiac Safety

9.6.1.1 Symptomatic LVSD

Symptomatic LVSD is defined as an LVSD event of NCI-CTCAE grades 3 to 5. Asymptomatic LVSD is defined as an LVSD event of NCI-CTCAE grades 1 and 2.

The symptoms or physical findings possibly associated with symptomatic LVSD or diagnosis of symptomatic LVSD will be taken from the "Cardiac questionnaire" DCS and "Cardiac symptoms" DCS.

The following listings will be presented:

- Listing of Cardiac Questionnaire by Trial Treatment and CRTN/Patient Number
- Listing of Cardiac Symptoms by Trial Treatment and CRTN/Patient Number

The following summary tables will be presented:

- Summary of Cardiac Questionnaire results by Treatment Cycle and Trial Treatment
- Summary of Cardiac Symptoms by Treatment Cycle and Trial Treatment

In the event that a patient has multiple cardiac questionnaires completed or multiple cardiac symptoms reported in the same cycle of treatment, the following conventions will apply when reporting the data in the summary tables:

- Cardiac questionnaire
  - Yes/No questions: count worst response, where 'Yes' is deemed worse than 'No'
  - Contributing factors & physical findings: count all unique responses
- Cardiac symptoms
  - Cardiac symptoms: count all unique responses
  - Most extreme intensity of each symptom: count worst response, based on most extreme intensity

Investigator Assessed Symptomatic LVSD

Investigator-assessed symptomatic LVSD events will be identified by selecting events from the AE GDM where the Investigator text (AETXT) = 'SYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION'. The number and percentage of patients with symptomatic LVSD events at any time during the study with NCI-CTCAE grades

and NYHA class will be summarized by treatment arm. A corresponding listing of symptomatic LVSD will also be presented by trial treatment and CRTN/patient number using the MARS template AE01. A separate listing will be produced of symptomatic LVSD events assessed by the Investigator that led to discontinuation of Study medication.

The MARS template AE11 will be used to produce the following summaries:

- Summary of symptomatic LVSD events that resulted in discontinuation of any study medication by trial treatment
- Summary of symptomatic LVSD events that resulted in interruption/modification of any study medication by trial treatment

A further listing will be produced of all symptomatic LVSD events, with the patients LVEF data closest to the onset date presented alongside. For each event, the LVEF value listed will be the last LVEF value prior to the onset date and the first LVEF value after the onset date. If the patient has an LVEF value on the actual date of onset, this value will be presented along with the closest value either before or after the date of onset.

CRC Adjudicated Symptomatic LVSD

The independent CRC reviews the list of patients with potential cardiac events or deaths (not related to breast cancer) and determines whether these events are symptomatic LVSD (non-fatal or fatal), other cardiac non-fatal events, non LVSD cardiac deaths, probable cardiac deaths, non–cardiac cardiovascular deaths, or non-cardiovascular deaths (for details refer to the CRC Charter). These events are recorded on a separate paper CRF and are not reconciled with the symptomatic LVSD events as assessed by the Investigator (and recorded on the "LVSD event" DCS).

A cardiac event adjudicated by the CRC is defined as a symptomatic LVSD (fatal and non-fatal), a non-LVSD cardiac death or a probable cardiac death (i.e. death without documented biology). The incidence of these cardiac events formed the basis of the stopping rule guidance for the DMC at the formal safety interim analysis.

The number and percentage of patients with CRC-adjudicated symptomatic LVSD events at any time during the study with NCI-CTCAE grades and New York Heart Association (NYHA) classification will be summarized by treatment arm. The summary of symptomatic LVSD, other cardiac and non-cardiac events, deaths and non-evaluable events will be presented by treatment arm. A corresponding listing of symptomatic LVSD and other cardiac and non-cardiac events adjudicated by the CRC will be presented by trial treatment and CRTN/patient number. Any comments made by the CRC will also be listed by trial treatment. Due to the accumulating nature of the data that the CRC review at each adjudication, if a patient has multiple adjudications during the study, only the patients final adjudication will be presented in the summary tables and listings, to ensure there is no risk of double-counting the same event. Note that a patient may still have multiple events adjudicated at the same review.

Investigation of Risk Factors for Cardiac Dysfunction

Analyses will be performed to explore risk factors for cardiac dysfunction. For the purposes of the analysis, two distinct aspects of cardiac dysfunction will be evaluated. The first approach will be based on both asymptomatic and symptomatic LVSD events, and will be defined as any adverse event with the PT 'LEFT VENTRICULAR SYSTOLIC DYSFUNCTION'. The second approach will be based on CRC-adjudicated symptomatic LVSD events, identified as events where "symptomatic LVSD" have been ticked on the CRC CRF.

For both endpoints, a Kaplan-Meier analysis will initially be performed to assess the time to first event by treatment group, summarized in weeks. A Cox regression analysis will then be performed to explore the impact of the risk factors on the time to event.

In the analysis of time to first asymptomatic or symptomatic LVSD, the date of event is defined as the "date of onset" of the relevant AE. Patients without the event will be censored at their last known date.

In the analysis of time (weeks) to first symptomatic LVSD as adjudicated by the CRC, the date of event is defined as the "date of onset of symptomatic LVSD" on the CRC CRF. Patients without the event (not ticked as "symptomatic LVSD") or patients who have not been selected for CRC adjudication will be censored at their last known date.

The Cox regression analyses will include the following covariates as potential risk factors: prior anthracycline exposure, prior radiation therapy, prior trastuzumab therapy, age, smoking history, and underlying conditions of diabetes and hypertension.

In order to account for possible differences in length of follow-up or completion of cardiac evaluations over time between treatment groups a cumulative incidence analysis will be performed on the time to first CRC-determined symptomatic LVSD, including death as a competing event. Patients alive and with no CRC-adjudicated symptomatic LVSD are censored at the date last known to be alive. As a sensitivity analysis, the cumulative incidence analysis of CRC-adjudicated symptomatic LVSD will be performed with a competing risk of an IRF-assessed PFS event.

Table 37 Outputs for Symptomatic LVSD

Output Title	Output reference	Population
Listing of Cardiac Questionnaire by Trial Treatment and CRTN/Patient Number	L_CARDQ	All Patients (By Treatment Received)
Summary of Cardiac Questionnaire by Treatment Cycle and Trial Treatment	T_FCARDQ	Safety
Listing of Cardiac Symptoms by Trial Treatment and CRTN/Patient Number	L_CARDS	All Patients (By Treatment Received)

Output Title	Output reference	Population
Summary of Cardiac Symptoms by Treatment Cycle and Trial Treatment	T_FCARDS	Safety
Listing of Symptomatic LVSD Events Assessed by the Investigator by Trial Treatment and CRTN/Patient Number	L_AE01_LVSD_INV	All Patients (By Treatment Received)
Summary of Symptomatic LVSD Events Assessed by the Investigator by Trial Treatment	T_FLVSD	Safety
Listing of Symptomatic LVSD Events Assessed by the Investigator that Resulted in Discontinuation of Any Study Medication by Trial Treatment and CRTN/Patient Number	L_AE01_LVSD_DIS	All Patients (By Treatment Received)
Listing of Symptomatic LVSD Events Assessed by the Investigator with the Closest LVEF Assessments Before and After the Date of Onset by Trial Treatment and CRTN/Patient Number	L_AELVSDLVEF	All Patients (By Treatment Received)
Summary of Symptomatic LVSD Events Assessed by the Investigator that Resulted in Discontinuation of Any Study Medication by Trial Treatment	T_AE11_LVSD_DIS	Safety
Summary of Symptomatic LVSD Events Assessed by the Investigator that Resulted in Interruption/Modification of Study Medication by Trial Treatment	T_AE11_LVSD_INT	Safety
Summary of Events Determined by the CRC by Trial Treatment	T_FEVCRC	Safety
Summary of Symptomatic LVSD Events Determined by the CRC by Trial Treatment	T_FEVLVSDCRC	Safety
Listing of Patients with Symptomatic LVSD Events Determined by the CRC by Trial Treatment and CRTN/Patient Number	L_EVLVSDCRC	All Patients (By Treatment Received)
Summary of Other Cardiac (Non-Death) Events Determined by the CRC by Trial Treatment	T_FEVNDCRC	Safety
Summary of All Deaths Assessed by the CRC by Trial Treatment	T_FDEATHCRC	Safety

Output Title	Output reference	Population
Summary of Non Evaluable Events Determined by the CRC by Trial Treatment	T_FNEEVCRC	Safety
Summary of Time to First LVSD Event (weeks), as Assessed by the Investigator, by Trial Treatment	T_TTEV__ILVSD	Safety
Summary of Cox Regression for Investigator-Assessed LVSD (one Covariate without/with Treatment)	T_HRCCOX_ILVSD	Safety
Summary of Time to First Symptomatic LVSD (weeks) for Events Determined by the CRC by Trial Treatment	T_TTEV_LVSD	Safety
Kaplan-Meier Curve of Time to First Symptomatic LVSD (weeks) for Events Determined by the CRC by Trial Treatment	F_TTEV1_LVSD	Safety
Summary of Cox Regression for CRC-Determined Symptomatic LVSD (one Covariate without/with Treatment)	T_HRCCOX_LVSD	Safety
Cumulative Incidence Rate of First CRC-Determined Symptomatic LVSD With Death as a Competing Event by Trial Treatment	T_CIRLVSD_DEATH	Safety
Cumulative Incidence of Time to First CRC-Determined Symptomatic LVSD With Death as a Competing Event by Trial Treatment	F_CIRLVSD_DEATH	Safety
Cumulative Incidence Rate of First CRC-Determined Symptomatic LVSD With IRF-Assessed PFS as a Competing Event by Trial Treatment	T_CIRLVSD_IRF_PFS	Safety
Cumulative Incidence of Time to First CRC-Determined Symptomatic LVSD With IRF-Assessed PFS as a Competing Event by Trial Treatment	F_CIRLVSD_IRF_PFS	Safety
Listing of Patients with Events Determined by the CRC by Trial Treatment and CRTN/Patient Number	L_UD08_EVCRC	All Patients (By Treatment Received)
Listing of Comments Made by the CRC by Trial Treatment and CRTN/Patient Number	L_UD08_COMCRC	All Patients (By Treatment Received)

9.6.1.2 LVEF

LVEF measurements and change in LVEF from baseline will be summarized by treatment arm and treatment cycle. The LVEF measurements and change in LVEF from baseline will further by summarized by treatment arm and scheduled week. In addition to the individual weeks/cycles, the summary tables will include the 'Treatment End Visit', 'Final Treatment Value' and 'Worst Treatment Value'.

Within summary tables by cycle, if multiple values fall within a treatment cycle, the worst assessment within that cycle (i.e. lowest absolute value) will be used in the summaries.

A plot of mean change in LVEF from baseline over time with 95% confidence intervals by trial treatment will be presented.

The changes in LVEF will also be classified at both each treatment cycle and each scheduled week as:

- "Increase, no change, decrease from baseline < 10% points",
- "Absolute value < 50% and decrease from baseline ≥ 10% to < 15% points",
- "Absolute value < 50% and decrease from baseline ≥ 15% points",
- "Absolute value >= 50% and decrease from baseline ≥ 10% points"
- "No baseline value" (to account for patients who have a treatment cycle value but no baseline meaning the change cannot be calculated)

These categories will be summarized as LVEF change from baseline status over time by trial treatment and by cycle and also by trial treatment and by scheduled week.

The time (weeks) to first decrease in LVEF value to < 50% and decrease from baseline of ≥ 10% points will be summarized by trial treatment using the Kaplan-Meier approach. The date of event will be the assessment date associated with the LVEF on the first occasion the patient's LVEF fell to <50%, with a decrease from baseline of ≥ 10% points. Patients without the event will be censored in the analysis at their last known date in the treatment period.

In order to account for possible differences in length of follow-up or completion of cardiac evaluations over time between treatment groups a cumulative incidence analysis will be performed on the time to first decrease in LVEF value to < 50% and decrease from baseline of ≥ 10% points, including death as a competing event. Patients alive and with no decrease in LVEF value to < 50% and decrease from baseline of ≥ 10% points are censored at the date last known to be alive. As a sensitivity analysis, the cumulative incidence analysis of CRC-adjudicated symptomatic LVSD will be performed with a competing risk of an IRF-assessed PFS event.

The baseline LVEF value (measured by ECHO or MUGA) 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 difference in the maximum absolute decrease in LVEF measure between the two treatment arms will be assessed by the Wilcoxon test. The number (%) of patients whose worst treatment LVEF is <40% will also be presented.

A listing of LVEF measures will be presented by trial treatment and CRTN/patient number. A listing of patients with an LVEF absolute value < 50% that is a decrease from baseline of ≥ 10% points by trial treatment and CRTN/patient number will also be presented.

A listing of the history of prior LVEF will be presented by trial treatment and CRTN/Patient Number. This data will be taken from DCS page "Previous LVEF". Data from this page are not included in any of the other LVEF outputs, as it provides historical data only, and cannot be used as a substitute for baseline.

Table 38 Outputs for LVEF

Output Title	Output reference	Population
Listing of Cardiac Monitoring Assessments (LVEF) by Trial Treatment and CRTN/Patient Number	L_UD08_LVEF	All Patients (By Treatment Received)
Listing of Patients with an LVEF Absolute Value < 50% That is a Decrease from Baseline of >= 10% Points by Trial Treatment and CRTN/Patient Number	L_UD08_LVEF50	All Patients (By Treatment Received)
Summary of LVEF Absolute Values and Change from Baseline Over Time by Treatment Cycle and Trial Treatment	T_ULVEF_CY	Safety
Summary of LVEF Absolute Values and Change from Baseline Over Time by Scheduled Visit and Trial Treatment	T_ULVEF_SV	Safety
Summary of LVEF Change from Baseline Status Over Time by Treatment Cycle and Trial Treatment	T_UFLVEF_CY	Safety
Summary of LVEF Change from Baseline Status Over Time by Scheduled Visit and Trial Treatment	T_UFLVEF_SV	Safety
Summary of Time (Weeks) to First Decrease in LVEF Value to < 50% and Decrease from Baseline of ≥ 10% Points by Trial Treatment	T_TTEVLVEF	Safety
Kaplan-Meier Curve of Time to First Decrease in LVEF Value to <50% and Decrease from Baseline of >=10% Points by Trial Treatment	F_TTEV1_LVEF	Safety

Output Title	Output reference	Population
Cumulative Incidence Rate of First Decrease in LVEF Value to <50% and Decrease from Baseline of >=10% Points With Death as a Competing Event by Trial Treatment	T_CIRLVEF_DEATH	Safety
Cumulative Incidence of Time to First Decrease in LVEF Value to <50% and Decrease from Baseline of >=10% Points With Death as a Competing Event by Trial Treatment	F_CIRLVEF_DEATH	Safety
Cumulative Incidence Rate of First Decrease in LVEF Value to <50% and Decrease from Baseline of >=10% Points With IRF-Assessed PFS as a Competing Event by Trial Treatment	T_CIRLVEF_IRF_PFS	Safety
Cumulative Incidence of Time to First Decrease in LVEF Value to <50% and Decrease from Baseline of >=10% Points With IRF-Assessed PFS as a Competing Event by Trial Treatment	F_CIRLVEF_IRF_PFS	Safety
Summary of Maximum Decrease in LVEF Measures by Trial Treatment	T_UFLVEFMDEC	Safety
Plot of Mean Change in LVEF from Baseline Over Time (with 95% Confidence Intervals) by Trial Treatment	F_LVEF1_CY	Safety
Listing of History of Prior LVEF by Trial Treatment and CRTN/Patient Number	L_UD08_LVEFHIST	All Patients (By Treatment Received)

9.6.2 Events to Monitor

9.6.2.1 MedDRA SMQs / Adverse Event Grouped Terms (AEGTs)

The prospective grouping of MedDRA preferred terms (PTs) from one or more MedDRA System Organ Classes relating to defined medical conditions supports identification and investigation of potential signals in statistical analyses. This grouping of PTs is especially relevant for diagnoses which are not well characterized.

When available, Standardized MedDRA Queries (SMQs) are suggested because this constitutes a globally recognized and consistent set of PTs by regulatory authorities. For most SMQs a narrow and wide version exists. The narrow version maximizes specificity

but is less sensitive. SMQs containing wide sets of PTs (consisting of both the narrow and wide version) maximize sensitivity but are less specific with false positive rates.

For the following diagnoses SMQs (narrow or wide version) are used and where no SMQs are available baskets of Roche Standard MedDRA Adverse Event Grouped Terms (AEGTs) have been used.

The Events to Monitor will be identified from the following sources.:

- **'Diarrhoea'**: from the single PT 'Diarrhoea'
- **'Rash'** : from the Roche Standard AEGT 'EGFR Associated Rash'
- **'SAEs suggestive of CHF'** : identified as serious events from the SMQ (wide) 'Cardiac Failure'
- '**Hypersensitivity, Anaphylaxis'** : identified from the Roche Standard AEGT 'Anaphylaxis and hypersensitivity', containing the MedDRA SMQ (narrow 'Anaphylactic Reaction' plus all MedDRA PTs containing 'hypersensitivity'.
- '**Mucositis'** : identified from the Roche Standard AEGT 'Mucositis of gastrointestinal tract'
- **'Leukopenia'**: identified from the SMQ (narrow) 'Haematopoietic Leukopenia'
  - **'Febrile neutropenia'**: by selecting the PT 'Febrile neutropenia' – subgroup of the search for 'Leukopenia'
- **'Leukopenic Infection'**: by selecting events from the 'Infections and Infestations' SOC with a start date ≤14 days after the start date of a grade ≥3 event in the SMQ (narrow) 'Leukopenia'
  - **'Febrile neutropenic infection'**: by selecting events from the 'Infections and Infestations' SOC with a start date ≤14 days after the start date of a grade ≥3 event of the PT 'febrile neutropenia' – subgroup of the search for 'Leukopenic infection'
- **'QT Prolongation'**: by selecting the SMQ (wide) 'Torsade de pointes/QT prolongation'
- **Interstitial lung disease**: by selecting the SMQ 'Interstitial lung disease (narrow)'
- **Drug related hepatic dysfunction**: by selecting events from the SMQ (wide) 'Drug related hepatic disorders – comprehensive search'. Note that this SMQ is comprised of 8 individual SMQs, as follows:

1. SMQ 'Liver neoplasms benign, (incl cysts and polyps)'
2. SMQ 'Liver malignant tumours'
3. SMQ 'Liver tumours of unspecified malignancy'
4. SMQ 'Liver related coagulation and bleeding disturbances'
5. SMQ 'Liver related investigations, signs and symptoms'
6. SMQ 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions'
7. SMQ 'Cholestasis and Jaundice of hepatic origin'
8. SMQ 'Hepatitis, non infectious'

The above categories of AEs will be summarized using the MARS AE11 template, including all events reported during the overall study treatment period (see Section 4.3.2 for definition). The exception to this is the summaries of leukopenic infections and febrile

neutropenic infections, which will be summarized by NCI-CTCAE grade and treatment group, using the MARS template AE15. The overall incidence of events leading to discontinuation and dose modification by each of the above categories will be summarized. The exception to this is diarrhoea and febrile neutropenia, since these are identified by a single PT rather than a group of PTs and therefore the information is already readily available in the main AE summary tables.

The 'SAEs suggestive of CHF' events will also be summarized for the follow-up period (see Section 9.2.6 for further details).

Further analyses of the above adverse events (where applicable) and further safety parameters of special interest are defined in the following sections.

A glossary of the SMQs/AEGTs will be produced using MARS template AE09.

9.6.2.2 Analysis of Events By Patient-Years

It is of interest to evaluate the incidence of selected events in relation to the duration of follow-up.

These AEs will be summarized by patient-years by trial treatment. The AE rates and the corresponding 80% and 90% confidence intervals will be presented by treatment arm.

The individual patient-years in the study will be calculated as:

(date of most recent follow up with patient – date of study Day 1 + 1)/365.25

Date of most recent follow up of patient will be the last available date out of all available data during the treatment period. Any pre-treatment data (including DEMO) and safety follow-up date will therefore not be considered. The start dates as well as the end dates will be used provided these dates are on or before the end of the overall treatment period.

The total number of patient years is the sum of years of all patients.

The number of events will be the total number of the specified adverse events occurring during the treatment period of each patient, prior to withdrawal or treatment completion. All events will be included in the total. Adverse events occurring after withdrawal from the study or during safety follow-up will not be included in the calculation.

The number of events per patient-year is then calculated as:

(total number of events/total number of patient-years) (this is then multiplied by 100 for number of events per 100 patient-years)

80% and 90% confidence intervals for the number of events per 100 patient-years will also be displayed. The confidence interval is calculated assuming that the incidence of adverse events follows a Poisson distribution, and is derived from an exact method for calculating the CI of the mean of a Poisson distribution using the following formulas.

$$LL = \frac{1}{2}\chi^2_{2n,\left(\frac{1-\alpha}{2}\right)} \times \left(\frac{100}{years}\right)$$

$$UL = \frac{1}{2}\chi^2_{2(n+1),\left(\frac{1+\alpha}{2}\right)} \times \left(\frac{100}{years}\right)$$

Where LL and UL are the lower and upper limits of the confidence interval respectively; 100α is the confidence level of the interval; 'years' is the total number of patient years observed; n is the total number of adverse events observed; $\chi^2_{2n,\left(\frac{1-\alpha}{2}\right)}$ is the $\frac{1-\alpha}{2}$ percentile of the Chi-squared distribution with 2n degrees of freedom and similarly $\chi^2_{2(n+1),\left(\frac{1+\alpha}{2}\right)}$ is the $\frac{1+\alpha}{2}$ percentile of the Chi-squared distribution with 2(n+1) degrees of freedom.

For 80% confidence intervals, $\frac{1-\alpha}{2} = 0.1$ and $\frac{1+\alpha}{2} = 0.9$

For 90% confidence intervals, $\frac{1-\alpha}{2} = 0.05$ and $\frac{1+\alpha}{2} = 0.95$

The value of $\chi^2_{2n,\left(\frac{1-\alpha}{2}\right)}$ and $\chi^2_{2(n+1),\left(\frac{1+\alpha}{2}\right)}$ can be derived using the "cinv" SAS function within the datastep.

For example, assuming the number of adverse events observed (n) = 20, then use the following function to derive the chi-square component of the formula:

80% CI: *varname = cinv(0.1,40)* for the lower limit and *varname = cinv(0.9,42)* for the upper limit.

90% CI: *varname = cinv(0.05,40)* for the lower limit and *varname = cinv(0.95,42)* for the upper limit

These analyses will be conducted for QT prolongation events (based on the SMQ (wide) 'Torsade de pointes/QT prolongation') and for the SMQs relating to hematological/pulmonary toxicity events (Leukopenia, Leukopenic Infection, Febrile Neutropenia (PT), Febrile Neutropenic Infection, Interstitial Lung Disease, Hypersensitivity/Anaphylaxis (AEGT)). See Section 9.6.2.1 for the definition of leukopenic infections and febrile neutropenic infections.

9.6.2.3 Analyses of Duration and Time to Adverse Events

For the incidence of diarrhoea and of rash (identified from the AEGTs "Diarrhoea (Pertuzumab)" and "Rash (Pertuzumab)", defined in Section 9.6.2.1), it is of interest to further characterize the time to onset and duration of these events. This will be summarized by treatment arm based on the following variables:

- Total number of episodes (all grades)
- Total number of unresolved episodes
- Number of patients with at least 1 episode by treatment cycle (determined from the date of onset relative to the date of infusion)
- Total number of episodes by NCI-CTCAE grade (grade 1 to grade 5)
- Number of episodes per patient

- Duration of episode (both the total duration over all episodes and the duration of the longest episode)
- Number (%) of patients requiring treatment for this AE, as recorded on the "Adverse Event" eCRF page.
- Time to first episode and time to onset of most severe episode (worst intensity), both calculated in days, from Study day 1.

Imputation rules for partial/invalid dates defined in Section 4.5.1.1 and 4.5.2.1 will be applied. AEs with an outcome of 'unresolved' or 'missing' at time of clinical cutoff will be included. The last known date for the patient after the datacut has been applied (defined in Section 4.3.3) will be used to calculate duration. The incidence of partial dates will be reviewed based on AE listings of diarrhoea and rash events in order that the potential effect of including imputed dates in these analyses can be considered. If the event start date is completely missing or the outcome is 'resolved' or 'death' and the end date is completely missing, then the event will not be considered for duration calculations.

9.6.2.4 Immunogenicicity

Immunogenicicity is identified by patients who test positive for Human Anti-Human Antibodies (HAHA) against pertuzumab.

The profile of adverse events associated with immunogenicity is of interest and will be investigated in the following manner.

A listing of all AEs reported during the overall treatment period by patients who test positive for HAHA will be produced using MARS template AE01, in order to assess the profile of AEs within this group of patients. A separate summary table of these AEs, based on the MARS AE11 template, will only be deemed necessary if > 10 patients test positive for HAHA.

Table 39 Outputs for Events to Monitor

Output Title	Output reference	Population
Summary of Rash (AEGT) by Trial Treatment	T_AE11_RASH	Safety
Summary of SAEs Suggestive of CHF (SMQ wide Cardiac Failure) by Trial Treatment	T_AE11_SC	Safety
Summary of QT Prolongation (SMQ) Adverse Events by Trial Treatment	T_AE11_QT	Safety
Summary of Interstitial Lung Disease (SMQ) by Trial Treatment	T_AE11_IL	Safety
Summary of Anaphylaxis and Hypersensitivity (AEGT) Events by Trial Treatment	T_AE11_HYP	Safety
Summary of Leukopenia Events by Trial Treatment	T_AE11_L	Safety
Summary of Leukopenic Infection Events by	T_AE15_LI	Safety

Output Title	Output reference	Population
Trial Treatment		
Summary of Febrile Neutropenic Infection Events by Trial Treatment	T_AE15_FI	Safety
Summary of Mucositis (AEGT) by Trial Treatment	T_AE11_MUC	Safety
Summary of Drug Related Hepatic Disorder (SMQ) Events by Trial Treatment	T_AE11_HEP	Safety
Summary of Events Leading to Discontinuation or Interruption/Modification of Study Medication by Identified/Potential Risk and Trial Treatment	T_FAEGT1DIS	Safety
Glossary of Basket Names and Preferred Terms for SMQs and Adverse Event Group Terms (AEGTs)	L_UD09_AEGT	Safety
Summary of Hematology/Pulmonary Toxicity (AEGT) Adverse Events per Patient Years by Trial Treatment	T_AEPY_HEM	Safety
Summary of QT Prolongation (SMQ) Adverse Events per Patient Years by Trial Treatment	T_AEPY_CAR	Safety
Summary of Incidence and Duration of Diarrhoea by Trial Treatment	T_UINCDUR_DIAR	Safety
Listing of Diarrhoea by Trial Treatment and CRTN/Patient Number	L_AE01_DIAR	All Patients (By Treatment Received)
Summary of Incidence and Duration of Rash (AEGT) by Trial Treatment	T_UINCDUR_RASH	Safety
Listing of Rash (AEGT) by Trial Treatment and CRTN/Patient Number	L_AE01_RASH	All Patients (By Treatment Received)
Listing of Adverse Events in Patients Positive for HAHA by Trial Treatment and CRTN/Patient Number	L_AE01_HAHA	All Patients (By Treatment Received)

9.6.3 Human Anti-Human Antibody (HAHA) Against Pertuzumab

A listing of HAHA against pertuzumab will be presented by trial treatment and CRTN/patient number. A summary table of HAHA against pertuzumab will be presented by cycle and by trial treatment.

Table 40 Outputs for HAHA

Output Title	Output reference	Population
Listing of Human Anti-Human Antibody (HAHA) Against Pertuzumab by Trial Treatment and CRTN/Patient Number	L_UD08_HAHA	All Patients (By Treatment Received)
Summary of Human Anti-Human Antibody (HAHA) Against Pertuzumab by Treatment Cycle and Trial Treatment	T_FHAHA	Safety

9.7 Vital Signs

All vital sign analyses will be performed on the Safety analysis population.

Vital signs (supine systolic blood pressure, supine diastolic blood pressure, supine pulse rate and temperature) recorded pre- and post-infusion will be taken from the "Vitals (pertuzumab)" "Vitals (trastuzumab)", "Vitals (docetaxel)" DCS pages. Vitals signs and physical measurements, including weight, will be taken from the "Vitals (follow-up)" DCS. Vital signs data collected at unscheduled visits will be remapped to treatment cycles according to the rules specified in Section 4.8.2.

For time-matched baselines, the baseline value is the pre-dose value at each visit.

All vital sign data will be listed with change from baseline values using time-matched baseline for scheduled visits using MARS template VS04. The listing will be presented in time order by treatment cycle. Vital signs collected at unscheduled visits that have been remapped to treatment cycles will be included in this listing, although the change from baseline will not be presented, as the time of the assessment is not recorded, and therefore there is no corresponding time-matched baseline available.

The actual values and the change from baseline values for systolic blood pressure, diastolic blood pressure, pulse rate and temperature will be summarized for all visits and time points where vital signs are collected. Vital signs collected at unscheduled visits will be excluded from this summary table. It is not anticipated that multiple scheduled assessments could be remapped to the same treatment cycle, as if, for example, pre-dose assessments were taken, and the patient then failed to start the infusion, these data would be moved to an unscheduled visit during the data cleaning process. However, if this situation does arise at the time of a data-cut, the pre- and post-infusion assessments taken last will be included in the summary table, as this is the default processing of our MARS reporting system. The mean, standard deviation, median, minimum and maximum will be presented by treatment arm using MARS template VS13.

9.8 ECOG Scores

Analysis of ECOG scores will be performed on the Safety analysis population.

Weight and ECOG status (from DCS pages "Vitals (screen)", "Weight – ECOG", "ECOG", "Additional ECOG" and "Vitals (follow-up)") will be listed for all patients by trial treatment and CRTN/patient number using the MARS template VS03. A summary table of change from baseline in ECOG score over time will be presented by treatment arm (T_FECOG). Any unscheduled measurements will be remapped to a treatment cycle according to the rules specified in Section 4.8.2. If there is more than one measurement within a treatment cycle, the highest score will be selected for summaries. For each cycle, the change from baseline will be calculated and each patient who has a measurement will be assigned to the following categories:

- Improved: the score decreased by any amount from baseline
- Unchanged: the score remained the same as baseline
- Worsened: the score increased by any amount from baseline.

In addition to the individual treatment cycles, ECOG data will also be summarized for the 'Treatment End Visit', 'Final Treatment Value' and 'Worst Treatment Value'.

9.9 Physical Examination, ECG and Chest X-rays

Clinically significant findings on physical examination noted on DCS pages "Physical exam (screen)" and "Physical exam", abnormal ECG noted on the "ECG (12-lead)" DCS and abnormal findings noted in the "Chest X-ray" DCS will be listed by patient and treatment arm for all patients using the MARS template VS03.

9.10 Comments

All comments will be listed by trial treatment and CRTN/Patient Number (CM01).

Table 41 Outputs for Physical Examination and Other Assessments

Output Title	Output reference	Population
Listing of Vital Signs by Trial Treatment and CRTN/Patient Number with Change from Baseline (Time-Matched Baseline)	L_VS04	All Patients (By Treatment Received)
Summary of Vital Signs Over Time by Treatment Cycle and Trial Treatment	T_VS13	Safety
Listing of Weight and ECOG Status by Trial Treatment and CRTN/Patient Number	L_VS03_WTEC	All Patients (By Treatment Received)
Summary of Change from Baseline for ECOG Performance Status Over Time by Treatment Cycle and Trial Treatment	T_FECOG	Safety

Output Title	Output reference	Population
Patient Listing of Physical Examination, ECG and Chest X-Ray Results by Trial Treatment and CRTN/Patient Number	L_VS03_PHYS	All Patients (By Treatment Received)
Listing of Comments by Trial Treatment and CRTN/Patient Number	L_CM01	All Patients (By Treatment Received)

10. FOLLOW-UP ANALYSES

Follow-up analysis for overall survival will be performed when 385 deaths have occurred.

11. CHANGES AND ADDITIONS AFTER DATABASE CLOSURE

Not applicable at this time.

12. REFERENCES

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Ca Inst 2000;92(3):205–216.

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

Appendix 1 Protocol Violators List

Protocol violations under consideration for the final analysis include all violations of inclusion/exclusion criteria and violations on study that are deemed to impact patient efficacy or safety.

The first review of protocol violations will be performed prior to the DCC unblinding the study for the interim analysis. A further review will take place prior to unblinding the study for the final analysis. Protocol violations identified by Clinical Science will be recorded on a formatted excel spreadsheet, provided by Statistical Programming and Analysis (SPA). The finalised list will be stored and approved in RAPID to signify to PDDB that the final PVs are ready prior to unblinding the study.

If any PVs are identified both by programming and on the Science spreadsheet, the record on the Science spreadsheet will be retained, as this version is likely to have additional explanatory comments, and the duplicate record identified programmatically will be removed from the PV dataset. Similarly, if duplicate records are identified within the Science spreadsheet, only one version of the record will be retained. This is to ensure that an individual PV appears only once in the listing, and will not be counted multiple times within the summary table.

Please note that for any lab test exclusions (e.g. Exc #14) if the lab value is prefixed with a '<' sign then take numeric value and subtract 0.0001. If a '>' then add 0.0001.

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
Inc #1	Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. **Patients with measurable and non-measurable disease are eligible.** Patients with only bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for	Breast cancer not histologically or cytologically confirmed	**Inclusion**	Science to review using I-Review. Locally breast cancer amenable to curative therapy. Science to check this on the basis of prior breast history and prior therapy for breast cancer

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
	central HER2 testing and subsequent biomarkers analysis. Locally recurrent disease must not be amenable to resection with curative intent. Note: Patients with de-novo Stage IV disease are eligible.			
Inc #2	HER2-positive (defined as 3+ IHC or FISH amplification ratio ≥ 2.0) MBC 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 if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.)	Not confirmed HER 2 positive by central lab	**Inclusion**	Programmed: based on the "HER2 test" DCS (Central testing results) IHC result +++ CISH/FISH positive = non violators
Inc #3	Age ≥ 18 years	Age <18	**Inclusion**	Programmed: based on the "Personal data" DCS DOB must be ≥ 18 years = non violator
Inc #4	Left Ventricular Ejection Fraction (LVEF) ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA	Baseline LVEF <50% or missing	**Inclusion**	Programmed: Baseline LVEF result ≥ 50% = non violator. Unscheduled visits are considered if prior to first dose of any study medication

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
Inc #5	Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1	Baseline ECOG status >1 or missing	**Inclusion**	Programmed using the "Vitals (screen)" DCS. Check Baseline ECOG result 0 or 1 only = non violator Unscheduled visits are considered if prior to first dose of any study medication
Inc #6	Protocol A or B: For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method [condoms, diaphragm], intrauterine devices, or abstinence).	Women with reproductive potential not willing to use an effective method of contraception at baseline	**Inclusion**	Protocol A or B (i.e. consent to A or B given, consent not given to Protocol C) Programmed: based on the "Personal data" DCS Female reproductive status not = 'childbearing potential without contraceptive protection' and not missing = non violator
	Protocol C: For women of childbearing potential and men with partners of child-bearing potential, agreement to use a highly-effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy.	i) Women with reproductive potential and men with partners of child-bearing potential not willing to use highly-effective method of contraception or 2 effective methods of contraception at baseline ii) Contraception use not continuing for duration of study treatment and for at least 6 months after last dose of study treatment	**Inclusion** **On-Study**	Patients consenting to Protocol C (irrespective of consent to A & B) i) Violators will be identified by both programming & science. Programmed violations: Based on the "Personal data" DCS Violator if Female reproductive status is 'childbearing potential without contraceptive protection' or missing Violator if Male reproductive status

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				is 'No' or missing. Science review violations: Violator if Female reproductive status is 'childbearing potential with contraceptive protection' and the entries in the 'specify' field(s) are not considered to represent 1 highly effective method or 2 effective methods of contraception Violator if male reproductive status is 'yes' and the entry in the 'specify' field is not considered an effective method of contraception ii). Science review: check that contraception use continuing to be added to SDV plan. If violator, monitor to complete PD99& Science to notify stats of violation if PD99 completed
Inc #7	Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure	- No signed informed consent	**Inclusion**	Programmed: based on the DCS pages "Informed consent A", "Informed consent B" and "Informed consent C" If patient has consented to >1 version of the protocol, check that

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
		- No approval by Institutional Review Board/Independent Ethics Committee		the earliest informed consent date is prior to randomization date Programmed: based on DCS pages "Protocol Amendment B" and "Protocol Amendment C" If a patient has only consented to Protocol A, no approval by IRB/IEC will need to be identified by Monitors as a PV and notified to stats by Science
Exc #1	History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC which must be stopped prior to randomization). This includes any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC. One prior hormonal "regimen" for MBC may include more than one hormonal therapy, for example, if the switch is not related to disease progression, such as toxicity or local standard practice, this will be counted as one "regimen". If a patient receives hormonal therapy for MBC and is	-history of anticancer therapy for MBC (including any EGFR , or anti-Her2 agents or vaccines , or cytotoxic) - history of more than one prior hormonal regimen for MBC	**Exclusion**	Science to review using I-Review

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
	switched to a different hormonal therapy due to disease progression, this will be counted as two "regimens" and the patient is not eligible.			
Exc #2	History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting	History of tyrosine kinase/HER inhibitors for breast cancer (exc. neo/adjuvant trastuzumab)	**Exclusion**	Science to review using I-Review
Exc #3	History of systemic breast cancer treatment in the neo-adjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months	Disease-free interval < 12 months	**Exclusion**	Programming: Eligibility question on "Eligibility" DCS. If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary
Exc #4	History of persistent Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy	History of Grade ≥ 2 hematologic toxicity from adj. therapy	**Exclusion**	Programming: eligibility question on "Eligibility" DCS If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary. Check med hist for neutropenia (query if >2) then cross check with tick box

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
Exc #5	Current peripheral neuropathy of NCI-CTCAE, Version 3.0, Grade ≥ 3 at randomization	Grade ≥ 3 neuropathy at randomization	**Exclusion**	Programming: eligibility question on "Eligibility" DCS If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary. Check med hist for neuropathy (query if >3) then cross check with tick box
Exc #6	Protocol B: History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell carcinoma Protocol C: History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that has been previously treated with curative intent	Protocol B: Other malignancy within the last 5 years (exc. cervical or basal cell carcinoma) Protocol C: Other malignancy within the last 5 years (exc. cervical, basal cell carcinoma or squamous cell carcinoma of the skin)	**Exclusion**	Science to review using I-Review.
Exc #7	Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases	Current clinical or radiographic evidence of CNS metastases	**Exclusion**	Science to review using I-Review. Target and non target lesions at screening must not include brain/CNS. Science to flag patients with site code=5 (brain). Also check site=other (code=35) in case

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				incorrectly entered. Any violators identified to be notified to stats.
Exc #8	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 (e.g., liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin) • If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.	Maximum recommended cumulative anthracycline dose exceeded	**Exclusion**	Programmed (unless 'other'). Violation = doxorubicin or liposomal doxorubicin > 360 mg/m2, epirubicin > 720 mg/m2, mitoxantrone > 120 mg/m2, idarubicin > 90 mg/m2. However, if patient is given both doxorubicin and epirubicin, based on a 1:2 ratio on the remaining doxorubicin out of the 360 mg/m2 allowed, if this is exceeded the patient is excluded, for example: If 300 mg/m2 of doxorubicin is given then 60 mg/m2 of equivalent doxorubicin is remaining, if 120 mg/m2 of epirubicin is given (equivalent to 60 mg/m2 of doxorubicin), total dose is 360 mg/m2 and patient is included, however, if 150 mg/m2 of epirubicin is given (equivalent to 75 mg/m2 of doxorubicin), then the total dose is 375mg/m2 and patient is excluded.

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				Other combination ratios: doxorubicin:mitoxantrone = 3:1, doxorubicin:idarubicin = 4:1, Science to check for 'other' using I-Review. If any additional anthracyclines identified, science will add to PV spreadsheet.
Exc #9	Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina	i) Unstable angina ii) Uncontrolled hypertension (at least one vital sign)	**Exclusion**	Both unstable angina and uncontrolled hypertension = Science review using I-Review (vitals, medhist) and DM alerts;
Exc #10	History of Congestive Heart Failure (CHF) of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia)	History of CHF or serious cardiac arrhythmia requiring treatment	**Exclusion**	Science to review using I-Review (review of preferred terms).
Exc #11	History of myocardial infarction within 6 months of randomization	MI within 6 months of randomization	**Exclusion**	Programming: Eligibility question on "Eligibility" DCS If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary.
Exc #12	History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant	LVEF <50% during/after prior trastuzumab neo-adjuvant or	**Exclusion**	Programming: Eligibility question on "Eligibility" DCS

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
	therapy	adjuvant therapy		If no = non violator Note: Science to closely check consistency of this data ("Previous LVEF" DCS LVEF result <50% & prior trastuzumab trt) on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary.
Exc #13	Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy	Dyspnea or other diseases due to advanced malignancy	**Exclusion**	Science to review using I-Review.
Exc #14	Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization: All protocol versions • Absolute neutrophil count < 1,500 cells/mm^3 • Platelet count < 100,000 cells/mm^3 • Hemoglobin < 9 g/dL • Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome) • Serum creatinine > 2.0 mg/dL or 177 µmol/L • International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 × ULN (unless on therapeutic	Inadequate organ function (confirmed <= 28 days before randomization)	**Exclusion**	Programmed using baseline labs from the "Hematology" and "Blood chemistry" DCS pages. If at baseline any criteria defined in the 'Protocol defined Inc/Exc Criteria' column are met or any of the tests are missing then violator. Note that any abnormalities are only a violator if the assessment is no more than 28 days prior to randomisation Note: for Serum Creatinine, programming only need to check for value >177 µmol/L, as the data

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes

	coagulation)
	
	Protocol A & B
	• AST (SGOT) and ALT (SGPT) > 2.5 × ULN
	• AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. (unless bone metastases are present)
	
	Protocol C
	• AST (SGOT) and ALT (SGPT) > 2.5 × ULN
	• AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. Serum alkaline phosphatase may be > 2.5 x ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) < 1.5 x ULN
				will be converted to these units, and 2.0 mg/dL is equivalent to 177 µmol/L.
				
				Note for AST/ALT & Alk Phos:
				Protocol A & B:
				If (AST or ALT >1.5 x ULN) AND serum Alk Phos > 2.5 x ULN AND bone mets No = Violator
				If (AST or ALT >1.5 x ULN) AND serum Alk Phos > 2.5 x ULN AND bone mets Yes = Non Violator
				i.e. need to check for bone mets to determine if a violation or not
				
				Protocol C:
				If (AST or ALT >1.5 x ULN) AND serum Alk Phos > 2.5 x ULN = Violator.
				i.e. there is no need to check for bone mets as this is only acceptable if AST/ALT <1.5 x ULN, and we have already determined that AST or ALT is >1.5 x ULN
				
				Other criteria to be determined as follows:

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				Gilbert's Syndrome: check for preferred term 'Gilbert's syndrome' on either the "Disease other than breast cancer" DCS (where status = active with/without treatment) or the "Adverse event" DCS (where start date within 28 days prior to randomization) Bone mets: check for tumor assessment at screening or baseline = bone scan ('How assessed' = code 9 (Bone scan)) on the "Target lesions (screening)" DCS page) OR code of organ site = bone ("Code of organ site" = code 3 (Bone) on "Non-target lesions (screening)" DCS page.)

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
Exc #14 cont.				Treatments for therapeutic coagulation (refer to document 'Cleopatra Treatments for Therapeutic Coagulation' stored in Rapid with the DRAM), from conmed page looking at 'previous' tick box, or from previous treatment CRF pages, where treatment started or ended within 28 days of randomization,
Exc #15	Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures)	Severe, uncontrolled systemic disease	**Exclusion**	Science to review using I-Review.
Exc #16	Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment	Major surgical procedure or injury <= 28 days prior to 1st study treatment	**Exclusion**	Programming: Eligibility question on "Eligibility" DCS If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary.
Exc #17	Pregnant or lactating women	i) Positive pregnancy test or missing result ii) Lactating women	**Exclusion**	Programming: "Pregnancy test (serum)" DCS and "Pregnancy Test (urine)" DCS at screening or baseline All patients have a urine test. If

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				positive, a serum test is performed for confirmation: If urine result negative = non violator If urine result positive and serum result negative = non violator If urine result positive and serum result positive or missing = violator If urine result missing = violator and "Personal Data" DCS - Female reproductive status = 'Surgically sterilized' or 'post-menopausal '= non violator. Lactating women: science to review using I-Review
Exc #18	History of receiving any investigational treatment within 28 days of randomization	Treatment with investigational drug <= 28 days before randomization	**Exclusion**	Science to review using I-Review.
Exc #19	Current known infection with HIV, HBV, or HCV	Infection with HIV, HBV, HCV	**Exclusion**	Science to review using I-Review.
Exc #20	Receipt of IV antibiotics for infection within 14 days of randomization	IV antibiotics for infection <= 14 days before randomization	**Exclusion**	Science to review using I-Review.
Exc #21	Current chronic daily treatment with corticosteroids (dose of > 10 mg/ day methylprednisolone equivalent) (excluding inhaled steroids)	Chronic daily treatment with corticosteroids	**Exclusion**	Science to review using I-Review.

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
Exc #22	Known hypersensitivity to any of the study drugs	Known hypersensitivity to any of the study drugs	**Exclusion**	Programming: Eligibility question on "Eligibility" DCS If no = non violator Note: Science to closely check this data on an ongoing basis and raise PD99 if appropriate to ensure eligibility is updated prior to database closure if necessary.
Exc #23	Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol	Patient assessed by the Investigator to be unable/ unwilling to comply with the requirements of the protocol	**Exclusion**	Science to notify
Exc #24	Concurrent Interventional or Non-Interventional Studies (NIS) are not permitted	Patient concurrently participating in an Interventional or Non-interventional study	**Exclusion**	This is a new exclusion criteria added to protocol C. For patients only consenting to protocol A and/or B, violations of this criteria will be identified by Science (following notification from monitor from SDV checks) & Science will inform stats. For protocol C patients this can be derived programmatically: Protocol A & B: Science to notify stats Protocol C:

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				Programming: Eligibility question on "Eligibility" DCS
Other criteria to consider at baseline	Baseline windows: i) CT/MRI scans = 28 days ii) MUGA or ECHO = 42 days iii) Bone scans = 28 days	Assessment outside allowed baseline window: i) CT/MRI scans (28 days) ii) MUGA or ECHO (42 days) iii) Bone scans (28 days)	**Inclusion**	Programmed Note: baseline windows counted from date of 1st dose of study treatment (Study day 1) For CT scans: if patient has a CT scan (assessment methods 1-6 from "Target lesions (screening)" DCS) OR (a valid non target lesion assessment (DCS page "Non-target lesions (screening)" and no target lesions on DCS page "Target lesions (screening)"), AND 'Date of assessment' on "Target lesions (screening)" is <=28 days prior to Study day 1 = no violation. MUGA/ECHO: if 'date of assessment' of baseline LVEF (from "LVEF" DCS) is <=42 days prior to Study day 1 = non violator Bone scans: if 'date of bone scan' from "Bone scan" DCS at baseline is <= 28 days prior to Study day 1 =

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				non violator
Post baseline	Safety population exclusion	Did not receive study medication	**Safety exclusion**	Programmed
Post baseline	Concurrent treatment with other anticancer, hormone therapy, chemotherapy, immunotherapy or any other therapy not part of the protocol–specified anticancer therapy	Concurrent therapy with any anticancer therapy not part of protocol-specified anticancer therapy	**On-study**	Science to review using I-Review.
Post baseline	Concurrent investigational agents of any type	Concurrent use of Investigational agents	**On-study**	Science to review using I-Review.
Post baseline	Chronic or high dose oral corticoid therapy: high dose is considered as > 20 mg of dexamethasone a day or equivalent for > 7 consecutive days (standard definition, not provided in the protocol).	Chronic or high dose oral corticoid therapy	**On-study**	Science to review using I-Review.
Post baseline	Immunosuppressive therapy such as: TNF-alpha, anti-T cell antibodies	Immunosuppressive therapy	**On-study**	Science to review using I-Review.
Post baseline	Herbal remedies for cancer therapy, unless it was started before study entry	Herbal remedies for cancer therapy started after study entry	**On-study**	Science to review using I-Review.
Post baseline	Docetaxel dose increased to 100 mg/m2 despite the following toxicities = febrile neutropenia, grade 4 neutropenia for > 5 days, or ANC < 100/ul for more than 1 day, or non-hematological toxicities of grade > 2 (NCI CTC, version 3	Docetaxel dose increased to 100 mg/m^2 despite toxicities	**On-study**	Science to review using I-Review.
Post baseline	Docetaxel administration continued despite the toxicities listed in table 3 page 82 of the protocol	Docetaxel administration continued despite toxicities requiring withdrawal of treatment	**On-study**	Science to review using I-Review.
Post baseline	Study treatment continued despite LVEF value < 40% or LVEF between 40 and 45% and 10% points below	Study treatment continued despite LVEF value < 40% or	**On-study**	Programmed – using LVEF data and study medication intake dates.

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
	baseline or lower.	LVEF between 40 and 45% and 10% points below baseline or lower		Refer to algorithm in Appendix 6 Note: when checking that the LVEF has returned to normal after a low value, check that the LVEF assessment ate is 3 weeks +/- 7 days from the previous assessment, and occurs prior to the next infusion
Post baseline	Tumor assessment not performed every 9 weeks (to be recorded on the "deviation from schedule" eCRF or "reason(s) for unscheduled tumor assessment" eCRF)	Tumor assessment not performed every 9 weeks	**On-study**	Programmed using tumor assessment DCS pages ("Target lesions", "Non-target lesions"). Check assessment dates starting from randomization visit. Expect assessments at 9 weeks, 18 weeks, 27 weeks etc until treatment end. Allowed window = +/- 7 days. i.e. non-violator if assessment is done 9 weeks +/- 7 days, 18 weeks +/- 7 days etc.
Post baseline	ECHO/ MUGA or ECG missing or not done every 9 weeks	ECHO/MUGA or ECG missing or not done every 9 weeks	**On-study**	Programmed using LVEF eCRF pages. Check assessment dates starting from randomization visit. Expect assessments at 9 weeks, 18 weeks, 27 weeks etc until treatment end. Allowed window = +/- 1 week. i.e. non-violator if assessment is done 9 weeks +/- 1 week, 18 weeks

Inc/Exc Number	Protocol defined Inc/Exc Criteria	Text for Inc/Exc Violation	Violation Type	Notes
				+/- 1 week etc.
Post baseline	If patient is randomized, the same method of LVEF assessment, ECHO or MUGA, must be used throughout the study	Same method of LVEF assessment (ECHO or MUGA) not used during the study	**On-study**	Programmed using LVEF eCRF pages
Post baseline	Women who become pregnant during the study	Pregnancy during the study	**On-study**	Science to review using I-Review.
Post baseline	Overdosage of any of the 3 study medications (defined as >10% of planned dose)	Overdosage: patient receives >10% of planned dose of any of study medications (pertuzumab, trastuzumab or docetaxel)	**On-study**	Science to review using I-Review.
Post baseline	Dose of docetaxel not reduced as per-protocol despite toxicities	Dose of docetaxel not reduced despite toxicities as defined in Section 6.7.2 table 3 of the protocol	**On-study**	Science to review using I-Review.
Post baseline	Pregnancy test not done during the study	Pregnancy test not done during study medication	**On-study**	Science to review using I-Review.
Post-baseline	Patient received a treatment they were not randomized to receive (Patient mis-randomized)	Received different treatment to the randomized treatment or did not receive the full combination of randomized treatments at any time during the study	**On-study**	Programmed: check that all 3 randomized treatments have been taken at any point during the study, and no additional treatments have been taken. If not, then violator

Appendix 2 Laboratory Parameters – Worst Value

The following table provides for each laboratory parameter an indication of whether the 'worst' value is represented by the lowest or highest value.

Laboratory Analysis	Laboratory Parameter	Worst value
Hematology	Hemoglobin	Low
	Hematocrit	Low
	Platelet count	Low
	RBC Count	Low
	Leukocytes (Total)	Low
	Neutrophils	Low
	Lymphocytes	Low
	Monocytes	Low
	Eosinophils	Low
	Basophils	Low
	Leukocytes (Other cells)	Low
	Prothrombin international normalised ratio (INR)	Low or High*
	aPTT	Low or High*
	PTT	Low or High*
Blood chemistry	Serum creatinine	High
	Total bilirubin	High
	Total protein	Low
	Albumin	Low
	ALT (SGPT)	High
	AST (SGOT)	High
	Alkaline phosphatase	High
	Glucose	Low or High*
	Urea (BUN)	High
	Uric acid	High
	Sodium	Low or High*
	Potassium	Low or High*
	Calcium	Low or High*
	Chloride	High
	Bicarbonate	Low or High*
	LDH	High
	GGT	High
	Magnesium	Low
	Alpha-1-acid glycoprotein (AGP)	Low or High*

*When summarising absolute values the value that in absolute terms is furthest outside the Normal Range (NR) will be taken (if there is one or more value outside the NR) or the value that is closest to either the lower or higher limit (if there are two values that lie within the NR). In the unlikely event that the values are equal distance from the normal range then the highest value will be considered. Any other occurrences will be listed only. These rules will also be applied when selecting the value to use when calculating the change from baseline.

Appendix 3 Visit Labels

Treatment labels will be included on listings based on both the assessment identifier (CPE) from the eCRF and also the remapped treatment cycle, assigned based on actual dates of study treatment infusions. The order in which these are shown (i.e. CPE or remapped label) will depend on how data are summarized. Refer to Section 4.11 for full details. The unique labels in this study are shown below, with examples of how to interpret the label. A 20 character limit will be set, made up of 9 characters for each label (remapped & CPE) and 2 characters for the parentheses. If based on the labels shown below the 9 character limit for either label is exceeded blank spaces and hyphens between words will be omitted, or the word will be abbreviated (e.g. 'Post-Trt' and 'Post-Tx' will become 'PstTrt'; 'UnschedTA1' will become 'UnschTA1'; 'Week 108 On-Tx' will become 'Wk108OnTx',) and this will be applied to all occurrences of similar labels within the domain.

Order:	*1: Remapped label (CPE label)*	*2: CPE label (Remapped label)*	*Interpretation*
1	Pre-Trt(Screen 1)	Screen 1(Pre-Trt)	*data have been recorded on a screening eCRF page and are pre-treatment based on study treatment dates*
2	Pre-Trt(Unsched)	Unsched(Pre-Trt)	*data have been recorded on an unscheduled eCRF page and are pre-treatment based on study treatment dates*
3	Cycle 1(Cycle 1)	Cycle 1(Cycle 1)	*data have been recorded on a Cycle 1 eCRF page and fall during Cycle 1 based on study treatment dates*
4	Cycle 1(Unsched)	Unsched(Cycle 1)	
5	Cycle 3(UnschedTA1)	UnschedTA1(Cycle 3)	*data have been recorded on the first unscheduled tumor assessment page, but the tumor assessment took place during Cycle 3 based on study treatment dates*
6	Cycle 9(Week 27)	Week 27(Cycle 9)	
7	Cycle 11(Cycle 12)	Cycle 12(Cycle 11)	*data have been recorded on a Cycle 12 eCRF page but fall during Cycle 11 based on study treatment dates*
8	Cycle 36(Week 108 On-Tx)	Week 108 On-Tx(Cycle 36)	*Patient has been on treatment for >100 weeks. CPE will include 'On-Tx' to distinguish them from some post-treatment CPEs that refer to weeks>100 eg. 'Week 108 wk 9 post-trt v1'*

Order:	*1: Remapped label (CPE label)*	*2: CPE label (Remapped label)*	*Interpretation*
9	Trt End(Trt End)	Trt End(Trt End)	*data have been recorded on the treatment discontinuation page of eCRF and fall during the window for this visit relative to last date of study treatment*
10	Trt End(Unsched)	Unsched(Trt End)	
11	Post-Trt(Trt End)	Trt End(Post-Trt)	*data have been recorded on the treatment discontinuation page of eCRF but fall after the window for this visit relative to last date of study treatment so classed as post-treatment*
12	Post-Trt(Unsched)	Unsched(Post-Trt)	
13	PstTrtV11(Unsched)	Unsched(PstTxV11)	

For labs, where a window is assigned to define pre- and post-infusion assessments in addition to treatment cycle, the following are examples of conventions to be followed:

Order:	*Remapped label (CPE label)*	*Interpretation*
1	Pre-Trt(Screen 1)	*data have been recorded on a screening eCRF page and are pre-treatment based on study treatment dates*
2	Pre-Trt(Cyc 1 D1)	*data have been recorded on a cycle 1 pre-infusion eCRF page and are pre-treatment based on study treatment dates*
3	Cyc 1 D8(Cyc 1 D8)	*data have been recorded on cycle 1 day 8 eCRF page and are within study day window for cycle 1 day 8*
4	Cyc 1 D8(Unsched)	*data have been recorded at an unscheduled assessment and are within study day window for cycle 1 day 8*
5	Cyc 2 D1(Cyc 2 D1)	*data have been recorded on cycle 2 day 1 eCRF page and are within study day window for cycle 2 day 1 pre-infusion assessment*

Order:	*Remapped label (CPE label)*	*Interpretation*
6	Cyc 2(Cyc 2 D1)	*data have been recorded on cycle 2 day 1 eCRF page and fall during cycle 2 based on study treatment dates but are not within windows for either cycle 2 day 1 or cycle 2 day 8*
7	Cyc 1(Cyc 1 D8)	*Data have been recorded on cycle 1 day 8 eCRF page and fall during cycle 1 based on study treatment dates but are not within window for cycle 1 day 8*

Appendix 4 Tumor Response

Tumor assessments will be made based upon the RECIST criteria version 1.0 (Response Evaluation Criteria in Solid Tumors [Therasse et al. 2000]). The RECIST criteria are the international standard for the evaluation of the efficacy of anti-tumor agents and have been developed as a collaborative effort by the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. A brief summary of the RECIST criteria and how they are applied in the pertuzumab project is given below:

Tumor response is assessed compared to baseline sum of longest diameters (SLD) of the target lesions, whilst PD is assessed compared to the nadir SLD, i.e. the smallest value of the SLD. Non-target lesions and the presence/absence of new lesions are also taken into consideration when determining the overall response at each follow-up visit.

The following derivations of overall response are specified in the IRF Charter. Note that the following tables of derivations are for information only. The overall response will appear in the datasets from both the eCRF and the IRF, and will not need to be derived as part of the statistical analysis:

Table 42 Derivation of Overall Response per Follow-up Time Point (Post-Baseline Visit)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

An "unable to assess" (UA) assessment of target lesions or non-target lesions results in an overall response assessment of UA, unless PD can be derived from any lesion category. Some relevant combinations are listed in the table below.

Table 43 Overall Response per Follow-up (Post-Baseline Visit) in Case of an UA Lesion Category

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
UA	Non-PD	No	UA
Non-PD	UA	No	UA
UA	UA	No	UA
UA	UA	Yes	PD

Evaluation of Best Overall Response (BOR)

After a response is assigned at each follow-up time point (i.e. at each post-baseline visit), the best overall response across all time points will be established by applying the RECIST confirmation criteria below:

- The best overall response is the best confirmed response recorded from the start of the treatment until PD.

- To be assigned a status of confirmed PR or CR, changes in tumor assessment must be confirmed by repeat assessments to be performed no less than four weeks after the criteria for response are first met.
- In the case of SD, measurements must have met the SD criteria at least once after start of treatment at a minimum interval of six weeks.
- As no scanning dates are disclosed to the reader, the read software will check for the observance of the minimal confirmation periods and notify the reader if a time point assumed to be confirmatory does not meet the adequate time interval.

Response confirmation requires the following more detailed rules supplementing the basic RECIST rules:

- Once a CR is observed (confirmed or unconfirmed) any unequivocal reappearance of disease results in progression. That is, neither a PR nor SD may follow a CR.
- For confirmation of PR:
  - The confirming 2nd PR does not need to be consecutive: 1 or more SDs can occur between the initial and the confirmatory PR. However, an interim PD is not allowed.
  - A CR will confirm an unconfirmed PR.
- Unconfirmed CR or PR will be defined as a BOR of SD, provided the requirement for at least a 6-week interval since start of treatment has been respected. An unconfirmed CR or PR occurring less than 6 weeks after the start of treatment will be defined as UA.
- Once a PR is confirmed, the status shall remain PR or improve to CR until criteria for PD are met. Specifically, an SD may not follow a confirmed PR (or CR).

The confirmation of response process is summarized in the following table:

Table 44 Confirmation Process and the Best Overall Response

First Best Response (not yet confirmed)	All Later Best Response (confirmation)	Best Overall Response
CR	CR	CR
CR	Missing/PD	SD
CR	PR or SD (Not Allowed)	
PR	PR or unconfirmed CR	PR
PR	SD or missing	SD
PR	PD	SD
SD	SD, unconfirmed CR or unconfirmed PR	SD

Note: the minimal intervals for confirmation of a CR or PR (at least 4 weeks after the 1st response of CR/PR) and for a best overall response of SD (at least 6 weeks after start of treatment) must be observed when defining the best overall response. In this study, given the frequency of scheduled tumor assessments, the earliest opportunity for a best overall response of SD is expected to be 9 weeks.

The best overall response will be used to derive the endpoint of Objective Response (OR).

A patient is considered to be a responder for OR if their BOR is either confirmed CR or confirmed PR. Patients with BOR of SD, PD or with insufficient post baseline information are considered to be non-responders for OR.

The "Date of First Response" in subjects with a confirmed CR or PR, used to calculate the duration of response, is the date when the criteria for CR or PR are first met, which is subsequently confirmed by a further CR/PR at least 28 days later. The earliest opportunity for confirmation of a best overall response of CR or PR is expected to be 13 weeks, although the date of first response could occur after 9 weeks.

A descriptive presentation of these rules for determining overall best response is provided in the table below.

Tumor assessments							**Best overall response**	**Endpoint (Objective Response)**
Baseline	Week 9	Week 18	Week 27	Week 36	Week 45	Week 54		
-	SD	SD	PR	PR	PR	PD	PR	Responder
-	SD	PR	SD	SD	PR	PD	PR	Responder
-	SD	SD	CR	CR	PD	-	CR	Responder
-	SD	SD	SD	SD	SD	SD	SD	Non-Responder
-	SD	SD	PR	SD	SD	SD	SD	Non-Responder
-	SD	SD	SD	CR	PD	-	SD	Non-Responder
-	SD	SD	CR	PD	-	-	SD	Non-Responder
-	PD (new lesion and carry on with therapy)[1]	SD	PR	PR	-	-	PD	Non-Responder
-	SD	SD	SD	-			SD	Non-Responder

1. Note that this option is not permitted in the protocol, but may occur and study treatment may continue until an intervention occurs to ensure the study treatment is discontinued.

There is a possibility that a patient's tumor may be "unable to assess" (UA) during the study, in which case assumptions can be made about that UA, providing later tumor assessments are made with responses CR/PR/SD. The UA will be assumed to be the worst case scenario, other than PD.

A PR/CR can be confirmed by an assessment not directly after the first PR/CR, so long as there is no deterioration of disease control in between. As an extreme, a patient could still have a PR/CR at Week 9, UA at Week 18 and Week 27 and then a PR/CR at Week 36 and still be confirmed.

Tumor assessments							UA should be interpreted as	Best overall response	Endpoint
Baseline	Week 9	Week 18	Week 27	Week 36	Week 45	Week 54			
-	**UA**	SD	SD	SD	SD	PD	SD[1]	SD	
-	SD	**UA**	SD	SD	SD	SD	SD[1]	SD	
-	SD	SD	**UA**	PR	SD	PD	SD[2]	SD	
-	SD	PR	**SD/UA**	PR	PR	PD	SD	PR[4]	OR
-	SD	CR	**UA**	**UA**	CR	PD	CR	CR[4]	OR
-	SD	SD	**UA**	**PD**	-	-	UA	SD	

1. Since an SD is reported at the assessment before and after the UA, the UA can be assumed to be an SD
2. Since the UA follows an SD and precedes a PR, though not confirmed, the UA can be assumed to be SD
4. A PR can be confirmed by an assessment not directly after the first PR, so long as there is no progressive disease in between. A CR can only be confirmed by an assessment not directly after the first CR is the interim assessments are UA. As an extreme a patient could still have a PR at Week 9, SD/UA at Week 18 and Week 27 and then a PR at Week 36 or even later.

After a confirmed PR is observed, only a further PR, CR or PD can be detected, though an SD can be detected after an unconfirmed PR, providing it does not meet the criteria of PD. However, after a confirmed or unconfirmed CR is observed, only a further CR or PD can be detected.

Appendix 5 Algorithm For Response for Target Lesions According to RECIST

Tumor measurements

A. RECIST criteria:

Response evaluation for target lesions: the longest diameter *only* for all target lesions is measured and the following responses recorded

- Complete response (CR): the disappearance of all target lesions.
- Partial Response (PR): at least a 30% decrease in the sum of the longest diameter as compared to the baseline sum longest diameter.
- Stable Disease (SD): neither a sufficient shrinkage to qualify for partial response nor a sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameters, either at screening or since start of treatment.

Progressive Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameters of the target lesions (the nadir) recorded at screening or since start of treatment or the appearance of one or more new lesions. If during treatment a decrease in the sum of the longest diameters is observed, then the smallest sum since the initiation of treatment is taken as the reference point for the assessment of progressive disease. If there is no change or an increase in the sum of the longest diameters since the initiation of treatment, then the baseline sum is taken as the reference point.

B. Target Lesions:

- Pull out all information for target lesions, from DCS pages ‘Target lesions (screening)’ and ‘Target lesions’.
- To derive the number of target lesions reported: at each visit, count up all lesions where lesion size >=0. Do not count any lesions where the size=NK, NM, ND, UA or missing. If BML is recorded, the size will be recorded as >0, so will be accounted for in the number of lesions.
- In order to get baseline sum of longest diameters (SLD): from DCS page ‘Target lesions (screening)’, sum the ‘Size (mm)’ variable across all target lesions. This is the “baseline sum of longest diameters”=baseline.
- Do the same for each visit for which target lesions were measured (DCS page ‘Target lesions’) to derive a visit SLD. The SLD is derived at all visits, irrespective of any missing or inconsistent data compred to the baseline assessment.

- For each lesion listed at screening, check at each visit for consistency the following:
  a) Organ Site: In other words, if a patient has lesion #1=liver and lesion #2= kidney, lesions #1 and #2 should always be liver and kidney.
  b) Lesion Number
  c) Method of Assessment: The method of assessment should always be the same for a given lesion across visits. For example, if lesion #1 (liver) is assessed by CT scan, this lesion should always be assessed by CT scan.
- % change from baseline: Lesions listed at screening should be listed at each tumor assessment. If there are any missing lesions (listed at screening and not listed at later tumor assessment) or missing or inconsistent data, do not calculate '%change from baseline' for that timepoint. However for subsequent tumor assessments, calculate '%change from baseline' if all lesions listed at screening are accounted for and no measurements are missing or inconsistent. Percent change from baseline=((SLD visit – SLD baseline)/SLD baseline)*100.
- % change from nadir: 'Smallest sum longest diameter' (i.e. nadir) includes screening and is the smallest SLD value to date, excluding current visit. '%change from nadir'= ((SLD visit – SLD nadir)/SLD nadir)*100. Any tumor assessments with missing or inconsistent data, compared to baseline, will not be considered for the nadir value. If the nadir=0 and the current SLD=0, set the % change from nadir to zero. If the nadir =0 and current SLD>0, set the % change from nadir to missing (infinite value)

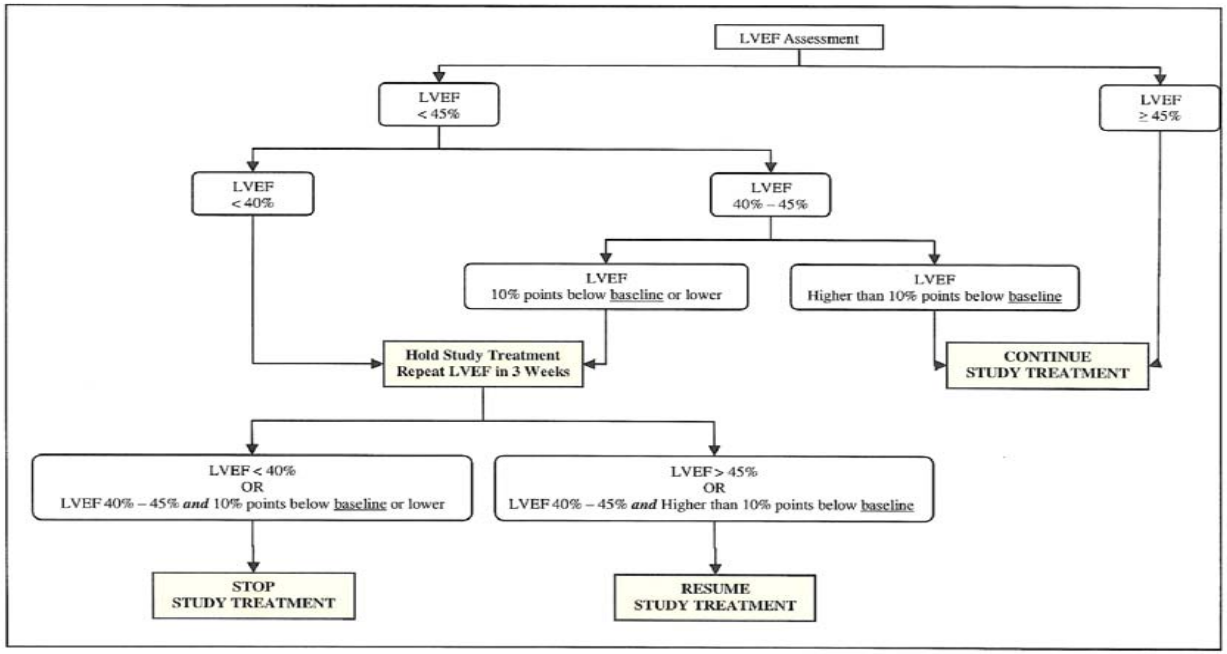
C. Non-Target Lesions

- To derive the number of non-target lesions reported: at each visit, count up all lesions either 'PRESENT' or 'ABSENT'. Do not count any lesions reported as 'NOT ASSESSED'.

Appendix 6 LVEF Algorithm

For patients whose LVEF drops to values lower than 45%, the decision to stop or continue study treatment is based on the algorithm shown in Figure 4.

Figure 4 Algorithm for Continuation and Discontinuation of Pertuzumab/Placebo and Trastuzumab Based on LVEF Assessments



LVEF=left ventricular ejection fraction.
Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year after the Treatment Discontinuation Visit, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the Treatment Discontinuation Visit.

F. HOFFMANN-LA ROCHE LTD / GENENTECH, INC

CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER WO20698C/TOC4129G

RO4368451 IND NUMBER BB-IND 9900

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PROTOCOL APPROVAL

Protocol Number / Version: WO20698 / C

Date: See last date in electronic signature manifestation below.

Protocol approved by: See electronic signature manifestation below.

Name	Reason for Signing	Date and Time (UTC)
Neate, Colin	Project Statistician	22-Jun-2009 16:31:04
Ross, Graham	Clinical Science Leader	23-Jun-2009 10:14:29

This protocol is intended for use in a life-threatening indication: Yes ☑ No ☐

SYNOPSIS OF PROTOCOL TOC4129G/WO20698C

TITLE	A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated Her2-Positive Metastatic Breast Cancer
SPONSOR	F. Hoffmann-LaRoche Ltd. and Genentech, Inc.
CLINICAL PHASE	III
INDICATION	Patients who have HER2-positive metastatic breast cancer (MBC) and have not received chemotherapy or biologic therapy for their metastatic disease
OBJECTIVES	**Primary Objectives** The primary objective of this study is to compare progression-free survival (PFS) based on tumor assessments by an independent review facility (IRF) between patients in the two treatment arms: placebo + trastuzumab + docetaxel vs. pertuzumab + trastuzumab + docetaxel. **Secondary Objectives** • To compare overall survival (OS) between the two treatment arms • To compare PFS between the two treatment arms based upon investigator assessment of progression • To compare the overall objective response rate between the two treatment arms • To compare the duration of objective response between the two treatment arms • To compare the safety profile between the two treatment arms • To compare time to symptom progression, as assessed by the FACT Trial Outcome Index - Physical Functional Breast (TOI-PFB) • To evaluate if biomarkers from tumor tissues or blood samples (e.g., HER3 expression, Fcγ, and serum ECD/HER2 and/or HER ligands concentrations) correlate with clinical outcomes
TRIAL DESIGN	Phase III, randomized, double-blind, placebo-controlled
NUMBER OF PATIENTS	The study will enroll 800 patients from approximately 250 sites worldwide.
TARGET POPULATION	The study population for this trial is patients with HER2-positive MBC who have not previously been treated with chemotherapy and/or biologic therapy for their MBC. Patients with Stage IV disease at initial disease presentation as well as those who have progressed following either neo-adjuvant or adjuvant therapy with a disease-free interval of at least 12 months will be included, and they may have received trastuzumab and/or taxanes in the adjuvant setting.

LENGTH OF STUDY	A total of approximately 800 patients (approximately 400 per arm) will be enrolled. It is estimated that the accrual will be approximately 40 patients per month after a 9-month ramp-up period over an approximate 26.5-month timeframe. An Interactive Voice Response System (IVRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.
INVESTIGATIONAL DRUG	**Blinded Pertuzumab/Placebo** Pertuzumab/placebo will be administered as an IV loading dose of 840 mg for Cycle 1, and 420 mg for subsequent cycles. Pertuzumab/placebo will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed. If the patient misses a dose of pertuzumab/placebo for 1 cycle (i.e., the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab/placebo (840 mg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.
COMPARATOR DRUGS	**Trastuzumab** Trastuzumab will be administered as an IV loading dose of 8 mg/kg for Cycle 1, and 6 mg/kg for subsequent cycles. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline. Trastuzumab will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed. If the patient misses a dose of trastuzumab for 1 cycle (i.e. the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of trastuzumab (8 mg/kg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1 and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later. **Docetaxel** Docetaxel will be administered as an IV dose of 75 mg/m^2 every 3 weeks. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for >5 days or ANC < 100/µL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

TREATMENT SCHEDULE	For the first cycle of treatment, blinded pertuzumab/placebo will be given on Day 1 over 60 minutes followed by a 60-minute observation period. Trastuzumab and docetaxel will be administered on Day 2 of Cycle 1 using the labeled guidelines for administration. If the administrations of all three agents are well tolerated in Cycle 1, they may be given sequentially on Day 1 in subsequent cycles thereafter. If a subject cannot tolerate all three drugs given on the same day, the Cycle 1 dosing schedule (pertuzumab/placebo on Day 1, trastuzumab and docetaxel on Day 2) will be followed. If one or both of the monoclonal antibody study drugs needs to be permanently discontinued or is held for more than two cycles, the subject will be taken off the study treatment. However, if docetaxel needs to be permanently discontinued for reasons related to toxicity, the subject can continue on monoclonal antibody study drugs.
INCLUSION CRITERIA	Disease-Specific Inclusion Criteria: 1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. Patients with measurable and/or non-measurable lesion are eligible. Patients with *only* bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for central HER 2 testing and subsequent biomarkers analysis. Locally recurrent disease must not be amenable to resection with curative intent. Note: Patients with de-novo Stage IV disease are eligible. 2. HER2-positive (**defined as 3+ IHC or FISH amplification ratio ≥ 2.0**) MBC 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 if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.) General Inclusion Criteria: 3. Age ≥ 18 years 4. Left Ventricular Ejection Fraction (LVEF) ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (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 7.4.2, page 100 of the protocol). **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.** 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1

INCLUSION CRITERIA Cont'd	6. For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly-effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy. For further details see Section 7.2.6, page 92 . 7. Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure
EXCLUSION CRITERIA Cont'd	**Cancer-Related Exclusion Criteria:** 1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC which must be stopped prior to randomization). Anticancer therapy for MBC includes any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC. One prior hormonal "regimen" for MBC may include more than one hormonal therapy, for example, if the switch is not related to disease progression, such as toxicity or local standard practice, this will be counted as one "regimen". If a patient receives hormonal therapy for MBC and is switched to a different hormonal therapy due to disease progression, this will be counted as two "regimens" and the patient is not eligible 2. History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting 3. History of systemic breast cancer treatment in the neo-adjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months 4. History of persistent Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy 5. Current peripheral neuropathy of NCI-CTCAE, Version 3.0, Grade ≥ 3 at randomization 6. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that has been previously treated with curative intent. 7. Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.

EXCLUSION CRITERIA	8. 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 (e.g., liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin) • If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin. **Hematological, Biochemical, and Organ Function** 9. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina 10. History of CHF of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia) 11. History of myocardial infarction within 6 months of randomization 12. History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy 13. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy **General Exclusion Criteria** 14. Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization: • Absolute neutrophil count < 1,500 cells/mm^3 • Platelet count < 100,000 cells/mm^3 • Hemoglobin < 9 g/dL • Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome) • AST (SGOT) or ALT (SGPT) > 2.5 × ULN • AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. Serum alkaline phosphatase may be > 2.5 × ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) < 1.5 × ULN • Serum creatinine > 2.0 mg/dL or 177 µmol/L • International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 × ULN (unless on therapeutic coagulation) 15. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures) 16. Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment 17. Pregnant or lactating women 18. History of receiving any investigational treatment within 28 days of randomization 19. Current known infection with HIV, HBV, or HCV

EXCLUSION CRITERIA Cont'd	20. Receipt of IV antibiotics for infection within 14 days of randomization 21. Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids) 22. Known hypersensitivity to any of the study drugs 23. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol 24. Concurrent Interventional or Non–Interventional Studies (NIS) are not permitted
ASSESSMENTS:	
• Efficacy	The primary endpoint is PFS based on IRF evaluations. PFS is defined as the time from randomization to the first documented radiographical progressive disease, as determined by the IRF using current RECIST (Therasse et al. 2000), or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions. Overall survival is the key secondary endpoint, and is defined as the time from the date of randomization to the date of death from any cause.
• Safety	Safety outcome measures are as follows: • Incidence of **Symptomatic left ventricular systolic dysfunction** [Congestive Heart Failure (CHF)] and asymptomatic left ventricular ejection fraction (LVEF) events • LVEF measurements over the course of the study • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Laboratory test abnormalities
• Pharmacokinetics/ QT (Substudy)	A **subset** of principal investigators and patients will participate in a pharmacokinetic, drug-drug interaction, and QTc interval substudy as detailed in a separate protocol. Separate IRB/IEC approval and Informed Consent Form will be required for participation in the substudy.
• Quality of Life/ Pharmacoeconomics	**Patient-Reported Outcomes Assessments** This study will use the Functional Assessment of Cancer Therapy-Breast (FACT-B), Version 4. The FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer (see Appendix 6, page 135 of the protocol). Patients will rate all items on a five-point scale ranging from "not at all" to "very much." The FACT-B provides supplemental domain valuative ratings or utility weights, thus providing an estimate of the relative importance of each quality of life domain to an individual patient. The FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. The FACT-B has been used extensively and has demonstrated reliability, validity, and sensitivity to change over time. Only female patients on this study will be asked to complete the FACT-B questionnaire.

• Quality of Life/ Pharmacoeconomics Cont'd	**<u>Pharmacoeconomic Assessments</u>** An economic assessment comparing various costs between the two treatment arms will be conducted by evaluating hospitalizations while on study treatment. The number of hospital visits, number of days admitted, and type of visits (emergency room vs. inpatient care) will be collected. This information will be collected from information submitted on AE and SAE electronic case report forms (eCRFs).
OPERATIONAL PROCEDURES	This protocol will be co-sponsored by Genentech, Inc., and F. Hoffmann-La Roche, Inc. These Sponsors will oversee the management of this study and will be responsible for clinical operations including site management and source data verification. Genentech and Roche will identify potential sites for participation in this study. Study networks will be assessed by Genentech and Roche and, where necessary, a Corporate Compliance Group-approved risk mitigation plan will be implemented. The Sponsors will perform pre-trial evaluations at individual sites. The Sponsors will oversee selection, approval, and monitoring of all clinical study sites. Patient eligibility verification will be conducted on all patients identified for enrollment into the study. Overall monitoring will be managed by the study Sponsors. Statistical analyses and clinical study report preparation will be managed by the Roche staff. A **central IRB** will be utilized when possible to ensure timely submission and approval of site regulatory documents for sites not required to use a local IRB. An **Interactive Voice Response System (IVRS)** will be utilized for collection of patient screening information, randomization, and drug management. Unblinding will not be permitted during the study except for safety issues that arise during study treatment. An **Independent Review Facility (IRF)** will be used to determine tumor response. Images (CT/MRI) will be acquired according to a standard protocol and will be transmitted to the independent reviewers. In addition, relevant clinical information such as results from tumor-marker assessments will be forwarded, as needed, to the independent reviewers to aid with assessment of disease progression and response. Full details will be listed in the Independent Imaging Review Charter. **The central independent review of MRI and CT scans will <u>NOT</u> determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.** Investigators' tumor assessments will not be reconciled with IRF tumor assessments. An independent **Data Monitoring Committee** (**DMC)** will monitor safety, review results from the interim analyses, and make recommendations regarding continuation of the study. The DMC will meet periodically to review safety summaries prepared by an independent Data Coordinator Center (DCC). The safety summaries will provide adequate information to assess overall safety in addition to cardiac-specific concerns. Members of the DMC will be external to Genentech and Roche, and will follow a charter that outlines their roles and responsibilities. Enrollment will not be deferred while the DMC performs a review. An independent **Data Coordinating Center (DCC)** will perform all safety and efficacy analyses that will be reviewed by the DMC during the trial.

OPERATIONAL PROCEDURES Cont'd	An independent **Cardiac Review Committee (CRC)** will evaluate potential congestive heart failure events during the study for an independent central determination of CHF rates for reporting to the DCC and DMC. The CRC will follow a charter that outlines their roles, responsibilities, and processes.
SAMPLE COLLECTION	Archival tumor samples from the primary tumor (or metastatic sites, if the primary tumor is not available) will be submitted from all subjects during screening and submitted to a central pathology laboratory for assessment of HER2 status via IHC and FISH for study eligibility, as well as for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 25 unstained freshly cut slides of 4 µm will be submitted (the number of slides submitted may be reduced pending on the regulatory and or IEC requirements of some counties). The slides must be sent to the central lab within 2 days of being cut. From submitted tumor blocks, at the central laboratory a maximum of 15 slides will be cut and 2 cores will be removed in order to construct tissue microarrays (TMAs) for later analysis. The remaining part of the tumor block will be returned to the institution. HER2 testing will be prioritized and the tissue will subsequently be used for assessment of biomarkers. For the assessment of tumor tissue biomarkers, a variety of analysis methodologies may be used, including but not limited to, qRT-PCR, IHC, in-situ hybridization, and gene expression profiling. At the end of the collection process, the most suitable analytical methodologies will be selected and employed. **Tissue Microarray (TMA) Construction** The tumor blocks will also be used to set up a TMA: a maximum of 2 tissue cores of 1.5 mm each will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissue cores from different patients. This process protects the tissue against oxidation and allows for long-term storage and later analysis. For later analysis, tissue sections can be generated using the latter tissue microarray. This technology will allow a high throughput (many patient samples on one glass slide) analysis of biomarkers. **DNA/RNA Extraction** The submitted tumor blocks will be used to generate sections on glass slides for the extraction of tumor DNA and RNA for later analysis. These slides will be prepared in a central lab to ensure the same quality for all samples and in later studies. Note that as tumorigenesis is a multiple-step process linked to somatic events, DNA analysis will focus on sporadic mutations specifically found in tumor tissue but not inherited changes found in the whole body. For this purpose, some sections containing tumor will be taken from the block and used for the extraction process. The tumor tissue samples will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed.

SAMPLE COLLECTION Cont'd	**Metastatic Tumor Tissue Samples for Biomarker Analysis (Optional)** If a biopsy of the patient's metastatic tumor tissue is available, it will be submitted from consenting patients at baseline (after the patient has been determined to be eligible for the study, but before the first administration of study medication) for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Biopsy samples should be submitted and processed as described in Section 5.4.7.1, page 73 of the protocol. **Serum Samples for ECD/HER2 and HER Ligands Analysis** For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment. Biomarker assessments with these samples will include levels of ECD/HER2, selected HER ligands, and/or markers thought to be important for HER family signaling or response to HER inhibitors and HER activation. At this time the significance of ECD/HER2 is not known, but because of its potential importance it will be measured as part of the panel of potential biomarkers of therapeutic effect. Leftovers of samples may be used for re-testing or developing and validating existing and/or new diagnostic tests related to pertuzumab or trastuzumab, or both. **Whole Blood Sample for Fcγ Polymorphism Analysis (Clinical Genotyping)** A whole blood sample (3 mL) for assessment of Fcγ polymorphism will be collected from patients at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication). An analysis of Fcγ-receptor polymorphism will be correlated with clinical outcome in order to further evaluate the mechanism of action of both trastuzumab and pertuzumab. Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the individual countries. **Serum and Plasma for Biomarker Sample Repository (BSR) Research (Optional)** Blood samples for extraction of serum and plasma samples (approximately 5 mL per sample) for biomarker discovery, validation, and application will be collected from consenting patients. These samples are collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study every 9 weeks at the time of every tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18.**

SAMPLE COLLECTION Cont'd	The collected BSR samples will be stored with the study Sponsor's facility or a contract laboratory facility for up to 15 years after the end of the associated study (database closure), at which time the samples will be destroyed. These samples will be used only for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and will help to better understand the pathogenesis, course, and outcome of breast cancer and related diseases and adverse events. The collected blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data related to HER2-positive breast cancer disease or response to pertuzumab and/or trastuzumab. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined.
STUDY DURATION	Patients should remain in the treatment phase of the study until investigator-assessed radiographic or clinical progressive disease, unmanageable toxicity, or study termination by Genentech and Roche. Patients will not receive open-label pertuzumab after discontinuation from study treatment. After discontinuation of study treatment, tumor assessments will continue until IRF-assessed progression. In addition, patients will be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and Roche. Tumor assessments will be conducted every 9 weeks from the date of randomization. Delays in treatment administration will not impact the timing of the tumor assessments. If a tumor assessment must be performed early/late, subsequent assessments will be conducted according to the original schedule of every 9 weeks from the date of randomization. Tumor assessments must be conducted until IRF-determined progressive disease (PD), even if treatment has been discontinued due to an investigator-determined PD or unacceptable toxicity. After termination of study treatment, patients will continue be followed for survival until death, loss to follow-up, or study termination by Genentech and Roche.
SAFETY PROCEDURES	There have been reports of CHF with trastuzumab and pertuzumab treatment. Because of this, left ventricular systolic dysfunction is a potential safety concern for patients who receive the treatments outlined in this study. While on study treatment, patients will be monitored for cardiac events with regular assessments of left ventricular function with either Echocardiography or MUGA. (Echocardiography is the preferred method. The same assessment method, ECHO or MUGA, the same institution/facility, and the same assessor should be used throughout the study, to the extent possible.) For patients who experience Grade 1 or 2 left ventricular systolic dysfunction (i.e., asymptomatic decrease in LVEF), an algorithm is provided in Section 7.3.1.1, page 94 of the protocol outlining under which circumstances treatments have to be held and LVEF assessed prior to treatment continuation. Patients who experience **symptomatic left ventricular systolic dysfunction (CHF)** (NCI-CTCAE Grade ≥ 3) will have study treatment discontinued. **Symptomatic left ventricular systolic dysfunction** will be reported in an expedited manner to the Sponsors for timely monitoring.

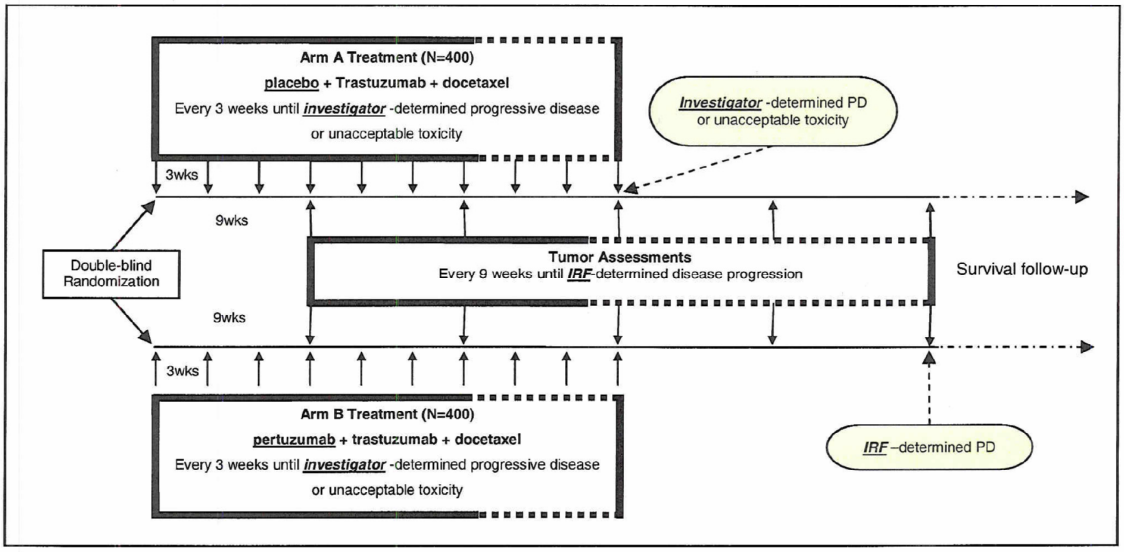
SAFETY PROCEDURES Cont'd	Clinical studies have demonstrated a higher incidence of myelosuppression when trastuzumab is administered with chemotherapy. Limited, non-comparative data from Phase I/II studies suggest that the combination of pertuzumab and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic AEs while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor support will be allowed in this protocol.
SAMPLE SIZE	A sample size of 800 patients is needed to provide 80% power to detect a 33% improvement in OS (HR=0.75) at the two-sided significance level of 5%. Since both PFS and OS analyses are event-driven, and to avoid prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial is designed to enroll sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of the final PFS analysis. Assuming that the median OS in the control arm is 36 months and OS is exponentially distributed, one interim analysis at 50% of total required deaths, and a Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary, approximately 385 deaths will be required. In addition, assuming that the accrual rate is approximately 40 patients per month after a 9-month ramp-up period, 800 patients will need to be enrolled and followed for an additional 29.5 months to obtain 385 deaths. The enrollment period is estimated to be 26.5 months, and 50% of the required deaths will be reached at around 33.5 months. Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it is estimated that 381 IRF-assessed PFS events, corresponding to approximately 448 investigator-assessed events, will have occurred when 50% of the required deaths (193 deaths) is reached. Table 6, page 112 in the protocol lists the power for final PFS analysis at the two-sided significance level of 5% with 381 IRF-assessed PFS events. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.
STATISTICAL METHODS	**Efficacy Analyses** Analyses of PFS, OS, and time to symptom progression will be based on the intent-to-treat (ITT) population, defined as patients who have been randomized. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only responders will be included in the analysis. All efficacy analyses will be based on the treatment arm to which patients were randomized. **Analysis of Primary Variable** The primary endpoint is PFS based on IRF assessments. For patients who discontinue study treatment due to reasons other than death or IRF-assessed progression, every effort will be made to continue tumor assessments until IRF-determined progressive disease or patient death. 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 IRF-evaluable tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day).

STATISTICAL METHODS Cont'd	For patients whose IRF-determined progression event is not available, surrogating death at any time as a progressive event can artificially prolong the PFS time because of a much longer life expectancy in this patient population compared with PFS. Therefore, only deaths within 18 weeks of the last tumor assessments will be included as an event in the primary analysis. However, a sensitivity analysis will be performed including all deaths as an event. The log-rank test, stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia), will be used to compare PFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis. The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazard model, stratified by prior treatment status and region, will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% confidence interval (CI). **The aforementioned analyses will be performed in demographic subgroups as appropriate. For example analysis may be performed in patient subgroups based on racial origin provided there is a reasonable sample size in the subgroups of interest.** **Secondary Variables** **Overall survival.** Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. 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. To minimize the chance of a biased OS estimate resulting from scheduled survival follow-up every 18 weeks, immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.) **PFS based on investigator assessments.** 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 investigator tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day). Analysis methods are the same as those described for the primary endpoint. **Objective response.** Only patients with measurable disease at baseline will be included in the analysis of the objective response. Patients without a post-baseline tumor assessment will be considered to be non-responders. Analysis of objective response will be based on IRF assessments. An estimate of the objective response rate and its 95% CI will be calculated for each treatment arm. The difference in objective response rate will also be provided with 95% CIs. The Mantel-Haenszel χ^2 test stratified by prior treatment status and region will be used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test result will also be provided as a sensitivity analysis.

STATISTICAL METHODS Cont'd	Duration of objective response. Only patients with an objective response will be included in the analysis of duration of objective response. The method for handling censoring is the same as that described for the primary endpoint. Analysis of duration of objective response will be based on IRF assessments. **Median** duration of objective response **for each arm** will be estimated using the Kaplan-Meier approach. **The hazard ratio between the two arms will also be estimated** using Cox regression. **Time to symptom progression.** A decrease of five points in TOI-PFB is considered symptom progression. Data for patients who do not have an observed symptom progression will be censored at the last observed TOI-PFB assessment date. If baseline TOI-PFB assessment is unavailable, or if there is no post-baseline TOI-PFB assessment performed, data will be censored at the time of randomization plus 1 day. Analysis methods are the same as those described for the primary endpoint. **Biomarker analyses.** To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes will be summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers. Markers to be considered include the status of HER receptors, HER ligands, Fc-γ, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis will be put on markers that have shown association with clinical outcome in patients treated with pertuzumab in previous studies: qRT-PCR markers: tumor gene expression profiles associated with HER2 activation Baseline serum markers: levels of ECD/HER2 and HER ligands Efficacy outcomes considered for this analysis will include PFS, objective response rate, and OS. The PFS and objective response will be based on the IRF assessments. The biomarker analyses at the time of protocol development do not take the form of testing fixed hypotheses involving specific cutoffs or other pre-specified prediction rules. It is planned for the Statistical Analysis Plan (to be generated prior to unblinding of this trial) to use all available scientific evidence from independent studies or publications to specify testable prediction rules. In addition, this plan will specify in due detail how data-adaptive prediction rules will be derived (e.g., systematic cutoff search) and how the inherent multiplicity/bias will be corrected in order to prevent biased conclusions. The difference in treatment benefit across biomarker statuses defined by a suitable prediction rule will be evaluated by testing the interaction effect of treatment and the prediction status using Cox regression for PFS and OS, and using logistic regression for response rate. These models involving an interaction term will also be used to estimate the conditional efficacy outcomes, conditional on biomarker prediction status or treatment arm, including and excluding the stratification factors into the model.

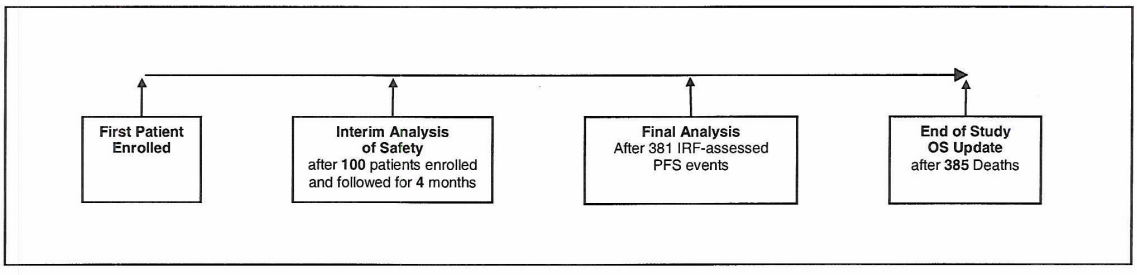
STATISTICAL METHODS Cont'd	Clinical covariates can be of prognostic value and could interact with treatment benefit and with biomarker status. Candidates here are baseline variables of prognostic value describing tumour properties and morbidity status or common lab values. Biomarker prediction will be checked involving relevant clinical covariates, which could be part of the biomarker prediction function, if necessary. **Safety Analyses** The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, cardiac-specific AEs, LVEF measurements, and laboratory test results. Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually receive.

Figure 1 Study Design: Patient Treatment and Assessment



PD=progressive disease; IRF=Independent Review Facility.

Figure 2 Study Design: Analysis Timing



IRF=Independent Review Facility; PFS=progression-free survival

Table 1 Schedule of Assessments

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post -Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Informed consent	x [c]								
Complete Medical History, including Demographics	x [d]								
Review of Inclusion and Exclusion criteria	x								
Complete Physical Examination, and Vital Signs	x								
Symptoms- directed Physical Exam, and Vital Signs			x [e]			x			
12 Lead Electrocardiogram (ECG)	x		**Perform every 9 weeks at the time of the LVEF [f]**			x [f]			
Chest X- ray	x		If clinically indicated			x [g]	If clinically indicated		
ECOG Performance Status	x		x			x	Every 9 weeks at the time of each tumor assessment [h, i]		
Fact-B- Quality of Life (Females Only)		x [u]	Every 9 weeks within 3 days prior to each tumor assessment [i]						
Tumor Assessments	x		Perform every 9 weeks from randomization until IRF- confirmed progressive disease [i]						
LVEF by ECHO or MUGA	x [j]		Perform every 9 weeks from randomization [k]			x	**Every 6 months in the first year, then annually for up to 3 years [k]**		
Bone scan[z]	x		If clinically indicated [i]			x [g]	If clinically indicated until IRF-confirmed progressive disease [i]		
Adverse Events	x [l]		Ongoing [m]				Ongoing [m]		
Concomitant Meds and Cancer –related Surgery /Procedures			Ongoing			**Ongoing**			

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post -Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Pertuzumab / Placebo Administration			x [n]						
Trastuzumab Administration			x [o]						
Docetaxel Administration			x [p]						
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [c]								
Hematology, at local lab		x [q]	x [q]	x [q]		x			
Biochemistry, at local lab		x [q]	x [q]			x			
INR and aPTT **or PTT**, at local lab		x	x [r]						
Pregnancy test, at local lab (If applicable)		x [s]			x [s]	x [s]	**3 and 6 months post Treatment Discon Visit[s]**		
Serum for Trastuzumab PK, to central lab		x [t, u]							
Serum for Antibodies to Pertuzumab, to central lab		x [u]	**Perform every 9 weeks at the time of the TA[v]**			x			
Serum for HER2 ECD& HER Ligands, to central lab		x [u]	Every 9 weeks at the time of each tumor assessment [i]						
Whole Blood for FCγ Polymorphism (clinical genotyping), to central lab		x [u, w]							
Samples requiring separate informed consent									
Metastatic Tumor for Biomarkers, to central lab		x [u]							
Serum & Plasma Biomarker Sample Repository (BSR), to central lab		x [u]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post-treatment) [i, x]						

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post -Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Record Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies								x [y]	
Survival information							x	x [y]	

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Complete medical history and demographics (i.e. age, sex, race and ethnicity**)** and all medications taken the last 90 days prior to randomization will be collected

[e] Symptom-directed physical examination including vital signs and weight will be assessed on Day 1 of every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

[f] 12 lead ECG will be performed at baseline**, then every 9 weeks from the date of randomization during the study treatment at the time of LVEF assessments and then at the Treatment Discontinuation Visit**.

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

[h] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

Table 1 Schedule of Assessments (Cont.)

[i] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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 have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes). Bone scan should be preformed as clinically indicated (In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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). If treatment is discontinued due to Progressive Disease, on sites other than bone, a bone scan should be performed immediately (this would replace the bone scan at the Study Discontinuation visit) and submitted to the Independent Review Facility with all corresponding tumor assessment data (CT/MRI scans, etc).

[j] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.

[k] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization until Treatment Discontinuation Visit, then every 6 months in the first year , then annually for up to 3 years **after the Treatment Discontinuation Visit**. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to 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 values return 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.**

[l] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[m] See Section 7.2, page 88 for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[o] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[p] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.

[q] See Section 5.4.3, page 69 below for specific required tests. 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. An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.

[r] 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.

Table 1 Schedule of Assessments (Cont.)

[s] For women of childbearing potential and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization, pregnancy tests must be performed via serum β-HCG at baseline. A urine pregnancy test should be performed during the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit and every three months thereafter until six months post Treatment Discontinuation Visit . Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[t] Collect and submit only for patients that have received prior trastuzumab.

[u] Collect and submit only if patient is determined to be eligible and will be randomized onto the study. May be collected up to and including study Day 1 prior to the first study drug dose.

[v] Serum samples for antibodies to pertuzumab will be collected at baseline and every 9 weeks from the date of randomization at the time of each tumor assessment during the treatment period and at the Treatment Discontinuation visit.

[w] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18.

[y] Collect post–study treatment cancer-related medical or surgical procedures and therapies and survival information every 18 weeks after the treatment discontinuation visit during the follow-up period until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

[z] In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
AST (SGOT)	Aspartate Aminotransferase
BSR	Biomarker Sample Repository
CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CT	Computed Tomography
DFI	Disease-Free Interval
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECD	Extracellular Domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EEG	Electroencephalogram
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organization for Research and Treatment of Cancer
ESF	Eligibility Screening Form

GLOSSARY OF ABBREVIATIONS

EU	European Union
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence *in situ* Hybridization
GGT	Gamma-Glutamyl Transferase
HER2	Human Epidermal Growth Factor Receptor 2
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	Independent Review Facility
ITT	Intent to Treat
IV	Intravenous
JVP	Jugular Venous Pressure
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-Activated Protein Kinase
MBC	Metastatic Breast Cancer
MDASI	M.D. Anderson Symptom Inventory
MRI	Magnetic Resonance Imaging
MUGA	Multigated Angiogram
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

GLOSSARY OF ABBREVIATIONS

NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PTT	Partial Thromboplastin Time
aPTT	Activated Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
TOI-PFB	Trial Outcome Index-Physician Function Breast
ULN	Upper Limit of Normal

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND

1.1 Background

1.1.1 Breast Cancer

Breast cancer is the most common cancer in women, with a global prevalence of more than 1 million patients and a mortality rate of approximately 400,000 deaths per year (International Agency for Research on Cancer; http://www-dep.iarc.fr; Globocan 2002). While improved early detection and advances in systemic therapy for early stage disease have resulted in a small decline in breast cancer mortality since 1989, metastatic breast cancer (MBC) remains largely incurable with a median survival of approximately 24 months (www.seer.cancer.gov). Factors associated with poor survival include age $\geq$ 50 years, visceral disease, shorter disease-free interval (DFI), aneuploid tumors, tumors with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor receptor 2 (HER2) status (Chang 2003).

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

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

With the growing understanding of the biology of breast cancer, multiple new targets for anti-cancer therapies are being identified. Trastuzumab, which targets the HER2 receptor, is approved for use as monotherapy or in combination with chemotherapy in the metastatic setting, and in combination with chemotherapy as adjuvant treatment for HER2-positive breast cancer. The optimal management of MBC now takes into account not only a patient's general condition, medical history, tumor burden, and receptor status, but also the HER2 status.

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and non-overlapping toxicity, which can be combined with established treatments for breast cancer.

1.1.2 Human Epidermal Growth Factor Receptors (HER)

Evidence suggests that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. The HER tyrosine kinase receptor family is comprised of four receptors: HER1 (EGFR), HER2, HER3, and HER4. These receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers. Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signalling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase (MAPK) pathway for cellular proliferation.

HER2 and HER3 have unique characteristics compared with HER1 and HER4. HER2 has no known ligand and, in a state of overexpression, can form active homodimers and initiate tyrosine kinase signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors is also increased, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using micro-array technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate tyrosine kinase signaling through several mechanisms (Jones et al. 2006).

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

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

HER2 has emerged as an important prognostic and potential predictive factor in breast cancer. Approximately 25% of patients overexpress HER2 (also known as c-*erb*B2 or *neu*). In the laboratory, HER2 overexpression results in oncogenic transformation and more aggressive tumor behavior. Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER), absence of *bcl2*, and absence of lobular architecture. Despite associations with other known negative prognostic factors, HER2 overexpression has

been independently associated with poorer disease-free survival (DFS) and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000).

1.1.3 Trastuzumab (rhuMAb HER2, Herceptin®)

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

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

A randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first-line treatment for HER2-positive MBC (Marty et al. 2005). A total of 186 patients received at least one dose of protocol therapy. The addition of trastuzumab to 100 mg/m^2 docetaxel for at least six cycles resulted in superior clinical efficacy with improved overall response rates (61% vs. 34%; P = 0.0002), overall survival (median, 31.2 vs. 22.7 months; P = 0.0325), time to progressive disease (median, 11.7 vs. 6.1 months; P = 0.0001), time to treatment failure (median, 9.8 vs. 5.3 months; P = 0.0001), and duration of response (median, 11.7 vs. 5.7 months; P = 0.009). There was little difference in the number and severity of adverse events between the arms. Grade 3 to 4 neutropenia was seen more commonly with the combination (32%) than with docetaxel alone (22%), and there was a slightly higher incidence of febrile neutropenia in the combination arm (23% vs. 17%). More patients in the combination arm had left ventricular ejection fraction (LVEF) decreases ≥ 15% compared with the docetaxel alone arm (17% vs. 8%), and 1 patient (1%) in the combination arm experienced symptomatic heart failure. An additional patient who was assigned to the trastuzumab + docetaxel treatment arm experienced congestive heart failure (CHF) after discontinuation of study treatment and during treatment with an investigational anthracycline. The CHF event in this second patient was attributed by the investigator as related to the investigational anthracycline (Marty et al. 2005).

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

1.1.4 Trastuzumab Pharmacokinetics

Analyses in clinical studies showed that trastuzumab has dose-dependent, non-linear pharmacokinetics, with faster clearance and shorter half-life at doses of < 100 mg. The volume of distribution approximates the serum volume. Early studies of the recommended dose indicated that the half-life was approximately 6-10 days. However, based on recent data from pharmacokinetic re-analysis, the half-life is approximately 28.5 days (95% confidence interval, 25.5-32.8 days). The washout period is up to 24 weeks (95% confidence interval, 18-24 weeks). Steady state pharmacokinetics should be reached by approximately 20 weeks (95% confidence interval, 18-24 weeks). The estimated mean AUC was 578 mg/day/L and the estimated peak and trough concentrations were 110 mg/L and 66 mg/L, respectively.

Overall, the pharmacokinetic (PK) profile probably reflects a composite of 1) interaction with tumor cell-bound HER2; 2) complexing with shed HER2 antigen extracellular domain (ECD); and 3) non-specific elimination similar to that observed with endogenous IgG. Serum concentrations are decreased in the presence of shed antigen and this is probably related to a faster clearance of the antibody-antigen complex than of free trastuzumab. Importantly, however, baseline shed antigen concentrations in the clinical studies did not show any correlation with clinical efficacy.

The approved dose of trastuzumab is a 4-mg/kg initial dose followed by a 2-mg/kg dose given every 7 days. This dosing regimen was based upon clinical efficacy in a randomized Phase III study (Slamon et al. 2001). Since the initial approval, the half-life of trastuzumab has been determined to be approximately 28.5 days, which supports a dosing of every 3 weeks vs. weekly. PK data are available from two studies evaluating the safety, tolerability, and pharmacokinetics of trastuzumab administered every 3 weeks to women with HER2-positive (IHC 3+ or FISH+) metastatic breast cancer (Baselga et al. 2005; Leyland-Jones et al. 2003).

All patients in these two studies received trastuzumab every 3 weeks by IV infusion. The initial infusion was given over 90 minutes at a dose of 8 mg/kg. All subsequent infusions were given over 90 minutes at a dose of 6 mg/kg. Data from Baselga et al. (2005) indicate that serum concentrations of trastuzumab increased, and steady state concentrations (in the range 50-60 ng/mL) were achieved after approximately eight to ten doses. Serum trough levels appeared to be comparable over the study period, although trough concentrations were slightly lower with the every-3-week regimen compared with previous studies of the weekly regimen.

In one study (Leyland-Jones et al. 2003), the cumulative dose during an every-3-week regimen arm interval was identical between the every-3-week regimen arm and the weekly regimen arm. As expected, data show that mean trough trastuzumab concentrations were approximately 20% lower at the end of each cycle than those concentration levels at the same time point using weekly dosing. However, the average exposure at any time during the treatment is comparable between the two regimens.

1.1.5 Pertuzumab (rhuMAb 2C4)

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

Like trastuzumab, pertuzumab is produced in Chinese hamster ovary (CHO) cell cultures and purified by protein-A column affinity chromatography, followed by ion-exchange column chromatography. Because of the high degree of homology between pertuzumab and trastuzumab, procedures similar to those developed for trastuzumab are used for the manufacturing process, the in-process controls, and the characterization of pertuzumab. No bovine-derived raw materials are used in the manufacture of pertuzumab.

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

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

Both pertuzumab and trastuzumab target the HER2 receptor but bind at distinct epitopes on the receptor. Consequently, ligand-activated downstream signaling is blocked by pertuzumab but not by trastuzumab. Pertuzumab, therefore, may not require HER2 overexpression to exert its activity as an anti-tumor agent. In addition, there is a potential role for the combination of pertuzumab and trastuzumab in HER2-overexpressing diseases, due to their complementary modes of action.

1.1.5.1 Summary of Non-Clinical Studies

In Vitro Studies

In vitro studies show that pertuzumab blocks ligand-activated HER2 signaling, whereas trastuzumab does not. In the breast carcinoma cell line MCF-7, pertuzumab, but not trastuzumab, blocked heregulin-induced activation of the PI3-kinase cell survival pathway, as indicated by a lack of activation of a key enzyme (Akt) in this pathway (Agus et al. 2002). The ability of pertuzumab to inhibit ligand activation of HER2 has also been demonstrated in transfected cell lines of fibroblast origin and with purified soluble receptors (Sliwkowski et al. 1994; Fitzpatrick et al. 1998).

Furthermore, pertuzumab blocks heregulin-dependent *in vitro* growth of a number of breast cancer cell lines as well as cell lines derived from other solid tumors (Lewis et al. 1996; Schaefer et al. 1997; Mann et al. 2001). For example, in the heregulin-secreting MDA-MB-175VII breast carcinoma cell line, which expresses low to moderate levels of HER2 protein (1+ by immunohistochemistry), cell proliferation was inhibited in a dose-dependent fashion by both pertuzumab and trastuzumab, but the magnitude of the inhibition was far greater with pertuzumab (Schaefer et al. 1997). The calculated pertuzumab concentration at which half-maximal growth inhibition (IC_{50}) occurred was 120 ng/mL or 0.8 nM, and is consistent with biochemical measurements of pertuzumab inhibition of heregulin binding or receptor activation (Agus et al. 2002; Fitzpatrick et al. 1998; Lewis et al. 1996). The combination of trastuzumab and pertuzumab was shown to have a synergistic growth-inhibiting effect on BT474 breast tumor cells, which express high levels of HER2, underscoring the complementary mechanism of action of the two drugs (Nahta et al. 2004).

In Vivo Studies

The effects of pertuzumab on cell lines derived from a number of human solid tumors have been investigated in murine xenograft models. Pertuzumab was tested for its antitumor activity either as a single agent or in combination with various cytotoxic or biologic therapies.

Single-Agent Studies: Pertuzumab shows activity in xenograft models of lung adenocarcinoma, breast carcinomas, and both androgen-dependent and androgen-independent prostate (Agus et al. 2000; Fiebig 2003a; Fiebig 2003b; Fiebig 2003c). For example, growth inhibition ranging between 50% and 70% compared with control was observed with pertuzumab in six out of 18 non-small cell lung cancer (NSCLC) xenografts (Fiebig 2003b). Similar studies using six different human mammary tumor explants revealed one clear responder with more than 90% growth inhibition (Fiebig 2003a) while one out of four ovarian tumor explants was inhibited by more than 70% (Fiebig 2003c). A dose of 6 mg/kg pertuzumab administered once per week produced maximal growth inhibition of human tumor xenografts in mice, which could not be augmented by higher doses (Friess et al. 2002).

Combination Therapy Studies: Pertuzumab can augment the therapeutic effect of cytotoxic agents regardless of their mode of action, as shown in various human lung, breast, and ovarian tumor xenograft models in immunodeficient mice. This was shown with the tubulin inhibitor paclitaxel, the topoisomerase inhibitor irinotecan, the alkylating agent cisplatin, and the antimetabolite drugs gemcitabine and capecitabine, respectively (Friess 2002a; Friess 2002b; Friess 2003; Hasmann et al. 2003; Hasmann and Dettmar 2004; Metz 2004). The augmentation by pertuzumab of the chemotherapeutic effects of various agents with differing modes of action is possibly explained by the deprivation of PI3-kinase-mediated cellular survival signals after inhibition of HER2 activation.

Pertuzumab enhances the antitumor activity of other HER pathway inhibitors. For example, pertuzumab augmented the activity of the EGFR kinase inhibitor erlotinib (Tarceva®) in human lung cancer xenograft models (Friess et al. 2003; Friess 2003; Friess et al. 2005). The combination of pertuzumab and trastuzumab synergistically inhibits the growth of xenografts derived from HER2-overexpressing NSCLC Calu-3 cells (Friess 2005) and from KPL-4 breast cancer cells (Friess et al. 2006). The synergistic action of pertuzumab and trastuzumab may be explained by their complementary modes of action: while pertuzumab prevents the ligand-activated formation of HER2 heterodimers and homodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Furthermore, as the two antibodies are not competing for the same binding epitope on HER2, their combination may lead to a higher antibody load, resulting in increased tumor-cell killing via antibody-dependent cell-mediated cytotoxicity (ADCC).

In conclusion, these results justify further clinical evaluation of pertuzumab in combination with chemotherapy drugs such as paclitaxel, gemcitabine, and capecitabine, and other HER pathway inhibitors with complementary mechanisms of action.

1.1.5.2 Summary of Clinical Studies

Pertuzumab has been studied in several Phase I or II clinical trials in solid tumors, including breast, prostate, ovarian, and lung cancer. Unlike trastuzumab, pertuzumab in all studies except one was administered as fixed doses of 840 mg IV as the initial dose followed by 420 mg IV every 3 weeks, or as fixed doses of 1050 mg IV every 3 weeks. This dose was established through population-based PK modeling and analysis in female patients (Ng et al. 2006). Pertuzumab was given until evidence of progressive disease or toxicity.

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

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

Modest clinical activity has been observed in patients with HER2-negative tumors who have received pertuzumab either as a single agent or in combination with cytotoxic chemotherapy. Partial responses (PRs) have been observed in < 5% of patients with ovarian cancer and HER2-negative breast cancer. No objective tumor responses were observed in patients with hormone-resistant prostate cancer or in patients with advanced non-small cell lung cancer. Stable disease (SD) of at least 6 months has been observed in approximately 5-7% of patients.

Pertuzumab has been evaluated in Phase II studies in combination with trastuzumab in patients with HER2-positive MBC who have previously received trastuzumab for metastatic disease. One study, conducted by the National Cancer Institute (NCI), enrolled 11 patients with previously treated HER2-positive MBC. Two out of the 11 patients exhibited a PR (Portera et al. 2007). In the second study, BO17929, 66 enrolled patients that had previously been treated with trastuzumab for HER2-positive MBC received the combination of pertuzumab and trastuzumab every 3 weeks until disease progression. Of the 66 patients enrolled, 42 were included in the most recent preliminary analysis of the data. One patient is reported to have a complete response (CR), 5 patients had PRs, and 17 patients had SD of at least two cycles in duration in this preliminary analysis (Baselga et al. 2007).

The overall safety data suggest that the combination of pertuzumab and trastuzumab is well tolerated. The preliminary Phase II study data suggest that the incidence of clinical cardiac toxicity is similar to that reported for trastuzumab-based treatments. One patient who received the combination in the NCI trial (n=11) experienced Grade III CHF (Portera et al. 2007). Asymptomatic decreases in LVEF have also been observed in 4 other patients; 3 patients' LVEF were back to normal within 3 months after discontinuation of pertuzumab and trastuzumab. It should be noted that 2 of these patients reported by Portera et al. had experienced LVEF decline during a previous trastuzumab treatment. The most common adverse events observed when pertuzumab is given with trastuzumab include diarrhea, nail changes, allergic reactions, anemia, and thrombocytopenia. The majority of adverse events reported in these trials are of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Grade 1-2 in severity. One patient had a Grade 3 allergic reaction. In study BO17929, of the 42 patients treated with pertuzumab and trastuzumab, 1 patient has experienced an LVEF decrease of greater than 10 percentage points from baseline to an absolute value less than 50%. This patient remained asymptomatic and discontinued treatment after Cycle 3 due to disease progression (Baselga et al. 2007).

Currently there are insufficient data available to determine cardiac toxicity risk-factors for the combination of pertuzumab and trastuzumab. Because current preliminary data suggest that the incidence of clinical cardiac toxicity in patients receiving combination pertuzumab/trastuzumab-based treatments is similar to that reported for trastuzumab-based treatments, this study will include regular cardiac LVEF monitoring of all patients, and will implement the treatment delay/stopping algorithm for LVEF decline as is the standard for patients receiving trastuzumab-based regimens (see Section 7.3.1.1.

1.1.6 Docetaxel

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

1.1.6.1 Docetaxel Pharmacokinetics

The pharmacokinetics of docetaxel has been evaluated in cancer patients in a variety of studies and in a population PK analysis. For details, please refer to the currently approved prescribing information.

1.1.6.2 Combination Studies with Anti-HER2 Monoclonal Antibodies

Both trastuzumab and pertuzumab have been administered with docetaxel in doses ranging between 60 mg/m^2 and 100 mg/m^2. Currently, no single chemotherapy regimen is considered to be the global standard of care for women with HER2-positive MBC that has progressed following trastuzumab administered in the adjuvant setting.

See Section 1.1.3 for a summary of a randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first-line treatment for HER2-positive MBC.

Patients with a range of tumor types received pertuzumab with docetaxel every 3 weeks until progressive disease or unacceptable toxicity (Study BO17021). No tumor responses were observed in this study of 19 patients. The maximum tolerated dose of docetaxel when given with pertuzumab was determined to be 75 mg/m^2. Dose-limiting toxicities (DLTs) were observed, including one case of Grade 4 febrile neutropenia and one case of Grade 3 fatigue.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare PFS based on tumor assessments by an independent review facility (IRF) between patients in the two treatment arms.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To compare overall survival (OS) between the two treatment arms
- To compare PFS between the two treatment arms based upon investigator assessment of progression
- To compare the overall objective response rate between the two treatment arms
- To compare the duration of objective response between the two treatment arms
- To compare the safety profile between the two treatment arms
- To compare time to symptom progression, as assessed by the FACT Trial Outcome Index - Physical Functional Breast (TOI-PFB)
- To evaluate if biomarkers from tumor tissues or blood samples (e.g., HER3 expression, Fcγ, and serum ECD/HER2 and/or HER ligands concentrations) correlate with clinical outcomes

3. STUDY DESIGN

3.1 Overview of Study Design

This study is a Phase III, randomized, double-blind, placebo-controlled, multicenter international clinical trial. 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 study. Patients could have received one prior hormonal treatment for MBC. Patients may have received systemic breast cancer treatment in the neo-adjuvant or adjuvant setting, provided that the patient has experienced a DFI of ≥ 12 months from completion of adjuvant systemic treatment (excluding hormonal therapy) to metastatic diagnosis. Patients may have received trastuzumab and/or a taxane during the neo-adjuvant or adjuvant treatment. HER2-positive status using archival paraffin-embedded tumor tissue will be confirmed in a central laboratory by IHC and/or FISH.

A total of 800 patients will be randomized in a 1:1 ratio to one of two treatment arms:

Arm A:

- **Pertuzumab placebo:** every 3 weeks until progressive disease or unacceptable toxicity
- **Trastuzumab:** 8 mg/kg IV loading dose, followed by 6 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity

- **Docetaxel:** 75 mg/m^2 IV every 3 weeks**.** On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. (At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3]).

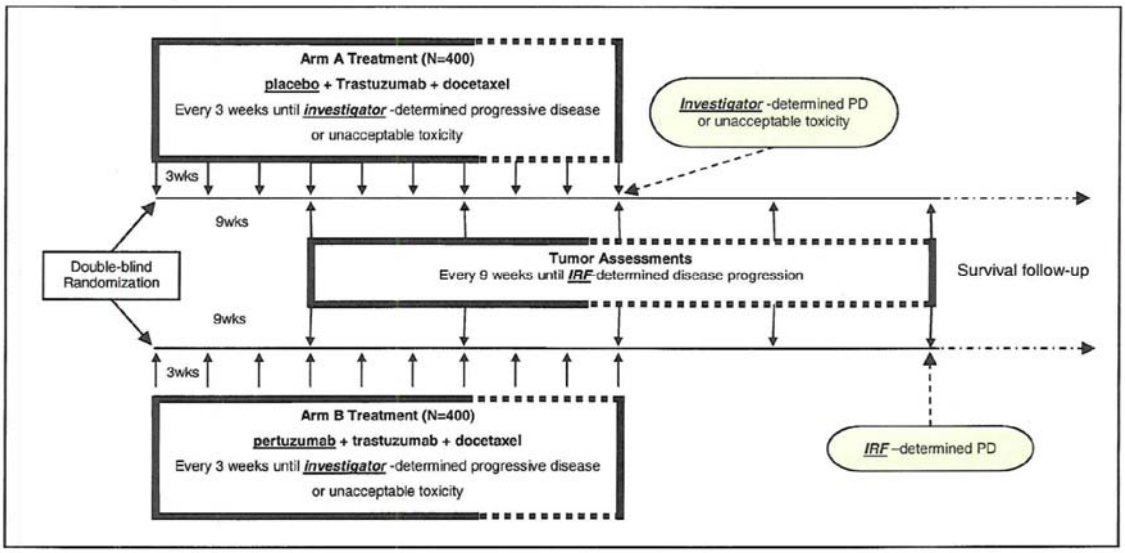
Arm B:

- **Pertuzumab:** 840 mg IV loading dose, followed by 420 mg IV every 3 weeks until progressive disease or unacceptable toxicity
- **Trastuzumab:** 8 mg/kg IV loading dose, followed by 6 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity
- **Docetaxel:** 75 mg/m^2 IV every 3 weeks. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. (At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3]).

Patients should remain in the treatment phase of the study until investigator-assessed radiographic or clinical progressive disease, unmanageable toxicity, or study termination by Genentech and Roche. Patients will not receive open-label pertuzumab after discontinuation from study treatment. After discontinuation of study treatment, tumor assessments will continue until IRF-assessed progression. In addition, patients will be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and Roche.

Tumor assessments will be conducted every 9 weeks from the date of randomization. Delays in treatment administration will not impact the timing of the tumor assessments. If a tumor assessment must be performed early/late, subsequent assessments will be conducted according to the original schedule of every 9 weeks from the date of randomization. Tumor assessments must be conducted until IRF-determined progressive disease (PD), even if treatment has been discontinued due to an investigator-determined PD or unacceptable toxicity (see Figure 1).

Figure 1 Study Design: Patient Treatment and Assessment



PD=progressive disease; IRF=Independent Review Facility.

A Data Monitoring Committee (DMC) will monitor patient safety. In addition to the DMC, an independent Cardiac Review Committee (CRC) will review cardiac data generated during the course of the study and report their findings to the DMC for review every 6 months beginning 9 months after the first patient is enrolled and at the safety interim analysis.

An Independent Review Facility (IRF) will evaluate progressive disease and overall tumor response through a periodic review of all radiographic (e.g., MRI, CT, bone scans, chest x-ray, etc.), as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and photographic data, if available, generated from all patients.

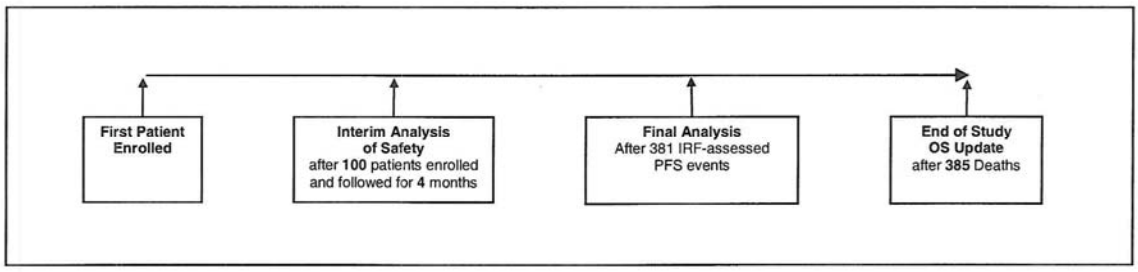
No interim analysis of efficacy is planned for this study. One safety-only interim analysis will occur after 100 patients have been enrolled and followed for at least 4 months. If the DMC does not recommend stopping the trial due to safety concerns at the interim analysis, the final primary efficacy analysis will take place when approximately 381 IRF-assessed PFS events (corresponding to approximately 448 investigator-assessed events) have occurred. The primary efficacy analysis will be based on tumor assessments by the IRF.

At the time of the final PFS analysis, it is expected that 193 patients will have died. An analysis of Overall Survival (OS) will be conducted at the same time as the primary efficacy analysis of PFS. Patients who are still on study will continue to be followed for safety and survival (see Figure 2).

3.1.1 End of Study

The trial will end when approximately 385 deaths have been reported or the trial is terminated by the Sponsors. An OS update will be provided at the end of the study (see Figure 2).

Figure 2 Study Design: Analysis Timing



IRF=Independent Review Facility; PFS=progression-free survival.

3.2 Number of Patients/Assignment to Treatment Groups

A total of approximately 800 patients (approximately 400 per arm) will be enrolled. It is estimated that the accrual will be approximately 40 patients per month after a 9-month ramp-up period over an approximate 26.5-month timeframe. An Interactive Voice Response System (IVRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.

A complete block randomization scheme will be applied to achieve balance in treatment assignment within each of the eight strata, as defined by prior treatment status (de novo vs. prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia). Unblinding of treatment assignment will not be permitted during the study except for safety issues that may arise during study treatment. An approval from the Sponsor‘s medical monitor(s) must be obtained prior to any unblinding of treatment code.

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.

3.3 Centers

A total of approximately 800 patients will be enrolled from approximately 250 sites worldwide.

4. STUDY POPULATION

4.1 Overview

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

4.2 Inclusion Criteria

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

Disease-Specific Inclusion Criteria:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. Patients with measurable and/or non-measurable disease are eligible.

   Patients with *only* bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for central HER 2 testing and subsequent biomarkers analysis.

   Locally recurrent disease must not be amenable to resection with curative intent. Note: Patients with de-novo Stage IV disease are eligible.

2. HER2-positive (**defined as 3+ IHC or FISH amplification ratio ≥ 2.0**) MBC 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 if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.)

General Inclusion Criteria:

3. Age ≥ 18 years

4. Left Ventricular Ejection Fraction (LVEF) ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (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 7.4.2). **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.**

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1

6. For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly-effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy. For further details see Section 7.2.6

7. Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure

4.3 Exclusion Criteria

Cancer-Related Exclusion Criteria:

1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC which must be stopped prior to randomization).

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

   One prior hormonal "regimen" for MBC may include more than one hormonal therapy, for example, if the switch is not related to disease progression, such as toxicity or local standard practice, this will be counted as one "regimen".

   If a patient receives hormonal therapy for MBC and is switched to a different hormonal therapy due to disease progression, this will be counted as two "regimens" and the patient is not eligible.

2. History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting.

3. History of systemic breast cancer treatment in the neo-adjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months

4. History of persistent Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy

5. Current peripheral neuropathy of NCI-CTCAE, Version 3.0, Grade ≥ 3 at randomization

6. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that has been previously treated with curative intent.

7. Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.

8. 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 (e.g., liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin)
   - If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

Hematological, Biochemical, and Organ Function:

9. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina
10. History of CHF of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia)
11. History of myocardial infarction within 6 months of randomization
12. History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy
13. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy

General Exclusion Criteria:

14. Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization:
    - Absolute neutrophil count < 1,500 cells/mm^3
    - Platelet count < 100,000 cells/mm^3
    - Hemoglobin < 9 g/dL
    - Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)
    - AST (SGOT) or ALT (SGPT) > 2.5 × ULN
    - AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. Serum alkaline phosphatase may be > 2.5 × ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) < 1.5 × ULN.
    - Serum creatinine > 2.0 mg/dL or 177 μmol/L
    - International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 × ULN (unless on therapeutic coagulation)
15. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures)
16. Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment
17. Pregnant or lactating women

18. History of receiving any investigational treatment within 28 days of randomization
19. Current known infection with HIV, HBV, or HCV
20. Receipt of IV antibiotics for infection within 14 days of randomization
21. Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids)
22. Known hypersensitivity to any of the study drugs
23. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol
24. Concurrent Interventional or Non-Interventional Studies (NIS) are not permitted.

4.4 Concomitant Medication and Treatment

Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, etc., according to standard of care when necessary.

All protocol-allowed medications taken by the patient for concomitant disease should continue as necessary during the study and be recorded on the electronic case report form (eCRF). The following list of allowed medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard of care practice.

The following treatments/procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions associated with pertuzumab and/or trastuzumab
- Medication to treat diarrhea (e.g., loperamide)
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for docetaxel and ASCO clinical guidelines (Smith et al. 2006).
- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site
- Inhaled steroids for asthma
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion
- Palliative surgical procedures. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings.

- As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start.
- The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.
- Anti-coagulation therapy for maintenance of patency of permanent indwelling IV catheters is permitted.
- Palliative radiotherapy. Radiotherapy is only allowed during the study treatment period for the indication of bone lesions present at baseline. If a patient requires radiation therapy to a new lesion, that new lesion would, per Response Evaluation Criteria in Solid Tumors (RECIST), qualify as progressive disease.
- Acceptable methods of contraception must be used when the female patient or female/male partner is not surgically sterilized or does not meet the study definition of post-menopausal (≥ 12 months of amenorrhea). For further details see Section 7.2.6.

The following treatments are not permitted:

- Treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy
- Any oral, injected or implanted hormonal methods of contraception.
- Concurrent investigational agents of any type
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

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

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

4.5 Criteria for Premature Withdrawal

Patients may withdraw from the study at any time for any reason. Investigators may withdraw patients from the study and/or from study treatment in the event of intercurrent illness, adverse events, protocol violation, administrative reasons, or for other reasons. Patients who prematurely withdraw from study treatment will continue being followed for post-treatment assessments unless patients withdraw from the study. Excessive patient withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

If a patient decides to withdraw, all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

In case a patient decides to prematurely discontinue study treatment ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.6 Replacement Policy

4.6.1 For Patients

Patients randomized into the study will not be replaced.

4.6.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 1 Schedule of Assessments

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post - Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Informed consent	x [c]								
Complete Medical History, including Demographics	x [d]								
Review of Inclusion and Exclusion criteria	x								
Complete Physical Examination, and Vital Signs	x								
Symptoms- directed Physical Exam, and Vital Signs			x [e]			x			
12 Lead Electrocardiogram (ECG)	x		**Perform every 9 weeks at the time of the LVEF [f]**			x [f]			
Chest X- ray	x		If clinically indicated			x [g]	If clinically indicated		
ECOG Performance Status	x		x			x	Every 9 weeks at the time of each tumor assessment [h, i]		
Fact-B- Quality of Life (Females Only)		x [u]	Every 9 weeks within 3 days prior to each tumor assessment [i]						
Tumor Assessments	x		Perform every 9 weeks from randomization until IRF- confirmed progressive disease [i]						
LVEF by ECHO or MUGA	x [j]		Perform every 9 weeks from randomization [k]			x	**Every 6 months in the first year, then annually for up to 3 years [k]**		
Bone scan[z]	x		If clinically indicated [i]			x [g]	If clinically indicated until IRF-confirmed progressive disease [i]		
Adverse Events	x [l]		Ongoing [m]				Ongoing [m]		
Concomitant Meds and Cancer -related Surgery/Procedures			Ongoing			**Ongoing**			

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post - Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Pertuzumab/Placebo Administration			x [n]						
Trastuzumab Administration			x [o]						
Docetaxel Administration			x [p]						
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [c]								
Hematology, at local lab		x [q]	x [q]	x [q]		x			
Biochemistry, at local lab		x [q]	x [q]			x			
INR and aPTT **or PTT**, at local lab		x	x [r]						
Pregnancy test, at local lab (If applicable)		x [s]			x [s]	x [s]	**3 and 6 months post Treatment Discon Visit[s]**		
Serum for Trastuzumab PK, to central lab		x [t, u]							
Serum for Antibodies to Pertuzumab, to central lab		x [u]	**Perform every 9 weeks at the time of the TA[v]**			x			
Serum for HER2 ECD& HER Ligands, to central lab		x [u]	Every 9 weeks at the time of each tumor assessment [i]						
Whole Blood for FCγ Polymorphism (clinical genotyping), to central lab		x [u, w]							
Samples requiring separate informed consent									
Metastatic Tumor for Biomarkers, to central lab		x [u]							
Serum & Plasma Biomarker Sample Repository (BSR), to central lab		x [u]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post-treatment) [i, x]						

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post - Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Record Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies								x [y]	
Survival information							x	x [y]	

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

[b] Treatment discontinuation visit should occur 4-6 weeks (28-42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Complete medical history and demographics (i.e. age, sex, race and ethnicity**)** and all medications taken the last 90 days prior to randomization will be collected

[e] Symptom-directed physical examination including vital signs and weight will be assessed on Day 1 of every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

[f] 12 lead ECG will be performed at baseline**, then every 9 weeks from the date of randomization during the study treatment at the time of LVEF assessments and then at the Treatment Discontinuation Visit**.

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

[h] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[i] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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 have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes). Bone scan should be preformed as clinically indicated (In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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). If treatment is discontinued due to Progressive Disease, on sites other than bone, a bone scan should be performed immediately (this would replace the bone scan at the Study Discontinuation visit) and submitted to the Independent Review Facility with all corresponding tumor assessment data (CT/MRI scans, etc).

[j] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.

Table 1 Schedule of Assessments (Cont.)

[k] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization until Treatment Discontinuation Visit, then every 6 months in the first year , then annually for up to 3 years **after the Treatment Discontinuation Visit**. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to 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 values return 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.**

[l] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[m] See Section 7.2 for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[o] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[p] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.

[q] See Section 5.4.3 below for specific required tests. 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. An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.

[r] 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.

[s] For women of childbearing potential and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization, pregnancy tests must be performed via serum β-HCG at baseline. A urine pregnancy test should be performed during the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit and every three months thereafter until six months post Treatment Discontinuation Visit . Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[t] Collect and submit only for patients that have received prior trastuzumab.

[u] Collect and submit only if patient is determined to be eligible and will be randomized onto the study. May be collected up to and including study Day 1 prior to the first study drug dose.

[v] Serum samples for antibodies to pertuzumab will be collected at baseline and every 9 weeks from the date of randomization at the time of each tumor assessment during the treatment period and at the Treatment Discontinuation visit.

[w] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18.

[y] Collect post-study treatment cancer-related medical or surgical procedures and therapies and survival information every 18 weeks after the treatment discontinuation visit during the follow-up period until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

[z] In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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

5.1 Screening Examination and Eligibility Screening Form

All patients must provide written Informed Consent (IC) before any study-specific assessments or procedures are performed.

An Eligibility Screening Form (ESF) documenting the patient's fulfillment of the entry criteria is to be completed by the investigator/designee for all patients considered for the study and subsequently included or excluded. Patients who are considered for study entry but fail to meet the eligibility requirements should also have an ESF completed with the reason for lack of eligibility given, since this provides information on the selected trial population. This screening information will be collected via the IVRS and will not be entered into the clinical trial database. All ESFs should be kept in the study files at the sites. Additionally, copies of records of all prior trastuzumab dosing and ECHO/MUGA reports should be retained with the study files at the investigative sites, for randomized and screen-failure patients.

5.2 Procedures for Enrollment of Eligible Patients

Patients will be randomly assigned to one of the two treatment groups. The patient identification numbers are to be allocated sequentially in the order in which the patients are enrolled using the IVRS.

The investigator or designee will then be able to enter the patients' data into the eCRF, which will be used for electronic data capture (EDC). A Patient Enrollment and Identification Code List must be maintained by the investigator.

The treatment randomization list will be generated by the Sponsor and incorporated into IVRS. The password-protected and/or encrypted electronic drug kit number randomization list will be kept in a central repository by the Sponsor's unblinding statistician. An open key to the code will not be available at the study site, to the Sponsor's monitors, project statisticians, or the project team at either Genentech or Roche (see Unblinding, Section 6.8).

5.3 Procedures for Screening and Baseline

- Tumor tissue for HER2 status and biomarker analyses. After signing an informed consent and before randomization into the study, patients must have HER2 positive breast cancer defined as 3+ by IHC or FISH amplification ratio ≥ 2.0 as determined by a designated central laboratory. Results obtained from the central laboratory will be recorded in the eCRF (e.g., IHC 0, 1+, 2+ or 3+; FISH Positive or Negative). The actual FISH amplification ratio will be obtained by the Sponsor directly from the designated central laboratory. The diagnosis may be made on the primary breast cancer specimen, or on a biopsy of a metastatic site if primary tumor is not available. It is highly recommended that FFPE tumor blocks are sent to the central laboratory; however, if this is not possible, 25 unstained and freshly cut slides per tumor specimen will be submitted. Blocks will be returned to the originating institution; slides sent to the central laboratory will not be returned (see Section 5.4.7.1).

The following screening tests and procedures must be completed between Day -28 days and Day -1 (except where indicated). Day -1 is defined as the day before the initiation of study treatment (i.e., there is no Day 0). The timing of all procedures is summarized in Table 1. (Specific data points to be collected will be detailed in the eCRF.)

- Complete medical history and demographics **(i.e., age, sex, race and ethnicity)** including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or therapy.

- Review of inclusion and exclusion criteria

- Complete physical exam, including vital signs (blood pressure, pulse rate, and body temperature) and physical measurements (body weight and height). In the physical examination, particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated Jugular Venous Pressure (JVP), sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG

- Chest X-ray

- ECOG performance status (see Appendix 2)

- Functional Assessment of Cancer Therapy-Breast Symptom Index (FACT-B) questionnaire must be administered to female patients within 7 days prior to initiation of study treatment or on study Day 1 provided that the FACT-B is taken prior to the first study drug dose. The FACT-B should be collected and submitted only if the patient is determined to be eligible and will be randomized onto the study. (see Section 5.5).

- Tumor assessment should be performed as specified in Section 5.4.4. **All patients should have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study** (except as specified for bone scans in the absence of radioactive isotopes)**.** To ensure comparability, the techniques used for tumor assessment at screening/baseline should be consistent with those used subsequently in the study, e.g., MRI, CT, bone scans, etc., as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available. A CT or MRI brain scan is to be performed at screening only in patients with signs or symptoms suggesting CNS involvement or other unexplained neurological symptoms, and during the study, if clinically indicated. **The central independent review will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessment. All patients must have their LVEF assessed by 2D echocardiography (ECHO) or multigated-angiography (MUGA) as part of the screening procedure. The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. ECHO is the preferred method because it can detect wall-motion abnormalities. LVEF is to be calculated using the modified Simpson method, and must be ≥ 50% at baseline as determined by the local facility before a patient can be enrolled in the study. The investigator must decide which method of LVEF assessment (ECHO or MUGA scan) will be used for each patient at baseline, and the same method and the same institution/facility should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with the LVEF result. **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.**

- Bone scan (In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)

- Adverse events. Only serious adverse events (SAEs) related to study-specific procedures are to be collected during the screening/baseline period.

- Hematology, blood chemistry, INR, and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) should be performed at a local laboratory **within 7 days** prior to the first administration of study medication (see Section 5.4.3 for specific tests required). Because the toxicity of docetaxel is influenced by liver function (see Section 7.3.2.5), no protocol exceptions/waivers will be granted for out-of-range liver function tests, as described in the inclusion criteria.

- Pregnancy Test. A serum β-HCG test **must** be performed for all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization. Testing should be performed at a local laboratory **within 7 days** prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.4.3).

- Serum sample for trastuzumab pharmacokinetics should be collected **within 7 days** prior to the first administration of study medication (or on study Day 1 provided that the sample is taken prior to the first study drug dose), *only if the patient has received prior trastuzumab therapy* and is eligible for and will be enrolled into the study. The samples will be submitted to the central laboratory.

- Serum sample for testing for antibodies to pertuzumab should be collected **within 7 days** prior to the first administration of study medication (or on study Day 1, provided that the sample is taken prior to the first study drug dose), only if the patient is eligible for, and will be enrolled into, the study.

- Serum sample for HER2 family ECD and HER ligands should be collected **within 7 days** prior to the first administration of study medication (or on study Day 1 provided that the sample is taken prior to the first study drug dose), only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.3).

- Whole blood sample for Fcγ polymorphism should be collected **within 7 days** prior to the first administration of study medication (or on study Day 1 provided that the sample is taken prior to the first study drug dose), only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.4). Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the involved countries.

- Samples requiring supplemental informed consent

  If the patient has signed the appropriate supplemental informed consent(s), the following samples are required to be collected and submitted. Patients will be permitted to separately consent for each item individually. All samples will be collected **within 7 days** prior to the first administration of study medication (or on study Day 1 provided that the sample is taken prior to the first study drug dose). All samples should be collected only after the patient has been determined to be eligible for, and will enroll into the study, but prior to the first study drug dose:

  – Metastatic tumor tissue for biomarkers for pertuzumab/trastuzumab response (see Section 5.4.7.2)

  – Serum and plasma samples for Biomarker Sample Repository (BSR) research (see Section 5.4.7.5)

5.4 On-Study Clinical Assessments and Procedures

The following assessments and procedures will be completed for randomized patients according to the Schedule of Assessments (see Table 1). (Specific data points to be collected will be detailed in the e CRF.)

5.4.1 Treatment Period Assessments and Procedures

During the treatment period, a window of ± 3 days will apply to all visits and assessments, unless otherwise specified.

- Symptom-directed physical examination including vital signs and weight on Day 1 of every cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG **will be done every 9 weeks** from the date of randomization during the study treatment at the time of LVEF assessments.

- Chest X-ray as clinically indicated

- ECOG performance status before administration of each study treatment (see Appendix 2)

- FACT-B questionnaire must be completed by female patients within 3 days prior to each tumor assessment.

- Tumor assessments **All patients should have a minimum of 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). Tumor assessments (CT scans, MRI scans, etc.) will be performed as specified in Section 5.4.4 every 9 weeks after the date of randomization and will continue until IRF-confirmed progressive disease. 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. To ensure comparability, the techniques used for tumor assessment at Screening/Baseline should be consistent with those used subsequently in the study. Brain CT/MRI scans should be performed on patients with symptoms/signs suggestive of CNS involvement or other unexplained neurological symptoms. **The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessment must be performed every 9 weeks after the date of randomization. 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. More frequent LVEF monitoring may be performed as needed for cardiac safety (see Section 7.3.1.1). The same method of LVEF assessment (ECHO or MUGA scan) and the same institution/facility used at baseline should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with each LVEF result.

- Bone scan as clinically indicated (In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)

- Adverse Events (AEs) including SAEs should be documented according to NCI-CTCAE, Version 3.

- Concomitant medications and cancer-related surgery or procedures should be documented at each visit; including prescription, over-the-counter, and herbal/homeopathic remedies and/or therapies, as well as any cancer-related diagnostic, therapeutic, or surgical procedures performed.

- Hematology and blood chemistry will be collected and submitted to a local laboratory within 3 days prior to administration of each study treatment, and when clinically indicated (see Section 5.4.3). **An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.**

- INR and aPTT or PTT will be collected and submitted to a local laboratory for all patients receiving therapeutic doses of anti-coagulants before the start of every chemotherapy cycle, and when clinically indicated.

- Pregnancy test. For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization. A urine pregnancy test **must** be administered within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated). Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3). Pregnancy test results must be available prior to the drug infusion.

- Serum sample for HER2 family extracellular domain and HER ligands will be collected every 9 weeks at the time of each tumor assessment.

- Serum samples for antibodies to Pertuzumab will be collected every 9 weeks after the date of randomization, at the time of each tumor assessment during the treatment period.

- Samples requiring supplemental informed consent

  – Serum and plasma samples for BSR Research will be collected every 9 weeks at the time of each tumor assessment.

- Pertuzumab/placebo administration every 3 weeks. The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered within 3 days of randomization. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity (see Section 6 for details).

- Trastuzumab administration every 3 weeks. The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity (see Section 6).

- Docetaxel administration every 3 weeks. The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. (see Section 6).

5.4.2 Post-Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit)

During the post-treatment follow-up period, a window of ±3 days will apply to all visits and assessments, except for follow-up survival information collection which will have a window of ± 7 days. The treatment discontinuation visit should occur 4-6 weeks (28-42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last). (Specific data points to be collected will be detailed in the eCRF.)

- Symptom-directed physical examination and vital signs (pulse rate, blood pressure, body temperature, and weight) will be performed at the treatment discontinuation visit. Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG **will be performed at the treatment discontinuation visit**

- Chest X-Ray will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and as clinically indicated through Week 18 post-treatment.

- ECOG performance status will be performed at the treatment discontinuation visit, and at the time of each tumor assessment, until IRF-determined progressive disease.

- FACT-B questionnaire must be completed by female patients within 3 days prior to each tumor assessment.

- Tumor assessments. For patients who discontinue study treatment for reasons other than death or IRF-determined progression events, efforts should be made to continue to collect scheduled tumor assessments every 9 weeks (63 Days) ± 3 days until patient death or IRF-determined progressive disease. 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. **The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.**

- LVEF assessments. For all patients, LVEF assessments should be conducted **at the treatment discontinuation visit, then every 6 months in the first year, then annually for up to 3 years after the Treatment Discontinuation Visit**. Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year **after the Treatment Discontinuation Visit**, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years **after the Treatment Discontinuation Visit**. The LLN for the LVEF facility will be reported along with the LVEF results.

- Bone scan will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and if clinically indicated until IRF-confirmed progressive disease (In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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). **If treatment is discontinued due to Progressive Disease, on sites other than bone, a bone scan should be performed immediately (this would replace the bone scan at the Study Discontinuation visit) and submitted to the Independent Review Facility with all corresponding tumor assessment data (CT/MRI scans, etc).**

- Adverse Events. All AEs and SAEs should be collected through the treatment discontinuation visit. Cardiac adverse events occurring up to 12 months after last administration of study medications must be reported irrespective of causal relationship or treatment assignment. **Symptomatic left ventricular systolic dysfunction (NCI-CTCAE ≥ Grade 3), irrespective of causal relationship and treatment assignment must be reported up to 3 years after the treatment discontinuation visit** See Section 7.2.4 for full details of post-treatment discontinuation visit AE reporting requirements.

- Hematology and blood chemistry will be collected and submitted to a local laboratory at the treatment discontinuation visit (see Section 5.4.3).

- Pregnancy test. For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization. A urine pregnancy test **must** be administered at the treatment discontinuation visit and then every three months thereafter until six months post Treatment Discontinuation Visit. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3).

- Concomitant medications and cancer-related surgery or procedures should be collected through the time of the treatment discontinuation visit.

- Serum sample for testing for antibodies to pertuzumab should be collected at the treatment discontinuation visit.

- Serum sample for HER2 family extracellular domain and HER ligands will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease.

- Samples requiring supplemental informed consent

  – Serum and plasma samples for biomarker repository sample research will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18**.

- Post-study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be recorded **every 18** weeks **± 1 week (7 days) after the treatment discontinuation visit during the follow-up period,** including the dates and description of the procedure(s) or therapies, and any clinical findings.

- Survival information will be collected via telephone or clinic visits every 18 weeks ± 1 week (7 days) after the treatment discontinuation visit until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Requests to withdraw consent must be documented in the source documents and signed by the investigator. Immediately prior to the data cutoffs for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

5.4.3 Local Laboratory Assessments

All local laboratory sample collection and testing will be scheduled as indicated in Table 1. Additional assessments may be performed as clinically indicated. Normal ranges for the local laboratory parameters must be supplied to the study Sponsors before the study starts.

The following tests will be performed at a local laboratory:

Hematology. Hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells). Additional tests may be performed per the institution's standard practice. Testing will be performed at baseline**, within 3 days** before the start of **every chemotherapy cycle, on Day 8 of each treatment cycle during chemotherapy**, at the treatment discontinuation visit, and when clinically indicated.

Blood chemistry. Na^+, K^+, bicarbonate, Cl^-, BUN/Urea, Ca^{++}, **Mg,** uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, LDH, total bilirubin, creatinine, non-fasting blood glucose. Additional tests may be performed per institution's standard practice. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the treatment discontinuation visit, and when clinically indicated. For patients involved in the separate PK/DDI/QTc substudy, alpha-1-acid glycoprotein test will also be required, as detailed in that substudy protocol.

Coagulation. All patients will have INR and aPTT or PTT testing at baseline. Patients on therapeutic doses of anti-coagulants should have INR and aPTT or PTT measurements repeated during the study, at least before the start of every chemotherapy cycle, and when clinically indicated.

Pregnancy test. For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization, pregnancy tests **must** be performed via serum β-HCG at baseline. A urine pregnancy test should be administered during the treatment period within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated) and at the treatment discontinuation visit and then every three months thereafter until six months post Treatment Discontinuation Visit. Any positive urine pregnancy test must be confirmed via serum β-HCG. Treatment period pregnancy test results must be available prior to the drug infusion.

The relevant laboratory assessments should be available prior to each administration of study treatment for dose modification or delay requirements as specified in Section 7.3. These assessments must be performed within 3 days prior to the administration of study treatment at each cycle.

NOTE: Hematology, blood chemistry, coagulation and serum β-HCG tests are only valid as part of baseline eligibility screening if they have been performed within 7 days of randomization.

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. Any abnormalities that are discovered during patient assessment should be further investigated where clinically indicated, in order to ensure that patients are fit to be included in the study and to receive study medication.

5.4.4 Tumor Assessments

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

The minimum screening examinations should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals). **PET scans will not be considered for assessment of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).**

  CT scans should be performed with a contrast agent. The CT portion of a combination PET/CT scan is generally not performed with contrast, therefore **PET/CTs are generally not acceptable**. However, if the site has acquired a high quality diagnostic CT scan including the application of contrast agent (which may be performed with modern PET/CT scanners), the CT scan portion may be adequate for submission and evaluation. For patients with known allergies to the contrast media, it is acceptable to perform a chest CT scan without contrast and an MRI scan for the abdomen (ideally at baseline and every tumor assessment thereafter).

- CT or MRI scan of the brain and/or spine where there is clinical suspicion of CNS metastases

- An isotope bone scan (with bone X-ray[s] as necessary) at baseline (In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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). It should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions.
- Medical photography to monitor chest wall recurrences (i.e., subcutaneous skin lesions)

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.

The same assessment technique must be used throughout the study for evaluating a particular lesion (e.g., if a CT scan is used to assess metastatic lung lesions at baseline then a CT scan must be used at all subsequent tumor assessments to assess metastatic lung lesions). The same investigator should assess all tumor responses for each patient.

For patients with multiple measurable lesions, a maximum of five lesions per organ and 10 lesions in total that are representative of all involved organs should be designated as target lesions and recorded and measured at screening.

All other lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the treatment period and follow-up, if applicable, until confirmed evidence of progressive disease. Tumor lesions that are situated within a field of previous irradiation can be considered measurable if these lesions have shown clinical evidence of progression and can be reproducibly measured over time. Patients who have metastatic disease that is confined to the bone are not eligible for response evaluation but will be included in the PFS analysis if the criteria for progressive disease is satisfied (i.e., new bone lesions after treatment initiation).

Complete and partial responses should be confirmed between 4 and 6 weeks (28 and 42 Days) after response is observed. This confirmation should not cause the next planned regular tumor assessment to be delayed. The complete and partial responses can be also confirmed at the next scheduled tumor assessment if it occurs between 4 and 6 weeks (28 and 42 Days) after the initial response.

In case of SD, follow-up assessments must have met the RECIST SD criteria at least once after study entry at a minimum interval of 6 weeks.

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

Tumor assessments will be performed every 9 weeks after the date of randomization. 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. For patients who discontinue study treatment for reasons *other than* death or IRF-determined progression events, efforts should be made to continue to perform scheduled tumor assessments every 9 weeks (63 Days) until patient death or IRF-determined progressive disease.

After the cutoff date for the final PFS analysis, tumor assessments will no longer be collected.

5.4.4.1 Independent Review of MRI/CT Scans

The central independent review of tumor assessment scans, etc., will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.

The IRF will assess response, non-response, or progression (CR, PR, SD, or PD, according to current RECIST [Therasse et al. 2000]) during the study.

Images must be acquired according to an imaging protocol described in the Imaging Guidelines provided by the IRF and must be transmitted to the IRF. In addition, bone scans, x-rays, cytologic data (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and relevant clinical information including medical photography will be forwarded to the IRF to aid in the tumor response assessment. Full details are listed in the IRF Charter and in the Imaging Guidelines.

NOTE: At the end of the study, investigator RECIST data and the IRF RECIST data will NOT be reconciled.

5.4.5 Anti-Therapeutic Antibodies to Pertuzumab

Within 7 days prior to the first administration of study medication**, then every 9 weeks, at the time of the tumor assessments,** and at the time of the treatment discontinuation visit, serum samples (5 mL blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study Sponsors.

Serum samples will be assayed for anti-pertuzumab antibody titers. The assay is to be developed.

These samples will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and checked. This research may take several years to complete, at which time the samples will be destroyed.

5.4.6 Trastuzumab Serum Concentration

Within 7 days prior to the first administration of study medication, a single serum sample (5 mL blood draw) for testing of trastuzumab concentration will be collected from all patients who have received prior trastuzumab therapy and are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory.

These samples will be assayed for trastuzumab concentrations using a receptor-binding ELISA. The assay uses immobilized antigen HER2-ECD to capture trastuzumab from serum samples. The MQC for trastuzumab in human serum measured by this assay is 156 ng/mL.

These samples will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and checked. This research may take several years to complete, at which time the samples will be destroyed.

5.4.7 Tumor and Blood Biomarker Samples

The procedures for the collection, handling, and shipping of laboratory samples being submitted to the central laboratory for testing or subsequent shipment to the study Sponsors will be specified in a central laboratory manual. Biological samples taken from all patients may be infectious and will be classified as UN3373 Biological Substance, Category B, for shipping purposes.

The tumor tissue and blood samples described in Sections 5.4.7.1, 5.4.7.3, and 5.4.7.2 and 5.4.7.5 (if consented for and collected), will be used for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and/or prognostic for breast cancer. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined but may include determination of markers of tumor genesis pathways or mechanisms of response to anti-HER2 therapies. The collected tumor tissue and blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data. Tumor tissue and blood samples remaining after the pre-defined biomarker assessments (e.g., aliquots of tumor cell RNA or DNA) may be used for re-testing, developing, and validating diagnostic assays related to HER2 positive breast cancer or the prediction of response to pertuzumab and/or trastuzumab, or further assessment of the defined marker panels.

5.4.7.1 Tumor Tissue Samples for HER2 Status and Biomarker Analysis

Archival tumor samples from the primary tumor (or metastatic sites, if the primary tumor is not available) will be submitted from all subjects during screening and submitted to a central pathology laboratory for assessment of HER2 status via IHC and FISH for study eligibility, as well as for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction.

Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 25 unstained freshly cut slides of 4 μm will be submitted (the number of slides submitted may be reduced pending on the regulatory and or IEC requirements of some counties). The slides must be sent to the central lab within 2 days of being cut. From submitted tumor blocks, at the central laboratory a maximum of 15 slides will be cut and 2 cores will be removed in order to construct tissue microarrays (TMAs) for later analysis. The remaining part of the tumor block will be returned to the

institution. HER2 testing will be prioritized and the tissue will subsequently be used for assessment of biomarkers.

For the assessment of tumor tissue biomarkers, a variety of analysis methodologies may be used, including but not limited to, qRT-PCR, IHC, in-situ hybridization, and gene expression profiling. At the end of the collection process, the most suitable analytical methodologies will be selected and employed.

Tissue Microarray (TMA) Construction

The tumor blocks will also be used to set up a TMA: a maximum of 2 tissue cores of 1.5 mm each will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissue cores from different patients. This process protects the tissue against oxidation and allows for long-term storage and later analysis.

For later analysis, tissue sections can be generated using the latter tissue microarray. This technology will allow a high throughput (many patient samples on one glass slide) analysis of biomarkers.

DNA/RNA Extraction

The submitted tumor blocks will be used to generate sections on glass slides for the extraction of tumor DNA and RNA for later analysis. These slides will be prepared in a central lab to ensure the same quality for all samples and in later studies.

Note that as tumorigenesis is a multiple-step process linked to somatic events, DNA analysis will focus on sporadic mutations specifically found in tumor tissue but not inherited changes found in the whole body. For this purpose, some sections containing tumor will be taken from the block and used for the extraction process.

The tumor tissue samples will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed.

5.4.7.2 Metastatic Tumor Tissue Samples for Biomarker Analysis (Optional)

If a biopsy of the patient's metastatic tumor tissue is available, it will be submitted from consenting patients at baseline (after the patient has been determined to be eligible for the study, but before the first administration of study medication) for the assessment of tumor tissue biomarkers for pertuzumab/trastuzumab response prediction. Biopsy samples should be submitted and will be processed as described in Section 5.4.7.1.

5.4.7.3 Serum Samples for ECD/HER2 and HER Ligands Analysis

For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment **until IRF-determined progressive disease**. Biomarker assessments with these samples will include levels of ECD/HER2, selected HER ligands, and/or markers thought to be important for HER family signaling or response to HER inhibitors and HER activation. At this time the significance of ECD/HER2 is not known, but because of its potential importance it will be measured as part of the panel of potential biomarkers of therapeutic effect. Leftovers of samples may be used for re-testing or developing and validating existing and/or new diagnostic tests related to pertuzumab or trastuzumab, or both.

The serum samples for ECD/HER2 and HER ligand analysis will be stored at the study Sponsors' facility or a contract laboratory facility for up to 7 years after database closure, at which time the samples will be destroyed.

5.4.7.4 Whole Blood Sample for Fcγ Polymorphism Analysis (Clinical Genotyping)

A whole blood sample (3 mL) for assessment of Fcγ polymorphism will be collected from patients at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication). An analysis of Fcγ-receptor polymorphism will be correlated with clinical outcome in order to further evaluate the mechanism of action of both trastuzumab and pertuzumab. Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the individual countries.

Blood samples for Fcγ polymorphism analysis and the DNA extracted from them will be stored at the study Sponsors' facility or a contract laboratory facility until this testing is completed and has been checked. The research may take several years to complete, after which time the samples will be destroyed.

5.4.7.5 Serum and Plasma for Biomarker Sample Repository (BSR) Research (Optional)

Blood samples for extraction of serum and plasma samples (approximately 5 mL per sample) for biomarker discovery, validation, and application will be collected from consenting patients. These samples are collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study every 9 weeks at the time of every tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18.**

The collected BSR samples will be stored with the study Sponsor's facility or a contract laboratory facility for up to 15 years after the end of the associated study (database closure), at which time the samples will be destroyed. These samples will be used only for research purposes to identify dynamic biomarkers that may be predictive of response to pertuzumab and trastuzumab treatment (in terms of dose, safety, tolerability, and efficacy) and will help to better understand the pathogenesis, course, and outcome of breast cancer and related diseases and adverse events.

The collected blood samples may be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data related to HER2-positive breast cancer disease or response to pertuzumab and/or trastuzumab. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined.

5.4.7.6 Ethics Approval and Consenting Process for Optional Tumor and Blood Samples

Sampling for the above optional biomarkers is contingent upon the appropriate Institutional Review Board's approval or Independent Ethics Committee's approval of sampling for the optional exploratory biomarker assessments and written informed consent of the patient. If an Institutional Review Board/Independent Ethics Committee (IRB/IEC) does not approve the sampling for the optional assessments, those sections will not be applicable at that site.

Collection of optional blood and tumor samples requires a separate patient consent. Individual patients may refuse the collection, storage, and use of any of the optional samples above; however, this will *not* exclude them from participation in this study. If the subject consents, the samples must be collected and submitted as described above.

5.5 Quality of Life Assessments

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system under development since October 1987 began with the creation of a patient-reported general core questionnaire called the Functional Assessment of Cancer Therapy, or FACT-G. Today's FACIT System (Version 4) has been translated in over 40 languages and consists of the FACT-G questionnaire and numerous other patient reported body organ or site specific questionnaires (referred to as "Additional Concerns") developed by David Cella of the Center on Outcomes Research Education (Brady et al. 1997).

5.5.1 The FACT-B Subscale

This study will use the Functional Assessment of Cancer Therapy-Breast (FACT-B), Version 4. The FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer (see Appendix 6). Patients will rate all items on a five-point scale ranging from "not at all" to "very much". The FACT-B provides supplemental domain valuative ratings or utility weights, thus providing an estimate of the relative importance of each quality of life domain to an individual patient. The FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. The FACT-B has been

used extensively and has demonstrated reliability, validity, and sensitivity to change over time.

Only female patients on this study will be asked to complete the FACT-B questionnaire.

5.5.2 Administration of the FACT-B

Paper FACT-B questionnaires will be utilized in this study and will be completed by female patients pre-treatment (at baseline) and within 3 days prior to each tumor assessment. (QoL data will not be collected via the eCRF system).

The QoL evaluations have been specifically linked to on-study tumor assessments (rather than treatment cycles) to avoid biased data collection. Patients should complete the QoL assessment on schedule prior to each tumor assessment even if protocol therapy is no longer being administered due to toxicities or investigator-determined progressive disease.

5.6 Pharmacoeconomic Assessments

An economic assessment comparing various costs between the two treatment arms will be conducted by evaluating hospitalizations while on study treatment. The number of hospital visits, number of days admitted, and type of visits (emergency room vs. inpatient care) will be collected. This information will be collected from information submitted on AE and SAE eCRFs.

5.7 Post-Study Provisional Care

Patients who discontinue this study for progressive disease or other reasons will receive treatment according to the local standard of care. Any post-study cancer treatment will be recorded. Information on patient outcomes and information on post-progression anti-cancer therapies will be captured as far as reasonably possible on a post-progression follow-up form.

5.8 Pharmacokinetic, Drug-Drug Interaction, and QTc Interval Substudy

A **subset** of principal investigators and patients will participate in a pharmacokinetic, drug-drug interaction, and QTc interval substudy as detailed in a separate protocol. Separate IRB/IEC approval and Informed Consent Form will be required for participation in the substudy.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Formulation of Pertuzumab/Placebo and Trastuzumab

Each lot of the recombinant antibodies produced for clinical purposes meets USP requirements for sterility and safety. In addition, each lot is extensively characterized and meets the required specifications for identity, purity, and potency.

6.1.1 Pertuzumab/Placebo

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20.

Each 20-cc vial contains approximately 420 mg of pertuzumab (14.0 mL/vial). Pertuzumab is intended for use only in clinical trials.

The formulation of the pertuzumab/placebo is equivalent to pertuzumab, without the active agent.

For further details, see the pertuzumab Investigator Brochure (IB).

6.1.2 Trastuzumab

In countries where permitted by local regulatory requirements, commercial Herceptin (trastuzumab) will be obtained directly by the site for use during this study. In other countries, investigational trastuzumab will be supplied by the study Sponsors.

Trastuzumab will be a freeze-dried preparation at a nominal content of either 440 mg or 150 mg per vial. Vial size will also vary by country.

Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

For further details, see the trastuzumab Summary of Product Characteristics and local prescribing information.

6.2 Labeling of Pertuzumab/Placebo and Trastuzumab

Pertuzumab/placebo and trastuzumab will be labeled according to the regulatory requirements in each country, as well as in accordance with International Conference of Harmonization (ICH) Good Clinical Practice.

6.2.1 Pertuzumab/Placebo

The study Sponsors will provide pertuzumab to all study sites labeled for investigational use only.

6.2.2 Trastuzumab

Where permitted by regulatory requirements, sites will obtain and utilize standard trastuzumab.

For sites that will not obtain trastuzumab due to regulatory requirements, the study Sponsors will provide trastuzumab labeled for investigational use only.

6.3 Storage, Preparation, and Administration of Pertuzumab/Placebo and Trastuzumab

6.3.1 Storage of Pertuzumab/Placebo and Trastuzumab

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

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

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

6.3.2 Preparation of Pertuzumab/Placebo and Trastuzumab

6.3.2.1 Blinded Pertuzumab/Placebo

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

The indicated volume of pertuzumab/placebo solution should be withdrawn from the vials and added to a 250-cc IV bag of 0.9% sodium chloride injection. Gently invert the bag to mix the solution. DO NOT SHAKE VIGOROUSLY. Visually inspect the solution for particulates and discoloration prior to administration. The entire volume within the bag should be administered as a continuous IV infusion. The volume contained in the administration tubing should be completely flushed using a 0.9% sodium chloride injection.

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

A rate-regulating device may be used for all study-drug infusions. When the study drug IV bag is empty, 50 mL of 0.9% Sodium Chloride Injection may be added to the IV bag or an additional bag will be hung, and the infusion may be continued for a volume equal to that of the tubing to ensure complete delivery of the study drug.

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

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

6.3.2.2 Trastuzumab

Each vial of trastuzumab 150 mg is reconstituted with 7.2 mL of Sterile Water for Injection (SWFI). This formulation does not contain a preservative and is suitable for single use only.

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

Use of other reconstitution solvents is not allowed.

Appropriate aseptic techniques should be used. Trastuzumab should be carefully handled during reconstitution. The following instructions have to be followed:

1. Using a sterile syringe, slowly inject the sterile water for injections in the vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.

2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

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

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

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

Determine the volume of the solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent dose of 6 mg trastuzumab/kg body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions, since it causes aggregation of the protein. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for a maximum of 24 hours from reconstitution (do not store above 30°C). No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Trastuzumab may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions. Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial.

6.4 Docetaxel

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

6.5 Study Treatment Administration Sequence

Study treatment cycles are 3 weeks (21 days) in length. The first dose of pertuzumab/placebo (Cycle 1, Day 1) should be administered within 3 days of the date of randomization. The first dose of trastuzumab should be administered 24 hours later (Cycle 1, Day 2), followed by the first dose of docetaxel. If the initial infusions of all three agents are well tolerated as determined by the investigator, subsequent cycles of trastuzumab and docetaxel may also be administered on Day 1 of the cycle. When all drugs are given on the same day they will be administered in the following sequence:

Pertuzumab/Placebo → Trastuzumab → Docetaxel.

6.6 Dose and Schedule of Pertuzumab/Placebo, Trastuzumab, and Docetaxel

6.6.1 Pertuzumab/Placebo Dose and Schedule

Pertuzumab/placebo will be administered as an IV loading dose of 840 mg for Cycle 1, and 420 mg for subsequent cycles.

Pertuzumab/placebo will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of pertuzumab/placebo for 1 cycle (i.e., the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab/placebo (840 mg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

6.6.2 Trastuzumab Dose and Schedule

Trastuzumab will be administered as an IV loading dose of 8 mg/kg for Cycle 1, and 6 mg/kg for subsequent cycles. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline.

Trastuzumab will be administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of trastuzumab for 1 cycle (i.e. the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of trastuzumab (8 mg/kg) should be given. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1 and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.

6.6.3 Docetaxel Dose and Schedule

Docetaxel will be administered as an IV dose of 75 mg/m^2 every 3 weeks. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

Table 2 Study Treatment Dose and Schedule

Cycle	Blinded Pertuzumab/Placebo	Trastuzumab	Docetaxel
Cycle 1	Day 1: 840mg loading dose over 60 min followed by a 60 minute observation period	Day 2: 24 hrs after pertuzumab 8 mg/kg loading dose over 90 min followed by a 60 minute observation period	Day 2: After trastuzumab obs. period 75 mg/m^2 over 1 hour observe according to institution standards
Cycle 2 [a)]	Day 1: 420mg over 60 min followed by a 30 min, or 60 min obs. period [e)]	Day 1: After pertuzumab observation period 6 mg/kg over 30 min, or 90 min [c)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After trastuzumab observation period 75 mg/m^2 (or 100 mg/m^2 [g)]) over 60 min observe according to institution standards
Other Cycles *(every 21 days)*	Day 1: 420mg [b)] over 30 min, or 60 min[d)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After pertuzumab observation period 6 mg/kg [f)] over 30 min, or 90 min [c)] followed by a 30 min, or 60 min obs. period [e)]	Day 1: After trastuzumab observation period 75 mg/m^2 (or 100 mg/m^2 [g)]) over 60 min observe according to institution standards for a total of 6 cycles or more [h]

a) If the administrations of all three agents are well tolerated in Cycle 1, they may all be given on Day 1 in subsequent cycles in the following sequence: pertuzumab/placebo → trastuzumab → docetaxel. If a patient cannot tolerate all three drugs given on the same day, the Cycle 1 dosing schedule (pertuzumab/placebo on Day 1, trastuzumab + docetaxel on Day 2) will be followed.

b) Pertuzumab/placebo should be re-loaded (840mg) if the agent is interrupted for 1 cycle (i.e., the 2 sequential administration times are at least 6 weeks apart). If reloading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

Table 2 Study Treatment Dose and Schedule (Cont.)

c) If the first infusion of trastuzumab is tolerated without infusion-associated adverse events (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.
d) If the first two infusions of blinded pertuzumab/placebo are tolerated without infusion-associated adverse events (fever and/or chills), the third and subsequent infusions may be delivered over 30 minutes.
e) If the first infusion of pertuzumab/placebo or trastuzumab is well tolerated without infusion-associated adverse events, the subsequent observational periods may be reduced from 60 minutes to 30 minutes.
f) Trastuzumab should be reloaded (8 mg/kg) if the agent is interrupted for 1 cycle (i.e., the 2 sequential administration times are at least 6 weeks apart). If reloading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1, i.e., pertuzumab/placebo on Day 1, and trastuzumab and docetaxel on Day 2. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.
g) At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).
h) On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.

6.7 Dose Delays and Modifications

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

6.7.1 Pertuzumab/Placebo and Trastuzumab Dose Delays and Modifications

Pertuzumab/placebo and trastuzumab doses may be delayed due to toxicities. If pertuzumab/placebo or trastuzumab is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment, and the patient will continue to be followed post-treatment as described in Section 5.4.2.

Pertuzumab/placebo or trastuzumab dose modifications are <u>not</u> permitted.

6.7.2 Docetaxel Dose Delays and Modifications

Docetaxel may be delayed due to toxicities. If docetaxel is delayed for more than 3 weeks with no recovery the patient should be withdrawn from docetaxel treatment. If docetaxel needs to be permanently discontinued, the patient will continue on pertuzumab/placebo and trastuzumab.

At the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle of 75 mg/m^2 without any of the following toxicities: febrile neutropenia, Grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).

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

Table 3 Docetaxel Dose Adjustments

Docetaxel Dose	When
75 mg/m^2	Starting dose Administer only if neutrophil count is > 1500 cell/mm^3
100 mg/m^2	At the discretion of the treating physician, after at least 1 cycle of 75 mg/m^2 without any of the following toxicities: Febrile neutropenia Grade 4 neutropenia for > 5 days ANC < 100/μL for more than 1 day Other non-hematological toxicities of Grade > 2 (NCI-CTCAE, Version 3).
55 mg/m^2 (or 75 mg/m^2 if dose previously increased to 100 mg/m^2)	25% reduced dose in case of any of the following toxicities: Febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1,500 cells/mm^3) Platelet count < 100,000 cells/mm^3 (after recovering to a platelet count ≥ 100,000 cells/mm^3) Severe or cumulative cutaneous reactions
Permanently Discontinue Docetaxel	After any of the following toxicities: Severe hypersensitivity reactions (Section 7.3.2.2) Peripheral neuropathy > Grade 3 Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery Febrile neutropenia or neutrophils < 500 cells/mm^3 without recovery Platelet < 100,000 cells/mm^3 without recovery Total bilirubin > ULN without recovery Serum transaminase (AST/ALT) levels > 1.5 × ULN concurrent with serum alkaline phosphatase levels > 2.5 × ULN without recovery

ANC=absolute neutrophil count; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

See also Section 7.3.

6.8 Study Treatment Unblinding

As per regulatory reporting requirements, Genentech and Roche will unblind the identity of the study medication for all unexpected (as per the IB) serious adverse events that are considered by the investigator to be related to the blinded study drug (pertuzumab/placebo). Unblinding for other reasons is not permitted. All cases of safety unblinding require the approval of the Medical Monitor.

Unblinding for interim analysis, or ongoing safety monitoring by a DMC, will be performed through an independent Data Coordinating Center (DCC) to ensure integrity of the study.

All other individuals directly involved in this study will remain blinded until the final analysis of the primary efficacy endpoint.

6.9 Assessment of Compliance

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Dose reductions and titrations of docetaxel must be recorded.

Accurate records must be kept for each study drug provided by the Sponsors, pertuzumab and trastuzumab (investigational). These records must contain at least the following information:

- Documentation of drug shipments received from the Sponsors (date received and quantity)

A Drug Dispensing Log must be kept current and contain the following information:

- The study number of the patient to whom the study medication was dispensed
- The date(s), drug kit number, and quantity of the study medication dispensed to the patient

Copies of the dispensing and inventory logs must be available for inspection by the monitor. Instructions for the destruction of unused, partially used or empty vials of pertuzumab/placebo and investigational trastuzumab, are detailed in Section 6.10.

6.10 Destruction of Study Drug

All pertuzumab/placebo, trastuzumab, and docetaxel supplies, including unused, partially used or empty vials, must be destroyed on site as per the site's specific procedures for handling and disposing of hazardous drugs or returned to the Sponsor or designated agent for destruction**.** The specific procedures for destruction of investigational pertuzumab/placebo and investigational trastuzumab are to be provided to the monitor who will verify them as acceptable and in line with the Sponsor's SOPs.

6.10.1 Partially Used or Empty Vial Destruction

To assist with storage capacity and functionality, it is acceptable for sites to destroy the partially used or empty pertuzumab/placebo and investigational trastuzumab vials before inspection by the site monitor so that only the empty boxes stating the drug kit number and patient information and dispensing date written on the label can be used for reconciliation of destroyed supplies.

6.10.2 Unused Vial Destruction

Unused pertuzumab/placebo and investigational trastuzumab drug supplies, including medication that has been exposed to storage temperatures outside of the protocol-specified range, may be destroyed on site after written approval from the Sponsors, provided that such disposition does not expose humans to risks from the drug or returned to the Sponsor or designated agent for destruction.

Written documentation of destruction must contain the following:

- Identity (drug kit numbers or patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed

- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsors with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of the responsible person who discarded the investigational product in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events and Laboratory Abnormality Definitions

7.1.1 Clinical AEs

Per the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that worsen during a study are to be reported as AEs.

7.1.1.1 Intensity

Intensity of all adverse events will be graded according to the NCI-CTCAE, Version 3.0 on a 5-point scale (Grades 1–5) and reported in detail on the eCRF.

Adverse events not listed on the NCI-CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening/disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.1.2 Adverse Event Relationship to Drug

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration
- Assessment that it may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappearance or decrease on cessation or reduction in dose
- Reappearance on re-challenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

7.1.1.3 Serious Adverse Events

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills one or more of the following criteria:

- It is fatal (i.e., results in death; NOTE: Death is an outcome, not an event).
- It is life threatening. (NOTE: The term "life threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.)
- It requires in-patient hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability/incapacity.
- It is a congenital anomaly/birth defect.
- It is medically significant or requires intervention to prevent one or other of the outcomes listed above.

The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2** (see Appendix 1).

7.1.1.4 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST, or other criteria as determined by the protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic clinical deterioration may occur in some patients. In this situation, progressive disease is evident in the patient's clinical symptoms but is not supported by the tumor measurements. Or, the progressive disease is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.2 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eForms of the eCRF.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE eForm in the eCRF:

- Accompanying clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

7.2 Reporting and Follow-Up of Adverse Events and Laboratory Abnormalities

7.2.1 Reporting of Non-Cardiac, Non-Serious Adverse Events

For all patients that have received at least one dose of study medication, all new non-cardiac, non-serious AEs (related and unrelated) must be collected during the study through the treatment discontinuation visit. These events will be reported via the eCRF.

7.2.2 Reporting of Serious Adverse Events (Immediately Reportable)

For all patients who have received at least one dose of study medication, any clinical AE or abnormal laboratory test value that is *serious* (as defined in Section 7.1.1.3 above) and which occurs during the course of the study, regardless of the treatment arm, must be reported to the Sponsors **within *one* working day** of the investigator becoming aware of the event (expedited reporting).

Related SAEs (cardiac and non-cardiac) ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated non-cardiac SAEs must be collected and reported during the study through the treatment discontinuation visit.

Adherence to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2** will be required. Complete information can be found in Appendix 1.

7.2.3 Reporting of Cardiac Adverse Events

All cardiac AEs occurring during the study and up to 12 months after last administration of study medications must be reported irrespective of causal relationship (related and unrelated) or **seriousness** (serious or non-serious). **Symptomatic left ventricular systolic dysfunction NCI-CTCAE ≥ Grade 3 (CHF) must be reported for up to 3 years after the study treatment discontinuation**.

***Symptomatic* Left Ventricular Systolic Dysfunction**

Symptomatic left ventricular systolic dysfunction (congestive heart failure, CHF) should be reported **as an SAE an as a diagnosis,** and not as individual signs and symptoms thereof. **Symptomatic left ventricular dysfunction** must also be reported on the **Symptomatic Left Ventricular Systolic Dysfunction eCRF form**. Specific related signs and symptoms will be entered on the eCRF. **Symptomatic left ventricular systolic dysfunction should be** graded according to NCI-CTCAE Version 3.0 for "left ventricular systolic dysfunction" and the NYHA classification (see Appendix 3).

***Asymptomatic* Left Ventricular Systolic Dysfunction**

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

- An asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50% must be reported as an AE
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment must be reported in an expedited manner by using the SAE form and classifying the event as Non-Serious Event of Special Interest (see Section 3a on page 1 of the SAE form)

In both cases, it should be reported as left ventricular systolic dysfunction and graded according to NCI-CTCAE, Version 3.0.

The following table summarizes the reporting conventions for left ventricular systolic dysfunction:

Table 4 Reporting Conventions for Left Ventricular Systolic Dysfunction

Observation	How to report	Term to be reported	Grading
Asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50%	AE (eCRF AE eform)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE eform) and Non-Serious Event of Special interest (SAE form)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Symptomatic left ventricular systolic dysfunction (Congestive Heart Failure)	**Symptomatic Left Ventricular Systolic Dysfunction** eCRF and SAE (SAE form)	**Symptomatic left ventricular systolic dysfunction**	NCI-CTCAE for "left ventricular systolic dysfunction" and NYHA criteria
Asymptomatic decline in LVEF to a value higher than 10 percentage points below Baseline, or Asymptomatic decline to a value 10 percentage points below baseline or lower, but ≥ 50%	Record on LVEF eCRF, not AE eCRF	N/A	N/A

LVEF=left ventricular ejection fraction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; AE=adverse event; SAE=serious adverse event; eCFR=electronic case report form.

Note: Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the Treatment Discontinuation Visit.

7.2.3.1 Cardiac Review Committee Document Review

Patients with potential cardiac events to be reviewed by the CRC will be identified from the study database according to the specifications detailed in the CRC charter.

In order for the CRC to adequately review potential cardiac events, copies of specific source documents will be required by the CRC: copies of chest X-ray reports, ECG readings, cardiac consultations, clinic visit notes, LVEF reports, documentation of medications received. The study Sponsors or designee will contact the study site to request the required source documents for identified patients. The CRC will review these source documents along with patient data profiles to independently determine whether or not the patient experienced a cardiac event according to the cardiac event definition defined in the CRC charter. The CRC cardiac event evaluations will be provided to the DCC for submission to the DMC for review during the periodic safety reviews. The independent CRC cardiac event evaluations will not be provided to the study sites.

7.2.4 Follow-up of AEs and Post-Treatment AE Collection

During the treatment period through the treatment discontinuation visit, all AEs (regardless of seriousness or causality) should be reported and continue to be followed until one of the following occurs:

- Resolved or improved to baseline
- Investigator confirmation that no further improvement can be expected
- Death

AEs that are *ongoing* at the time of the treatment discontinuation visit should be followed depending on the event type:

- All Cardiac AEs (regardless of seriousness or causality), and all SAEs (regardless of causality) should be followed until resolution/stabilization/death up to 1 year after the last dose.
- Non-cardiac, non-serious AEs (regardless of causality) should be followed only until the Treatment Discontinuation Visit.

Only the following *new* adverse events that start *after* the treatment discontinuation visit should be reported:

- Cardiac events (regardless of causality or seriousness) that start up to 1 year after the last dose should be reported. These events should be followed until resolution/stabilization/death up to 1 year after the start of the event. **Symptomatic left ventricular systolic dysfunction (regardless of causality) that start up to 3 years after the last dose should be reported. These events should be followed until resolution/stabilization/death or until investigator confirmation that no further improvement can be expected or until the survival follow-up for the study is complete.**
- Treatment-related SAEs should be reported at any time regardless of the start date. These events should be followed until resolution/stabilization/death up to 1 year after the start of the event.

7.2.5 Follow-Up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found, or until the test values are determined to be not clinically significant by the investigator. If a clear explanation is established, it should be recorded on the eCRF.

7.2.6 Pregnancy

ICH M3 Guidance require precautions to be taken to minimize risk to fetus or embryo when including women of childbearing potential. This includes highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy monitoring and continued pregnancy testing up to 6 months following last dose of study drug (follow-up period based on PK considerations).

Reproductive toxicity data was recently published in the Investigator Brochure, and of particular interest is that pertuzumab caused oligohydramnios, delayed renal development and embryo-fetal deaths in pregnant cynomolgus monkeys. There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy.

For women of childbearing potential (who have not undergone surgical sterilization) and men with partners of childbearing potential, agreement to use a highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

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

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

Or two of the following effective forms of contraception:

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

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

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

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

Postmenopausal is defined as ≥ 12 months of amenorrhea.

For male patients with a female partner of childbearing potential, co-operation of female partner is required (use two forms of contraception as stated above) during the study and for at least 6 months following the last dose of study treatment when a highly effective form of contraception is not appropriate.

Based on PK considerations, contraception must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to the Sponsor including the partners of male patients. The investigator should counsel the patient/partner, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient/partner should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of study medication must also be reported to the investigator.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 6 months following the last dose of either monoclonal antibody.

Experimental studies have reported that IgGs are present in both the pre-ejaculate and the seminal plasma (Moldoveanu et al 2005). To date there has been no clinical studies to assess the IgG profile in the pre-ejaculate and seminal plasma in male patients receiving pertuzumab or trastuzumab. Therefore, as a precaution male patients with female partners of child bearing potential are required to use highly effective form of contraception or use two forms of contraception as outlined above. Similarly, vaginal absorption of pertuzumab is unknown and therefore male patients with pregnant partners are required to use condoms for the duration of the pregnancy, and then revert to contraceptive methods as outlined above. This is to ensure that the fetus is not exposed to the study

medication through vaginal absorption. Similarly, sperm donation should not occur for at least 6 months after the last dose of study treatment.

7.3 Dose Modifications for Toxicity

The NCI-CTCAE Version 3.0 will be used to grade toxicity.

Pertuzumab/placebo, trastuzumab, and docetaxel will be given as specified in Section 6. Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections.

7.3.1 Pertuzumab/Placebo and Trastuzumab

Pertuzumab/placebo and trastuzumab administration may be delayed to assess or treat AEs such as cardiac adverse events, myelosuppression, or other events. No dose reduction will be allowed for pertuzumab/placebo or trastuzumab.

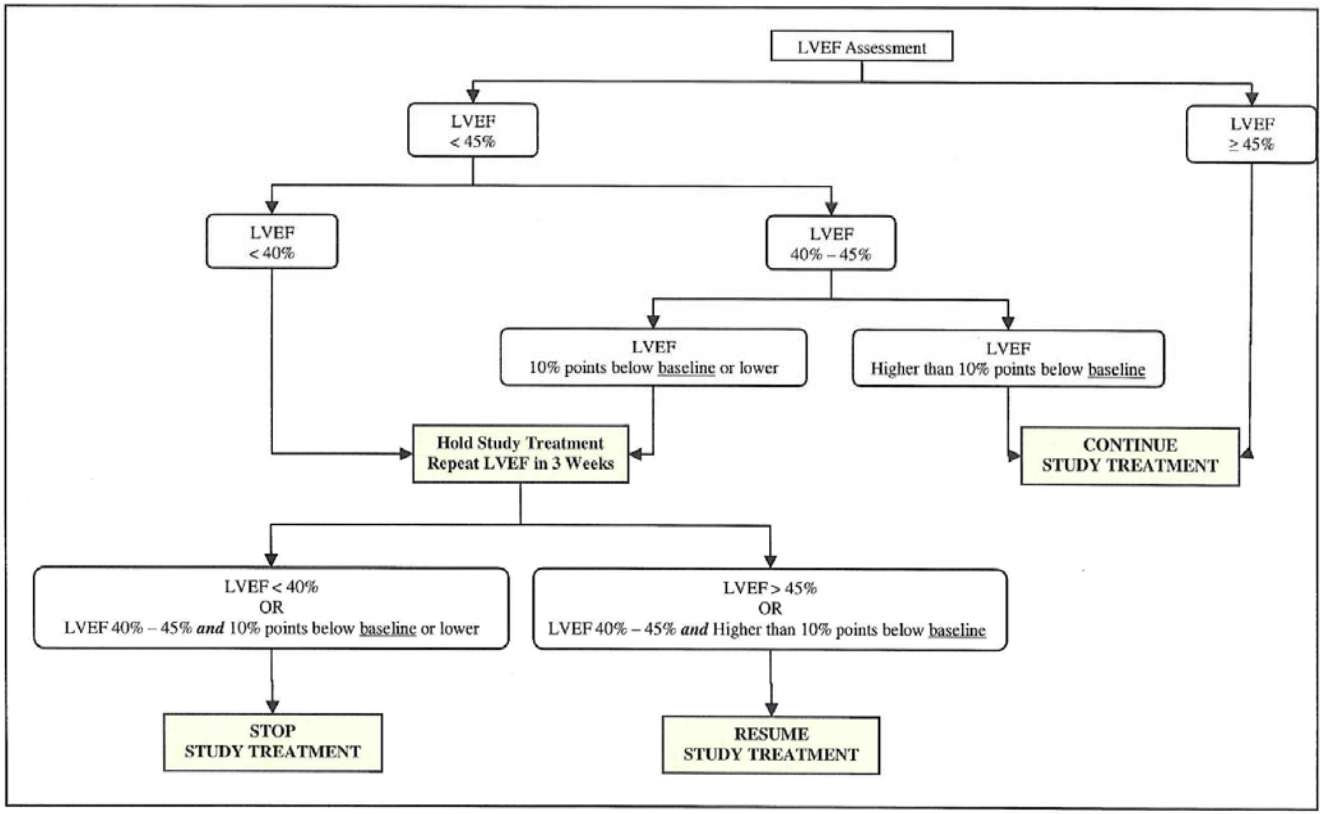
7.3.1.1 Cardiac Safety

All patients must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly according to the schedule of assessments. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Pertuzumab/placebo and trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting congestive heart failure, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. Congestive heart failure should be treated and monitored according to standard medical practice.

At the present time, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure the safety of patients in the trial, pertuzumab/placebo and trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented and confirmed with a repeat assessment within 3 weeks of the first assessment, using the same assessment method.

For patients whose LVEF drops to values lower than 45%, the decision to stop or continue study treatment is based on the algorithm shown in Figure 3.

Figure 3 Algorithm for Continuation and Discontinuation of Pertuzumab/Placebo and Trastuzumab Based on LVEF Assessments



LVEF=left ventricular ejection fraction.

Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year after the Treatment Discontinuation Visit, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the Treatment Discontinuation Visit.

7.3.1.2 Infusion-Associated Symptoms and Allergic Reactions

Administration of monoclonal antibodies, including pertuzumab and trastuzumab, may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rashes, headache, nausea, vomiting, or allergic reactions.

Patients with extensive pulmonary disease, e.g., lymphangitis, multiple metastases, recurrent pleural effusions, and those with pre-existing pulmonary compromise who are treated with trastuzumab, may be at increased risk of serious infusion-associated symptoms. Therefore, careful consideration must be made before enrolling patients with chronic lung disease into the study.

Study treatment will be administered in a setting with emergency equipment and staff that is trained to monitor for and respond to medical emergencies. Patients who experience an NCI-CTCAE grade 4 allergic reaction, acute respiratory distress syndrome, or bronchospasm will be discontinued from study treatment.

Patients who experience infusion-associated symptoms may be managed by:

- Slowing or stopping the trastuzumab or pertuzumab/placebo infusion
- Supportive care with oxygen, beta agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab or pertuzumab infusions at the investigator’s discretion.

If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms.

7.3.1.3 Pertuzumab/Placebo or Trastuzumab: Incomplete Loading Dose

In case the whole loading dose of pertuzumab/placebo or trastuzumab could not be administered due to an infusion reaction or other reason, the following guidelines apply:

The patient should receive at least 50% of the loading dose in the first week. Therefore, if the patient receives less than 50% of the Cycle 1 dose, the patient should receive the remainder before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only approximately 50% of the scheduled loading dose (i.e., only 4 mg/kg instead of 8 mg/kg of trastuzumab; or only 420 mg instead of 840 mg of pertuzumab/placebo), the patient should receive the remaining dose (4 mg/kg of trastuzumab; or 420 mg of pertuzumab), preferably in the first week, and then regular maintenance doses (6 mg/kg of trastuzumab; 420 mg of pertuzumab/placebo) on Day 22, as routinely scheduled.

If the patient receives between 50-75% of the dose, the patient should receive the remainder before Day 22, preferably within the first two weeks of Cycle 1. For example, if a patient received only approximately 60% of the scheduled loading dose, the patient should receive the remaining 40%, within 2 weeks after the interrupted loading dose. Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.

If the patient received ≥ 75% of the loading dose, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22.

7.3.2 Docetaxel

The recommendations given in the prescribing information for docetaxel should be strictly followed.

The first dose of docetaxel should be given at a dose of 75 mg/m^2 and dose reductions should be applied in the event of toxicity. If docetaxel is withheld for more than 3 weeks with no recovery the patient should be withdrawn from docetaxel treatment. If docetaxel has been withdrawn, investigators may continue with pertuzumab/placebo and trastuzumab, if clinically appropriate.

7.3.2.1 Hematotoxicity

Neutrophil Count

Docetaxel should only be administered if the neutrophil count is ≥ 1,500 cells/mm^3.

If patients experience either febrile neutropenia or neutrophils < 500 cells/mm^3 for more than one week following docetaxel administration, docetaxel should be held until the patient is fully recovered and the neutrophil count is≥ 1,500 cells/mm^3. Treatment with docetaxel may be resumed with a 25% reduction in the dose. If patients continue to experience these reactions at a dose of 55 mg/m^2, docetaxel should be discontinued permanently.

Alternatively, prophylactic G-CSF may be used in patients who experienced febrile neutropenia or severe infection during the previous cycle, in order to maintain dose intensity as clinically indicated or according to the ASCO guidelines for growth factor support (Smith et al. 2006).

Platelet Count

- Patients with a platelet count of ≥ 100,000 cells/mm^3 on the day of treatment may receive docetaxel.
- Patients with a platelet count < 100,000 cells/mm^3 should not be given docetaxel. Docetaxel may be delayed for a maximum of 3 weeks.

- If the platelet count recovers to $\geq$ 100,000 cells/mm^3 after a decline to < 100,000 cells/mm^3, the patient should receive further cycles of docetaxel with a 25% reduction in the dose.
- If the platelet count does not recover to a level $\geq$ 100,000 cells/mm^3, the patient should discontinue docetaxel.

7.3.2.2 Hypersensitivity

Patients should be observed closely for hypersensitivity reactions, especially during the first and second docetaxel infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel; thus, facilities for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. These patients should not be re-challenged with the docetaxel. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Minor symptoms such as flushing or localized cutaneous reactions generally do not require interruption of therapy.

7.3.2.3 Peripheral Neuropathy

Patients who develop $\geq$ Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

7.3.2.4 Fluid Retention

Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion, or ascites that is possibly related to docetaxel should be closely monitored and the decision to continue or discontinue study treatment is at the discretion of the Investigator.

7.3.2.5 Hepatic Impairment

Patients should have adequate baseline liver function as stated in the inclusion criteria in Section 4.2. Liver function should be measured before each cycle to avoid docetaxel-associated toxicity.

According to the manufacturer, docetaxel should not be administered to patients who have total bilirubin > ULN or to patients with serum transaminase (AST/ALT) levels > 1.5 $\times$ ULN concurrent with serum alkaline phosphatase levels > 2.5 $\times$ ULN, as there is a higher risk of developing adverse reactions such as toxic death, including sepsis; gastrointestinal hemorrhage, which can be fatal; febrile neutropenia; infections; thrombocytopenia; stomatitis; and asthenia.

7.3.2.6 Cutaneous Reactions

Localized skin erythema of the extremities with edema followed by desquamation has been observed. According to the manufacturer, patients who are dosed at 100 mg/m^2 of docetaxel and experience severe or cumulative cutaneous reactions during docetaxel therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions at a dose of 75 mg/m^2, the dose should be reduced to 55 mg/m^2 or the treatment should be discontinued.

7.3.3 Dose Adjustment for Changes in Body Weight

Baseline body weight is used to calculate required doses of trastuzumab and docetaxel.

The trastuzumab dose should be recalculated only if the patient's weight changes by more than ±10% from baseline.

Docetaxel dose adjustments due to changes in body weight should be based upon the investigative site's institutional standards.

The pertuzumab dose should not be adjusted for body weight.

7.4 Warnings and Precautions for Pertuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate, other than those noted in the Investigator's Brochure.

7.4.1 Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Associated Symptoms

Monoclonal antibodies may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during or very shortly after an infusion. In the pertuzumab single-agent Phase II studies, 41% of patients experienced treatment-related adverse events occurring during or within 24 hours of an infusion. The true rate of infusion-associated reactions may be considerably lower since approximately 5% of patients had such events during an infusion (data from two studies).

To date, 6 patients who have received pertuzumab (approximately 1%) have experienced serious events compatible with infusion-associated reactions or hypersensitivity reactions, or both. Two of these serious events occurred during a pertuzumab infusion (hypersensitivity, urticaria). The remaining four serious cases (pulmonary edema, ARDS, anaphylaxis, hypertension, and dyspnea) occurred following a pertuzumab infusion. In 3 cases, pertuzumab was given after administration of gemcitabine (anaphylaxis, pulmonary edema, hypertension, and dyspnea). Only two of the six cases occurred in the context of the first pertuzumab infusion.

Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each pertuzumab infusion and for 60 minutes following the completion of the infusion for any adverse effects. If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may subsequently be premedicated with acetaminophen, diphenhydramine, or meperidine.

Infusion of pertuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience an NCI-CTCAE Grade 3 or 4 allergic reaction or acute respiratory distress syndrome should not receive additional pertuzumab.

7.4.2 Risk of Cardiotoxicity

Like trastuzumab, pertuzumab is directed at the HER2 receptor and may be associated with a risk of cardiac dysfunction.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan. In pertuzumab single-agent Phase II studies, a fall in LVEF of ≥ 10% to a LVEF value < 50% was observed in 7% of patients who had a post-baseline LVEF assessment. Nine of these patients had received prior anthracycline treatment. Overall, 3 symptomatic cardiac failure events have been reported in approximately 550 patients treated with pertuzumab across all studies. Two of these cases occurred in patients with MBC who had received prior anthracyclines.

Patients with significant cardiac disease or baseline LVEF below 50% are not eligible for this study. Risk factors for pertuzumab-associated cardiac dysfunction are not known at this time, and this risk should be carefully weighed against the potential benefit in patients who have received prior anthracyclines. During the screening/baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-related congestive heart failure, including all prior LVEF assessments.

Monitoring of LVEF is required while patients are receiving study treatment. If symptomatic left ventricular dysfunction develops (NCI-CTCAE Grade 3 or 4) with a drop in LVEF consistent with cardiac failure, the patient must discontinue study treatment. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice.

7.4.3 Risk of EGFR-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors. In the 7-week IV and 26-week toxicity studies in cynomolgus monkeys, there was a treatment-related increase in the incidence of diarrhea. Diarrhea has been observed in approximately 50% of patients being treated with pertuzumab in Phase II single-agent studies, and up to 70% of patients in combination therapy studies, and was NCI-CTC Grade 1 or 2 in the majority of cases. For patients experiencing diarrhea, early intervention with loperamide should be considered.

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

7.5 Warnings and Precautions for Trastuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for trastuzumab.

Trastuzumab therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Serious adverse reactions including cardiotoxicities, infusion reactions, hypersensitivity, allergic-like reactions, and pulmonary events have been observed in patients receiving trastuzumab therapy. These severe reactions were usually associated with the first infusion of trastuzumab and generally occurred during or immediately following the infusion. For some patients, symptoms progressively worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction.

7.5.1 Infusion Reactions, Allergic-Like Reactions, and Hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur, the trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients with dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

7.5.2 Pulmonary Events

Dyspnea, bronchospasm, asthma, and hypoxia can occur as part of an infusion reaction. These are most common with the first infusion, and their severity decreases with subsequent infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. Single cases of pulmonary infiltrates, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and respiratory insufficiency have been reported rarely. Acute respiratory distress syndrome (ARDS) has been reported with fatal outcome.

7.5.3 Cardiotoxicity

Heart failure (NYHA Class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death.

Table 5 Incidence and Severity of Cardiac Dysfunction in Metastatic Breast Cancer

	Trastuzumab Alone [a)] n=213	**Trastuzumab + Paclitaxel [b)] n=91**	**Paclitaxel Alone [b)] n=95**	**Trastuzumab + AC [b)] n=143**	**AC [b)] n=135**
Any cardiac dysfunction	7%	11%	1%	28%	7%
NYHA Class III-IV	5%	4%	1%	19%	3%

AC = anthracycline + cyclophosphamide; NYHA=New York Heart Association.

a) Open-label, single-agent Phase II study (94% received prior anthracyclines)

b) Randomized Phase III study comparing chemotherapy ± Herceptin to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel

Risk factors for trastuzumab-associated cardiotoxity include increased age, concomitant administration with anthracyclines, and declining LVEF while on trastuzumab treatment.

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with the standard medications for this purpose.

The half-life of trastuzumab is approximately 28.5 days (range, 25.5-32.8 days). Trastuzumab may persist in the circulation for up to 24 weeks (range, 18-24 weeks) after stopping trastuzumab treatment. Patients who receive anthracyclines during this period may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy up to 24 weeks after stopping trastuzumab. If anthracyclines are used then the patient should have careful cardiac surveillance.

Most patients who developed heart failure in the Phase III trials of trastuzumab in MBC improved with standard medical treatment. This included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

7.6 Warnings and Precautions for Docetaxel

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for docetaxel.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Efficacy Variable

The primary endpoint is PFS based on IRF evaluations. PFS is defined as the time from randomization to the first documented radiographical progressive disease, as determined by the IRF using current RECIST (Therasse et al. 2000), or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.

8.1.2 Secondary Efficacy Variables

The secondary efficacy variables are as follows:

Overall survival: OS is defined as the time from the date of randomization to the date of death from any cause.

PFS based on investigator assessment: PFS based on investigator assessment is defined as the time from randomization to the first documented radiographic progressive disease, as determined by the investigator using current RECIST (Therasse et al. 2000), or death from any cause, whichever comes first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.

Objective response: Objective response is defined as a CR or PR determined by the IRF using current RECIST (Therasse et al. 2000) on two consecutive occasions ≥ 4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response.

Duration of response: Duration of response is defined as the period from the date of initial confirmed PR or CR until the date of progressive disease or death from any cause. Tumor responses will be based on the IRF evaluations using current RECIST (Therasse et al. 2000).

Time to symptom progression: This is defined as the time from randomization to the first symptom progression in the FACT TOI-PFB. The TOI-PFB is a 24-item subscale generated using 3 subsections from the FACT-B questionnaire: Physical Well-being, Functional Well-being and Additional Concerns. A decrease of five points is considered clinically significant, and thus symptom progression.

Biomarker analysis: The relationship between molecular markers and efficacy outcomes will be evaluated.

8.1.3 Safety Variables

Safety of the treatment will be evaluated as follows:

- Incidence of CHF and asymptomatic LVEF events
- LVEF measurements over the course of the study
- Incidence and severity of AEs and SAEs
- Laboratory test abnormalities

8.2 Statistical and Analytical Methods

This study is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel relative to placebo + trastuzumab + docetaxel in patients with previously untreated MBC. The final analysis for the primary endpoint will take place when approximately 381 IRF-assessed PFS events have occurred. A data cutoff date will be determined when this number of events occurs, and the clinical data on or prior to the data cutoff date will be thoroughly cleaned. The treatment assignment will be unblinded, analyses will be performed, and a clinical study report will be prepared. Assuming there will be 15% fewer IRF-assessed PFS events compared to investigator-assessed events, it is estimated that approximately 448 investigator-assessed PFS events will have been reported at the data cutoff for final PFS analysis.

8.2.1 Statistical Model

The fixed-sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple statistical testing of IRF-assessed PFS, OS **and** objective response rate. The **three** variables will each be tested at an overall two-sided 5% significance level in the order specified. Additional details on the testing procedure will be specified in the statistical analysis plan.

8.2.1.1 Analysis of Primary Variable

The primary endpoint is PFS based on IRF assessments. For patients who discontinue study treatment due to reasons other than death or IRF-assessed progression, every effort will be made to continue tumor assessments until IRF-determined progressive disease or patient death. 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 IRF-evaluable tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day).

For patients whose IRF-determined progression event is not available, surrogating death at any time as a progressive event can artificially prolong the PFS time because of a much longer life expectancy in this patient population compared with PFS. Therefore, only deaths within 18 weeks of the last tumor assessments will be included as an event in the primary analysis. However, a sensitivity analysis will be performed including all deaths as an event.

The log-rank test, stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia), will be used to compare PFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazard model, stratified by prior treatment status and region, will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% confidence interval (CI).

The aforementioned analyses will be performed in demographic subgroup as appropriate, for example analysis may be performed in patient subgroups based on racial origin provided there is a reasonable sample size in the subgroups of interest.

8.2.1.2 Secondary Variables

Overall survival. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. 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. To minimize the chance of a biased OS estimate resulting from scheduled survival follow-up every 18 weeks, immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

PFS based on investigator assessments. 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 investigator tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day). Analysis methods are the same as those described for the primary endpoint.

Objective response. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Patients without a post-baseline tumor assessment will be considered to be non-responders. Analysis of objective response will be based on IRF assessments.

An estimate of the objective response rate and its 95% CI will be calculated for each treatment arm. The difference in objective response rate will also be provided with 95% CIs. The Mantel-Haenszel χ^2 test stratified by prior treatment status and region will be used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test result will also be provided as a sensitivity analysis.

Duration of objective response. Only patients with an objective response will be included in the analysis of duration of objective response. The method for handling censoring is the same as that described for the primary endpoint. Analysis of duration of objective response will be based on IRF assessments.

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

Time to symptom progression. A decrease of five points in TOI-PFB is considered symptom progression. Data for patients who do not have an observed symptom progression will be censored at the last observed TOI-PFB assessment date. If baseline TOI-PFB assessment is unavailable, or if there is no post-baseline TOI-PFB assessment performed, data will be censored at the time of randomization plus 1 day. Analysis methods are the same as those described for the primary endpoint.

Biomarker analyses. To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes will be summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers. Markers to be considered include the status of HER receptors, HER ligands, Fc-γ, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis will be put on markers that have shown association with clinical outcome in patients treated with pertuzumab in previous studies:

- qRT-PCR markers: tumor gene expression profiles associated with HER2 activation
- Baseline serum markers: levels of ECD/HER2 and HER ligands

Efficacy outcomes considered for this analysis will include PFS, objective response rate, and OS. The PFS and objective response will be based on the IRF assessments.

The biomarker analyses at the time of protocol development do not take the form of testing fixed hypotheses involving specific cutoffs or other pre-specified prediction rules. It is planned for the Statistical Analysis Plan (to be generated prior to unblinding of this trial) to use all available scientific evidence from independent studies or publications to specify testable prediction rules. In addition, this plan will specify in due detail how data-adaptive prediction rules will be derived (e.g., systematic cutoff search) and how the inherent multiplicity/bias will be corrected in order to prevent biased conclusions.

The difference in treatment benefit across biomarker statuses defined by a suitable prediction rule will be evaluated by testing the interaction effect of treatment and the prediction status using Cox regression for PFS and OS, and using logistic regression for response rate. These models involving an interaction term will also be used to estimate the conditional efficacy outcomes, conditional on biomarker prediction status or treatment arm, including and excluding the stratification factors into the model.

Clinical covariates can be of prognostic value and could interact with treatment benefit and with biomarker status. Candidates here are baseline variables of prognostic value describing tumour properties and morbidity status or common lab values. Biomarker prediction will be checked involving relevant clinical covariates, which could be part of the biomarker prediction function, if necessary.

See also Section 8.2.5.1, Biomarker Analyses.

8.2.2 Hypothesis Testing

The difference in primary endpoint, IRF-assessed PFS, between the two treatment arms will be compared using a two-sided log-rank test at 5% significance level stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia). The null hypothesis is that the survival distributions of PFS in the two treatment groups are the same. The alternative hypothesis is that the survival distribution of PFS in the treatment and the control arm are different:

$$\mathbf{H_0: S_{<pertuzumab>} = S_{<placebo>} \quad vs. \quad H_1: S_{<pertuzumab>} \neq S_{<placebo>}}$$

Additional tests will be performed to compare whether the distributions or the key summary statistics of the secondary endpoints between the two treatment arms are the same at a two-sided alpha level of 5%. The overall type I error rate for **the analysis of primary endpoint of PFS, OS and ORR** will be controlled **at 5%** using the fixed sequence testing procedure.

8.2.3 Types of Analyses

8.2.3.1 Efficacy Analysis

Analyses of PFS, OS, and time to symptom progression will be based on the intent-to-treat (ITT) population, defined as patients who have been randomized. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only responders will be included in the analysis. All efficacy analyses will be based on the treatment arm to which patients were randomized.

8.2.3.2 Exclusion of Data from Analysis

Intent-to-Treat Population:

All randomized patients will be included in the intent-to-treat population.

Other Efficacy Populations:

See Section 8.2.3.1 for patients who will be excluded from the analyses for objective response and duration of response.

Safety Population:

All patients who received any amount of study medication (docetaxel, pertuzumab/placebo, and/or trastuzumab) and have at least one post baseline safety assessment will be included in the safety population. Analyses will be based on the treatment they actually receive.

8.2.3.3 Interim Safety Monitoring and Interim Safety Analyses

There have been reports of CHF with trastuzumab and pertuzumab treatment. Because of this, left ventricular systolic dysfunction is a potential safety concern for patients who receive the treatments outlined in this study. While on study treatment, patients will be monitored for cardiac events with regular assessments of left ventricular function with either Echocardiography or MUGA. (Echocardiography is the preferred method. The same assessment method, ECHO or MUGA, the same institution/facility, and the same assessor should be used throughout the study, to the extent possible). For patients who experience Grade 1 or 2 left ventricular systolic dysfunction (i.e., asymptomatic decrease in LVEF), an algorithm is provided in Section 7.3.1.1 outlining under which circumstances treatments have to be held and LVEF assessed prior to treatment continuation. Patients who experience CHF (NCI-CTCAE Grade ≥ 3) will have study treatment discontinued. CHF will be reported in an expedited manner to the Sponsors for timely monitoring.

Clinical studies have demonstrated a higher incidence of myelosuppression when trastuzumab is administered with chemotherapy. Limited, non-comparative data from Phase I/II studies suggest that the combination of pertuzumab and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic AEs while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor support will be allowed in this protocol.

A DMC will be convened to monitor patient safety. In addition to the DMC, an independent CRC will review all suspected cases of left ventricular systolic dysfunction. This CRC will report their findings to the DMC every 6 months starting approximately 3 months after the first patient has been enrolled, and at the time of the interim analysis.

To closely monitor patient safety, the DMC will review serious adverse events and investigator-assessed CHF every month through the interim analysis, starting approximately 3 months after the first patient has been enrolled. After the interim safety review, the DMC will review serious AEs and investigator-assessed CHF every 3 months. Moreover, every 6 months, starting approximately 9 months after the first patient has been enrolled, the DMC will receive summaries of serious and non-serious AEs, incidence of CHF assessed by the CRC, and maximum decrease in LVEF measures, and will have a teleconference to discuss their safety findings (the Sponsors will not be allowed to participate in this teleconference).

Cardiac events of Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation/flutter, syncope and seizures will be included in the safety summary for interim DMC review. The incidence of these events will also be monitored by the Sponsors throughout the course of the study.

In addition to the periodic safety monitoring, an interim safety analysis is planned. The interim safety analysis will take place after 100 patients have been enrolled and followed for at least 4 months. The DMC will review all safety data from all patients enrolled and may recommend stopping the study if, among the patients who have been followed for at least 4 months, the incidence of cardiac events (as defined in the CRC charter) based upon the CRC assessment is at least 9.3% higher in the pertuzumab arm compared with the control arm. The DMC may also recommend stopping the study if, in their opinion, the incidence of other clinically significant toxicities, such as neutropenia, neutropenic sepsis, or severe pulmonary toxicity, is unacceptably high in the pertuzumab arm compared with the control arm.

Assuming that the cardiac event rate in the control arm is 5%, the stopping guidance for cardiac event rate is chosen so that the chance of falsely stopping the study at the interim analysis will be < 5% if there is no difference in event rate between two arms. If the event rate in the pertuzumab arm is 10%, the chance of stopping the trial at the interim analysis is approximately 19%. However, if the event rate in the pertuzumab arm is 15%; the chance of stopping the trial at the interim will increase to approximately 47%.

8.2.4 Safety Data Analysis

The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, cardiac-specific AEs, LVEF measurements, and laboratory test results. Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually receive.

Cardiac Safety. The number and percentage of patients with CHF (NCI-CTCAE Grades 3, 4, and 5) and asymptomatic LVEF events (NCI-CTCAE Grades 1 and 2) at any time during the study will be summarized by treatment arm. The summary of CHF will be based on assessments by the independent CRC. LVEF can be measured by either MUGA or ECHO.

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 difference in the maximum absolute decrease in LVEF measure between the two treatment arms will be assessed by the Wilcoxon test. LVEF measurements and change in LVEF from baseline will be summarized by treatment arm and scheduled visits in graphical and tabular format.

For each ECHO/MUGA evaluation following the initiation of study drug, the number and percentage of patients who have had trastuzumab and pertuzumab held and ECHO/MUGA repeated will be summarized. In addition, the change in LVEF at that timepoint will be summarized using descriptive statistics.

In addition, Cox regression model of time to first CHF and time to first CHF or asymptomatic LVEF events will be utilized to explore risk factors for cardiac dysfunction. Optional blood samples for assessment of candidate markers indicative of cardiac dysfunction will be collected periodically from consenting patients for exploratory analysis.

Adverse Events. Verbatim descriptions of treatment-emergent AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI-CTCAE, Version 3.0. All AEs, including SAEs, will be summarized by treatment arm and CTCAE grade. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Laboratory Data. Clinical laboratory tests will be performed at local laboratories. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTCAE, Version 3.0. Select laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm.

8.2.5 Other Analyses

8.2.5.1 Exploratory Biomarker Analysis

The objective of the further statistical analyses of biomarkers is the identification of those markers or combinations of markers which show best association with positive or negative clinical outcome of pertuzumab treatment or safety issues. Special emphasis will be on the identification of markers that discriminate between patients (subgroups) that specifically benefit from the treatment. These biomarker analyses will be explorative. Data on markers (e.g., IHC scores, ISH scores on tumor gene amplification, and DNA mutation data of tumor target genes) will be analyzed, depending on their availability.

According to experience, many biomarkers show a skewed statistical distribution across patients and within patient. Frequently there is also some biochemical background of this skewness; the variation process has a multiplicative structure. Biomarkers with skewed distributions may cause problems when linear statistical approaches (e.g., regression) are to be used. When used as covariates in statistical models, these biomarkers as well can obscure the results. Therefore, suitable transformations need to be found that transform these measurements into distributions with an approximate Gaussian shape. Typical choices in the biomarker area are transformations of the form log $(x + c)$. These transformations do not change the order of the values, such that non-parametric analyses based on ranks or cutoffs remain unchanged by the transformation. Such transformations are also a prerequisite when linear multivariate approaches (e.g., discriminant analysis and principal component analysis) are employed.

The basic statistics and interdependencies of the different markers will be descriptively investigated. Methodological analyses comparing different measurement approaches, e.g., IHC and qRT-PCR, will be performed with regard to reliability and validity.

Exploratory Statistical and Analytical Methods

During the course of an explorative analysis, numerous statistical tests will be performed. The p-values emerging from these analyses will not (and cannot) be interpreted in a confirmative sense; they will be seen as a special descriptive tool in order to guide the analyses toward improved prediction rules.

Markers will be evaluated on a univariate level regarding their potential for prediction (e.g., search or adaptation of cutoffs) of the clinical endpoints. Further multivariate techniques (e.g., linear discriminant analysis, multiple logistic regression, principal component analysis with rotation, cluster analysis, CART methodology) will be employed in order to study combinations of markers.

Biomarker and response correlations with clinical covariates will be investigated. It will be checked whether covariates can improve the prediction and whether there is an interaction with the biomarkers. Relevant covariates could become a part of an explorative biomarker prediction rule.

Candidate groupings derived from biomarker prediction rules will be checked with time-to-event variables (Kaplan-Meier curves, Cox proportional hazard model, log-rank test).

8.2.5.2 Pharmacoeconomic Analysis

The number of hospital visits, number of days admitted, and type of hospital visits (emergency room vs. in-patient care) will be summarized by treatment arm. The Fisher's exact test will be employed to compare the difference in these outcomes between the two treatment arms.

8.3 Sample Size

A sample size of 800 patients is needed to provide 80% power to detect a 33% improvement in OS (HR = 0.75) at the two-sided significance level of 5%. Since both PFS and OS analyses are event-driven, and to avoid prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial is designed to enroll sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of the final PFS analysis.

Assuming that the median OS in the control arm is 36 months and OS is exponentially distributed, one interim analysis at 50% of total required deaths, and a Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary, approximately 385 deaths will be required. In addition, assuming that the accrual rate is approximately 40 patients per month after a 9-month ramp-up period, 800 patients will need to be enrolled and followed for an additional 29.5 months to obtain 385 deaths. The enrollment period is estimated to be 26.5 months, and 50% of the required deaths will be reached at around 33.5 months.

Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it is estimated that 381 IRF-assessed PFS events, corresponding to approximately 448 investigator-assessed events, will have occurred when 50% of the required deaths (193 deaths) is reached. Table 6 lists the power for final PFS analysis at the two-sided significance level of 5% with 381 IRF-assessed PFS events. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.

Table 6 Statistical Power for Final PFS Analysis

Effect size	Power for Log-Rank test of PFS
40% improvement in PFS	90%
33% improvement in PFS	80%

PFS=progression-free survival.

All sample size calculations were performed using East® Version 4 (Cytel, Inc., Cambridge, MA).

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

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

An electronic data capture (EDC) system using electronic Case Report Forms (eCRFs) will be utilized for all data capture required for this study. Exceptions to this include radiographic tumor assessment films (including but not limited to chest X-rays, CT scans, MRI, and bone scans), ECHO/MUGA cardiac assessments, and paper quality-of-life questionnaires completed by the patients. Local clinical laboratory data, including hematology and serum chemistry will be transcribed by the site from the paper laboratory reports onto the eCRF. **In no case is the eCRF to be considered as source data for this trial.**

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche database will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the investigator.

Throughout the study the study management team will review data according to the Data Review Plan as described in the Data Quality Plan.

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up to date version of MedDRA (medical dictionary for regulatory activities terminology) for AEs and diseases and the INN (international non-proprietary name) drug terms and procedures dictionary for treatments and surgical and medical procedures.

Unblinding will not be permitted during the study except for safety issues that arise during study treatment. Treatment unblinding will take place right before the final analysis for the primary endpoint or at the time the DMC recommends trial stopping.

10. STUDY COMMITTEES

This study consists of three independent review committees: an IRF, a CRC, and a DMC. The IRF will be used to independently assess tumor responses. The DMC will be employed to review accumulating safety data for the combination of pertuzumab + trastuzumab + docetaxel. Because cardiac toxicity is a potential safety concern for the pertuzumab + trastuzumab treatment, an independent CRC will be convened to review cardiac assessments and report their findings to the DMC and the Sponsors. An independent data coordination center (DCC) will be employed to perform analyses for DMC reviews.

Independent Review Facility. An independent imaging group will be used to evaluate tumor assessments for determination of progression free survival as a part of the primary objective of the trial. Imaging studies (CT/MRI/bone scans) will be acquired according to a standard protocol and will be transmitted to the independent reviewers. In addition, relevant cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data will be forwarded, if available, to the independent reviewers to aid with assessment of progressive disease and response. Full details are listed in the Independent Imaging Review Charter. Investigator tumor assessments will not be reconciled with the IRF tumor assessments.

Independent Data Monitoring Committee. The DMC will be composed of a group of independent experts including at least one statistician, three medical oncologists, and one cardiologist external to the Sponsors.

The DMC will be responsible for monitoring the safety of patients in the study (see Section 8.2.3.3) for a brief description of the monitoring plan). The DMC will make recommendations to the Sponsors regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study for excessive toxicity. A separate DMC Charter will outline the committee's composition and the members' roles and responsibilities.

Cardiac Review Committee. A group of independent experts will form the Cardiac Review Committee to determine the cardiac event rates. This group will consist of cardiologists who are not Principal Investigators, DMC members, or active (contracted) Genentech or Roche consultants.

The committee members will review patient data profiles and source documents from all potential cases of left ventricular systolic dysfunction, as specified in the CRC charter. The independent cardiac assessments will be provided to the DMC for review every 6 months starting approximately 9 months after the first patient has been enrolled, and at each of the interim analyses. The detailed review process, definition of cardiac events, committee composition, and the member roles and responsibilities will be documented in the CRC charter.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC). For studies conducted in the United States or under U.S. IND, the investigator will additionally adhere to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators," part 50, "Protection of Human Patients," and part 56, "Institutional Review Boards."

In other countries where "Guidelines for Good Clinical Practice" exist, Roche/Genentech and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

It is the responsibility of the investigator or a person designated by the investigator (if acceptable by local regulations) to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, anticipated benefits, objectives, and potential hazards of the study. Appropriate forms for obtaining written informed consent will be provided by the investigator or by Roche/Genentech/designee.

For patients not qualified to give or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his or her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients, including those already being treated, should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.3 Independent Ethics Committees/Institutional Review Board

Independent Ethics Committees (non-U.S. Sites): This protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the patient, will be submitted by the investigator to an IEC. Approval from the committee must be obtained before starting the study and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IEC approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

Institutional Review Board (U.S. Sites): It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures will be reviewed and approved by an IRB. This board must operate in accordance with the current U.S. Federal Regulations. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsors and the investigator. Protocol modifications must be prepared by a representative of the Sponsors and initially reviewed and approved by the Clinical Science Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies, if required. Approval must be received by the investigator before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsors and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche, Genentech, and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

15. STUDY DOCUMENTATION, eCRFs, AND RECORD KEEPING

15.1 Investigator's Files/Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) investigator's study file; and (2) patient clinical source documents.

The investigator's study file will contain the protocol and amendments, IRB/IEC and governmental approval with correspondence, sample Informed Consent Form, drug records, staff curriculum vitae, and authorization forms and other appropriate documents and correspondence, etc. In addition, at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the investigator's study file.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include patient hospital/clinic records; physician's and nurse's notes; appointment book; original laboratory reports; ECG, EEG, X-ray, pathology and special assessment reports; signed Informed Consent Forms; consultant letters; and patient screening and enrollment logs.

The investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, Roche/Genentech must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Roche or Genentech to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator, in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made before storing outside of the site.

15.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

15.3 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit, or Genentech GCP/Quality Assurance Group or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

Data for this study will be captured via an EDC system by using an eCRF. An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change. For each patient randomized, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study treatment, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

This protocol will be co-sponsored by Genentech, Inc., and F. Hoffmann-La Roche, Inc. These Sponsors will oversee the management of this study and will be responsible for clinical operations including site management and source data verification.

Genentech and Roche will identify potential sites for participation in this study. Study networks will be assessed by Genentech and Roche and, where necessary, a Corporate Compliance Group-approved risk mitigation plan will be implemented. The Sponsors will perform pre-trial evaluations at individual sites. The Sponsors will oversee selection, approval, and monitoring of all clinical study sites. Patient eligibility verification will be conducted on all patients identified for enrollment into the study.

Overall monitoring will be managed by the study Sponsors. Statistical analyses and clinical study report preparation will be managed by the Roche staff.

The IVRS will be utilized for collection of patient screening information, randomization, and drug management. It is anticipated that a number of sites will be able to utilize a Central IRB (CIRB), and this will be managed by the Sponsors. Tissue and blood samples will be collected for this study and will be stored and assayed by a central analytical laboratory or the Sponsors. Data from central analytical laboratories will be sent directly to Roche electronically and will not be collected via CRF. Local clinical laboratory data including hematology and serum chemistry will be transcribed by the site from the paper source documents onto the eCRF**.**

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Roche/Genentech, e.g., patients' written Informed Consent Forms, in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

In accord with standard editorial and ethical practice, Roche/Genentech will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Roche/Genentech personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche/Genentech personnel. Authorship will be determined by mutual agreement.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal (results in death) (NOTE: death is an outcome, not an event)
- is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- required in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (Cont.)

Causality is initially assessed by the investigator. For SAEs, possible causes of the event **are** indicated by selecting one or more options (check all that apply):

- Pre-existing/Underlying disease - specify
- Study treatment - specify the drug(s) related to the event
- Other treatment (concomitant or previous) - specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

An SAE occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, an SAE that occurs after this time, if considered related to test “drug,” should be reported.

Such preliminary reports will be followed by detailed descriptions later, which will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

For SAEs, the following must be assessed and recorded on the AEs page of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (Cont.)

For sites outside of the United States

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor (see attached gcp_for000227 for details of administrative and contact information).

ROCHE HEADQUARTERS CONTACT for SAEs: Clinical Operations/Clinical Science (see attached gcp_for000227 for details of administrative and contact information).

Weekends, holidays, and after 5:00 p.m., call the local emergency contact number provided by the Monitor.

For United States sites

GENENTECH HEADQUARTERS CONTACT for SAEs: Drug Safety

Fax: (650) 225-4682 or (650) 225-5288

Weekends, holidays, and after 5:00 p.m., call 1-800-526-6367 and ask for the physician on call.

Appendix 2 ECOG Performance Status Scale (with Karnofsky Equivalent)

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

Appendix 3 NYHA Classification and Left Ventricular Systolic Dysfunction NCI CTCAE version 3.0Grading

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997	

Left Ventricular Systolic Dysfunction NCT CTC AE version 3.0 Grading

Grade1	**Asymptomatic , resting ejection fraction (EF) < 60-50%; shortening fraction (SF) < 30-24%**
Grade 2	**Asymptomatic , resting EF < 50%; SF < 24-15%%**
Grade 3	**Symptomatic CHF responsive to intervention; EF < 40-20%; SF < 15%%**
Grade 4	**Refractory CHF or poorly controlled ; EF < 20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated**
Grade 5	**Death**
Cancer Therapy Evaluation Program> Common Terminology Criteria for Adverse Event. Version 3.0 DCTD.NCI.NIH. DHHS March 31.2003 (http://ctep.cancer.gov. Published December 12.2003	

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000])

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, Ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000]) (Cont.)

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000]) (Cont.)

Response Criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (1)

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UA	Non-PD	No	UA
Non-PD	UA	No	UA

Appendix 4 Tumor Assessments (RECIST [Therasse et al. 2000]) (Cont.)

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of progressive disease at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of Overall Response

- The duration of overall response is measured from the time-measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for progressive disease are met, taking as reference the smallest measurements recorded since the treatment started

Appendix 5 National Cancer Institute-Common Toxicity Criteria AE v3.0

The Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE v3.0) can be found in the Roche handout entitled: ”National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0” or on the following web-site:

http://ctep.cancer.gov

Appendix 6 FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Appendix 6 FACT-B (Version 4) (Cont.)

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box □ and go to the next section.*					
GS7	I am satisfied with my sex life.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

Appendix 6 FACT-B (Version 4) (Cont.)

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

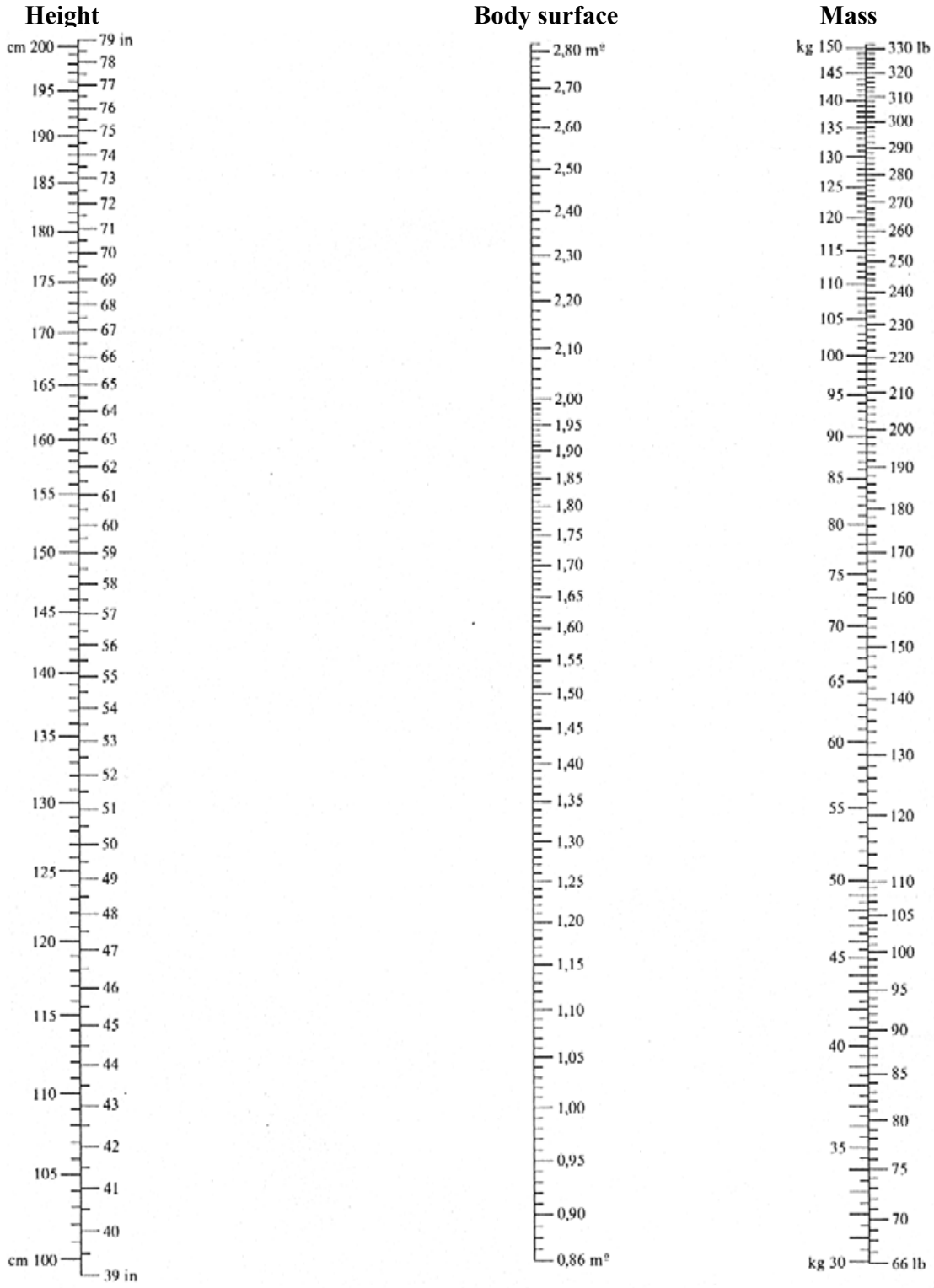
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

Appendix 6 FACT-B (Version 4) (Cont.)

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath.....	0	1	2	3	4
B2	I am self-conscious about the way I dress...	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive.....	0	1	2	3	4
B5	I am bothered by hair loss.....	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have.....	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix 7 Nomogram for the Determination of Body Surface Area



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

History of protocol amendments

Protocol A → Protocol B

AMENDMENT HISTORY FOR PROTOCOL TOC4129G/W020698

Background and Rationale for the Amendment:

Study TOC 4129g/W020698 is a Genentech and Roche-sponsored phase III, randomized, double blind, placebo-controlled, international study designed to evaluate the efficacy and safety of combining pertuzumab with trastuzumab + docetaxel compared with placebo+ trastuzumab+ docetaxel in previously untreated HER2 + metastatic breast cancer. The primary endpoint of the study is progression free survival, as determined by an independent radiological facility. A total of approximately 800 patients (400 per arm) will be randomized in a 1:1 ratio to one of two treatment arms.

Pertuzumab represents a promising new anti-HER2 agent with a novel mechanism of action targeting inhibition of HER dimerization. Non clinical and clinical data generated to date suggest that pertuzumab may provide broader blockade through inhibition of HER2 homo and hetero dimerization. The aim of the study is to provide with adequate efficacy and safety data to allow assessments of the benefit-risk ratio, as well as to support the registration of pertuzumab in patients with HER2 positive metastatic breast cancer, previously untreated for their metastatic disease.

The study protocol was reviewed by the FDA on 5th November 2007 and recommendations were made for some changes to the protocol. This amendment was issued following these recommendations.

The objectives of the amendment are:

As per discussion with FDA on 5th November 2007:

1. To collect all pre-study LVEF values during and post- trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study.
2. To collect additional ECGs during study treatment and to perform additional LVEF assessments post-study treatment discontinuation for up to 3 years.
3. To correct the reporting of cardiac heart failure (CHF) to symptomatic left ventricular systolic dysfunction accordingly to NCICTCAE version 3.0.
4. To clarify and update further the statistical analysis plan regarding duration of objective response and make further clarification in the Statistical Considerations and Analytical plan (section 8.2).
5. To collect additional samples for determination of anti-therapeutic antibodies to pertuzumab during study treatment.
6. To add an interim hematology blood test during study treatment.
7. To clarify and reinforce the minimum CT/MRI scans required at baseline and through the study.

8. To collect every 18 weeks post-study treatment cancer related medical or surgical procedures and therapies.

The sponsors would like to take the opportunity of this amendment to make the following additional changes to the protocol:

1. To clarify further the patient disease definition in the Inclusion Criteria 1: patients with measurable and non measurable disease will be eligible.
2. To complete the definition of HER2 positive patients in Inclusion Criteria 2 , as per the definition given in Section 5.3.
3. To-update the regulatory requirements section for the reporting of serious adverse events.
4. To update the reporting and follow up of cardiac adverse events, following additional LVEF assessments after study treatment discontinuation.
5. To correct the allowed methods of contraception.
6. To add collection of Magnesium electrolyte in all biochemistry tests performed at baseline and during study treatment.
7. To inform that the Informed consent form will be updated to include the changes concerning the additional ECG . LVEF assessments, and serum samples for antibodies to pertuzumab and correct as well the information regarding the allowed method of contraception during study treatment.

The following changes have been made to the protocol:

1. SUBJECT: INCLUSION CRITERIA

Reason for change:

To collect all pre-study LVEF values during and post trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study. The e-CRF will be revised to include this information.

Section 4.2 Inclusion Criteria

New text:

inclusion criteria 4: **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.**

Old text:

Not applicable

2. SUBJECT SCHEDULE OF ECG

Reason for change:

To perform and collect additional ECGs during study treatment.

Section 5.4.1: Treatment Period Assessments and Procedures: 12-lead ECG

New text:

12-Lead ECG **will be done every 9 weeks (within 3 days prior to study drug administration).**

Old text:

12-Lead ECG as clinically indicated

Section 5.4.2 Post- Treatment Follow-up Assessments and Procedures(Including Treatment Discontinuation Visit): 12-lead ECG

New text:

12-Lead ECG will be performed at the treatment discontinuation visit.

Old text:

12-Lead ECG will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and as clinically indicated through Week 18 post-treatment.

3. SUBJECT SCHEDULE OF LVEF

Reason for change:

To add LVEF assessments during follow-up period in order to allow long term follow-up of cardiac function. To update LVEF assessments follow-up schedule for patients for whom study treatment was discontinued for drop in the LVEF.

Section 5.4.2 Post –Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit): LVEF Assessments

New text:

LVEF assessments. For all patients, LVEF assessments at the treatment discontinuation visit **, then every 6 months in the first year, then annually for up to 3 years**. Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment.**

Old text:

LVEF assessments. For all patients, LVEF assessments should be conducted at Week 9 and Week 18 post-treatment. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.

Section 7.2.3 Reporting of Cardiac Adverse Events, Table 4 , Note to foot note

New text:

Note:. Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment.**

Old text:

Note: Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.

4. SUBJECT METHOD OF CODING SYMPTOMATIC AND ASYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION:

Reason for change:

In the current version of the protocol, symptomatic left ventricular systolic dysfunction is to be reported as congestive heart failure (CHF). In the amended version of the protocol, symptomatic left ventricular systolic dysfunction will be reported and graded according to NCI-CTCAE Version 3.0 for left ventricular systolic dysfunction. Table 4 Section 7.2.3 is also revised to include these changes.

Section 7.2.3 Reporting of Cardiac Adverse Events;

New text:

Symptomatic left ventricular systolic dysfunction (congestive heart failure, CHF) should be reported as an SAE and a diagnosis and not as individual signs and symptoms thereof. **Symptomatic left ventricular dysfunction** must also be reported on **the Symptomatic left Ventricular Systolic Dysfunction** eCRF. Specific related signs and symptoms will be entered on the eCRF. CHF should be graded according to NCI-CTCAE Version 3.0 for "left ventricular systolic dysfunction" and the NYHA classification (see Appendix 3).

Old text:

Symptomatic left ventricular systolic dysfunction should be reported as an SAE as congestive heart failure (CHF) and not as individual signs and symptoms thereof. CHF must also be reported on the Congestive Heart Failure eCRF. Specific related signs and symptoms will be entered on the eCRF. CHF should be graded according to NCI-CTCAE Version 3.0 for “left ventricular systolic dysfunction” and the NYHA classification (see Appendix 3).

These changes have been made as well in Table 4: Reporting Conventions for left Ventricular Systolic Dysfunction, as below.

New Table:

Observation	How to report	Term to be reported	Grading
Asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50%	AE (eCRF AE eform)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE eform) and Non-Serious Event of Special interest (SAE form)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Symptomatic left ventricular systolic dysfunction (Congestive Heart Failure)	**Symptomatic left ventricular systolic dysfunction** eCRF and SAE (SAE form)	**Left ventricular systolic dysfunction**	NCI-CTCAE for "left ventricular systolic dysfunction" and NYHA criteria
Asymptomatic decline in LVEF to a value higher than 10 percentage points below Baseline, or Asymptomatic decline to a value 10 percentage points below baseline or lower, but ≥ 50%	Record on LVEF eCRF, not AE eCRF	N/A	N/A

LVEF=left ventricular ejection fraction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; AE=adverse event; SAE=serious adverse event; eCFR=electronic case report form.

Old Table:

Observation	How to report	Term to be reported	Grading
Asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, *and* < 50%	AE (eCRF AE eform)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE eform) and Non-Serious Event of Special interest (SAE form)	Left ventricular systolic dysfunction	NCI-CTCAE for "left ventricular systolic dysfunction"
Symptomatic left ventricular systolic dysfunction (Congestive Heart Failure)	CHF eCRF and SAE (SAE form)	Congestive heart failure	NCI-CTCAE for "left ventricular systolic dysfunction" and NYHA criteria
Asymptomatic decline in LVEF to a value higher than 10 percentage points below Baseline, or Asymptomatic decline to a value 10 percentage points below baseline or lower, but ≥ 50%	Record on LVEF eCRF, not AE eCRF	N/A	N/A

LVEF=left ventricular ejection fraction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; AE=adverse event; SAE=serious adverse event; eCFR=electronic case report form.

5. SUBJECT: PREGNANCY TESTS

Reason for change:

To change the requirement of pregnancy testing from “should be” to “must be” performed. To add the following sentence “women who have undergone a surgical sterilization are exempt from pregnancy testing”.

Section 5.3 Procedures for Screening and Baseline

New text:

Pregnancy Test. A serum β-HCG test **must** be performed for all pre-menopausal women of childbearing potential and for all women < 2 years after the onset of menopause. Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. **Women who have undergone surgical sterilization are exempt from this assessment.**

Old text:

Pregnancy Test. A serum β-HCG test should be performed for all women of childbearing potential and for all women < 2 years after the onset of menopause. Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

Pregnancy test. For women of childbearing potential, a urine pregnancy test **must** be administered every 3 cycles within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated), regardless of the contraceptive method. Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory . Pregnancy test results must be available prior to the drug infusion. **Women who have undergone surgical sterilization are exempt from this assessment.**

Old text:

Pregnancy test. A urine pregnancy test should be administered every 3 cycles within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated). Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory. Pregnancy test results must be available prior to the drug infusion.

Section 5.4.2 Post- Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit)

New text:

Pregnancy test**.** A urine pregnancy test **must** be administered at the treatment discontinuation visit regardless of contraceptive method. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory. **Women who have undergone surgical sterilization are exempt from this assessment.**

Old text:

Pregnancy test. A urine pregnancy test should be administered at the treatment discontinuation visit. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory.

Section 5.4.3 Local Laboratory Assessments

New text:

For women of childbearing potential pregnancy tests **must** be performed via serum β-HCG at baseline. **Women who have undergone surgical sterilization are exempt from this assessment.**

Old text:

Women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline.

6. SUBJECT : ANTI-THERAPEUTIC ANTIBODIES TO PERTUZUMAB

Reason for change:

To increase the surveillance for antibody formation to pertuzumab. In the current version, serum samples for testing antibodies to pertuzumab will be collected from all patients who are eligible and will be enrolled into the study at baseline and at Treatment Discontinuation Visit . Additional samples will be collected during study treatment; prior to Cycle 3 then every 9 weeks through Treatment Discontinuation Visit.

Section 5.4.1Treatment Period Assessments and Procedures

New text:

Serum samples for antibodies to pertuzumab will be collected every 9 weeks, starting from Cycle 3, until Treatment discontinuation Visit.

Old text:

Not applicable

Section 5.4.5 Anti-Therapeutic Antibodies to Pertuzumab

New text:

within 7 days prior to the first administration of study medication **then every 9 weeks, starting from Cycle 3** and at the time of the treatment discontinuation visit, serum samples (5 ml blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study sponsors.

Old text:

within 7 days prior to the first administration of study medication and at the time of the treatment discontinuation visit, serum samples (5 ml blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study sponsors.

7. SUBJECT: STATISTICAL CONSIDERATIONS

Reason for change:

To clarify and update further the statistical analysis plan regarding duration of objective response and make further clarification in the Statistical Considerations and Analytical plan (Section 8.2).

Section 8.2.1 Statistical Model

New text:

The fixed-sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple statistical testing of IRF-assessed PFS, OS **and** objective response rate. These **three** variables will each be tested at an overall two-sided 5% significance level in the order specified**.**

Old text:

The fixed-sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple statistical testing of IRF-assessed PFS, OS, objective response rate and duration of response. These four variables will each be tested at an overall two-sided 5% significance level in the order specified.

Section 8.2.1.1 Analysis of Primary Variable

New text:

The aforementioned analyses will be performed in demographic subgroup as appropriate, For example, analysis may be performed in patient subgroups based on racial origin provided there is a reasonable sample size in the subgroups of interest.

Old text:

Not applicable

Section 8.2.1.2 Secondary Variables

New text:

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

Old text:

Duration of objective response will be estimated using the Kaplan-Meier approach. Comparisons between treatment arms using the unstratified log-rank test and estimation of hazard ratio using Cox regression will also be made.

Section 8.2.2 Hypothesis Testing

New text:

The overall type I error rate for the primary **end point of PFS, OS and ORR** will be controlled **at 5%** using the fixed sequence testing procedure.

Old text:

The overall type I error rate for the primary and the OS analysis will be controlled using the fixed sequence testing procedure.

8. SUBJECT: INTERIM HEMATOLOGY BLOOD TEST

Reason for change:

To add a hematology test on Day 8 of each treatment cycle during chemotherapy , in order to better characterize the safety profile of the combination of pertuzumab with docetaxel.

Section 5.4.1 Treatment period Assessments and Procedure: Hematology and Chemistry

New text:

Hematology and blood chemistry will be collected and submitted to a local laboratory within 3 days prior to administration of each study treatment, and when clinically indicated (see Section 5.4.3). **An additional hematology blood test will be performed on day 8 of each treatment cycle during chemotherapy.**

Old text:

Hematology and blood chemistry will be collected and submitted to a local laboratory within 3 days prior to administration of each study treatment, and when clinically indicated (see Section 5.4.3).

Section 5.4.3 Local Laboratory Assessments: Hematology

New text:

Hematology. Testing will be performed at baseline, within 3 days before the start of every chemotherapy cycle, **on Day 8 of each treatment cycle during chemotherapy,** at the treatment discontinuation visit, and when clinically indicated.

Old text:

Hematology. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the treatment discontinuation visit, and when clinically indicated

9. SUBJECT: TUMOR ASSESSMENT

Reason for change:

To accurately describe the specified tumor assessment scans required at baseline and during study treatment. All patients will have as a minimum a CT or MRI of chest and abdomen at baseline and through study treatment. PET scans will not be considered for assessment of efficacy at any time during the study.

Section 5.3 Procedures for Screening and Baseline

New text:

All patients should have a minimum of a chest and abdomen CT or MRI scan. PET scans will not be considered for assessment of efficacy at any time during the study.

Old text:

Not applicable

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

All patients should have a minimum of a chest and abdomen CT or MRI scan. PET scans will not be considered for assessment of efficacy at any time during the study.

Old text:

Not applicable

Section 5.4.4 Tumor Assessments

New text:

CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals). **PET scans will not be considered for assessment of efficacy at any time during the study.**

Old Text:

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

10. SUBJECT: POST STUDY TREATMENT CANCER RELATED MEDICAL OR SURGICAL PROCEDURES AND THERAPIES

Reason for change:

To collect and record post study treatment cancer related medical or surgical procedures and therapies every 18 weeks after study discontinuation.

Section 5.4.2 Post-Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation)

New text:

Post study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be collected and recorded **every 18 weeks during the follow-up period** , including the dates and description of the procedure(s) or therapies, and any clinical findings.

Old text:

Post–study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be recorded **,** including the dates and description of the procedure(s) or therapies, and any clinical findings.

CHANGES SUGGESTED BY THE SPONSORS:

11. SUBJECT: INCLUSION CRITERIA

Reason for change:

To clarify that patients with measurable and non-measurable disease are eligible (inclusion criteria 1). To add definition of FISH positive (FISH amplification ratio ≥2.0) in the inclusion criteria 2, as specified in Section 5.3; procedure for screening and baseline. To correct an error in criterion 8 which is in fact apart of criterion 7.

Section 4.2 Inclusion Criteria

New text:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. **Patients with measurable and non-measurable disease are eligible.**

2. HER2 positive **(defined as 3+ IHC or FISH amplification ratio ≥ 2.0)** MBC confirmed by a Sponsor-designated central laboratory.

Old text:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy.

2. HER2-positive (FISH-positive or IHC 3 +) MBC confirmed by a Sponsor-designated central laboratory.

12. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To correct an error in criterion 8 which is in fact apart of criterion 7.

Section 4.3 Exclusion Criteria

New text:

7 Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.

Old text:

7 Current clinical or radiographic evidence of central nervous system (CNS) metastases

8 CT or MRI scan of the brain is mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.

13. SUBJECT: GRADING OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Reason for change:

To add to Appendix 3, table of NCI CTCAE version 3.0, for grading of Left Ventricular Systolic Dysfunction.

Section Appendix 3

New Table:

Left ventricular systolic dysfunction NCT CTC AE Grading

Grade1	**Asymptomatic , resting ejection fraction (EF) < 60-50%; shortening fraction (SF) < 30-24%**
Grade 2	**Asymptomatic , resting EF < 50%; SF < 24-15%%**
Grade 3	**Symptomatic CHF responsive to intervention; EF < 40-20%; SF < 15%%**
Grade 4	**Refractory CHF or poorly controlled ; EF < 20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated**
Grade 5	**Death**
Cancer Therapy Evaluation Program> Common Terminology Criteria for Adverse Event. Version 3.0 DCTD.NCI.NIH. DHHS March 31.2003 (http://ctep.cancer.gov. Published December 12.2003	

Old Table:

Not applicable

14. SUBJECT: CONTRACEPTIVE METHODS

Reason for change:

To remove oral contraceptive pills and hormonal implants in the allowed method of contraception.

Section 4.2 Inclusion Criteria

New text:

For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method **[condoms, diaphragm], intrauterine devices, or abstinence**) and to continue its use for the duration of study treatment and for 6 months after the last dose of study treatment.

Old text:

For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) and to continue its use for the duration of study treatment and for 6 months after the last dose of study treatment

Section 7.2.6 Pregnancy

New text:

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy. In pre-menopausal patients of childbearing potential and women < 2 years after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment (**e.g, a reliable barrier method [condoms, diaphragm]; intrauterine devices; surgical methods, or abstinence**).

Old text:

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy patients of childbearing potential and women < 2 years after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment (e.g., birth control pills, barrier method [condoms, diaphragm]; intrauterine devices; surgical methods, or abstinence).

15. SUBJECT: REPORT OF SERIOUS ADVERSE EVENT

Reason for change:

To add the following sentence in Section 7.1.1.3 in order to comply with all regulatory requirements for reporting of serious adverse events: “The study will comply with all local regulatory requirements”.

Section 7.1.1.3 Serious Adverse Event

New text:

The study will comply with all local regulatory requirements. and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2 (see Appendix 1).

Old text:

The full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2, will be adhered to (see Appendix 1).

16. SUBJECT : REPORTING AND FOLLOW UP OF CARDIAC ADVERSE EVENTS

Reason for change:

To update the reporting and follow up of cardiac events following additional LVEF assessments post-study treatment for up to 3 years, in order to collect symptomatic left ventricular dysfunction for up to 3 years following the study treatment discontinuation.

Section 7.2.3 Reporting of Cardiac Adverse Events

New text:

All cardiac AEs occurring during the study and up to 12 months after last administration of study medications must be reported irrespective of causal relationship (related and unrelated) or **seriousness** (serious or non-serious). **Symptomatic left ventricular systolic dysfunction NCI CTCAE ≥ Grade 3 (CHF) must be reported for up to 3 years after the treatment discontinuation visit.**

Old text:

All cardiac AEs occurring during the study and up to 12 months after last administration of study medications must be reported irrespective of causal relationship (related and unrelated) or severity (serious or non-serious).

Section 7.2.4 Follow up of AEs and Post-Treatment AE Collection: Cardiac events

New text:

Symptomatic left ventricular systolic dysfunction (regardless of causality) that start up to 3 years after the last dose should be reported. These events should be followed until resolution/stabilization /death or until investigator confirmation that no further improvement can be expected or until the survival follow-up for the study is complete.

Old text:

Not applicable

Section 5.4.2 Post- Treatment Follow-up Assessments and Procedures (Including Treatment Discontinuation Visit): Adverse Events

New text:

Adverse Events. All AEs and SAEs should be collected through the treatment discontinuation visit. Cardiac adverse events occurring up to 12 months after last administration of study medications must be reported irrespective of causal relationship or treatment assignment. **Symptomatic left ventricular systolic dysfunction (NCICTCAE ≥ Grade 3) irrespective of causal relationship and treatment assignment must be reported up to 3 years after the treatment discontinuation visit.** See Section 7.2.4 for full details of post-treatment discontinuation visit AE reporting requirements

Old text:

Adverse Events. All AEs and SAEs should be collected through the treatment discontinuation visit. All cardiac adverse events occurring up to 12 months after last administration of study medications must be reported irrespective of causal relationship or treatment assignment.. See Section 7.2.4 for full details of post-treatment discontinuation visit AE reporting requirements.

Section 8.2.3.3 Interim Safety Monitoring and Interim Safety Analyses

Reason for change:

To update the interim safety Monitoring and Interim safety Analysis to include the collection of cardiac events such as Torsade de pointes, ventricular tachycardia, ventricular fibrillation/flutter, syncope and seizures.

New text:

Cardiac events of Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation/flutter, syncope, and seizures will be included in the safety summary for interim DMC review. The incidence of these events will also be monitored by the Sponsors throughout the course of the study.

Old text:

Not applicable

17. SUBJECT : BIOCHEMISTRY TEST

Reason for change:

To collect magnesium in biochemistry test at baseline and in all biochemistry tests during the study.

Section 5.4.3 Local Laboratory Assessments

New text:

Biochemistry test NA+, K+, bicarbonate, CL^-, BUN/Urea, C++, **Mg ,** uric acid , total bilirubin

Old text:

Biochemistry test NA+, K+, bicarbonate, CL^-, BUN/Urea, C++ **,** uric acid , total bilirubin

18. SUBJECT : DEMOGRAPHICS

Reason for change:

To update the information collected regarding demographics (i.e., age, sex, race and ethnicity).

Section 5.3 Procedures for Screening and Baseline

New text:

Complete medical history and demographics **(i.e., age, sex, race and ethnicity)** including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or therapies.

Old text:

Complete medical history and demographics including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or therapies.

Section 5. Schedule of Assessments: foot note d

New text:

Complete medical history and demographics **(i.e., age, sex, race and ethnicity)**, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or therapies.

Old text:

Not applicable.

19. SUBJECT BIOMARKER REPOSITORY SAMPLES

Reason for change:

To clarify collection of BSR samples.

Sections 5.4.2 and 5.4.7.5 and foot note Table 1

New text:

If IRF- determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment week 18.

Old text:

If IRF- determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected at the time of scheduled LVEF assessments every 9 weeks until post-treatment week 18.

20. SUBJECT: SCHEDULE OF ASSESSMENTS AND PROCEDURES

Reason for change:

To revise Table 1 for the schedule of assessments, as well as the foot note instructions to Table 1, in order to include all the modifications cited above.

Section 5 Schedule Of Assessments And Procedures

New Table:

Table 1 Schedule of Assessments

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles (9 weeks)	Treatment Discontinuation Visit [b]	Week 18 post Treatment	Every 18 weeks	Up to 3 years
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post -Treatment**	**126 Days Post-Treatment**	**Every 126 Days**	
Informed consent	x [c]								
Complete Medical History, including Demographics	x [d]								
Review of Inclusion and Exclusion criteria	x								
Complete Physical Examination, and Vital Signs	x		x			x			
Symptoms- directed Physical Exam, and Vital Signs			x [e]						
12 Lead Electrocardiogram (ECG)	x				**x** [f]	x [f]			
Chest X- ray	x		If clinically indicated			x [g]	If clinically indicated		
ECOG Performance Status	x		x			x	Every 9 weeks at the time of each tumor assessment [h, i]		
Fact-B- Quality of Life (Females Only)		x	Every 9 weeks within 3 days prior to each tumor assessment [i]						
Tumor Assessments	x		Perform every 9 weeks from randomization until IRF- confirmed progressive disease [i]						
LVEF by ECHO or MUGA	x [j]		Perform every 9 weeks from randomization [k]			x	**Every 6 months in the first year, then annually for up to 3 years [k]**		
Bone scan	x		If clinically indicated			x [g]	If clinically indicated until IRF-confirmed progressive disease [i]		
Adverse Events	x [l]		Ongoing [m]				Ongoing [m]		
Concomitant Meds and Cancer –related Surgery /Procedures			Ongoing			**Ongoing**			
Pertuzumab / Placebo Administration			x [n]						
Trastuzumab Administration			x [o]						
Docetaxel Administration			x [p]						

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles (9 weeks)	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks	Up to 3 years
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days Post Treatment**	**126 Days Post - Treatment**	**Every 126 Days**	
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [c]								
Hematology, at local lab		x [q]	x [q]	**x** [q]		x			
Biochemistry, at local lab		x [q]	x [q]			x			
INR and aPTT, at local lab		x	x [r]						
Pregnancy test, at local lab (If applicable)		x [s]			x [s]	x [s]			
Serum for Trastuzumab PK, to central lab		x [t, u]							
Serum for Antibodies to Pertuzumab, to central lab		x [u]			**x**[v]	x			
Serum for HER2 ECD& HER Ligands, to central lab		x [u]	Every 9 weeks at the time of each tumor assessment [i]						
Whole Blood for FCγ Polymorphism (clinical genotyping), to central lab		x [u, w]							
Samples requiring separate informed consent									
Metastatic Tumor for Biomarkers, to central lab		x [u]							
Serum & Plasma Biomarker Sample Repository (BSR), to central lab		x [u]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post-treatment) [i, x]						
Record Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies							ongoing [y]		
Survival information							x	x [y]	

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Complete medical history and demographics **(i.e. age, sex, race and ethnicity)** and all medications taken the last 90 days prior to randomization will be collected

[e] Symptom-directed physical examination including vital signs and weight will be assessed every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

[f] 12 lead ECG will be performed at baseline**, then every 9 weeks (within 3 days prior to study drug administration) during study treatment,** then at the study treatment discontinuation.

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

[h] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[i] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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 have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study.**

[j] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.**

[k] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization until Treatment Discontinuation Visit, **then every 6 months in the first year , then annually for up to 3 years**. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever occurs first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment.**

[l] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[m] See Section 7.2 for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[o] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[p] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity).

[q] See Section 5.4.3 below for specific required tests. 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. **An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.**

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

[s] For women of childbearing potential, pregnancy tests **must** be performed via serum β-HCG at baseline. During the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion. **Women who have undergone surgical sterilization are exempt from this assessment**.

[t] Collect and submit only for patients that have received prior trastuzumab.

[u] Collect and submit only if patient is determined to be eligible and will be randomized onto the study, but prior to the first study drug dose.

[v] **Serum samples for antibodies to Pertuzumab will be collected at baseline and every 9 weeks during study treatment, until Treatment Discontinuation Visit**.

[w] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18**.

[y] Collect post–study treatment cancer-related medical or surgical procedures and therapies **every 18 weeks during the follow-up period** and survival information until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

Old text:

Table 1 Schedule of Assessments

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Informed Consent	× [c]					
Complete Medical History, including Demographics	×					
Review of Inclusion and Exclusion Criteria	×					
Complete Physical Examination, and Vital Signs	×					
Symptom-directed Physical Exam, and Vital Signs			× [d]	×		
12-Lead Electrocardiogram (ECG)	×		If clinically indicated	×[e]	If clinically indicated	
Chest X-ray	×		If clinically indicated	× [e]	If clinically indicated	
ECOG Performance Status	×		×	×	Every 9 weeks at the time of each tumor assessment [f, g]	
FACT-B- Quality of Life (Females ONLY)		×	Every 9 weeks within 3 days prior to each tumor assessment [g]			
Tumor Assessments	×		Perform every 9 weeks from randomization until IRF-confirmed progressive disease [g]			
LVEF by ECHO or MUGA	× [h]		Perform every 9 weeks from randomization until 18 Weeks post-treatment [i]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Bone Scan	×		If clinically indicated	× [e]	If clinically indicated until IRF-confirmed progressive disease [g]	
Adverse Events	× [j]		Ongoing [k]		Ongoing [k]	
Concomitant Meds and Cancer-related Surgery/Procedures			Ongoing			
Pertuzumab/placebo Administration			× [l]			
Trastuzumab Administration			× [m]			
Docetaxel Administration			× [n]			
Samples						
Tumor for HER2 Eligibility & Biomarkers, to central lab	× [c]					
Hematology and Blood Chemistry, at local lab		× [o]	× [o]	×		
INR and aPTT, at local lab		×	× [p]			
Pregnancy Test, at local lab *(If applicable)*		× [q]	× (q3cycles) [q]	× [q]		
Serum for Trastuzumab PK, to central lab		× [r, s]				
Serum for Antibodies to Pertuzumab, to central lab		× [s]		×		
Serum for HER2 ECD & HER Ligands, to central lab		× [s]	Every 9 weeks at the time of each tumor assessment [g]			

Table 1 Schedule of Assessments (Cont.)

	Screening/ Baseline		Treatment Period [a]	Follow-Up [a]		
			Every Cycle *(Cycle = 21 Days)*	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks
Day	**-28 to -1**	**-7 to -1**	**1**	**28 – 42 Days Post-Treatment**	**126 Days Post-Treatment**	**Every 126 Days**
Whole Blood for Fcγ Polymorphism (clinical genotyping), to central lab		× [s,t]				
Samples requiring separate informed consent						
Metastatic Tumor for Biomarkers, to central lab		× [s]				
Serum & Plasma for Biomarker Sample Repository (BSR), to central lab		× [s]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post –treatment) [g, u]			
Record Post Study Treatment Cancer-related Medical or Surgical Procedures and Therapies				Ongoing [v]		
Survival Information					×	× [v]

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Symptom-directed physical examination including vital signs and weight will be assessed every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

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

[f] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[g] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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.

[h] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization.

[i] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever occurs first.

[j] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[k] See Section 7.2 for adverse event reporting and follow-up requirements.

[l] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[m] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[n] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity).

[o] See Section 5.4.3 below for specific required tests. 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.

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

[q] For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline. During the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[r] Collect and submit only for patients that have received prior trastuzumab.

[s] Collect and submit only if patient is determined to be eligible and will be randomized onto the study, but prior to the first study drug dose.

[t] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[u] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment week 18, BSR samples will continue to be collected at the time of the scheduled LVEF assessments every 9 weeks until post-treatment Week 18**.

[v] Collect post–study treatment cancer-related medical or surgical procedures and therapies and survival information until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

History of protocol amendments

Protocol B → Protocol C

AMENDMENT HISTORY FOR PROTOCOL TOC4129G/W020698

Background and Rationale for the Amendment:

Reproductive toxicity data was recently published in the Investigator Brochure version 8 February 2008, and of particular interest is that pertuzumab caused oligohydramnios, delayed renal development and embryo-fetal deaths in pregnant cynomolgus monkeys. To date no fetal studies in humans have been performed. Therefore, pertuzumab should not be used in pregnant women and women receiving pertuzumab should avoid pregnancy during study treatment and for at least 6 months after completion of study treatment, due to the long half life of the drug. Recently, one pregnancy was reported in the WO20697 study (A randomised, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer), the patient underwent a therapeutic termination at 7 weeks. Consequently, the decision was made to review the contraception requirements in conjunction with the recommendations from the MHRA and ICH M3 and to update the inclusion criterion and pregnancy section as deemed appropriate for this study.

The objectives of the amendment are:

1. To clarify the wording of inclusion/exclusion criteria.
2. To update the definition of postmenopausal women and to update the contraceptive requirements for women of child bearing potential, for male patients with partners of child bearing potential and pregnant partners as recommended by the MHRA in accordance with ICH M3
3. To provide clarification and to correct minor errors throughout the protocol which may lead to assessments or data collection at incorrect time points.
4. To allow the use of alternative methods of assessing bone disease in patients in circumstances where there is an isotope shortage meaning that a bone scan cannot be performed.
5. To provide further guidance for the completion of the FACT-B questionnaire.
6. To clarify docetaxel administration and discontinuation
7. To update the drug destruction policy

The following changes have been made to the protocol:

1. SUBJECT: INCLUSION CRITERIA

Reason for change:

To provide clarification for inclusion into the study of patients with only bone metastases.

Section Synopsis & 4.2 Inclusion Criteria

New text:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. Patients with measurable and/**or** non-measurable disease are eligible.

   Patients with *only* bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for central HER 2 testing and subsequent biomarkers analysis.

Old text:

1. Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. **Patients with measurable and non-measurable disease are eligible**

2. SUBJECT: INCLUSION CRITERIA

Reason for change:

To provide clarification for inclusion into the study using metastatic tumor samples.

Section Synopsis & 4.2 Inclusion Criteria

New text:

2. HER2-positive (**defined as 3+ IHC or FISH amplification ratio ≥ 2.0**) MBC 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 if the primary is not available)** be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.)

Old text:

2 HER2-positive (**defined as 3+ IHC or FISH amplification ratio ≥ 2.0**) MBC confirmed by a Sponsor-designated central laboratory. It is strongly recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor be submitted for central laboratory confirmation of HER2 eligibility; however, if that is not possible, 25 unstained and freshly cut slides will be submitted. (Tissue will subsequently be used for assessment of biomarkers.)

3. SUBJECT: INCLUSION CRITERIA

Reason for change:

To update the definition of postmenopausal women and to update the contraceptive requirements for women of child bearing potential, for male patients with partners of child bearing potential and pregnant partners as recommended by the MHRA in accordance with ICH M3.

Section Synopsis & 4.2 Inclusion Criteria

New text:

6. **For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly-effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy. For further details see Section 7.2.6.**

Old text:

6. For women of childbearing potential, agreement to use an effective form of contraception (patient and/or partner, e.g., surgical sterilization, a reliable barrier method **[condoms, diaphragm], intrauterine devices, or abstinence)** and to continue its use for the duration of study treatment and for 6 months after the last dose of study treatment**.**

Section 5.3 Procedures for Screening and Baseline

New text:

- Pregnancy Test. A serum β-HCG test **must** be performed for all women of childbearing potential, and for all women **not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization.** Testing should be performed at a local laboratory **within 7 days** prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.4.3).

Old text:

- Pregnancy Test. A serum β-HCG test **must** be performed for all women of childbearing potential and for all women < 2 years after the onset of menopause. Testing should be performed at a local laboratory **within 7 days** prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section **5.4.3**). **Women who have undergone surgical sterilization are exempt from this assessment.**

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

- Pregnancy test. **For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization.** A urine pregnancy test **must** be administered within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated). Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3). Pregnancy test results must be available prior to the drug infusion.

Old text:

- Pregnancy test. A urine pregnancy test **must** be administered within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated). Any positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3). Pregnancy test results must be available prior to the drug infusion. **Women who have undergone surgical sterilization are exempt from this assessment.**

4. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To provide clarification on prior hormonal regimen in the MBC setting.

Section Synopsis & 4.3 Exclusion Criteria

New text:

1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC **which must be stopped prior to randomization**).

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

   One prior hormonal "regimen" for MBC may include more than one hormonal therapy, for example, if the switch is not related to disease progression, such as toxicity or local standard practice, this will be counted as one "regimen".

   If a patient receives hormonal therapy for MBC and is switched to a different hormonal therapy due to disease progression, this will be counted as two "regimens" and the patient is not eligible.

Old text:

1. History of anticancer therapy for MBC (with the exception of one prior hormonal regimen for MBC).

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

5. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To amend exclusion criteria 6 to allow patients with past squamous cell carcinoma to be enrolled into the study.

Section Synopsis & 4.3 Exclusion Criteria

New text:

History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix**,** basal cell carcinoma **or squamous cell carcinoma of the skin that has been previously treated with curative intent.**

Old text:

History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell carcinoma.

6. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To provide clarification on the exclusion criteria relating to the transaminases and alkaline phosphatase.

Section Synopsis & 4.3 Exclusion Criteria

New text:

- AST (SGOT) **or** ALT (SGPT) > 2.5 × ULN
- AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. **Serum alkaline phosphatase may be > 2.5 × ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) < 1.5 × ULN.**

Old text:

- AST (SGOT) and ALT (SGPT) > 2.5 × ULN
- AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. **(unless bone metastases are present)**

7. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To allow collection of PTT in the absence of a PTT result, to allow the assessment of the exclusion criteria.

Section Synopsis & 4.3 Exclusion Criteria

New text:

- International normalized ratio (INR) and activated partial thromboplastin time **or partial thromboplastin time** (aPTT **or PTT**) > 1.5 × ULN (unless on therapeutic coagulation)

Old text:

- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless on therapeutic coagulation)

8. SUBJECT: EXCLUSION CRITERIA

Reason for change:

To confirm that patients participating in concurrent Interventional or Non-Interventional Studies (NIS) will not be randomized into the study.

Section Synopsis & 4.3 Exclusion Criteria

New text:

24 Concurrent Interventional or Non–Interventional Studies (NIS) are not permitted.

Old text:

Not applicable

9. SUBJECT: ADDITIONAL CONTRACEPTIVE REQUIREMENTS

Reason for change:

To provide additional information relating to the contraceptive requirements for the study as a consequence of the modification of inclusion criterion 6 and addition of inclusion criterion 7.

Section 4.4 Concomitant Medication and Treatment

New text:

- **Acceptable methods of contraception must be used when the female patient or female/male partner is not surgically sterilized or does not meet the study definition of post-menopausal (≥ 12 months of amenorrhea). For further details see Section 7.2.6.**

The following treatments are not permitted:

- Treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy
- **Any oral, injected or implanted hormonal methods of contraception.**

Old text:

Not applicable

10. SUBJECT: ADDITIONAL PREGNANCY TESTING REQUIREMENTS

Reason for change:

To update the pregnancy testing requirement after discontinuation of study treatment. For consistency with protocol and advice provided to the patient to avoid pregnancy for at least six months post discontinuation of study treatment. Pregnancy testing is now required every three months until six months post discontinuation of study treatment in women of child bearing potential.

Section 5.4.2 Post-Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit)

New text:

- Pregnancy test. **For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization.** A urine pregnancy test **must** be administered at the treatment discontinuation visit **and then every three months thereafter until six months post Treatment Discontinuation Visit**. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3).

Old text:

- Pregnancy test. A urine pregnancy test **must** be administered at the treatment discontinuation visit. A positive urine pregnancy test must be confirmed via serum β-HCG via the local laboratory (see Section 5.4.3). **Women who have undergone surgical sterilization are exempt from this assessment.**

Section 5.4.3 Local Laboratory Assessments

New text:

Pregnancy test. **For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization**, pregnancy tests **must** be performed via serum β-HCG at baseline. **A urine pregnancy test should be administered** during the treatment period within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated) and at the treatment discontinuation visit **and then every three months thereafter until six months post Treatment Discontinuation Visit**. Any positive urine pregnancy test must be confirmed via serum β-HCG. Treatment period pregnancy test results must be available prior to the drug infusion.

Old text:

Pregnancy test. For women of childbearing potential, pregnancy tests **must** be performed via serum β-HCG at baseline. During the treatment period within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated) and at the treatment discontinuation visit, a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Treatment period pregnancy test results must be available prior to the drug infusion. **Women who have undergone surgical sterilization are exempt from this assessment**.

11. SUBJECT: MODIFICATION TO THE SCHEDULE OF ASSESSMENT

Reason for change:

To update the Schedule of Assessment where appropriate, to delete unnecessary assessments and correct the time points at which an assessment is required. These modifications include:

1. Deletion of Complete Physical Examination during the Treatment Period and at the Treatment Discontinuation visit.
2. Insertion of Symptom Directed Physical Examination assessment at the Treatment Discontinuation visit.
3. Correction of the time point of 12 Lead Electrocardiogram (ECG) during the Treatment Period to specify that the assessment is to be performed every 9 weeks at the time of the LVEF.
4. Correction of the time point of ECOG Performance Status assessment during the Treatment Period to specify that the assessment is to be performed on Day 1 of every cycle.
5. Insertion of footnote 'u' to the Fact-B- Quality of Life (Females Only) to the assessment at Day -7 to -1.
6. Insertion of footnote 'i' to the Bone Scan assessment during the Treatment Period.
7. Insertion of footnote 'z' regarding alternatives to bone scans if there is an isotope shortage meaning a bone scan cannot be performed.
8. Correction of the time point of Pertuzumab/Placebo, Trastuzumab and Docetaxel administration during the Treatment Period to specify that the administration should occur on Day 1 of every cycle.
9. Insertion of PTT assessment to allow collection in the absence of APTT assessments and correction of the time point of INR and aPTT/PTT, during the Treatment Period to specify that the administration should occur on Day 1 of every cycle.
10. Insertion of pregnancy testing after discontinuation of study treatment, to specify that pregnancy testing will continue on a 3 monthly basis until six months post discontinuation of study treatment.
11. Correction of the time point of Serum for Antibodies to Pertuzumab assessment, during the Treatment Period to specify that the assessment is to be performed every 9 weeks at the time of the TA.
12. Correction of the time point of recording Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies during the Follow up Period to specify that the data will be collected every 18 weeks.
13. Correction of the time point of recording Survival information the Follow up Period to specify that the data will be collected every 18 weeks.

Section Synopsis & Section 5 Schedule of Assessments and Procedures

New text:

Table 1 Schedule of Assessments

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post - Treatment**	**126 Days Post-Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Informed consent	x [c]								
Complete Medical History, including Demographics	x [d]								
Review of Inclusion and Exclusion criteria	x								
Complete Physical Examination, and Vital Signs	x								
Symptoms- directed Physical Exam, and Vital Signs			x [e]			**x**			
12 Lead Electrocardiogram (ECG)	x		**Perform every 9 weeks at the time of the LVEF [f]**			x [f]			
Chest X- ray	x		If clinically indicated			x [g]	If clinically indicated		
ECOG Performance Status	x		**x**			x	Every 9 weeks at the time of each tumor assessment [h, i]		
Fact-B- Quality of Life (Females Only)		x [u]	Every 9 weeks within 3 days prior to each tumor assessment [i]						
Tumor Assessments	x		Perform every 9 weeks from randomization until IRF- confirmed progressive disease [i]						
LVEF by ECHO or MUGA	x [j]		Perform every 9 weeks from randomization [k]			x	**Every 6 months in the first year, then annually for up to 3 years [k]**		
Bone scan[z]	x		If clinically indicated [i]			x [g]	If clinically indicated until IRF-confirmed progressive disease [i]		
Adverse Events	x [l]		Ongoing [m]				Ongoing [m]		
Concomitant Meds and Cancer –related Surgery /Procedures			Ongoing			**Ongoing**			
Pertuzumab / Placebo Administration			x [n]						
Trastuzumab Administration			x [o]						
Docetaxel Administration			x [p]						

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles	Treatment Discontinuation Visit [b]	Week 18 post Treatment Discon Visit	Every 18 Weeks post Treatment Discon Visit	Up to 3 years post Treatment Discon Visit
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days Post Treatment**	**126 Days post Treatment Discon Visit**	**Every 126 Days post Treatment Discon Visit**	
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [c]								
Hematology, at local lab		x [q]	x [q]	**x** [q]		x			
Biochemistry, at local lab		x [q]	x [q]			x			
INR and aPTT **or PTT**, at local lab		x	x [r]						
Pregnancy test, at local lab (If applicable)		x [s]			x [s]	**x** [s]	**3 and 6 months post Treatment Discon Visit** [s]		
Serum for Trastuzumab PK, to central lab		x [t, u]							
Serum for Antibodies to Pertuzumab, to central lab		x [u]	**Perform every 9 weeks at the time of the TA** [v]			x			
Serum for HER2 ECD& HER Ligands, to central lab		x [u]	Every 9 weeks at the time of each tumor assessment [i]						
Whole Blood for FCγ Polymorphism (clinical genotyping), to central lab		x [u, w]							
Samples <u>requiring separate informed consent</u>									
Metastatic Tumor for Biomarkers, to central lab		x [u]							
Serum & Plasma Biomarker Sample Repository (BSR), to central lab		x [u]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post-treatment) [t, x]						
Record Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies								**x** [y]	
Survival information							x	**x** [y]	

Old text:

Table 1 Schedule of Assessments

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles (9 weeks)	Treatment Discontinuation Visit [b]	Week 18 post Treatment	Every 18 weeks	Up to 3 years
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days post -Treatment**	**126 Days Post-Treatment**	**Every 126 Days**	
Informed consent	x [c]								
Complete Medical History, including Demographics	x [d]								
Review of Inclusion and Exclusion criteria	x								
Complete Physical Examination, and Vital Signs	x		x			x			
Symptoms- directed Physical Exam, and Vital Signs			x [e]						
12 Lead Electrocardiogram (ECG)	x				**x** [f]	x [f]			
Chest X- ray	x		If clinically indicated			x [g]	If clinically indicated		
ECOG Performance Status	x		x			x	Every 9 weeks at the time of each tumor assessment [h, i]		
Fact-B- Quality of Life (Females Only)		x	Every 9 weeks within 3 days prior to each tumor assessment [i]						
Tumor Assessments	x		Perform every 9 weeks from randomization until IRF- confirmed progressive disease [i]						
LVEF by ECHO or MUGA	x [j]		Perform every 9 weeks from randomization [k]			x	**Every 6 months in the first year, then annually for up to 3 years [k]**		
Bone scan	x		If clinically indicated			x [g]	If clinically indicated until IRF-confirmed progressive disease [i]		
Adverse Events	x [l]		Ongoing [m]				Ongoing [m]		
Concomitant Meds and Cancer –related Surgery /Procedures			Ongoing			**Ongoing**			
Pertuzumab / Placebo Administration			x [n]						
Trastuzumab Administration			x [o]						
Docetaxel Administration			x [p]						

Table 1 Schedule of Assessments (Cont.)

	Screening/Baseline		Treatment Period [a]			Follow up [a]			
			Every Cycle (Cycle=21 days		Every 3 Cycles (9 weeks)	Treatment Discontinuation Visit [b]	Week 18 Post-Treatment	Every 18 Weeks	Up to 3 years
Day	**D-28 to -1**	**D-7 to -1**	**D1**	**D8**		**28-42 Days Post Treatment**	**126 Days Post - Treatment**	**Every 126 Days**	
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [c]								
Hematology, at local lab		x [q]	x [q]	**x** [q]		x			
Biochemistry, at local lab		x [q]	x [q]			x			
INR and aPTT, at local lab		x	x [r]						
Pregnancy test, at local lab (If applicable)		x [s]			x [s]	x [s]			
Serum for Trastuzumab PK, to central lab		x [t, u]							
Serum for Antibodies to Pertuzumab, to central lab		x [u]			**x**[v]	x			
Serum for HER2 ECD& HER Ligands, to central lab		x [u]	Every 9 weeks at the time of each tumor assessment [i]						
Whole Blood for FCγ Polymorphism (clinical genotyping), to central lab		x [u, w]							
Samples requiring separate informed consent									
Metastatic Tumor for Biomarkers, to central lab		x [u]							
Serum & Plasma Biomarker Sample Repository (BSR), to central lab		x [u]	Every 9 weeks at the time of each tumor assessment (until at least 18 weeks post-treatment) [i, x]						
Record Post Study Treatment cancer Related Medical or Surgical Procedures and Therapies							ongoing [y]		
Survival information							x	x [y]	

12. SUBJECT: MODIFICATION TO THE FOOTNOTES SUPPLEMENTING TABLE 1

Reason for change:

To update the Schedule of Assessment footnotes where appropriate. These modifications include: e, f, i, k, p, r, s. u, v, y and z.

Section 5 Schedule Of Assessments And Procedures

New text:

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Complete medical history and demographics (i.e. age, sex, race and ethnicity**)** and all medications taken the last 90 days prior to randomization will be collected

[e] Symptom-directed physical examination including vital signs and weight will be assessed **on Day 1 of** every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

[f] 12 lead ECG will be performed at baseline**, then every 9 weeks from the date of randomization during the study treatment at the time of LVEF assessments and then at the Treatment Discontinuation Visit**.

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

[h] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[i] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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 have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes). Bone scan should be preformed as clinically indicated (In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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). If treatment is discontinued due to Progressive Disease, on sites other than bone, a bone scan should be performed immediately (this would replace the bone scan at the Study Discontinuation visit) and submitted to the Independent Review Facility with all corresponding tumor assessment data (CT/MRI scans, etc).**

[j] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.

[k] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization until Treatment Discontinuation Visit, then every 6 months in the first year , then annually for up to 3 years **after the Treatment Discontinuation Visit**. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to 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 values return 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.**

[l] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[m] See Section 7.2 for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[o] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[p] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. **On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.**

[q] See Section 5.4.3 below for specific required tests. 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. **An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.**

[r] 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.

[s] For women of childbearing potential **and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization**, pregnancy tests **must** be performed via serum β-HCG at baseline. **A urine pregnancy test should be performed** during the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit **and every three months thereafter until six months post Treatment Discontinuation Visit** . Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[t] Collect and submit only for patients that have received prior trastuzumab.

[u] Collect and submit only if patient is determined to be eligible and will be randomized onto the study. **May be collected up to and including study Day 1 prior** to the first study drug dose.

[v] Serum samples for antibodies to pertuzumab will be collected at baseline **and every 9 weeks from the date of randomization at the time of each tumor assessment during the treatment period and at the Treatment Discontinuation visit.**

[w] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18.

[y] Collect post–study treatment cancer-related medical or surgical procedures and therapies and survival information **every 18 weeks after the treatment discontinuation visit during the follow-up period** until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

z **In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 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**

Old text:

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

[b] Treatment discontinuation visit should occur 4–6 weeks (28–42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever is discontinued last).

[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers are not limited to the 28-day window prior to Day 1 (first dose).

[d] Complete medical history and demographics **(i.e. age, sex, race and ethnicity)** and all medications taken the last 90 days prior to randomization will be collected

[e] Symptom-directed physical examination including vital signs and weight will be assessed every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g. elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

[f] 12 lead ECG will be performed at baseline**, then every 9 weeks (within 3 days prior to study drug administration) during study treatment,** then at the study treatment discontinuation.

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

[h] ECOG performance status only to be performed after the Treatment Discontinuation Visit in the absence of IRF-confirmed PD.

[i] Tumor assessments (and assessments performed at the time of tumor assessments) should be performed until IRF-confirmation of progressive disease. Always schedule tumor assessments every 9 weeks ± 3 days from the date of randomization. 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 have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study.**

[j] The baseline LVEF assessment should be performed as close as possible to, but at maximum of 42 days prior to randomization. **All pre-study LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study will be collected.**

[k] Perform more frequent LVEF assessments as needed for cardiac safety. Always schedule LVEF assessments every 9 weeks from the date of randomization until Treatment Discontinuation Visit, **then every 6 months in the first year , then annually for up to 3 years**. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of randomization. Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever occurs first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment.**

[l] Only SAEs related to study-specific procedures are to be collected during the Screening/Baseline period.

[m] See Section 7.2 for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) must be administered **within 3 days of randomization**. All doses of pertuzumab/placebo will be administered on Day 1 of the 21-day cycles. Pertuzumab/placebo will continue until investigator-assessed disease progression or unmanageable toxicity.

[o] The first dose of trastuzumab will be given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab will be administered on Day 1 after pertuzumab/placebo. Trastuzumab will continue until investigator-assessed disease progression or unmanageable toxicity.

[p] The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity).

[q] See Section 5.4.3 below for specific required tests. 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. **An additional hematology blood test will be performed on Day 8 of each treatment cycle during chemotherapy.**

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

[s] For women of childbearing potential, pregnancy tests **must** be performed via serum β-HCG at baseline. During the treatment period every 3 treatment cycles starting from Cycle 3 (and as clinically indicated), and at the treatment discontinuation visit a urine pregnancy test should be administered. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline and treatment period pregnancy test results must be available prior to drug infusion. **Women who have undergone surgical sterilization are exempt from this assessment**.

[t] Collect and submit only for patients that have received prior trastuzumab.

[u] Collect and submit only if patient is determined to be eligible and will be randomized onto the study, but prior to the first study drug dose.

[v] **Serum samples for antibodies to Pertuzumab will be collected at baseline and every 9 weeks during study treatment, until Treatment Discontinuation Visit**.

[w] Whole blood samples for Fcγ polymorphism will only be collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) will be collected every 9 weeks at the time of each tumor assessment until IRF-determined progressive disease. **If IRF-determined PD occurs prior to post-treatment Week 18, BSR samples will continue to be collected every 9 weeks until post-treatment Week 18**.

[y] Collect post–study treatment cancer-related medical or surgical procedures and therapies **every 18 weeks during the follow-up period** and survival information until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Immediately prior to the data cutoff for the final PFS analysis and final OS analysis, the investigative sites will contact every patient that is alive to confirm current survival status. (The study Sponsors will notify all investigators of the timing of this survival data sweep.)

13. SUBJECT: STUDY PROCEDURES FOR SCREENING AND BASELINE

Reason for change:

To allow collection of PTT in the absence of a PTT result.

Section Glossary of Abbreviations

New text:

PTT **Partial Thromboplastin Time**

Old text:

Not applicable

Section 5.3 Procedures for Screening and Baseline

New text:

- Hematology, blood chemistry, INR, and activated partial thromboplastin time (aPTT) **or partial thromboplastin time (PTT)** should be performed at a local laboratory **within 7 days** prior to the first administration of study medication (see Section 5.4.3 for specific tests required). Because the toxicity of docetaxel is influenced by liver function (see Section 7.3.2.5), no protocol exceptions/waivers will be granted for out-of-range liver function tests, as described in the inclusion criteria.

Old text:

- Hematology, blood chemistry, INR, and activated partial thromboplastin time (aPTT) should be performed at a local laboratory **within 7 days** prior to the first administration of study medication (see Section 5.4.3 for specific tests required). Because the toxicity of docetaxel is influenced by liver function (see Section 7.3.2.5), no protocol exceptions/waivers will be granted for out-of-range liver function tests, as described in the inclusion criteria.

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

- INR and aPTT **or PTT** will be collected and submitted to a local laboratory for all patients receiving therapeutic doses of anti-coagulants before the start of every chemotherapy cycle, and when clinically indicated.

Old text:

- INR and aPTT will be collected and submitted to a local laboratory for all patients receiving therapeutic doses of anti-coagulants before the start of every chemotherapy cycle, and when clinically indicated.

Section 5.4.3 Local Laboratory Assessments

New text:

Coagulation. All patients will have INR and aPTT **or PTT** testing at baseline. Patients on therapeutic doses of anti-coagulants should have INR and aPTT **or PTT** measurements repeated during the study, at least before the start of every chemotherapy cycle, and when clinically indicated.

Old text:

Coagulation. All patients will have INR and aPTT testing at baseline. Patients on therapeutic doses of anti-coagulants should have INR and aPTT measurements repeated during the study, at least before the start of every chemotherapy cycle, and when clinically indicated.

14. SUBJECT: STUDY PROCEDURES FOR SCREENING AND BASELINE

Reason for change:

To clarify the time points associated with the screening and baseline assessments.

Section 5.3 Procedures for Screening and Baseline

New text:

- Serum sample for trastuzumab pharmacokinetics should be collected **within 7 days** prior to the first administration of study medication **(or on study Day 1 provided that the sample is taken prior to the first study drug dose),** *only if the patient has received prior trastuzumab therapy* and is eligible for and will be enrolled into the study. The samples will be submitted to the central laboratory.

- Serum sample for testing for antibodies to pertuzumab should be collected **within 7 days** prior to the first administration of study medication **(or on study Day 1, provided that the sample is taken prior to the first study drug dose)**, only if the patient is eligible for, and will be enrolled into, the study.

- Serum sample for HER2 family ECD and HER ligands should be collected **within 7 days** prior to the first administration of study medication **(or on study Day 1 provided that the sample is taken prior to the first study drug dose),** only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.3).

- Whole blood sample for Fcγ polymorphism should be collected **within 7 days** prior to the first administration of study medication **(or on study Day 1 provided that the sample is taken prior to the first study drug dose),** only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.4). Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the involved countries.

- Samples requiring supplemental informed consent
  If the patient has signed the appropriate supplemental informed consent(s), the following samples are required to be collected and submitted. Patients will be permitted to separately consent for each item individually. All samples will be collected **within 7 days** prior to the first administration of study medication **(or on study Day 1 provided that the sample is taken prior to the first study drug dose)**. All samples should be collected only after the patient has been determined to be eligible for, and will enroll into the study, but prior to the first study drug dose:

Old text:

- Serum sample for trastuzumab pharmacokinetics should be collected **within 7 days** prior to the first administration of study medication, *only if the patient has received prior trastuzumab therapy* and is eligible for and will be enrolled into the study. The samples will be submitted to the central laboratory.

- Serum sample for testing for antibodies to pertuzumab should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study.

- Serum sample for HER2 family ECD and HER ligands should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.3).

- Whole blood sample for Fcγ polymorphism should be collected **within 7 days** prior to the first administration of study medication only if the patient is eligible for, and will be enrolled into, the study (see Section 5.4.7.4). Mandatory blood collection for polymorphic analysis will be pending on the regulatory and or IEC requirements of the involved countries.

- Samples requiring supplemental informed consent
  If the patient has signed the appropriate supplemental informed consent(s), the following samples are required to be collected and submitted. Patients will be permitted to separately consent for each item individually. All samples will be collected **within 7 days** prior to the first administration of study medication. All samples should be collected only after the patient has been determined to be eligible for, and will enroll into the study, but prior to the first study drug dose:

15. SUBJECT: STUDY PROCEDURES FOR THE TREATMENT PERIOD

Reason for change:

To provide clarification and to correct the time points at which assessments are required.

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

- Symptom-directed physical examination including vital signs and weight **on Day 1 of** every cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG **will be done every 9 weeks from the date of randomization during the study treatment at the time of LVEF assessments.**

Old text:

- Symptom-directed physical examination including vital signs and weight every cycle. Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

- 12-Lead ECG **will be done every 9 weeks (within 3 days prior to study drug administration).**

New text:

- Serum samples for antibodies to Pertuzumab will be collected every 9 weeks **after the date of randomization, at the time of each tumor assessment during the treatment period.**

Old text:

- **Serum samples for antibodies to Pertuzumab will be collected every 9 weeks, starting from Cycle 3 until Treatment Discontinuation Visit.**

16. SUBJECT: STUDY PROCEDURES FOR THE POST-TREATMENT FOLLOW UP PERIOD AND TREATMENT DISCONTINUATION VISIT

Reason for change:

To provide clarification and to correct the time points at which assessments are required. For the bone scan entry, alternatives to a bone scan have been entered to still allow bone disease to be assessed in light of an isotope shortage meaning that bone scans would not be able to be performed.

Section 5.4.2 Post-Treatment Follow-Up Assessments and Procedures (Including Treatment Discontinuation Visit)

New text:

- LVEF assessments. For all patients, LVEF assessments should be conducted **at the treatment discontinuation visit, then every 6 months in the first year, then annually for up to 3 years after the Treatment Discontinuation Visit.** Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year **after the Treatment Discontinuation Visit**, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years **after the Treatment Discontinuation Visit**. The LLN for the LVEF facility will be reported along with the LVEF results.

- Bone scan will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and if clinically indicated until IRF-confirmed progressive disease **(In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)**. **If treatment is discontinued due to Progressive Disease, on sites other than bone, a bone scan should be performed immediately (this would replace the bone scan at the Study Discontinuation visit) and submitted to the Independent Review Facility with all corresponding tumor assessment data (CT/MRI scans, etc).**

Old text:

- LVEF assessments. For all patients, LVEF assessments should be conducted **at the treatment discontinuation visit, then every 6 months in the first year, then annually for up to 3 years.** Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment**. The LLN for the LVEF facility will be reported along with the LVEF results.

- Bone scan will be performed at the treatment discontinuation visit (if not performed within the previous 28 days), and if clinically indicated until IRF-confirmed progressive disease.

New text:

- Post–study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be recorded **every 18** weeks ± 1 week (7 days) after the treatment discontinuation visit **during the follow-up period,** including the dates and description of the procedure(s) or therapies, and any clinical findings.

- Survival information will be collected via telephone or clinic visits every 18 weeks ± 1 week (7 days) **after the** treatment **discontinuation visit** until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche. Requests to withdraw consent must be documented in the source documents and signed by the investigator.

Old text:

- Post–study treatment cancer-related medical or surgical procedures and therapies. Any cancer-related diagnostic, therapeutic, or surgical procedure, or cancer therapy administered during the follow-up period, should be recorded **every 18** weeks **during the follow-up period,** including the dates and description of the procedure(s) or therapies, and any clinical findings.

- Survival information will be collected via telephone or clinic visits every 18 weeks ± 1 Week (7 Days) post-treatment until death, loss to follow-up, withdrawal of consent, or study termination by Genentech and/or Roche.

17. SUBJECT: METHODS OF TUMOR ASSESSMENT

Reason for change:

To provide clarification on the use of PET/CT scans in the study, also in light of what should happen if there is an isotope shortage and bone scans cannot be performed.

Section 5.4.4 Tumor Assessments

New text:

The minimum screening examinations should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals). PET scans will not be considered for assessment of efficacy at any time during the study **(except as specified for bone scans in the absence of radioactive isotopes)**.

  CT scans should be performed with a contrast agent. The CT portion of a combination PET/CT scan is generally not performed with contrast, therefore PET/CTs are generally not acceptable. However, if the site has acquired a high quality diagnostic CT scan including the application of contrast agent (which may be performed with modern PET/CT scanners), the CT scan portion may be adequate for submission and evaluation. For patients with known allergies to the contrast media, it is acceptable to perform a chest CT scan without contrast and an MRI scan for the abdomen (ideally at baseline and every tumor assessment thereafter).

Old text:

The minimum screening examinations should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals). **PET scans will not be considered for assessment of efficacy at any time during the study**

18. SUBJECT: BONE SCAN ALTERNATIVES

Reason for change:

To address the issue of there being an isotope shortage impacting on the ability of bone scans to be performed, alternative methods of assessment have been added to the protocol in these exceptional circumstances. Bone scans are still the mandated method unless the above situation presents.

Section 5.3 Procedures for Screening and Baseline

New text:

Tumor assessment should be performed as specified in Section 5.4.4. **All patients should have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).** To ensure comparability, the techniques used for tumor assessment at screening/baseline should be consistent with those used subsequently in the study, e.g., MRI, CT, bone scans, etc., as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available. A CT or MRI brain scan is to be performed at screening only in patients with signs or symptoms suggesting CNS involvement or other unexplained neurological symptoms, and during the study, if clinically indicated. **The central independent review will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.**

Old text:

Tumor assessment should be performed as specified in Section 5.4.4.. All patients should have a minimum of a chest and abdomen CT scan. PET scans will not be considered for assessments of efficacy at any time during the study. To ensure comparability, the techniques used for tumor assessment at screening/baseline should be consistent with those used subsequently in the study, e.g., MRI, CT, bone scans, etc., as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available. A CT or MRI brain scan is to be performed at screening only in patients with signs or symptoms suggesting CNS involvement or other unexplained neurological symptoms, and during the study, if clinically indicated. The central independent review will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.

New text:

Bone scan **(In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)**

Old text:

Bone scan

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

Tumor assessments **All patients should have a minimum of 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).** Tumor assessments (CT scans, MRI scans, etc.) will be performed as specified in Section 5.4.4 every 9 weeks after the date of randomization and will continue until IRF-confirmed progressive disease. 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.. To ensure comparability, the techniques used for tumor assessment at Screening/Baseline should be consistent with those used subsequently in the study. Brain CT/MRI scans should be performed on patients with symptoms/signs suggestive of CNS involvement or other unexplained neurological symptoms. **The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.**

Old text:

Tumor assessments All patients should have a minimum of a chest and abdomen CT or MRI scan. PET scans will not be considered for assessment of efficacy at any time during the study. Tumor assessments (CT scans, MRI scans, etc.) will be performed as specified in Section 5.4.4 every 9 weeks after the date of randomization and will continue until IRF-confirmed progressive disease. 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. To ensure comparability, the techniques used for tumor assessment at Screening/Baseline should be consistent with those used subsequently in the study. Brain CT/MRI scans should be performed on patients with symptoms/signs suggestive of CNS involvement or other unexplained neurological symptoms. The central independent review will NOT determine patient treatment. All treatment decisions will be made by the investigator using local assessments.

New text:

Bone scan as clinically indicated **(In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)**

Old text:

Bone scan as clinically indicated

Section 5.4.4 Tumor Assessments

New text:

An isotope bone scan (with bone X-ray[s] as necessary) at baseline **(In the absence of radioactive isotopes, MRI scan [with gadolinium enhancement if required] or F18 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)**. It should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions.

Old text:

An isotope bone scan (with bone X-ray[s] as necessary) at baseline. It should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions.

19. SUBJECT: ANTI-THERAPEUTIC ANTIBODIES TO PERTUZUMAB

Reason for change:

To correct the time points at which assessments are required and to update the method of analysis for anti-pertuzumab antibody titers.

Section 5.4.5 Anti-Therapeutic Antibodies to Pertuzumab

New text:

Within 7 days prior to the first administration of study medication**, then every 9 weeks, at the time of the tumor assessments,** and at the time of the treatment discontinuation visit, serum samples (5 mL blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study Sponsors.

Serum samples will be assayed for anti-pertuzumab antibody titers. **The assay is to be developed.**

Old text:

Within 7 days prior to the first administration of study medication **, then every 9 weeks, starting from Cycle 3** and at the time of the treatment discontinuation visit, serum samples (5 mL blood draws) for testing for antibodies to pertuzumab will be collected from all patients who are eligible for and will be enrolled into the study. The samples will be submitted to a central laboratory or the study Sponsors.

Serum samples will be assayed for anti-pertuzumab antibody titers using a bridging electro-chemi-luminescence assay (ECLA). This assay measures anti-pertuzumab antibodies at a titer of > 1.0 (1:10 dilution), with a relative sensitivity equivalent to approximately 200 ng/mL of an affinity-purified CDR-specific antibody from a hyper-immunized cynomolgus monkey.

20. SUBJECT: SERUM SAMPLE COLLECTION

Reason for change:

To clarification of the time points at which the serum samples will be collected until RF-determined progressive disease.

Section 5.4.7.3 Serum Samples for ECD/HER2 and HER Ligands Analysis

New text:

For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment **until IRF-determined progressive disease**.

Old text:

For assessment of serum biomarkers that may indicate response to pertuzumab and trastuzumab, serum samples (from an approximately 5 mL blood draw) will be collected at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication) and during the study at the time of each tumor assessment.

21. SUBJECT: CLARIFICATION OF FACT-B QUESTIONNAIRE

Reason for change:

To provide clarification and further guidance for the completion of the FACT-B questionnaire.

Section 5.3 Procedures for Screening and Baseline

New text:

- Functional Assessment of Cancer Therapy-Breast Symptom Index (FACT-B) questionnaire must be administered to female patients within 7 days prior to initiation of study treatment **or on study Day 1 provided that the FACT-B is taken prior to the first study drug dose. The FACT-B should be collected and submitted only if the patient is determined to be eligible and will be randomized onto the study**. (see Section 5.5).

Old text:

- Functional Assessment of Cancer Therapy-Breast Symptom Index (FACT-B) questionnaire must be administered to female patients within 7 days prior to initiation of study treatment (see Section 5.5).

22. SUBJECT: CLARIFICATION OF DOCETAXEL DOSING

Reason for change:

To provide clarification for administration and discontinuation of docetaxel.

Section 3.1 Overview of Study Design (applicable to Arm A and B) & Section 6.6.3 Docetaxel Dose and Schedule

New text:

- Docetaxel: 75 mg/m^2 IV every 3 weeks. **On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician. (A**t the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3]).

Old text:

- **Docetaxel:** 75 mg/m^2 IV every 3 weeks **for at least 6 cycles until progressive disease or unacceptable toxicity** (at the discretion of the treating physician, the docetaxel dose will be increased to 100 mg/m^2 for patients who tolerate at least 1 cycle without any of the following toxicities: febrile neutropenia, grade 4 neutropenia for > 5 days or ANC < 100/μL for more than 1 day, or other non-hematological toxicities of Grade > 2 [NCI-CTCAE, Version 3]).

Section 5.4.1 Treatment Period Assessments and Procedures

New text:

- Docetaxel administration every 3 weeks. The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. **On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.** (see Section 6).

Old text:

- Docetaxel administration every 3 weeks. The first dose of docetaxel will be given at Docetaxel administration every 3 weeks. The first dose of docetaxel will be given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel will be administered on Day 1 after trastuzumab. Docetaxel will continue a minimum of 6 Cycles (or until investigator-assessed disease progression or unmanageable toxicity) (see Section 6).

Section 6.6.3 Docetaxel Dose and Schedule, Table 2 (insertion of footnote h)

New text:

h) On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.

Old text:

Not applicable

23. SUBJECT: MODIFICATION TO THE PREPARATION OF DRUG

Reason for change:

To update the specification of the allowed 0.9% sodium chloride infusion bag .

Section 6.3.2.1 Blinded Pertuzumab/Placebo

New text:

The solution of pertuzumab/placebo for infusion diluted in **PVC** or non-PVC polyolefin bags containing 0.9% sodium chloride injection may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use.

Old text:

The solution of pertuzumab/placebo for infusion diluted in polyethylene or non-PVC polyolefin bags containing 0.9% sodium chloride injection may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use.

24. SUBJECT: MODIFICATION TO THE PREPARATION OF DRUG

Reason for change:

To update the specification of the permitted diluents for trastuzumab reconstitution, thereby deleting the reference to ‘as supplied’. No diluents are supplied with the study medication.

Section 6.3.3.2 Trastuzumab

New text:

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

Old text:

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

25. SUBJECT: MODIFICATION TO THE DRUG DESTRUCTION POLICY

Reason for change:

To update the drug destruction policy in the appropriate sections "Partially Used or Empty Vial Destruction and Unused Vial Destruction"

Section 6.9 Assessment of Compliance

New text:

Copies of the dispensing and inventory logs must be available for inspection by the monitor. **Instructions for the destruction of unused, partially used or empty vials of pertuzumab/placebo and investigational trastuzumab, are detailed in Section 6.10.**

Old text:

This inventory must be available for inspection by the monitor. All supplies, including partially used or empty vials of pertuzumab/placebo and trastuzumab (investigational), and copies of the dispensing and inventory logs, must be retained at the site for review by the Roche/Genentech Monitor, unless destruction has been authorized by Roche/Genentech or required by local or institutional regulations (see Section 6.10).

Section 6.10 Destruction of Study Drug

New text:

All pertuzumab/**placebo**, trastuzumab, and docetaxel supplies, including **unused**, partially used or empty vials, must be destroyed on site as per the site's specific procedures for handling and disposing of hazardous drugs **or returned to the Sponsor or designated agent for destruction.** The specific procedures for destruction of investigational pertuzumab/**placebo** and **investigational** trastuzumab are to be provided to the monitor who will verify them as acceptable and in line with the Sponsor's SOPs.

6.10.1 Partially Used or Empty Vial Destruction

To assist with storage capacity and functionality, it is acceptable for sites to destroy the **partially used or empty pertuzumab/placebo and investigational trastuzumab** vials before inspection by the site monitor so that only the empty boxes stating the drug kit number and patient information and dispensing date written on the label can be used for reconciliation of destroyed supplies.

6.10.2 Unused Vial Destruction

Unused pertuzumab/placebo and **investigational** trastuzumab drug supplies, including medication that has been exposed to storage temperatures outside of the protocol-specified range, may be destroyed **on site after** written approval from the Sponsors, provided that such disposition does not expose humans to risks from the drug **or returned to the Sponsor or designated agent for destruction.**

Written documentation of destruction must contain the following:

Old text:

All pertuzumab, trastuzumab, and docetaxel supplies, including partially used or empty vials, must be destroyed on site as per the site's specific procedures for handling and disposing of hazardous drugs. The specific procedures for destruction of investigational pertuzumab and trastuzumab are to be provided to the monitor who will verify them as acceptable and in line with the Sponsor's SOPs.

To assist with storage capacity and functionality, it is acceptable for sites to destroy the vials before inspection by the site monitor so that only the empty boxes stating the drug kit number and patient information and dispensing date written on the label can be used for reconciliation of destroyed supplies.

Unused pertuzumab/placebo and trastuzumab (investigational) drug supplies, including medication that has been exposed to storage temperatures outside of the protocol-specified range, may only be destroyed upon written approval from the Sponsors, provided that such disposition does not expose humans to risks from the drug.

Written authorization must be obtained from the Sponsors before destruction of pertuzumab/placebo and investigational trastuzumab.

Written documentation of destruction must contain the following:

26. SUBJECT: MODIFICATION TO PREGNANCY LANGUAGE

Reason for change:

To align the pregnancy section with the updated text as outlined in inclusion criteria 6 and 7 and the Concomitant Medication and Treatment. Please refer to point 2 and 6 for further details.

Section 7.2.6 Pregnancy

New text:

ICH M3 Guidance require precautions to be taken to minimize risk to fetus or embryo when including women of childbearing potential. This includes highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy monitoring and continued pregnancy testing up to 6 months following last dose of study drug (follow-up period based on PK considerations).

Reproductive toxicity data was recently published in the Investigator Brochure, and of particular interest is that pertuzumab caused oligohydramnios, delayed renal development and embryo-fetal deaths in pregnant cynomolgus monkeys. There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy.

For women of childbearing potential (who have not undergone surgical sterilization) and men with partners of childbearing potential, agreement to use a highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

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

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

Or two of the following effective forms of contraception:

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

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

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

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

Postmenopausal is defined as ≥ 12 months of amenorrhea.

For male patients with a female partner of childbearing potential, co-operation of female partner is required (use two forms of contraception as stated above) during the study and for at least 6 months following the last dose of study treatment when a highly effective form of contraception is not appropriate.

Based on PK considerations, contraception must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to the Sponsor **including the partners of male patients**. The investigator should counsel the patient/**partner,** and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient/**partner** should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of study medication must also be reported to the investigator.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 6 months following the last dose of either monoclonal antibody.

Experimental studies have reported that IgGs are present in both the pre-ejaculate and the seminal plasma (Moldoveanu et al 2005). To date there has been no clinical studies to assess the IgG profile in the pre-ejaculate and seminal plasma in male patients receiving pertuzumab or trastuzumab. Therefore, as a precaution male patients with female partners of child bearing potential are required to use highly effective form of contraception or use two forms of contraception as outlined above. Similarly, vaginal absorption of pertuzumab is unknown and therefore male patients with pregnant partners are required to use condoms for the duration of the pregnancy, and then revert to contraceptive methods as outlined above. This is to ensure that the fetus is not exposed to the study medication through vaginal absorption. Similarly, sperm donation should not occur for at least 6 months after the last dose of study treatment.

Old text:

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy. In patients of childbearing potential and women < 2 years after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment **(e.g., a reliable barrier method [condoms, diaphragm], intrauterine devices, surgical methods, or abstinence).** Based on PK considerations, contraceptive measures are recommended for at least 6 months following the last dose of either trastuzumab or pertuzumab.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to the Sponsor. The investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of study medication must also be reported to the investigator.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 6 months following the last dose of either monoclonal antibody.

27. SUBJECT: LVEF ASSESSMENTS

Reason for change:

To provide clarification on the follow up period for LVEF assessments following discontinuation of study treatment.

Section 7.2.3 Reporting of Cardiac Adverse Events

New text:

Note: Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years **after the Treatment Discontinuation Visit**

Old text:

Note: Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. **Thereafter, LVEF assessments will be performed annually for up to 3 years following discontinuation of study treatment.**

Section 7.2.3 Cardiac Safety Figure 3 (footnote)

New text:

Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year **after the Treatment Discontinuation Visit**, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years **after the Treatment Discontinuation Visit.**

Old text:

Patients for whom study treatment was permanently discontinued due to 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 values return to ≥ 50%, or 1 year, whichever comes first. **Thereafter, LVEF assessments will be performed annually for up to 3 years after the Treatment Discontinuation Visit following discontinuation of study treatment**.

28. SUBJECT: REFERENCES

Reason for change:

To insert an additional reference to support newly inserted text in Section 7.2.6 (Pregnancy).

Section 11 References

New text:

48. Moldoveanu Z, Huang W-Q, Kulhavy R, et al. Human Male Genital Tract Secretions: Both Mucosal and Systemic Immune Compartments Contribute to the Humoral Immunity. J Immunology, 2005; 175: 4127–4136.

Old text:

Not applicable

29. SUBJECT: TYOPGRAPHICAL ERRORS

Reason for change:

To amend typographical errors where appropriate.

Section 5.3 Procedures for Screening and Baseline

New text:

- Complete medical history and demographics **(i.e., age, sex, race and ethnicity)** including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or **therapy.**

Old text:

- Complete medical history and demographics **(i.e., age, sex, race and ethnicity)** including clinically significant diseases within the last 5 years, smoking history, breast cancer history including tumor characteristics (i.e., hormone receptor status, etc.), prior cancer therapies and procedures including any trastuzumab treatment, complete cardiovascular history including all prior LVEF values, and all medication taken over the last 90 days prior to randomization including prescription, over the counter, and herbal/homeopathic remedies and/or **therapy.**

30. SUBJECT: FORMATTING UPDATES

Reason for change:

Due to the insertion of inclusion and exclusion criteria and references the original text will be updated in chronological order