CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	125,409
Priority or Standard	Priority
Submit Date	December 6, 2011
Received Date	December 8, 2011
PDUFA Goal Date	June 8, 2012
Division / Office	DOP1 / OHOP
Reviewer Name(s)	Gideon Blumenthal, MD (efficacy) Nancy S. Scher, MD (safety) Patricia Cortazar, MD (CDTL)
Review Completion Date	May 16, 2012
Established Name	Pertuzumab
(Proposed) Trade Name	Perjeta
Therapeutic Class	Monoclonal antibody
Applicant	Genentech, Inc.
Formulation	420 mg/14mL (30mg/mL) in a single use vial
Dosing Regimen	Initial dose of 840 mg IV infusion, followed by 420 mg IV infusion every 3 weeks thereafter
Indication	In combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the clinical review team recommends full approval of biologics license application (BLA) 125,409 pertuzumab (Perjeta®) for the following indication:

> *Perjeta is a HER2/neu antagonist indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer, who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.*

The basis for this recommendation is a favorable benefit-risk profile for pertuzumab when added to trastuzumab and docetaxel in first-line HER2+ metastatic breast cancer (see section 1.2, 'Risk Benefit Assessment'). In the pivotal study, a clinically meaningful and statistically robust 6.1 month improvement in median Progression Free Survival (PFS) was observed, with a Hazard Ratio (HR) of 0.62 favoring the pertuzumab treatment arm. Furthermore, a planned interim analysis demonstrated a strong trend in improved Overall Survival (OS) favoring the pertuzumab treatment arm, with a HR of 0.64 that did not cross the statistical stopping boundary.

The safety profile of pertuzumab, when added to trastuzumab and docetaxel, was acceptable. Pertuzumab did increase the incidence of diarrhea, rash, mucosal inflammation, neutropenia and febrile neutropenia. There was no evidence of additive cardiac toxicity with the addition of pertuzumab to docetaxel and trastuzumab.

The clinical data in the pertuzumab HER2+ metastatic breast cancer (MBC) BLA differ markedly from the bevacizumab MBC efficacy supplement, which initially was granted accelerated approval but was subsequently revoked after failure to confirm clinical benefit[1]. The reasons for our recommendation for full approval of the pertuzumab BLA are as follows: a well designed, double-blind, placebo controlled study with prospective independent radiologic review and no evidence of differential bias between treatment arms, a clinically meaningful and statistically robust improvement in PFS with strong trend in OS in a targeted patient population selected by validated *in vitro* diagnostic tests, internal consistency, lack of negative studies, strong supportive phase 2 studies, and an acceptable toxicity profile.

The recommendation for full approval is contingent upon satisfactory resolution of manufacturing issues identified by the Division of Monoclonal Antibodies (see section 4.1, Chemistry Manufacturing and Controls).

1.2 Risk Benefit Assessment

Metastatic Breast Cancer (MBC) is a serious and life threatening condition, causing 39,250 deaths in the U.S. in 2011[2]. The HER2/neu receptor is over-expressed in 15-30% of MBC, and is associated with a poor prognosis and an aggressive phenotype.

Trastuzumab in combination with paclitaxel is the only approved first-line chemotherapy-based regimen for HER2+ MBC. There is a clear need for new therapies to treat HER2+ MBC to prolong life, substantially delay disease progression, and/or alleviate breast cancer related symptoms.

The pertuzumab BLA is primarily supported by a single, multinational, multicenter, double-blind, placebo-controlled, randomized phase 3 study (CLEOPATRA; TOC4129g; WO20698). The pivotal study enrolled a total of 808 patients with HER2+ metastatic breast cancer (MBC) who had not received HER2-directed therapy or chemotherapy in the metastatic setting. Patients were randomized 1:1 to receive pertuzumab in combination with trastuzumab and docetaxel (n=402) or placebo in combination with trastuzumab and docetaxel (n=406).

The assessment of benefit is based on the primary endpoint of progression free survival (PFS) by independent review and the key secondary endpoint of overall survival (OS). A statistically significant, clinically meaningful 6.1 month median difference in PFS was observed in patients randomized to receive pertuzumab. Median PFS was 18.5 months on the pertuzumab treatment arm, compared to 12.4 months on the control arm, with a hazard ratio of 0.62 (95% CI: 0.51, 0.75; P-value <0.0001).

These results withstood numerous sensitivity analyses, were consistent with the investigator PFS results, and were consistent across several key subgroups, with the exception of patients with disease confined to non-visceral metastasis (N=178, HR=0.96, 95% CI: 0.61, 1.52).

Although only 11% of patients received adjuvant trastuzumab (in the U.S., most patients present with early breast cancer and are treated with adjuvant trastuzumab-based therapy for HER2+ disease), the pertuzumab PFS benefit (HR=0.62, 95% CI: 0.35, 1.07) was preserved in this subgroup. Therefore, the pivotal study results appear to be applicable to the U.S. population.

The PFS results are supported by the planned interim OS analysis which demonstrated a strong trend in OS favoring the pertuzumab arm which did not reach statistical significance (HR = 0.64, p<0.0053, O'Brien Fleming boundary not crossed).

The efficacy results from the pivotal study are further supported by two Phase 2 studies. Neosphere (WO20697) is an open-label, multinational, multicenter, randomized study in neoadjuvant HER2+ early breast cancer. In this study, the observed pathologic complete response (pCR) rate in the treatment arm combining pertuzumab,

trastuzumab and docetaxel was 46%, compared to 29% in the treatment arm combining trastuzumab and docetaxel, and 24% in the arm combining pertuzumab and docetaxel.

In the single arm trial BO17929 in trastuzumab-resistant HER2+ MBC, the objective response rate (ORR) of combination trastuzumab and pertuzumab was 24%, with pertuzumab monotherapy yielding an ORR of 3%, and the combination of trastuzumab and pertuzumab in patients progressing on both antibodies yielding an ORR of 18%. The enhanced effect of combining trastuzumab and pertuzumab in HER2+ breast cancer is consistent across clinical studies, and also consistent with preclinical mouse xenograft breast cancer models.

In the safety analysis of the pivotal study, there was no evidence of additive cardiotoxicity with the addition of pertuzumab to trastuzumab and docetaxel. Pertuzumab did increase the incidence of diarrhea, rash, mucosal inflammation, neutropenia and febrile neutropenia, but these appeared to be clinically manageable. The higher incidence of febrile neutropenia observed in Asians in both treatment arms, and especially in the pertuzumab treatment arm, could not be explained by different drug exposure, body weight, or practice patterns.

In conclusion, pertuzumab, when added to trastuzumab and docetaxel in front-line HER2+ MBC, demonstrates a favorable risk-benefit profile. Full approval is recommended, contingent upon satisfactory resolution of manufacturing issues identified by the Division of Monoclonal Antibodies (see section 4.1, Chemistry Manufacturing and Controls).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide is required for marketing of pertuzumab.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Requirement (PMR):

1. Submit a protocol for a prospectively and actively enrolled Pregnancy Registry to collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Notice of a Pregnancy Registry and telephone contact number will be included in the package insert.

Rationale: Animal studies suggest that exposure to pertuzumab during pregnancy can result in oligohydramnios, delayed renal development, and embryo-fetal death. There is clinical data of oligohydramnios, pulmonary hypoplasia and death associated with trastuzumab. A Pregnancy Registry for pertuzumab would provide insight into the added risks of embryo-fetal harm.

The clinical team recommends the following Postmarketing Commitments (PMCs):

1. Submit the final results of MO27775 (PERTAIN): "A randomized, two-arm, open-label, multicenter, phase 2 trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first line patients with HER2 positive, Hormone Receptor positive, Metastatic Breast Cancer."

Rationale: In the pivotal study, the subgroup of patients with hormone receptor positive (HR+) disease (n=388) did not appear to benefit as much from pertuzumab (HR=0.72, 95% CI: 0.55, 0.95) as patients with hormone receptor negative (HR-) disease (n=408; HR=0.55, 95% CI: 0.42, 0.72). This is consistent with the results of the Neosphere neoadjuvant study, in which the pCR rate in the treatment arm combining trastuzumab with pertuzumab and docetaxel was 63% in HR- patients, and 26% in HR+ patients. The clinical review team was concerned about continued cross-talk between the estrogen and HER2 receptors, and requested that final results of the ongoing randomized phase 2b study combining pertuzumab, trastuzumab and aromatase inhibitor be submitted to the Agency as a PMC. This will provide insight into whether pertuzumab has activity when added to a hormonal-based regimen.

2. Submit the final Overall Survival results of the pivotal study (CLEOPATRA; TOC4129g; WO20698).

Rationale: The final OS results would verify the encouraging interim trend in improved OS favoring the pertuzumab treatment arm in the pivotal study.

2 Introduction and Regulatory Background

2.1 Product Information

Pertuzumab is an IgG1 (k) humanized monoclonal antibody (human-mouse monoclonal 2C4 heavy chain) with Fc framework identical to trastuzumab (Figure 1). The recombinant, humanized, immunoglogulin IgG1 (k) consists of two heavy chains (449 residues) and two light chains (214 residues).

Pertuzumab differs from trastuzumab at certain complimentarily determining regions (CDRs) – 12 Amino Acids (AA) on the light chain, and 29 AAs on the heavy chain. Pertuzumab is produced in Chinese Hamster Ovary cell cultures. The molecular weight is approximately 148 kDA.

Like trastuzumab, pertuzumab targets the Her2 receptor extra-cellular domain (ECD). Whereas trastuzumab binds to subdomain IV of the HER2 receptor ECD, pertuzumab binds to subdomain II.

When binding to subdomain IV of the HER2 extra-cellular domain, trastuzumab inhibits ligand-independent HER2 signaling, activates ADCC, and prevents HER2 extra-cellular domain shedding.

In contrast, pertuzumab binds to sub-domain II of the HER2 receptor extra-cellular domain (the dimerization domain). By binding to sub-domain II, pertuzumab inhibits ligand-dependent HER2 dimerization with other HER family members such as HER1 (EGFR), HER3 (ERBB3) and HER4 as well as homodimerization with HER2 (Figure 2). This inhibition of HER2 homo- and heterodimerization is thought to activate antibody-dependent cell-mediated cytotoxicity (ADCC) and inhibit downstream signaling of pathways crucial to cancer cell proliferation and survival such as PI3K and MAPK.

Table 1: Composition of Pertuzumab Drug Product (Applicant Table)

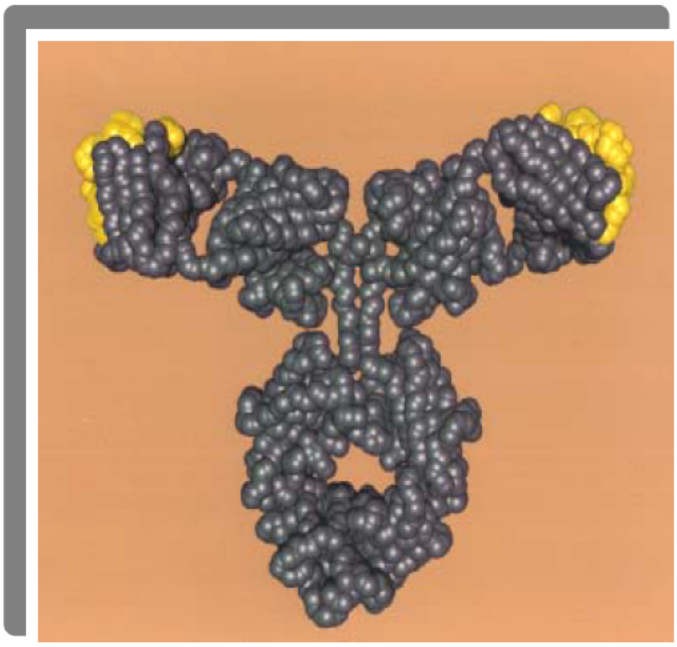
Composition of Pertuzumab Drug Product

Ingredients	Amount per Vial[a]	Concentration per Vial	Component Function	Pharmacopeia Specification
Pertuzumab	420 mg	30 mg/mL	Active Ingredient	-
L-Histidine	(b) (4)	(b) (4)	(b) (4)	USP/Ph. Eur.
(b) (4)				USP/Ph. Eur.
Sucrose				NF/Ph. Eur.
Polysorbate 20				NF/Ph. Eur.
(b) (4)				USP/Ph. Eur.

NA = not applicable; NF = National Formulary.

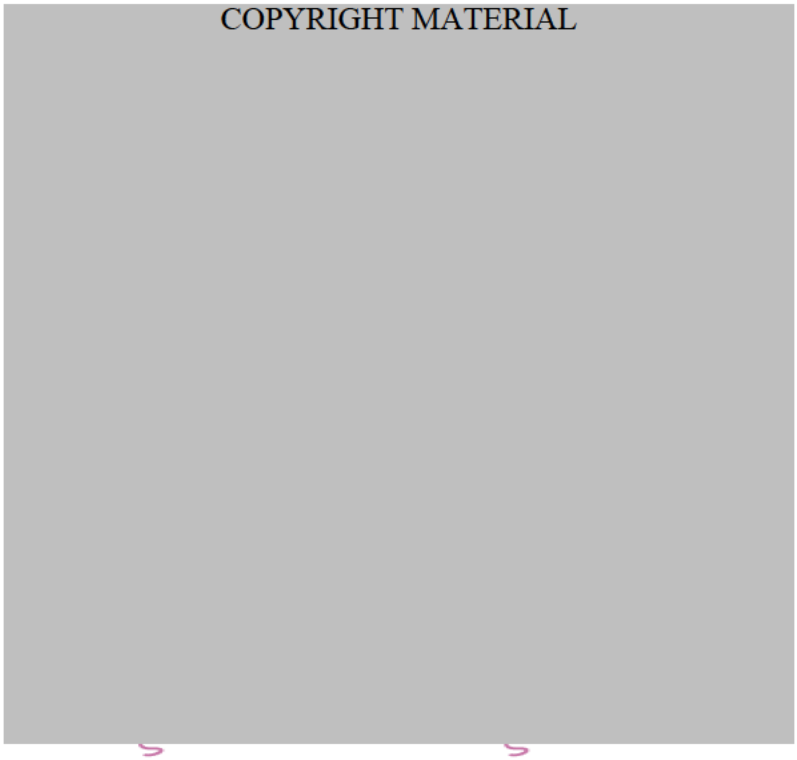
[a] Amounts listed depict the extractable content.

Figure 1: Pertuzumab structure



Source: Applicant briefing materials

Figure 2: Pertuzumab mechanism of action



Source: Baselga and Swain, Nature Cancer Reviews, 2009

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently two drugs approved in the U.S. for HER2+ metastatic breast cancer: the monoclonal antibody trastuzumab (Herceptin®, Genentech) and the small molecule tyrosine kinase inhibitor lapatinib (Tykerb®, GSK). FDA approvals for HER2+ MBC are listed in Table 2.

Table 2: FDA approvals for HER2 directed agents

Drug	Year	Indication	N	Comparator	Basis for approval
Trastuzumab (+ paclitaxel)	1998	HER2+ MBC	469 (188)	Chemotherapy (Paclitaxel or Adriamycin/ Cyclophosphamide)	**TTP:** HR 0.53, median Δ 2.7 mo combined; 4.2 mo paclitaxel subgroup. Later demonstrated **OS**: HR 0.80; median Δ 4.8 mo
Trastuzumab	1998	HER2+ MBC who received ≥ 1 chemotherapy regimens	222	N/A	**ORR:** 14% in single arm study
Lapatinib (+ capecitabine)	2007	HER2+ MBC after failure of anthracycline, taxane, trastuzumab	399	Capecitabine	**TTP**: IRC HR 0.57, median Δ 2 mo; INV HR 0.72, median Δ 1.2 mo
Lapatinib (+ letrozole) ***Accelerated Approval***	2010	Postmenopausal women with HR+, HER2+ MBC for whom hormonal therapy is indicated	219	Letrozole + placebo	**PFS:** HR 0.71, median Δ 5 mo

MBC = Metastatic Breast Cancer; HR+ = Hormone Receptor Positive; TTP = Time to Progression; OS = Overall Survival; ORR = Objective Response Rate; IRC = Independent Radiologic Charter; INV = Investigator
Source: drugs@fda.com

2.3 Availability of Proposed Active Ingredient in the United States

Pertuzumab is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Trastuzumab:

Trastuzumab carries the following Boxed Warnings:

- Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy.
- Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
- Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

In addition, trastuzumab has an associated 'Warnings and Precautions' for exacerbation of chemotherapy-induced neutropenia.

Lapatinib:

Lapatinib carries the following Boxed Warning:

- Hepatotoxicity: Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain.

In addition, lapatinib has associated 'Warnings and Precautions' for decreases in LVEF, diarrhea, interstitial lung disease/pneumonitis, QT prolongation, and fetal harm.

2.5 Summary of Regulatory Activity Related to Submission

- **May 2001**: pre-IND Meeting

- **June 2001**: IND submission

- **April 17, 2007**: Summary of Meeting Minutes for End of Phase 2 meetings to discuss design of CLEOPATRA (WO20698/TOC4129g)
    - FDA: Would accept a single pivotal study to support licensure only if results show a highly statistically significant effect on overall survival (OS) that is internally consistent across relevant subgroups and the magnitude

of effect is clinically meaningful such that the benefits outweigh the risks. FDA recommended that Genentech power the study to detect clinically meaningful difference in OS.
  - FDA: If the integrated analyses are highly statistically significant, but not internally consistent, the indication may be limited to the subgroup that drives the statistically significant result.
  - FDA: Independent Review Facility (IRF)-assessed PFS may be considered acceptable to support a request for accelerated approval, provided that the result is highly statistically significant and consistent relevant subgroups or is supported by confirmation of these findings in a second trial.
  - FDA: Sensitivity analyses should be performed to study the impact on analysis of PFS due to missing data/assessments, and any loss to follow-up or discontinuation of assessments not due to an event. Additionally, evaluate the agreement between IRF-determined PFS and investigator-determined PFS.
  - Genentech: Agreed to provide a detailed plan for evaluation of patients with NCI CTC Grade $\geq$ 2 cardiotoxicity
  - Genentech: Plan to start with Docetaxel dose of 75 mg/m^2 and increase to 100 mg/m^2 if the lower dose was tolerable. FDA stated this approach was acceptable.
  - FDA: protocol should specify prospective collection of possible cardiotoxicity risk factor data. The SAP should describe exploratory analyses correlating baseline factors and risk of cardiotoxicity. Genentech agreed.
  - FDA: DDI study of pertuzumab, docetaxel and trastuzumab necessary.

- **November 5, 2007**: Summary of Meeting Minutes for End of Phase 2 Type C meeting to discuss design of CLEOPATRA (WO20698/TOC4129g)
  - FDA: The protocol eligibility criteria do not require prior anthracycline for de novo Stage IV patients. Whether data derived from this study reflect the current standard of care for, and can be extrapolated to the US patient population will be a review issue.
  - FDA: IRF-assessed PFS may support accelerated approval provided the result is highly statistically significant across relevant subgroups or is supported by confirmation of these findings in a second trial.
  - FDA: SAP should include a subgroup analysis based on race as required by 21 CFR 314.50.
  - FDA: requested greater than 18 weeks post treatment LVEF assessments to further characterize potential cardiac risks. Genentech agreed, but some patients will be lost to follow-up.
  - FDA: recommend that DMC members have no ongoing financial relationships with Genentech or other commercial entities involved in the

manufacture or marketing of the product. Genentech stated that no DMC members are principal investigators on any Genentech trials.
  - Genentech: Most of docetaxel exposure occurs in 4 hours, with a > 80% exposure over 24 hours. Regarding trastuzumab PK, plan to collect trough samples in 40-50 patients. FDA recommended more sampling timepoints.
  - FDA and Genentech: Agreed to sampling anti-pertuzumab antibodies at baseline, before the second pertuzumab dose, every 3 cycles, and at study discontinuation.

- **May 2011**: Type C Meeting to reach agreement on BLA submission
  - FDA: Agency requested an additional PFS sensitivity analysis for patients discontinued due to toxicity. For time to cardiac event, Agency recommended analyses based on cumulative incidence considering non-cardiac death as competing events, akin to Figures 1-3 of Herceptin label.
  - FDA: Genentech will need to submit a PMA supplement if using an FDA approved HER2 test. If using a test kit that is not FDA approved, they will need to submit a PMA.

- **August 2011**: CMC pre-BLA meeting
  - Quality by design approach for Drug Product
  - Stability data
  - Statistical approach for qualification of the scaledown models

- **September 2011**: Type B pre-BLA meeting. Summary of meeting minutes:
  - FDA: The efficacy and safety results from study TOC4129g, a single study intended to support marketing approval, are sufficient to characterize the benefits and risks of pertuzumab and to form the basis of a BLA for the proposed indication. However, whether or not the application will support full or accelerated approval will be based on FDA's review.
  - Genentech: Final OS analysis in late 2013 at 385 events. Will provide a proposal by November, 2011 for the statistical analysis plan for conducting an additional OS analysis, should FDA request this.
  - Genentech: Will provide high level safety results and stand alone datasets for study BO22280.
  - FDA: determination of review designation will be made after a determination that the application can be filed and will be conveyed in the filing letter.
  - FDA: Based on the information in the meeting package, FDA is not requesting that a REMS be proposed, however a final determination on the need for REMS will be made during the review of the application.
  - FDA: Determination on the need for an ODAC review will be made after the BLA is submitted.

Reviewer Comment: *In 2007, the Agency suggested that a meaningful difference in PFS would support accelerated approval, and an OS improvement would support full approval. The current recommendation for full approval is based on: a well conducted pivotal study, a large magnitude of PFS benefit that is robust and internally consistent, an acceptable (and less than anticipated) toxicity profile, an early trend in improved OS, and supportive data from two phase 2 studies.*

2.6 Other Relevant Background Information

Metastatic Breast Cancer (MBC) is a serious and life threatening condition, causing 39,250 deaths in the U.S. in 2011[2]. In the United States, breast cancer is the most common female cancer, the second most common cause of cancer death in women (after lung cancer), and is the main cause of death in women between the ages of 45 and 55.

The HER2/neu receptor is over-expressed in 15-30% of MBC and is associated with a poor prognosis and an aggressive phenotype. With the incorporation of trastuzumab-based therapy for adjuvant early breast cancer and for MBC, the prognosis of HER2+ breast cancer has improved. However, new therapies are needed to prolong life, significantly delay disease progression, and/or improve cancer related symptoms.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, the study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country where the research was conducted, whichever provided greater protection to the individual. The study adhered to the January 1997 ICH Guideline for Good Clinical Practice. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

During one of 15 Applicant-conducted investigator site audits, critical findings of non-compliance were observed at one site, including:

- Failure to inform subjects in a timely manner of new information that might affect their willingness to continue participation.
- Failure to obtain consent to continue prior to performing further study-related activities.
- Investigational product accountability, reconciliation, and use records were incomplete and inadequate.
- IND safety reports not reported to the IRB in a timely fashion.

Per the Applicant, adequate corrective actions were undertaken. In addition, this investigator site only enrolled 2 patients onto the pivotal study. Therefore, these findings do not appear to compromise data integrity.

In addition, (b) (4), the Contract Research Organization (CRO) responsible for organizing the Cardiac Review Committee (CRC) review performed a process audit and observed the following:

- The process to identify and prepare potential cardiac events for review and adjudication by the CRC lacked robustness and the project guidelines lacked clarity.
- At the time of (b) (4) audit, the majority of triggers were not processed by the Clinical Event Validation and Adjudication (CEVA). Therefore, the CRC was unlikely to have reviewed all potential cardiac events in a timely manner, and the DMC was unlikely to have reviewed all relevant safety data in a timely manner.

According to the Applicant, (b) (4) took action to clear the backlog and perform a full reconciliation to ensure that all triggers were presented to the CRC for adjudication, and included in the clinical study database before database lock, such that the integrity of the endpoint data presented in the CSR was not compromised.

Reviewer Comment: *It appears that the Applicant and CRO took reasonable measures to institute corrective and preventive actions to address these deficiencies. Overall, the study appears to be compliant with GCP and the integrity of the data does not appear to be compromised.*

FDA Clinical Inspection Summary:

A draft of the Clinical Inspection Summary was provided by Robert Young, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, Office of Scientific Investigations (OSI). The OSI inspected three of the highest accruing sites, two in South Korea, and one in Brazil. A summary of the site inspections is provided in Table 3.

Table 3: Summary of OSI findings

Inspection	Site # (# of Subjects)	Inspection Date	Final Classification
Roberto Hegg Hospital Perola Bygton Av. Brigadeiro Luis Antonio 683 Sao Paulo, 01317-000 Brazil	Site 121228 (22 subjects)	April 16-20, 2012	Pending NAI
Sung-bae Kim ASAN Medical Center 388-1 Pungnap-dong Seoul, 138-736 Korea	Site 121117 (30 subjects)	April 9-13, 2012	Pending VAI
Seock Ah Im Seoul National Hospital 28 Yongon-dong, Chongro-gu Seoul, 110-744 Korea	Site 12116 (23 subjects)	April 2-6, 2012	Pending VAI
Genentech South San Francisco, CA 94080	Not Applicable	April 23-30, 2012	Pending NAI

NAI= No deviation from regulations; **VAI** = deviation from regulations; **pending** = preliminary classification based on information in 483 or preliminary communication with the field, Establishment Inspection Report (EIR) has not been received from the field, and complete review of EIR is pending.

The reasons for the pending VAIs from the two Korean sites are as follows:

- There were three instances of subjects who gained weight and received a 10 mg increase in trastuzumab over the average 350 mg they should have received. This 3% increase likely had no effect on safety or efficacy. Study monitors identified and corrected this problem early in the study.
- Subjects 7139 and 7504 did not meet the 12 month disease free interval exclusion criterion but were continued on the study under a waiver granted by the sponsor.
- Subject 7135's medication was incorrectly entered so that the first dose of docetaxel was 130 mg rather than the correct dose of 108 mg docetaxel. Subject 7138 missed a week 9 tumor assessment, and two patients' concomitant medications were not reported in a timely fashion.

Overall, the OSI reviewer's preliminary review is that data integrity was not compromised by these random and limited deviations and impact on the overall evaluation of the study is unlikely. The final OSI review is pending.

3.3 Financial Disclosures

The sponsor received financial disclosure information from 99.8% of principal investigators and sub-investigators on CLEOPATRA (WO20698/TOC4129g) and 100% of principal and sub-investigators on Studies WO20697 and BO17929, respectively.

Disclosable financial interests were recorded by 7 out of 1671 (<1%) investigators in study WO20698/TOC4129g, 2 out of 382 (<1%) in study WO20697, and 1 out of 141 (<1%) in BO17929. Table 4 summarizes the investigators with disclosable financial interests in the pertuzumab development program.

Table 4: Summary of Financial Disclosures (Applicant Table)

Study Protocol Number	Clinical Site Number	Investigator Name	Patient Enrollment	Disclosure
WO20698/ TOC4129g	(b) (6)	(b) (6)	(b) (6)	$95,937 honoraria for lecturing and advisory boards
WO20698/ TOC4129g				$50,000
WO20698/ TOC4129g				Not able to obtain the $ specific amount
WO20698/ TOC4129g				$712,647 worth of Genentech Stocks
WO20698/ TOC4129g				$70,000
WO20698/ TOC4129g				$32,000 worth of Roche Stock
WO20698/ TOC4129g				$286,562 in funds
WO20697				200,000 SEK
WO20697				Not able to obtain the $ specific amount
BO17929				Not able to obtain the $ specific amount

Source: BLA 125409 Section 1.3.4, financial disclosure

***Reviewer Comment**: The financial disclosures do not raise questions about data integrity in the pivotal study. Investigators with significant disclosable interests enrolled a small proportion of the total number of patients such that introduction of bias is unlikely.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review of BLA 125,409 was conducted by the Division of Monoclonal Antibodies (DMA) in the Office of Biotechnology Products/CDER, and the Biotech Manufacturing Assessment Branch (BMAB) in the Office of Manufacturing and Product Quality/Office of Compliance/CDER.

The DMA product quality reviewers were Dr. Kathryn King (Traditional Elements) and Laurie Graham (Quality by Design). The BMAB reviewers were Drs Bo Chi (Drug Substance) and Colleen Thomas (Drug Product). For full details, please see the CMC reviews.

Drug Substance Inspection:

The pertuzumab manufacturing process as described in Genentech's BLA 125409 includes a standard cell culture process (b) (4)

The pre-license drug substance inspection of the Genentech facility in Vacaville, CA was conducted on March 20 - 28, 2012 by BMAB and DMA reviewers.

During the FDA pre-approval inspection of the commercial API facility (March, 2012), DMA review staff noted a (b) (4) failure rate for the working cell bank thaw and subsequent growth at (b) (4) In addition, surviving thaws showed a (b) (4) These failure rates are inconsistent with previous pertuzumab manufacturing experience and have not been observed with other approved monoclonal antibodies manufactured at this facility.

Since completion of the inspection, DMA has had regular teleconferences (1-2 per week) with the Applicant in order to gain a better understanding of the scope, impact and potential for resolution of this issue. Review issues have focused on potential impact to product quality and process consistency. This was approached with the initial understanding that the problem was limited to the working cell bank thaw and (b) (4) (b) (4)

In April, the Applicant agreed to a three-pronged action plan recommended by the FDA:

- Extended characterization of drug substance derived from the current campaign (to mitigate risks to product quality associated with [redacted] (b) (4) productivity).
- Development of a new working cell bank (based on the possibility that the root cause for [redacted] (b) (4) productivity is due to instability of the current working cell bank).
- Confirm stability of the master cell bank. This is a critical source material, as it is the origin of all future WCBs; if both the MCB and the WCB are not stable, there could be no future source of pertuzumab.

[redacted] (b) (4)

[redacted] (b) (4) (b) (4)

The continued failures [redacted] (b) (4) in the production process of the current campaign with the working cell bank, and the lack of identification of a root cause(s) for the poor cell growth have increased DMA's concern regarding process consistency.

Use of the Master Cell Bank to generate product would provide the Agency with assurance of the stability of the MCB and a future source of product. [redacted] (b) (4), product quality data from pertuzumab produced by the MCB is required to assure that the MCB process is comparable to the WCB.

The initial and continued major concern in regard to this issue is whether the Applicant has a validated process and can consistently manufacture pertuzumab with product quality characteristics comparable to that used in their clinical trials. Based on DMA review, and given the ongoing failures with the current working cell bank, the Applicant has not yet demonstrated a consistent process that would ensure continued supply of commercial material.

As of the finalization of this clinical review, the product quality concerns have not been completely resolved, and the final CMC review is pending.

Drug product inspection:

The pre-license drug product inspection of the Roche facility in Manheim Germany was conducted on April 18 – 26, 2012 by Prabhu Raju of Team Biologics, Division of Domestic Field Investigations, Office of Regional Operations. The FDA-483 generated from the inspection will be reviewed by a compliance officer in the CDER-OC, which is pending at the time of finalization of the clinical review.

4.2 Clinical Microbiology

Please see CMC reviews by Drs Chi and Thomas.

As of the finalization of the clinical review, there were several outstanding microbiologic issues identified by FDA CMC reviewers. These include (summarized from information request dated May 15, 2012):

- [redacted] (b) (4)
- [redacted] (b) (4) [redacted] More effective methods of preventing bioburden accumulation may include screening raw materials for [redacted] (b) (4) [redacted]. Provide data to demonstrate the control of bioburden in cell culture media [redacted] (b) (4) [redacted] Alternatively screen raw materials for (b) (4) bioburden [redacted] (b) (4) [redacted] and [redacted] (b) (4) to prevent bioburden accumulation during non-sterile medium preparation operation.
- A revalidation of the hold time for non-sterile cell culture media with an adequate bioburden acceptance criterion at scale at the Vacaville facility (potential PMC).
- A commitment to perform a comprehensive risk assessment regarding cell culture microbial control and action plan. The risk assessment should consider the feasibility of [redacted] (b) (4). It should also consider implementation of [redacted] (b) (4) bioburden and endotoxin control of cell culture raw materials and the expanded use [redacted] (b) (4) [redacted]

4.3 Preclinical Pharmacology/Toxicology

For full details, please see Pharmacology/Toxicology review by Dr. Kimberly Ringgold.

Pharmacology:
Since the amino acid homology for Her2 was 99%, the cynomolgus monkey was selected as the appropriate model for nonclinical evaluation. Tumor growth was inhibited by pertuzumab doses of 30 – 90 mg/kg in the founder 2-134R tumor xenograft model, which is resistant to trastuzumab. Pertuzumab had antitumor activity in several cancer models, including breast, ovarian and NSCLC. In a HER2 over-expressing NSCLC xenograft, the combination of pertuzumab and trastuzumab was greater in activity (100% tumor growth inhibition) compared to either single agent alone.

Pharmacokinetics:
The PK profile of pertuzumab was studied in the monkey; the nonclinical species used for chronic toxicology and fetal toxicity studies. Pertuzumab was eliminated with a half-life of approximately 10 days. The plasma clearance and volume of distribution following intravenous administration were low (clearance = 5 mL/day/kg and volume of distribution, Vss = 70 ml/Kg).

Following IV administration for 25 weeks, pertuzumab exposures increased in a dose-proportional manner. Faster clearance was observed in the 150 mg/kg dose group. Pertuzumab PK increased in dose-proportional manner between all doses tested in pregnant monkeys and fetuses. Ratios of fetal to maternal pertuzumab levels were comparable.

General Toxicity:
Pertuzumab appeared to be well-tolerated in monkeys. Pertuzumab clinical findings were predicted from the nonclinical studies, and nonclinical findings (except oligohydramnios) were generally observed in the clinical studies. Nonclinical studies showed toxicities in the lung and gastrointestinal tract, which were expected given the distribution of HER2/neu antigen.

Reproductive and Developmental Toxicities:
Pertuzumab caused fetal lethality in pregnant monkeys treated with loading doses of $\geq$ 30 mg/kg followed by bi-weekly doses of $\geq$ 10 mg/kg (approximately 0.2 to 2 fold greater than the exposure at the recommended human dose by AUC). These malformations included paw hyper-extension/ hyper-flexion, microtia, small lungs, thin walls in the ventricular regions of the heart, fused caudal and sacral vertebra, and supernumerary lumber vertebra. Thus, administration of pertuzumab during pregnancy may pose a risk to the human fetus.

The Pharmacology/Toxicology review team recommended pregnancy category D for pertuzumab. The basis for this recommendation was that pertuzumab exhibited

embryo-fetal lethality at all doses tested. In addition, oligohydramnios was observed at all doses and a NOAEL for fetal effects was not determined.

Based on the pre-clinical findings of oligohydramnios with pertuzumab, and the known (boxed) clinical risk of oligohydramnios with trastuzumab, the pharmacology/toxicology, clinical, and safety teams recommend a post-marketing registry to collect clinical data on oligohydramnios risk.

Special Toxicity:
In vitro studies showed comparable binding affinity of pertuzumab for humans and monkeys. Pertuzumab did not cause lysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma in *in vitro* test systems. Cell surface staining with pertuzumab in human tissues was noted in the haired skin, placenta, parathyroid gland, tonsil, mammary gland, ureter, and urinary bladder tissues. Cytoplasmic staining was noted in the salivary gland and prostate gland as well as in the stomach, haired skin, and thymic cyst of human tissues. In monkey tissues, cell surface staining was noted in the sweat and sebaceous gland, mammary gland, placenta, ureter, urinary bladder, and prostate gland. Cytoplasmic staining was noted in adenohypophysis and salivary gland.

4.4 Clinical Pharmacology

For full details, see clinical pharmacology review by Dr. Pengfei Song.

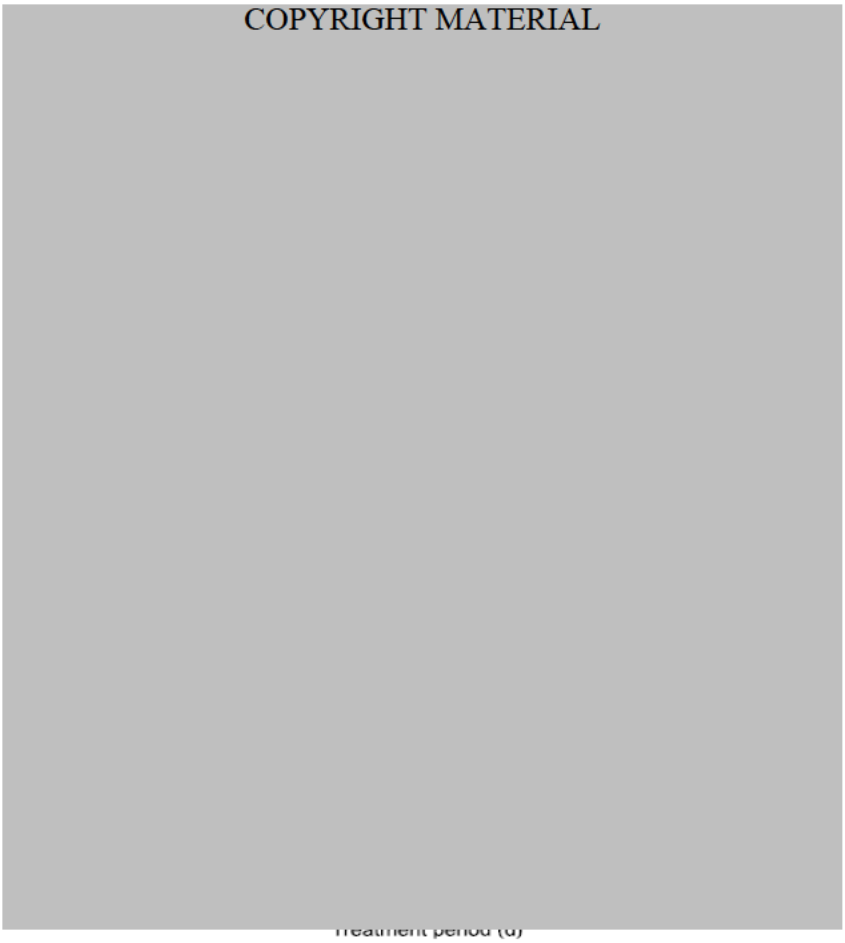
4.4.1 Mechanism of Action

Pertuzumab is a recombinant humanized monoclonal IgG1 antibody that targets HER2 by binding to the subdomain II of HER2 (as opposed to subdomain IV where trastuzumab binds). Binding of pertuzumab to the HER2 on human epithelial cells prevents HER2 from forming heterodimeric complexes with other members of the HER receptor family (including EGFR, HER3, HER4) and forming HER2 homodimers, resulting in inhibition of key intracellular signaling pathways critical to cell proliferation and survival, such as PI3K/Akt/mTOR, and MAPK. In addition, both pertuzumab and trastuzumab are purported to induce antibody-dependent cell-mediated cytotoxicity (ADCC).

4.4.2 Pharmacodynamics

Preclinical mouse models showed that the combination of trastuzumab and pertuzumab strongly enhanced antitumor effect and induces tumor regression in breast cancer xenografts, which was not achieved by either monotherapy. The enhanced efficacy of the combination was also observed after tumor progression on trastuzumab monotherapy (Figure 3). Pre-clinically, the data suggests that the enhanced antitumor activity is mainly due to the differing but complimentary mechanisms of action of trastuzumab and pertuzumab, namely inhibition of HER2 dimerization and prevention of p95HER2 formation.

Figure 3: Pertuzumab + Pertuzumab activity in HER2+ mouse xenograft model



Source: Scheuer W et al. Cancer Research 2009

4.4.3 Pharmacokinetics

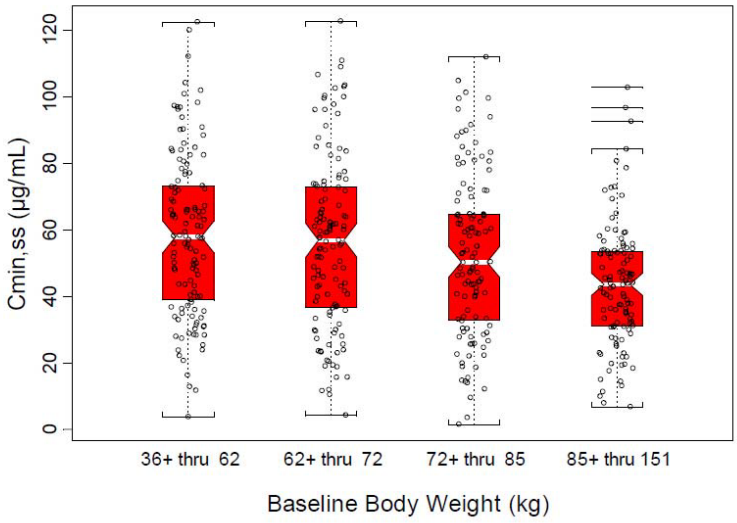
See clinical pharmacology review by Dr. Pengfei Song.

In Phase 1 studies (TOC2297 and JO17076), Pertuzumab demonstrated linear PK at doses ranging from 2 to 25 mg/kg with a half-life of about 18 days. A maximum tolerated dose was not achieved. Given the minimal pertuzumab toxicity in phase 1, combined with the long half-life two dosages were proposed for further evaluation: 1) 840 mg load/420 mg Q3W and 2) 1050 mg Q3W.

The serum pertuzumab concentration of 20 µg/mL was set as a target serum concentration based on the observation that the maximum suppression of tumor growth was achieved at ~5 - 25 µg/mL in xenograft mouse models. A population PK analysis predicted that > 90% of patients receiving the 840 mg /420 mg Q3W regimen would have steady-state trough serum concentrations higher than > 20 µg/mL. Since the target serum concentrations were achieved by the 840 mg /420 mg Q3W regimen, the higher dosage of 1050 mg Q3W was not selected for the pivotal trial.

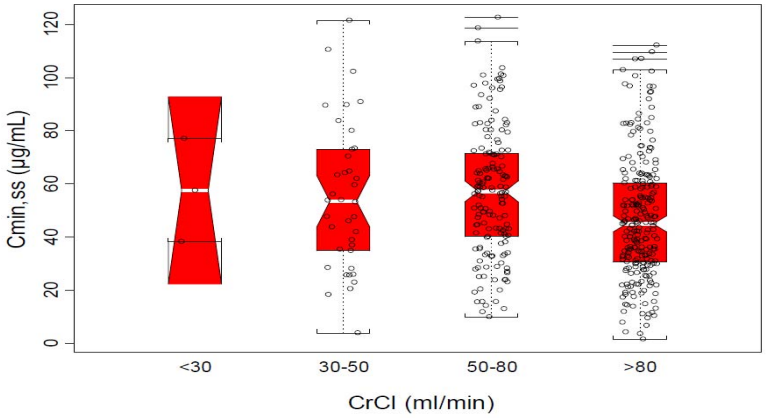
With a loading dose of 840 mg and a 420 mg maintenance dose every three weeks, the steady-state concentrations of pertuzumab were reached after the first maintenance dose. Based on a population PK analysis using data from 12 clinical trials, clearance (CL), central volume of distribution (V_C), and terminal elimination half-life of pertuzumab are 0.235 L/day, 3.11 L, and 18 days, respectively. Inter-individual variability of CL and V_C expressed as CV% are 34.9% and 18.7%, respectively. Though lean body weight and albumin were identified as significant covariates on the pertuzumab PK, the fixed dosage was acceptable, as their impacts on the pertuzumab PK were considered to be marginal (Figure 4). The population PK analysis did not identify age, race, gender, or mild/moderate renal impairment (Figure 5) as significant covariates on the PK of pertuzumab.

Figure 4: Pertuzumab Cmin by body weight (Applicant Figure)



Source: Population PK Report Figure 15

Figure 5: Pertuzumab Cmin by Creatinine Clearance (Applicant Figure)



Source: Population PK Report Figure 16

In a sub-study of the pivotal trial, no significant drug interactions were observed between pertuzumab and docetaxel (in the presence of trastuzumab) or between pertuzumab and trastuzumab (in the presence of docetaxel).

The incidence rate of positive anti-therapeutic antibodies (ATAs) to pertuzumab was 2.8% in the pertuzumab arm as compared to 6.2% in the placebo arm. The presence of

ATAs was not associated with hypersensitivity reactions, anaphylaxis or other adverse safety findings. Although ATA-positive patients appeared to have shorter PFS and lower response rate than ATA-negative patients, the benefit of pertuzumab treatment was preserved within both ATA-positive and ATA-negative subgroups.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Data from 17 clinical studies were submitted to the BLA. This included 3 clinical studies pertinent to the claimed indication (CLEOPATRA/WO20698/TOC4129g, Neosphere/WO20697, BO17929). Also included in the BLA are 5 phase 1a/1b patient PK and initial tolerability studies (TOC2297g, JO17076, BO17021, BO17003, WO20024); and 8 phase 2a/2b studies (BO16934, BO17931, TOC3258g, TOC2689g, TOC2572g, TOC2682g, BO17004, TOC3487s) in a variety of malignancies (MBC with low HER2, platinum sensitive/resistant ovarian cancer, non small cell lung cancer, castrate resistant prostate cancer); and 1 extension study (TOC2664).

Table 5 lists the clinical trials submitted in support of the NDA application. Data from CLEOPATRA (TOC4129g, WO20698) serves as the primary basis for evaluation of efficacy and safety.

Table 5: Key Clinical Studies Submitted (Reviewer Table)

Protocol	Study Design	Disease	Doses	N	Primary EP	Status
CLEOPATRA WO20698/ TOC4129g	Phase 3b, randomized, placebo controlled, double blind, multi-center, international	HER2+ MBC	Pertuzumab 420 mg q3w (840 mg load) Trastuzumab 6 mg/kg q3w (8mg/kg load) Docetaxel: 75 mg/m^2 q3w (option to increase to 100 mg/m^2)	808	PFS	Ongoing Full report for primary analysis submitted
Neosphere WO20697	Phase 2b, randomized, open label, four-arm study, multi-center, international	Neoadj HER2+ early BC	Pertuzumab 420 mg q3w (840 mg load) x 4 cycles Trastuzumab 6 mg/kg q3w (8mg/kg load) x 4 cycles neoadj and up to 1 year post-op Docetaxel: 75 mg/m^2 q3w (option to increase to 100 mg/m^2) x 4 cycles	417	pCR	Ongoing Full report for primary analysis submitted
BO17929	Phase 2b, single arm, open label, multi-center, international	HER2+ MBC pts who previously received trastuz	Pertuzumab 420 mg q3w (840 mg load) Trastuzumab 6 mg/kg q3w or 2mg/kg qw	95	ORR, CBR	Ongoing Full report for primary analysis submitted

EP= Endpoint; N= Number; MBC= metastatic breast cancer; PFS= progression free survival; pCR= pathologic complete response; ORR= objective response rate; CBR= clinical benefit rate

5.2 Review Strategy

The clinical review is based on the clinical study report for the pivotal study and the two supportive studies outlined in 5.1. The efficacy review was conducted by Dr. Gideon Blumenthal and the safety review by Dr. Nancy Scher. A statistical review was conducted by Dr. Somesh Chattopadhyay. Among the items reviewed were the case report forms, selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant, study reports for other pertuzumab clinical trials, research of the FDA data base for regulatory history of the pertuzumab IND, and a literature review of HER2+ MBC.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Phase 3 CLEOPATRA (TOC4129g/WO20698)

This BLA submission is primarily supports by results from a single industry-sponsored study, CLEOPATRA (U.S. study number TOC4129g; world study number WO20698), entitled:

> "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."

WO20698 Endpoints

Primary Endpoints:

- **PFS by Independent Review**: The primary endpoint of CLEOPATRA is to compare PFS based on tumor assessments by an independent review facility (IRF) between patients in the two treatment arms. PFS is defined as time from randomization to first documented radiographical progressive disease (PD), as determined by the IRF using RECIST 3.0[3] or death from any cause (within 18 weeks of last tumor assessment), whichever comes fist. Assessment of PD was based on a review of radiographic (MRI, CT, bone scans, chest x-ray, etc.) as well as cytological (e.g. relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.) and photographic data, if available. Carcinomatous meningitis diagnosed by cytology of cerebral spinal fluid was considered progressive disease. Medical photography was permitted to monitor chest wall recurrence of subcutaneous lesions.

Secondary Endpoints:

- **Overall Survival**: Defined as time from date of randomization to the date of death from any cause.

- **PFS based on investigator assessment**: same definition as primary endpoint, except progression assessed by investigator rather than IRF.

- **Objective response**: CR or PR determined by IRF using RECIST on two consecutive occasions > 4 weeks apart. Patient with bone only disease not included in the analysis.

- **Duration of response**: The date of initial confirmed PR or CR until the date of progressive disease or death from any cause.

- **Time to symptom progression**: Time from randomization to first symptom progression in the FACT TOI-PFB, a 24-item subscale using 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being and additional concerns. A decrease of 5 points is considered clinically significant.

WO20698 Statistical Methods:

Sample Size Determination:
A sample size of 800 patients needed to provide 80% power to detect a 33% improvement in OS (36 months median placebo vs. 48 months median pertuzumab; HR=0.75) at the two sided significance level of 5%. The trial was sized for approximately 50% of the required deaths at the time of final PFS analysis.

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 occur when 50% of the required deaths (193 deaths) is reached. A 40% improvement in PFS (median 10.5 months placebo vs. 14.7 months pertuzumab) would have 90% power at two-sided significance level of 5%, and a 33% PFS improvement (median 10.5 months placebo vs. 14 months pertuzumab) would have 80% power by log-rank test.

Analysis Populations:
Intent to Treat: all randomized patients

Other Analysis Populations: For Objective response and time to response, only patients with measurable disease at baseline included. For duration of response, only responders. For time to symptom progression based on FACT-B questionnaire, only female patients.

Safety Analysis Population: Patients who received any amount of any component of study treatment.

A summary of the various efficacy analyses are listed in Table 6**.**

Table 6: WO20698 Efficacy Analyses (Applicant Table)

Variable	Test	Stratification*
Primary endpoint: IRF-assessed PFS	Log-rank	prior treatment status, region
Secondary endpoints: time-to-event: investigator-assessed PFS, OS, time to symptom progression, duration of response	Cox regression	prior treatment status, region
objective response rate	Mantel–Haenszel χ^2	prior treatment status, region
	Fisher's exact	unadjusted (sensitivity)

* Strata: Prior treatment status: de novo vs prior (neo)adjuvant therapy;
Region: Europe, North America, South America, and Asia.

Source: CSR page 76

Testing hierarchy at the time of PFS analysis to adjust for multiplicity:

1. Test the primary endpoint, IRF-assessed PFS, at a two-sided 5% significance level. If positive, continue to Step 2.
2. Test OS at an overall two-sided 5% significance level. If positive, continue to Step 3.
3. Test ORR at an overall two-sided 5% significance level.

Sensitivity Analyses:

Six sensitivity analyses were proposed, with a definition provided in Table 7:

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

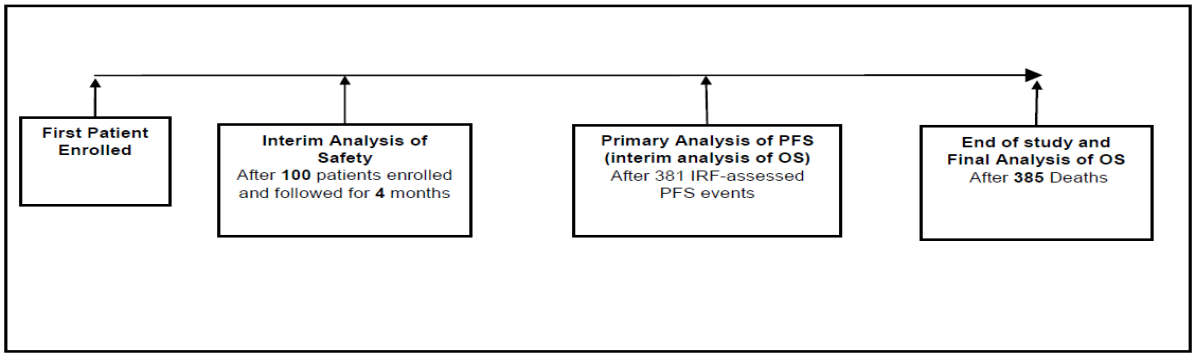
Table 7: WO20698 Sensitivity Analyses (Applicant Table)

	Factor Assessed	Censoring Rules
1	Possible differences between investigator and IRF tumor assessments	The earliest PD date as assessed by either the IRF or the investigator was used as the date of the PFS event.
2	Censoring at the time of next-line anti-cancer therapy (NACT)	Patients who started NACT prior to either IRF-assessed PD, death (within 18 weeks of last tumor assessment) or last IRF-evaluable tumor assessment were censored at the date of the last IRF-evaluable tumor assessment prior to the start of NACT.
3	IRF-assessed PFS during treatment	Only IRF-assessed PFS events occurring no later than 42 days after the last administration of any study treatment were included in the analysis.
4	Potential bias introduced by varied tumor assessment intervals as a result of a missing visit(s)	The missing assessment (or earliest missing assessment if more than one was missed) was replaced by an assessment of PD and the time to event was set as the expected day of the missing scheduled visit. If no assessment was missed, then the first PD date as assessed by the IRF was used as the date of the 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 was replaced by an assessment of PD.
5	Timing of death	All deaths, including those occurring 18 weeks after the last tumor assessment, were included as events in the analysis.
6	Patients stopping treatment early due to toxicity	Patients who discontinued all study treatment due to toxicity were censored at their last IRF-assessed tumor assessment on or before their treatment discontinuation date

Source: CSR page 78

Interim safety analysis:
An interim safety analysis was performed after 100 patients were enrolled and followed for at least four months (Figure 6). Analysis were presented to the independent data monitoring committee (DMC)

Figure 6: WO20698 Study Design: Analysis Timing (Applicant Figure)



IRF = Independent Review Facility; OS = overall survival; PFS = progression-free survival.
Source: CSR page 44

WO20698 Eligibility Criteria

Inclusion Criteria:
Disease-specific inclusion criteria:

- 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 were eligible.
    - Patients with bone only metastases were eligible provided they had some bone metastases that had not been previously irradiated and had tumor tissue samples from the primary tumor available for central HER2 testing and subsequent biomarker analysis.
    - Locally recurrent disease must not be amenable to resection with curative intent. Patients with de-novo Stage IV disease were eligible.
- HER2-positive (defined as 3+ IHC or FISH amplification ratio $\geq$ 2.0) MBC confirmed by a Sponsor-designated central laboratory. It was strongly recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor (or metastatic if the primary was not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that was not possible, 25 unstained and freshly cut slides were to be submitted. The tissue was subsequently used for assessment of biomarkers.

General inclusion criteria:

- Age $\geq$ 18 years
- LVEF > 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (ECHO preferred. If the patient was randomized, the

same method of LVEF assessment, ECHO or MUGA, was to be used throughout the study and to the extent possible the same institution. All available historic LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study were collected.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
- 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 was to continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners were pregnant should use condoms for the duration of the pregnancy.
- 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:
- History of anti-cancer therapy for MBC (with the exception of one prior hormonal regimen for MBC, which had to be stopped prior to randomization).
    - Anti-cancer therapy for MBC included 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 could have included more than one hormonal therapy. If a patient switched therapy due to toxicity or local standard practice, and not due to PD, this was counted as one 'regimen'.
    - If a patient received hormonal therapy for MBC and switched to a different hormonal therapy due to PD, this was counted as two 'regimens' and the patient was not eligible.
- 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 systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months.
- History of persistent NCI-CTCAE, Version 3.0 Grade $\geq$ 2 hematologic toxicity resulting from previous adjuvant therapy.
- Current peripheral neuropathy of Grade $\geq$ 3 at randomization.
- 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 was previously treated with curative intent.
- Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain was mandatory (within 28 days of randomization) in cases of clinical suspicion of metastases.
- History of exposure to the following cumulative doses of anthracyclines:

- Doxorubicin or liposomal doxorubicin > 360 mg/m^2
- epirubicin > 720 mg/m^2
- mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2
- other (i.e. liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin)
- if more than one anthracycline was used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

General exclusion criteria:

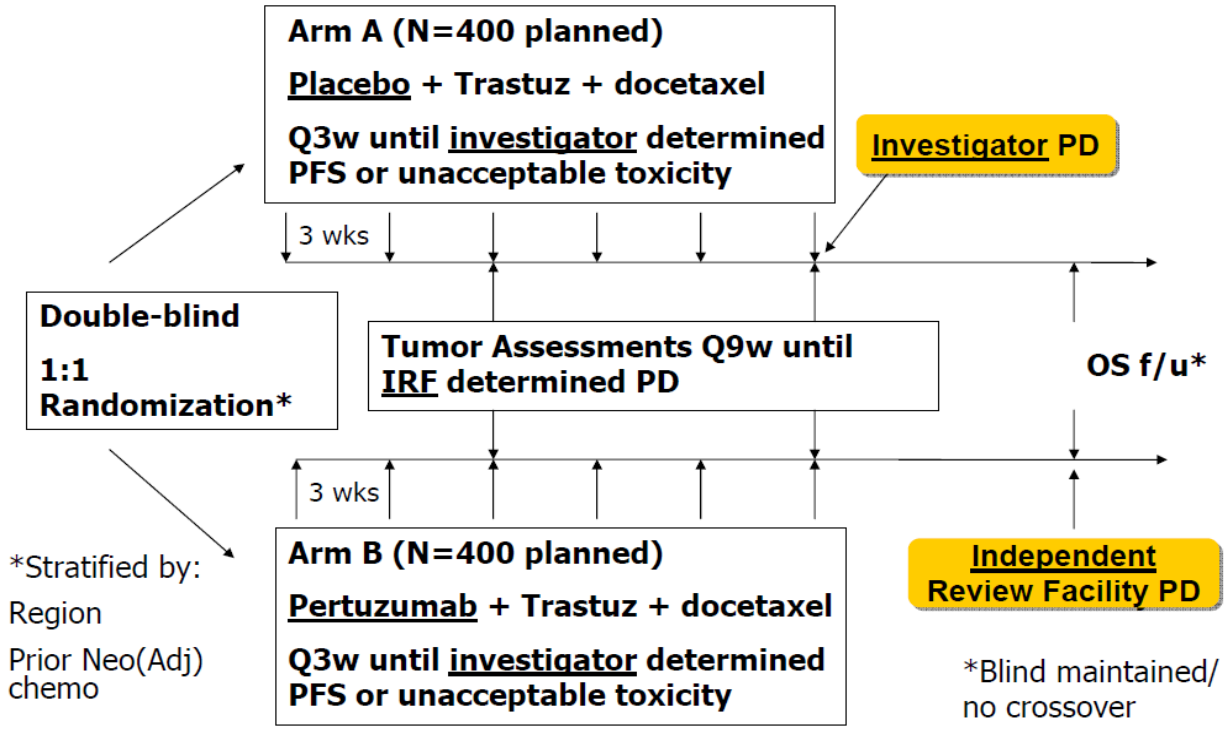
- Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina.
- History of congestive heart failure (CHF) of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception: atrial fibrillation, paroxysmal supraventricular tachycardia).
- History of myocardial infarction within 6 months of randomization.
- History of myocardial infarction within 6 months of randomization.
- History of LVEF decline to below 50% during or after prior trastuzumab neoadjuvant or adjuvant therapy.
- Current dyspnea at rest due to complications of advanced malignancy, or other diseases requiring continuous oxygen therapy.
- Inadequate organ function, evidenced by the following laboratory results within 28 days of randomization:
  - Absolute neutrophil count (ANC) < 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 had documented Gilbert's syndrome
  - AST or ALT > 2.5 x ULN
  - AST or ALT > 1.5 x ULN with concurrent serum alkaline phosphatase > 2.5 x ULN. Serum alkaline phosphatase may be > 2.5 x ULN only if bone metastases present and AST or ALT < 1.5 x ULN.
  - Serum creatinine > 2.0 mg/dL or 177μmol/L
  - International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 x ULN (unless on therapeutic coagulation).
- Current severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease; wound dealing disorders; ulcers; or bone fractures).
- Major surgical procedure or significant traumatic injury within 28 days of study treatment start or anticipation of the need for major surgery during the course of study treatment.
- Pregnancy or lactating women.
- History of receiving and investigational treatment within 28 days of randomization.

- Current known infection with HIV, HBV, or HCV.
- Receipt of IV antibiotics for infection within 14 days of randomization.
- Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
- Known hypersensitivity to any of the study drugs.
- Assessed by the investigator as unable or unwilling to comply with the requirements of the protocol.
- Participation in concurrent interventional or non-interventional studies was not permitted.

Reviewer Comment: *Unclear why patients with non measurable disease were eligible as these patients have better prognosis, potentially different tumor biology, and are more difficult to follow using PFS as an endpoint. Otherwise, the eligibility criteria appear reasonable.*

WO20698 Trial Design and treatment plan:

Figure 7: WO20698 study design (Reviewer Figure)



Reviewer Comment: *Well-designed study with 'real time' PFS analysis by independent review facility. If the investigator determined progressive disease (PD) but the independent review facility (IRF) disagreed, patients would continue with every 9 week tumor assessments until IRF determined PD. In addition, once PD was determined, the blind was maintained without cross-over. This design reduced informative censoring and reduced confounding variables in the PFS and OS analyses.*

A total of 800 patients planned for enrollment, randomized 1:1 to:

Arm A (Placebo + T + D)

- Pertuzumab placebo: IV infusion every 3 weeks (q3w)
- Trastuzumab: loading dose 8 mg/kg IV, followed by 6 mg/kg IV q3w
- Docetaxel 75 mg/m^2 IV q3w for at least six cycles

Arm B (Pertuzumab + T + D)

- Pertuzumab: loading dose 840 mg/kg IV, followed by 420 mg/kg IV q3w
- Trastuzumab: loading dose 8 mg/kg IV, followed by 6 mg/kg IV q3w
- Docetaxel 75 mg/m^2 IV q3w for at least six cycles

At the investigator's discretion, docetaxel could be increased to 100 mg/^{2} for patients who tolerated at least one cycle without significant toxicities.

Treatment continued until investigator-assessed radiographic or clinical progressive disease (PD), unacceptable toxicity or withdrawal of patient consent. If pertuzumab/placebo and/or trastuzumab had to be permanently discontinued or withheld for more than two cycles, the patient was taken off treatment. However, if docetaxel had to be permanently discontinued for reasons related to toxicity, the patient could continue pertuzumab/placebo and trastuzumab.

Imaging, medical photography and other relevant data relating to disease assessment were sent to the IRF on an ongoing basis. When PD was diagnosed by the investigator, the IRF was notified and all relevant data sent to IRF for expedited review. If progression not confirmed, IRF sent a notification to the investigator requesting that the patient continue to be scanned every 9 weeks, as per protocol. The investigator did not need to wait until IRF confirmation of PD before deciding what action to take and was free to initiate alternative anticancer treatment.

Rationale for Dose Selection:
Trastuzumab: standard every 3 week dose selected (rather than weekly regimen) for its greater convenience in combination with docetaxel and pertuzumab.

Docetaxel: 75 mg/m^2 selected rather than 100 mg/m^2. Investigators in Asia stated that the 100 mg/m^2 was too high to participate, and Western investigators indicated that in routine practice only a minority of patients are initiated on docetaxel 100 mg/m^2.

***Reviewer Comment**: Trastuzumab is approved in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer, and as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. In the adjuvant setting, it is indicated as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel or with docetaxel and carboplatin. Although it is not specifically labeled for combination with docetaxel in the metastatic setting, it is a commonly used first-line metastatic regimen. Docetaxel is indicated as a single agent for locally advanced or metastatic breast cancer after chemotherapy failure (60 mg/m^2 to 100 mg/m^2). By 2012 NCCN guidelines[4], docetaxel 80 – 100 mg/m^2 every 3 weeks is a preferred regimen with trastuzumab 4 mg/kg day 1 followed by 2 mg/kg IV weekly or 8 mg/kg load day 1 followed by 6 mg/kg IV every 3 weeks. Therefore, the control arm represents a reasonable 1st line option with multiple contemporary randomized phase 2 and 3 trials showing median TTP/PFS ranging from 11.1 to 12.8 months[5,6,7,8].*

WO20698 Formulation and Packaging:

Pertuzumab was provided as a single-use vial containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine (pH 6.0), 120 nM sucrose, and 0.02% polysorbate 20. Each 20-cc vial contained approximately 420 mg of pertuzumab (14.0 mL/vial).

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

WO20698 Randomization and Blinding:

An interactive Voice Response System used to collect patient screening information and randomize eligible patients in a 1:1 ratio. A complete block randomization scheme was applied to achieve balance in treatment assignment within each of eight strata: prior treatment status (de novo vs. prior adjuvant vs. prior neoadjuvant) and region (Europe, North America, South America and Asia). Unblinding was not permitted except for safety issues, which required approval from the medical monitor.

WO20698 Drug Administration:

Pertuzumab/placebo administered as an IV loading dose of 840 mg Cycle 1 and 420 mg in subsequent cycles. Trastuzumab was administered as an 8 mg/kg IV loading dose and 6 mg/kg in subsequent cycles. The dose of trastuzumab was recalculated if change in body weight exceeded +/- 10% from baseline. Docetaxel was administered

75 mg/m^2 IV every 3 weeks. For patients who tolerated at least one cycle without significant toxicity, docetaxel was increased to 100 mg/m^2 at the discretion of the investigator. Docetaxel dose adjustments for changes in body weight were based on the investigative site's usual practice.

Treatment cycles were 21 days in duration. The first dose of pertuzumab/placebo (Cycle 1, Day 1) was to be administered within 3 days of randomization. The first dose of trastuzumab was to be administered 24 hours later, followed by the first dose of docetaxel. If all three agents were well tolerated, in subsequent cycles all 3 drugs were to be administered day 1 of the cycle in the following sequence: pertuzumab/placebo --> trastuzumab --> docetaxel.

The first infusion of trastuzumab was to be administered over 90 minutes and pertuzumab/placebo after 60 minutes. If the first infusion of trastuzumab and the first two infusions of blinded pertuzumab/placebo were tolerated without infusion associate adverse events (AEs), subsequent infusions could be delivered over 30 minutes. Treatment with pertuzumab/placebo and trastuzumab was to continue until investigator-assessed PD or unmanageable toxicity. Treatment with docetaxel continued for a minimum of six cycles, unless the patient experienced unacceptable toxicity or PD. After 6 cycles, continuation of docetaxel was at the investigator's discretion.

Dose Delay and Modification:

If administration of any individual study drugs were delayed for a day or more, administration of the other two agents is delayed as well.

If a patient missed a dose of pertuzumab/placebo for > 1 cycle (i.e. the two doses were 6 weeks or more apart), patients would be re-loaded (840 mg) with pertuzumab. Similarly, if a patient missed > 1 cycle of trastuzumab, s/he would be re-loaded with trastuzumab 8mg/kg. If a re-loading dose was required, the 3 study medications would be administered as in cycle 1 (pertuzumab/placebo day 1, trastuzumab and docetaxel day 2).

If pertuzumab/placebo or trastuzumab were delayed more than 2 cycles or had to be permanently discontinued, the patient would be withdrawn from study treatment and would be monitored post-treatment. Pertuzumab/placebo or trastuzumab dose modifications were not permitted.

If docetaxel dose was delayed > 3 weeks with no recovery, docetaxel would be permanently discontinued but pertuzumab/placebo and trastuzumab would be continued. The docetaxel dose could be increased at the investigator's discretion to 100 mg/m2 for patients tolerating at least one cycle without: febrile neutropenia, grade 4 neutropenia > 5 days or ANC < 100/uL for > 1 day or non hematologic toxicities > Grade 2. Docetaxel was modified according to Table 8. The schedule of assessments is provided in Table 9.

Table 8: WO20698 Docetaxel Dose Adjustments (Applicant table)

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.

Source: WO20698 protocol table 3

Table 9: WO20698 Schedule of Assessments (Applicant Table)

	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 [l]			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]						
Samples									
Tumor for HER2 Eligibility & Biomarkers, to central lab	x [q]								
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]							
1. Serum for Antibodies to Pertuzumab, to central lab					4. Perform every 9 weeks at the time of the TA[v]	5.			
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, u]						
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 applied to all visits and assessments, except for follow-up survival information collection which had a window of ± 7 days.
[b] Treatment discontinuation visit to occur 4-6 weeks (28-42 days) after the last administration of study drug (pertuzumab/placebo, trastuzumab, or docetaxel, whichever was discontinued last).
[c] Signing of the Informed Consent and submission of tumor sample for HER2 Eligibility and Biomarkers were 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 to be collected
[e] Symptom-directed physical examination including vital signs and weight was assessed on Day 1 of every treatment cycle. Vital signs (blood pressure, pulse rate, and body temperature) were recorded before and after infusion of each study medication (pertuzumab/placebo, trastuzumab, and docetaxel). Particular care was 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 was 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.

Source: CSR Section 2.5

[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) to be performed until IRF-confirmation of PD. Tumor assessments were scheduled every 9 weeks ± 3 days from the date of randomization. If a tumor assessment was performed early or late, subsequent assessments were conducted according to the original schedule of every 9 weeks from the date of randomization. All patients had a minimum of a chest and abdomen CT scan. PET scans were not considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes). Bone scans were preformed as clinically indicated. (In the absence of radioactive isotopes, an MRI scan (with gadolinium enhancement if required) or an F18 PET scan was an acceptable form of assessment of the skeleton for the presence of bone metastases. Skeletal survey with plain x-rays was acceptable if there were no suitable alternatives). If treatment was discontinued due to PD, on sites other than bone, a bone scan was 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 was 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 were collected.

[k] More frequent LVEF assessments were performed as needed for cardiac safety. LVEF assessments were scheduled 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 was performed early or late, subsequent assessments were 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 continued to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months , until the LVEF values returned to ≥ 50%, or 1 year after the Treatment Discontinuation Visit, whichever occured first. Thereafter, LVEF assessments were performed annually for up to 3 years after the Treatment Discontinuation Visit.

[l] Only SAEs related to study-specific procedures were collected during the Screening/Baseline period.

[m] See Section 7.2 of the protocol for adverse event reporting and follow-up requirements.

[n] The first dose of pertuzumab/placebo (Cycle 1, Day 1) was administered within 3 days of randomization. All doses of pertuzumab/placebo were administered on Day 1 of the 21-day cycles. Pertuzumab/placebo continued until investigator-assessed disease PD or unmanageable toxicity.

[o] The first dose of trastuzumab was given at Cycle 1, Day 2. If well tolerated as determined by the investigator, all subsequent cycles of trastuzumab were administered on Day 1 after pertuzumab/placebo. Trastuzumab continued until investigator-assessed PD or unmanageable toxicity.

[p] The first dose of docetaxel was given at Cycle 1, Day 2 after trastuzumab. If well tolerated as determined by the investigator, all subsequent cycles of docetaxel were administered on Day 1 after trastuzumab. On or prior to Cycle 6, docetaxel was discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the patient and treating physician.

[q] See Section 5.4.3 of the protocol for specific required tests. Laboratory tests were 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 were performed within 7 days prior to study treatment start, they were not repeated on Day 1 of the start of study treatment. An additional hematology blood test was performed on Day 8 of each treatment cycle during chemotherapy.

[r] During the treatment period, patients receiving therapeutic doses of anti-coagulants had 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 had not undergone surgical sterilization, pregnancy tests were performed via serum β-HCG at baseline. A urine pregnancy test was 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] Collected and submitted only for patients that received prior trastuzumab.

[u] Collected and submitted only if a patient was eligible and randomized onto the study. Could be collected up to and including study Day 1 prior to the first study drug dose.

[v] Serum samples for antibodies to pertuzumab were 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 were only collected and submitted from sites where permitted by local regulatory and EC requirements.

[x] Serum and plasma samples for biomarker sample repository (BSR) were collected every 9 weeks at the time of each tumor assessment until IRF-determined PD. If IRF-determined PD occured prior to post-treatment Week 18, BSR samples were collected every 9 weeks until post-treatment Week 18.

[y] Post-study treatment cancer-related medical or surgical procedures and therapies and survival information was collected 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 cut-off for the final PFS analysis and final OS analysis, the investigative sites are to contact every patient that was alive to confirm current survival status. (The study Sponsors are to notify all investigators of the timing of this survival data sweep.)

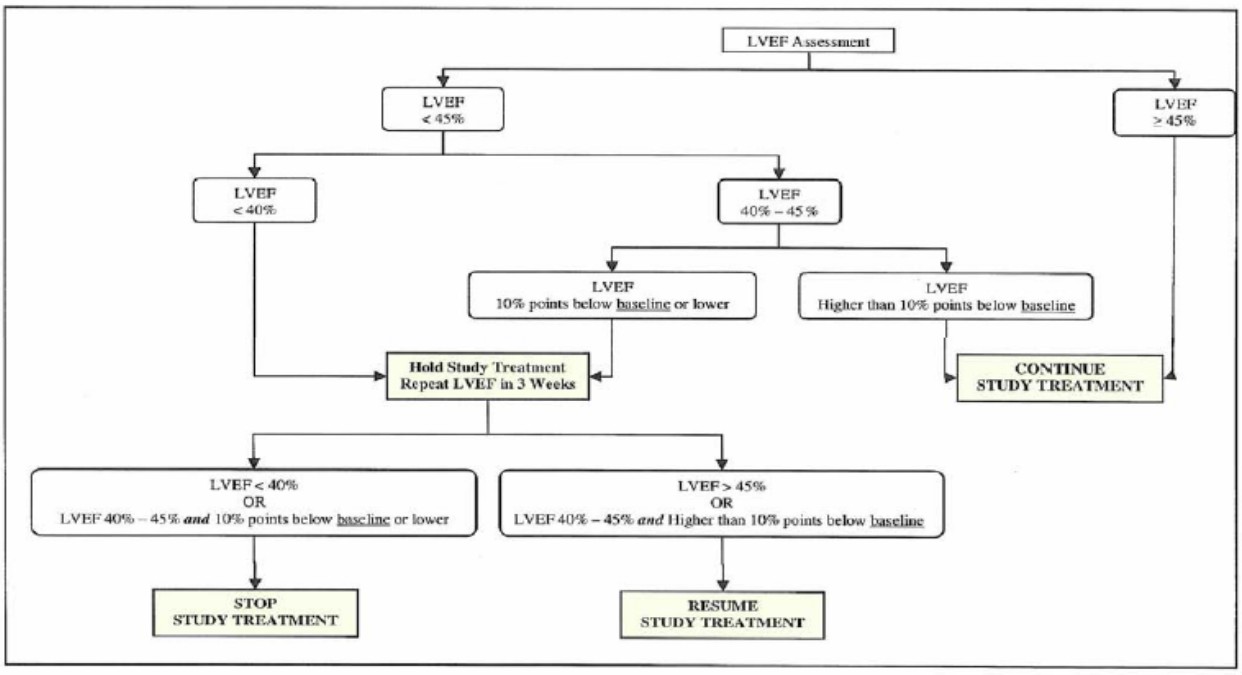
[z] In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan was an acceptable form of assessment of the skeleton for the presence of bone metastases. Skeletal survey with plain x-rays was acceptable if there was no suitable alternative

Source: CSR Section 2.5

WO20698 Cardiac Monitoring Algorithm:

The algorithm for continuation and discontinuation of pertuzumab/placebo and trastuzumab based on LVEF assessments is presented in Figure 8. Patients who were permanently discontinued due to a drop in LVEF would have repeat assessments of 3 months, until the LVEF values returned to > 50%, or 1 year. Thereafter, LVEF assessments would be performed annually for 3 years.

Figure 8: WO20698 Cardiac Monitoring Algorithm (Applicant Figure)



Source: CSR Section 2.6.4.2, Figure 3

WO20698 Protocol Amendments

Protocol Version A, September 2007: In response to EMA and FDA comments, in the original protocol the sponsor increased the sample size from 600 to 800 to power for OS.

Protocol Version B, December 2007: In response to FDA recommendations.
Key changes:

- Inclusion criteria 4 modified to include collection of historic LVEF values during and after adjuvant trastuzumab adjuvant treatment
- LVEF assessments were added during follow-up. The LVEF assessment follow-up schedule for patients discontinuing study treatment for drop in LVEF also updated.
- Surveillance for Anti pertuzumab antibodies increased. Additional samples collected during study treatment, prior to cycle 3 then every 9 weeks
- Hematology test was added on day 8 of each treatment cycle.
- On-study tumor assessments more precisely defined. At baseline, patients were to have a minimum chest and abdomen CT or MRI, and PET scans were allowed for assessing efficacy.

Protocol Version C June 23, 3009:
Following new reproductive toxicity findings in pregnant cynomolgus monkeys and the subsequent reporting of a pregnancy in a pertuzumab study (WO20697) requiring a therapeutic termination at 7 weeks. Key changes included:

- Definition of postmenopausal women and the contraceptive requirements for women of childbearing potential, male patients with partners of childbearing potential, and pregnant partners were updated to align with ICH M3 guidelines
- Pregnancy testing after treatment discontinuation was added.

Other key changes:

- Patient with only bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue from the primary tumor available for central HER2 testing.
- One prior hormonal regimen for MBC may include more than one hormonal therapy, for example, if the switch is not related to disease progression. If the switch is related to disease progression, this will be counted as two "regimens" and the patient is not eligible.
- Alkaline phosphatase may be > 2.5 x ULN only if bone metastases are present and AST and ALT < 1.5x ULN.
- Clarified time points for LVEF assessment. For all patients, LVEF assessments should be conducted at treatment discontinuation, every 6 months in the first year, then annually for up to 3 years after treatment discontinuation visit.

5.3.2 Phase 2b Neoadjuvant WO20697 (Neosphere)

Title: "A randomized, 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"

Design: Patients were randomized to receive neoadjuvant therapy:

- Arm A: trastuzumab plus docetaxel
- Arm B: trastuzumab plus docetaxel plus pertuzumab
- Arm C: trastuzumab plus pertuzumab
- Arm D: pertuzumab plus docetaxel

Key inclusion: Locally advanced, inflammatory or early stage HER2+ breast cancer. Patients with metastatic disease were excluded.

Pertuzumab dose: 840 mg load IV; then 420 mg IV every 3 weeks x 4 cycles

Trastuzumab dose: 8 mg/kg load IV then 6 mg/kg every 3 weeks x 4 cycles neoadjuvant and up to 1 year total post surgery

Docetaxel dose: 75 mg/m^2 escalating if tolerated to 100 mg/m^2 IV every 3 weeks for 4 cycles

Post Surgery standard of care: 5FU 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV every 3 weeks for 3 cycles. Hormonal therapy in HR+ patients and/or radiotherapy as per local practice after post-operative chemotherapy.

Primary Endpoint: pCR (absence of invasive neoplastic cells at microscopic examination of tumor remnants after surgery following primary systemic therapy) in the breast.

Secondary Endpoints: Tumor response, clinical response, time to response, breast conserving therapy rate, disease free interval, progression-free survival, and biomarker evaluation.

Safety: Adverse Events, Laboratory Parameters, LVEF by Echo or MUGA, Vital signs

Statistics: A pCR rate of 25% was expected in Arm A and Arm D. A pCR rate of 40% in Arm B or Arm C would be of clinical interest. The following three individual hypotheses were tested using a two-sided Cochrane Mantel-Haenszel test:

Arm A versus Arm B
- Null hypotheses: pCR A rate = pCR B rate
- Alternative hypothesis: pCR A rate $\neq$ pCR B rate

Arm A versus Arm C
- Null hypotheses: pCR A rate = pCR C rate
- Alternative hypothesis: pCR A rate $\neq$ pCR C rate

Arm D versus Arm B
- Null hypotheses: pCR D rate = pCR B rate
- Alternative hypothesis: pCR D rate $\neq$ pCR B rate

As there were three individual comparisons, a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk of 0.2. With a sample size of 400 (100 per arm) the study would have 80% power to detect an absolute percentage difference of 15% between arms for each of the three primary comparisons.

The comparisons were stratified by:
- operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, and N, M0) and inflammatory (T4d, any N, M0)
- ER and/or PgR status (positive vs. both negative)

PFS: time from date of randomization to progressive disease or death

DFS: only for patients who underwent surgery. Time from date of primary surgery to the first documentation of progressive (recurrent) disease or death.

PFS and DFS results are to be submitted in a follow-up report.

5.3.3 Single Arm Phase 2b BO17929 in trastuzumab-resistant HER2+ MBC

Title: "An exploratory phase II, single arm, multicenter study to evaluate the efficacy and safety of the combination of pertuzumab and Herceptin® (trastuzumab) in patients with HER2-positive metastatic breast cancer.

Design: Open-label, single-arm, multinational, multicenter trial to evaluate the efficacy and safety of eight cycles of pertuzumab in combination with trastuzumab (cohorts 1 and 2). An additional cohort (cohort 3) evaluated the safety and efficacy of single-agent pertuzumab. Patients in cohort 3 could have trastuzumab added following progression on pertuzumab monotherapy.

Key eligibility: Females with HER2+ MBC who had progressed on trastuzumab-based therapy as last previous treatment.

Dose/ Schedule:

Pertuzumab: 840 mg IV load over 60 ± 10 minutes, thereafter 420 mg IV over 30 ± 10 minutes every 3 weeks
Trastuzumab: 2mg/kg IV over 30 minutes weekly or 6 mg/kg IV over 90 minutes every 3 weeks

At cycle 1 trastuzumab was administered day 1 and pertuzumab day 2. Thereafter, they were both administered day 1. Patients who completed 8 cycles and did not progress were eligible to continue study medication until progression, intolerable toxicity or death

Primary Endpoints: OR and CBR rate in cohorts 1 and 2 according to RECIST.

Secondary Endpoints: TTP, PFS, OS in cohorts 1 and 2, and OR/CBR in cohort 3

Safety: AEs, laboratory parameters, LVEF by ECHO or MUGA, Vital signs and performance status.

Tumor assessments: On or after Day 15 of cycles 2, 4, 6 and 8 and every 4 cycles thereafter.

Statistics:
Objective Response (OR): documented and confirmed CR or PR
Clinical Benefit Rate (CBR): objective response at any time and for at least 4 weeks or best response of stable disease that lasts at least 6 months (or 8 cycles of therapy).

Interim analysis: 24 evaluable enrolled. An optimum design, with a null hypothesis for OR rate ≤ 7%, a one-sided alpha = 0.10 and power = 60% to detect a clinically meaningful OR rate of ≥ 13%. Specifically, the trial could be stopped for lack of activity if ≤ 1 response out of 24 patients was observed at the first stage.

Final analysis: 58 evaluable patients enrolled and ≥ 8 patients with response or ≥ 14 patients with clinical benefit response, 67% power to reject null hypothesis when OR is ≥ 13% or clinical benefit response rate ≥ 25%, at a one-sided alpha of ≤ 0.1.

6 Review of Efficacy

6.1 Indication

Genentech proposed the following indication in their BLA submission:

> "Perjeta is indicated in combination with Herceptin® (trastuzumab) and docetaxel for patients with HER2-positive metastatic [redacted] (b) (4) breast cancer, who have not received previous treatment [redacted] (b) (4)

6.1.1 Methods

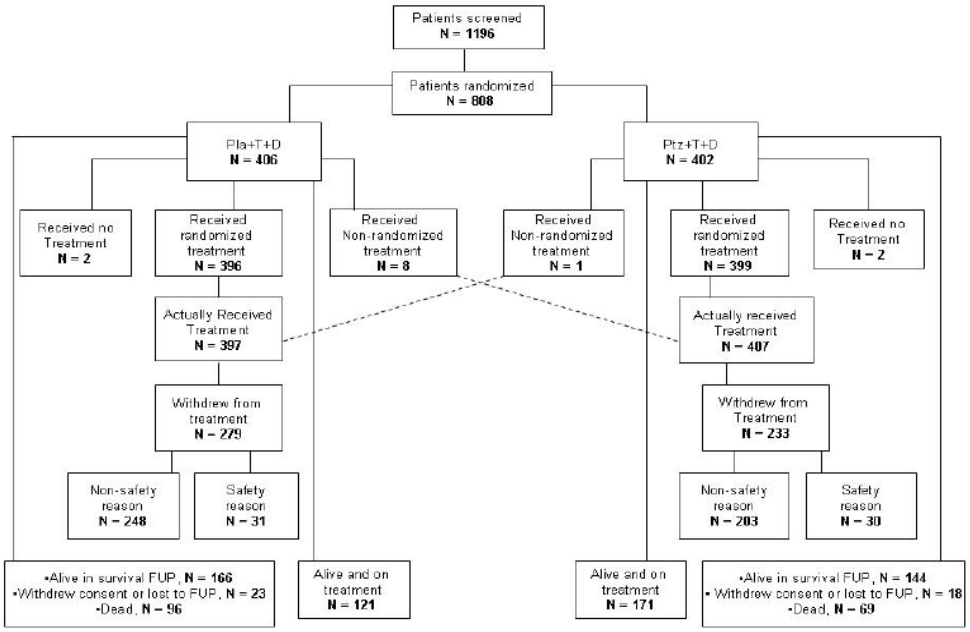
This review will focus primarily on the efficacy results of the single randomized controlled trial, WO20698 (CLEOPATRA)[9]. For information on WO20698 study design, see section 5.3.1. For the statistical review, please see Dr. Somesh Chattopadhyay's review.

In addition to the pivotal study, a review of efficacy data from the randomized phase 2b study WO20697 (NEOSPHERE), and from the single arm phase 2 study in metastatic breast cancer BO17929 will be included in sections 6.1.11 and 6.1.12, respectively. For a summary of the study designs of WO20697 and BO17929, see sections 5.3.2 and 5.3.3.

6.1.2 WO20698 Subject Disposition

From the first patient visit February 12, 2008 to data cut-off May 13, 2011, a total of 1196 patients were screened, and patients were enrolled from 204 centers in 25 countries. A total of 808 patients were randomized, 406 to the placebo arm and 402 to the pertuzumab arm, comprising the ITT population (Figure 9).

Figure 9: WO20698 Patient Disposition (Applicant Figure)



BEST POSSIBLE COPY

Source : CSR figure 4

The safety analysis population excluded two patients in each arm that received no study medication after randomization. There were 8 patients assigned to placebo who incorrectly received at least one dose of pertuzumab, and 1 patient assigned to pertuzumab who incorrectly received placebo at every cycle. The Safety Analysis population therefore included a total of 804 patients, 397 in the placebo arm and 407 in the pertuzumab arm.

At the time of clinical data cut-off 121 patients (30%) on placebo and 171 patients (43%) on pertuzumab were still alive and on treatment. An additional 166 patients (41%) on placebo and 144 patients (36%) on pertuzumab were alive and in survival follow-up. With respect to patients who had withdrawn consent or were lost to follow-up, there were 23 (6%) such patients on placebo and 18 (5%) on pertuzumab. There were 96 patients (24%) on placebo and 69 patients (17%) on pertuzumab who died.

The median time on study, including post-treatment follow-up was 73.1 weeks on placebo and 77.1 weeks on pertuzumab. The blind was broken for 25 patients (12 placebo, 13 pertuzumab).

6.1.3 WO20698 Protocol Violations

Inclusion/Exclusion
Approximately 12% in each treatment arm were categorized as violating inclusion criteria, but the majority of these infractions were due to being outside the 28-day screening window. Violations in exclusion criterion occurred in 24% of patients on the placebo arm and 20% on the pertuzumab arm. Most of these were violations of exclusion criteria 14, requiring minimum laboratory test requirements for bone marrow, liver and renal function. Of these, about half were due to missing aPTT or INR measurements at screening. Four patients were randomized despite entry criteria violations but never treated. Three of these patients had ALT and AST levels > 2.5 x ULN and one withdrew consent prior to study drug administration.

On-Study procedures:
About 40% of patients in each arm had on-study violations due to LVEF assessments or tumor assessments performed outside the protocol-defined window of 9 weeks +/- 7 days.

Early Withdrawals due to protocol violations:
One placebo patient withdrew after 1 cycle because she had no treatment-free interval between adjuvant therapy and diagnosis of metastatic disease. One pertuzumab patient withdrew after 1 cycle due to brain lesions on baseline assessment, and another pertuzumab patient withdrew after 1 cycle due to LVEF reduction to 38% while on adjuvant trastuzumab.

Reviewer Comment: *Overall, the protocol violations were relatively minor and do not appear to compromise the integrity of WO20698.*

6.1.4 WO20698 Demographics

Table 10 presents the breakdown of enrollment by country. The three highest accruing countries were the U.S (14%), Brazil (12%), and South Korea (12%), respectively. By region, Asia had the highest accrual (32%), followed by Western Europe (23%), Central/ South America (16%), USA/Canada (15%), and Russia/Eastern Europe (14%).

Of the 3 highest accruing sites, 2 were in South Korea (Ulsan College of Medicine, Seoul N=30; Seoul National University Hospital N=23) and 1 in Brazil (Hospital Perola Bygton, Sao Paulo, N=22). The highest accruing US sites were in Nashville TN (Sarah Cannon Research Institute, N=6) and Bakersfield CA (N=6).

Table 10: WO20698 Enrollment by country (Reviewer Table)

Country	# Pts	% (808)
USA	116	14.4
Brazil	100	12.4
South Korea	94	11.6
Russia	71	8.8
Spain	58	7.2
Japan	53	6.6
Germany	44	5.4
Thailand	38	4.7
United Kingdom	34	4.2
Poland	33	4.1
Philippines	30	3.0
France	24	3.0
Italy	24	2.5
Singapore	20	2.2
China	18	1.6
Argentina	13	0.7
Mexico	6	0.7
Costa Rica	6	0.7
Latvia	6	0.6
Finland	5	0.6
Guatemala	5	0.5
Croatia	4	0.4
Macedonia	3	0.2
Canada	2	0.1
Ecuador	1	0.1

Source: cent.xpt

Reviewer Comment: *Diverse international representation, including 14% from U.S. High accrual from Asia (32%).*

Table 11 presents demographic information. There was under-representation of African Americans (3.7% overall). There were more patients with ECOG performance status (PS) of 0 on pertuzumab arm (68%) than placebo (61%). Baseline tumor characteristics (Table 12) and prior breast cancer treatments (Table 13) are also summarized. Almost all patients had metastasis at study entry. Of the 19 patients categorized as having locally recurrent disease at baseline, 7 actually had metastases noted on their baseline disease assessment. Therefore, the number of true locally recurrent patients overall was 1%.

Table 11: WO20698 Baseline patient demographics (Reviewer Table)

Patient Characteristics	Total (N=808)	Placebo + T + D (N=406)	Pertuzumab + T + D (N=402)
Gender			
Female (%)	806 (99.8)	404 (99.5)	402 (100)
Male (%)	2 (0.2)	2 (0.5)	0 (0)
Age (years)			
Mean (sd)	53.5 (11.1)	53.5 (11.4)	53.4 (10.9)
Median (Range)	54 (22 – 89)	54 (27 – 89)	54 (22 – 89)
< 65 (%)	681 (84.3)	339 (83.5)	342 (85.1)
≥ 65 (%)	127 (15.7)	67 (16.5)	60 (14.9)
< 75 (%)	789 (97.6)	392 (96.6)	397 (98.8)
≥ 75 (%)	19 (2.4)	14 (3.4)	5 (1.2)
Race			
American Indian/Alaskan Native (%)	7 (0.9)	4 (1.0)	3 (0.7)
Asian (%)	261 (32.3)	133 (32.8)	128 (31.8)
Black (%)	30 (3.7)	20 (4.9)	10 (2.5)
Other (%)	30 (3.7)	14 (3.4)	16 (4.0)
White (%)	480 (59.4)	235 (57.9)	245 (60.9)
Ethnicity			
Hispanic	83 (10.3)	44 (10.8)	39 (9.7)
Non-Hispanic/ Unknown	725 (89.7)	362 (89.2)	363 (90.2)
Weight at baseline (kg)			
Mean (sd)	67 (15.1)	66 (14.7)	67 (15.4)
Median (Range)	65 (39 - 142)	65 (39 – 142)	65 (39 – 129)
Reproductive status			
Postmenopausal (%)	512 (63.5)	251 (62.1)	261 (64.9)
ECOG Performance Status			
0 (%)	522 (64.6)	248 (61.1)	274 (68.2)
1 (%)	282 (34.9)	157 (38.7)	125 (31.1)
2 (%)	3 (0.4)	0 (0)	3 (0.7)
3 (%)	1 (0.1)	1 (0.2)	0 (0)
Smoking Status			
Current Smoker (%)	75 (9.3)	41 (10.1)	34 (8.5)
Never Smoker (%)	629 (77.8)	315 (77.6)	314 (78.1)
Former Smoker (%)	104 (12.9)	50 (12.3)	54 (13.4)
Baseline LVEF			
Mean (SD)	65.2 (6.6)	65.5 (6.5)	64.9 (6.7)
Median (Range)	65 (50 – 88)	65 (50 – 88)	65 (50 – 88)

Reviewer Comment: *There was a slight imbalance in ECOG performance status, with more favorable PS 0 patients on pertuzumab arm. This imbalance did not appear to bias the study results. Black patients, who have a higher proportion of stage IV tumors at diagnosis, were under-represented in the pivotal study.*

Table 12: WO20698 Baseline Tumor Characteristics (Reviewer Table)

Tumor Characteristics	Total (N=808)	Placebo + T + D (N=406)	Pertuzumab + T + D (N=402)
Disease Type			
Non-Visceral Disease (%)	178 (22)	90 (22)	88 (22)
Visceral Disease (%)	630 (78)	316 (78)	314 (78)
Measurable Disease per IRF (%)	679 (89)	336 (89)	343 (89)
Non Measurable Disease per IRF (%)	87 (11)	43 (11)	44 (11)
Metastatic Disease (%)	797 (99)	400 (99)	397 (99)
Locally Recurrent (%)	11 (1)	6 (1)	5 (1)
Tumor Grade			
Anaplastic (%)	3 (<1)	1 (<1)	2 (<1)
Moderately Differentiated (%)	264 (33)	132 (33)	132 (33)
Poorly Differentiated (%)	255 (32)	125 (31)	130 (32)
Unknown (%)	255 (32)	131 (32)	124 (31)
Well differentiated (%)	30 (4)	16 (4)	14 (4)
Histology			
Ductal	736 (91)	368 (91)	368 (92)
Lobular	38 (5)	18 (4)	20 (5)
Medullary	4 (<1)	3 (<1)	1 (<1)
Tubular	6 (<1)	4 (1)	2 (<1)
Mucinous	13 (2)	3 (<1)	10 (3)
Comedo	33 (4)	16 (4)	17 (4)
Inflammatory	16 (2)	10 (3)	6 (2)
Hormone Receptor Status			
Negative (%)	408 (51)	196 (48)	212 (53)
Positive (%)	388 (48)	199 (49)	189 (47)
Unknown (%)	12 (1)	11 (3)	1 (<1)
HER 2 Status IHC			
0+ (%)	2 (<1)	--	2 (<1)
1+ (%)	4 (<1)	2 (<1)	2 (<1)
2+ (%)	79 (10)	32 (8)	47 (12)
3+ (%)	721 (89)	371 (92)	350 (87)
HER 2 Status FISH			
Negative (%)	5 (<1)	4 (1)	1 (<1)
Positive (%)	767 (95)	383 (94)	384 (96)
HER 2 Status IHC/FISH Combined			
--/FISH Positive	2 (<1)	1 (<1)	1 (<1)
IHC 0+/FISH Positive	2 (<1)	--	2 (<1)
IHC 1+/FISH Positive	4 (<1)	2 (<1)	2 (<1)
IHC 2+/FISH Negative	1 (<1)	1 (<1)	--
IHC 2+/FISH Positive	78 (10)	31 (8)	47 (12)
IHC 3+/--	36 (4)	19 (5)	17 (4)
IHC 3+/FISH Negative	4 (<1)	3 (1)	1 (<1)
IHC 3+/FISH Positive	681 (84)	349 (86)	332 (83)

Table 13: WO20698 Prior Breast Cancer Treatment (Reviewer Table)

Prior Treatment Characteristics	Total (N=808)	Placebo + T + D (N=406)	Pertuzumab + T + D (N=402)
Prior Systemic Therapy			
De Novo (%)	432 (54)	214 (53)	218 (54)
Adjuvant/Neoadjuvant (%)	376 (47)	192 (47)	184 (46)
Prior Anthracycline (%)	314 (39)	164 (40)	150 (37)
Prior Taxane	185 (23)	94 (23)	91 (23)
Prior Trastuzumab	88 (11)	41 (10)	47 (12)
Prior Hormonal Therapy	221 (27)	107 (26)	114 (28)
Radiation			
Prior Radiation	346 (43)	175 (43)	171 (43)
Surgery			
Prior Surgery	571 (71)	286 (70)	285 (71)

Reviewer Comment: *Only 11% of patients received prior adjuvant or neoadjuvant trastuzumab. This was a key review issue since in the U.S., most patients present with local breast cancer and the majority of HER2+ patients receive adjuvant trastuzumab.*

In addition, 52% of HR+ patients received adjuvant hormonal therapy, and 13% of HR+ patients received 1st line metastatic hormonal therapy. In the U.S., most patients with HR+ disease would receive adjuvant hormonal therapy. For HR+ HER2+ metastatic disease, the decision whether to start with hormonal therapy (in combination with anti-HER2 therapy) or chemotherapy (in combination with trastuzumab) is a clinical decision and depends on the pace of the disease and whether there is impending visceral crisis.

6.1.5 WO20698 Analysis of Primary Endpoint(s)

As of the May 2011 cut-off, 433 IRF-confirmed PFS events had occurred, 242 (60%) in the placebo arm and 191 (48%) in the pertuzumab arm. The median PFS in the pertuzumab arm was 18.5 months, and in the placebo arm 12.4 months, (HR=0.62, 95% CI, 0.51 to 0.75; p<0.0001) as summarized in Table 14 and Figure 10.

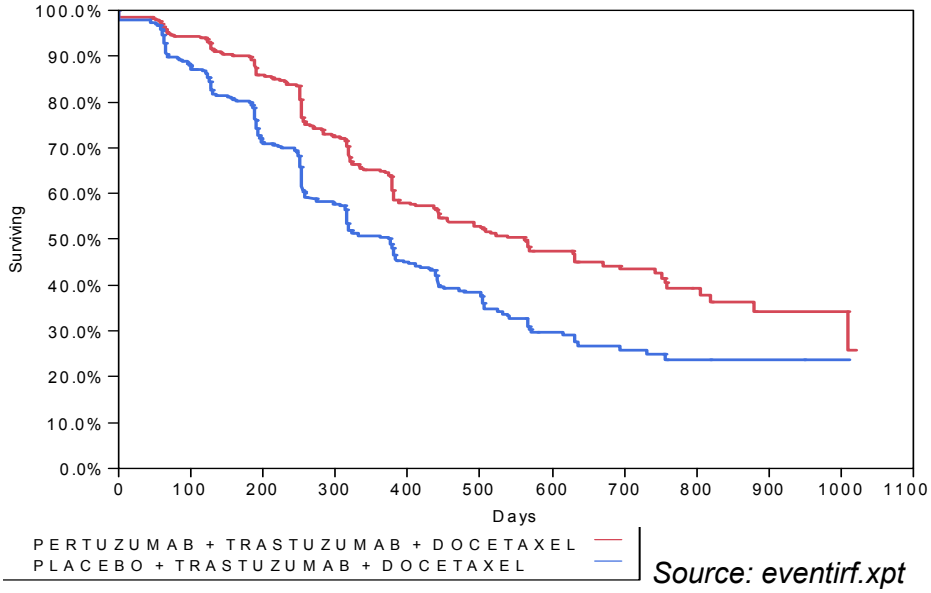
Table 14: WO20698 Primary endpoint: IRF assessed PFS (Reviewer Table)

	Placebo + T +D N=406	Pertuzumab + T + D N=402
Number of events (%)	**242 (60)**	**191 (48)**
Disease Progression (%)	226 (56)	180 (45)
Death within 18 weeks (%)	16 (4)	11 (3)
Censored (%)	**164 (40)**	**211 (52)**
Median PFS (months)	**12.4**	**18.5**
Hazard Ratio (stratified)*	**0.62**	
95% CI	(0.51 to 0.75)	
p- value	<0.0001	

*stratified by prior treatment and region
Source: eventirf.xpt

Reviewer comment: *A clinically meaningful 6.1 month improvement in median PFS. Control arm performance (12.4 month median) was consistent with contemporary front-line HER2+ MBC docetaxel + trastuzumab trials[5,6,7,8]. In the trastuzumab study which lead to MBC approval[10], the median TTP for chemotherapy + trastuzumab was 7.4 months. However, this was a different patient population, with 26% of patients HER2 2+ by IHC, and 22% of patients having received high dose chemotherapy followed by hematopoietic stem cell rescue, which is no longer used to treat breast cancer.*

Figure 10: WO20698 KM curve IRF-assessed PFS (Reviewer Figure)



Source: eventirf.xpt

Sensitivity Analyses:
See Table 7 for definition of sensitivity analyses, and results are listed in Table 15. Briefly, the sensitivity analyses were as follows:

- Sensitivity analysis 1: PD date is earliest of IRF or Investigator assessed PD
- Sensitivity analysis 2: Censor to last tumor assessment prior to start of next line anti-cancer therapy
- Sensitivity analysis 3: Only IRF-assessed PFS events occurring ≤ 42 days after last administration of study treatment
- Sensitivity analysis 4: The earliest missing assessment before a PFS event replaced by PD
- Sensitivity analysis 5: Included all deaths (including ≥ 18 weeks after last tumor assessment) as an event
- Sensitivity analysis 6: Patients who discontinue due to toxicity were censored at last tumor assessment.

Table 15: WO20698 PFS Sensitivity analyses (Reviewer Table)

PFS analyses	Median (months)		HR	P-value	# events	# censored
	Placebo + T +D	Pertuz +T +D				
IRF PFS	12.4	18.5	0.62 (0.51,0.75)	<0.0001	433	375
Investigator PFS	12.4	18.5	0.65 (0.54,0.78)	<0.0001	451	357
Sensitivity Analysis 1	10.4	14.6	0.66 (0.55,0.79)	<0.0001	500	308
Sensitivity Analysis 2	12.3	18.7	0.58 (0.48,0.71)	<0.0001	404	404
Sensitivity Analysis 3	12.4	20.8	0.58 (0.47,0.71)	<0.0001	385	423
Sensitivity Analysis 4	12.3	18.5	0.62 (0.51,0.75)	<0.0001	433	375
Sensitivity Analysis 5	12.4	17.2	0.63 (0.52,0.76)	<0.0001	451	357
Sensitivity Analysis 6	12.3	18.5	0.61 (0.50,0.74)	<0.0001	421	387

Source: eventirf.xpt

Reviewer Comment: *IRF PFS, investigator PFS, and all sensitivity analyses are internally consistent with HRs ranging from 0.58 to 0.66 and median differences ranging from 4.2 months to 8.4 months. This indicates that the results of the pivotal study are robust and clinically meaningful.*

6.1.6 WO20698 Analysis of Secondary Endpoints(s)

Overall Survival:
At the May 2011 cut-off, a planned interim OS analysis was performed, comprising 43% of the events planned at the final analysis. For this planned interim analysis, 96 patients (24%) died on the placebo arm and 69 patients (17%) died on pertuzumab. This yielded a hazard ratio of 0.64, and a p value of 0.0053, which did not cross the O'Brien Fleming statistical boundary (Table 16, Figure 11).

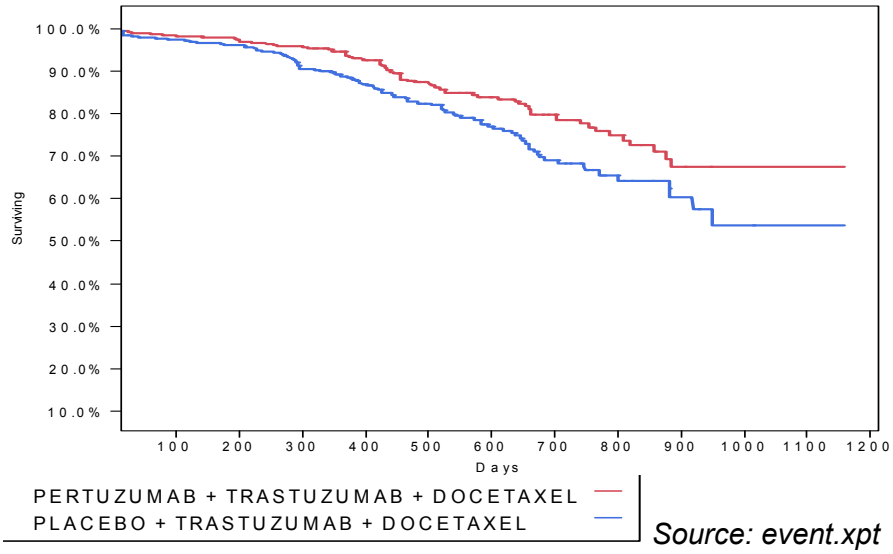
At the 3 month safety update, using a November 2011 cut-off, the sponsor reported 207 deaths, 116 on placebo and 91 on pertuzumab. The blind continues until the final OS analysis at 385 events, projected in 2013.

Table 16: WO20698 Overall Survival Analysis ITT (Reviewer Table)

	Placebo + T +D N=406	Pertuzumab + T + D N=402
Number of events (%)	**96 (24)**	**69 (17)**
Censored (%)	**310 (76)**	**333 (83)**
Median OS (months)	**NR**	**NR**
Hazard Ratio (stratified)*	**0.64**	
95% CI	(0.47 to 0.88)	
p- value	0.0053*	

*O'Brien Fleming boundary not crossed (α required p≤0.0012)
Source: event.xpt

Figure 11: WO20698 Overall Survival KM curve ITT (Reviewer Figure)



Source: event.xpt

Reviewer Comment: *Strong trend favoring pertuzumab arm which did not yet meet statistical significance. There were internal discussions during the BLA review to potentially ask for an additional interim OS analysis. However, given the robustness of the PFS data and the strong trend in OS, we decided to forgo a request for an additional analysis and require submission of the planned final OS analysis as a post-marketing commitment.*

PFS based on investigator assessment:

Table 17 summarizes PFS by investigator, and Table 18 highlights concordance rates between investigator and independent review facility PFS.

Table 17: WO20698 Investigator-assessed PFS (Reviewer Table)

	Placebo + T +D N=406	Pertuzumab + T + D N=402
Number of events (%)	**250 (62)**	**201 (50)**
Censored (%)	**156 (38)**	**201 (50)**
Median PFS (months)	**12.4**	**18.5**
Hazard Ratio (stratified)*	**0.65**	
95% CI	(0.54 to 0.78)	
p- value	<0.0001	

Reviewer Comment*: Investigator PFS with almost identical HR and median PFS as central review, further supporting robustness of the finding.*

Table 18: WO20698 PFS concordance IRF and Investigator (Reviewer Table)

	Placebo + T +D N=406	Pertuzumab + T + D N=402
Agreement (%)	**272 (67)**	**269 (67)**
Agreed event within 30 days	140 (35)	99 (23)
No event	132 (33)	176 (44)
Disagreement (%)	**134 (33)**	**134 (33)**

Reviewer Comment: *No evidence of differential discordance between placebo and pertuzumab treatment arms. The 33% disagreement between IRF and Investigator in the pivotal study is consistent with what has been observed in other phase 3 oncology trials[11].*

Objective Response Rate:
The IRF assessed objective response rate was 69% in the placebo arm and 80% in the pertuzumab arm (Table 19). The ORR by investigator assessment was 68% placebo and 77% pertuzumab, respectively.

Table 19: WO20698 Objective response rate (Reviewer Table)

	Placebo + T + D	Pertuzumab + T + D
ORR by IRF (%), n= 502	**233 (69.3)**	**269 (80.2)**
Complete Response (CR)	14 (4.2)	19 (5.5)
Partial Response (PR)	219 (65.2)	256 (74.6)
ORR by Investigator (%), n= 537	**253 (68.2)**	**284 (77.4)**

***Reviewer Comment**: Addition of pertuzumab improved ORR, consistent with PFS and interim OS results. Interesting to note that an 11% improvement in ORR translated into a 6.1 month difference in median PFS.*

Duration of Response:
The median duration of response was 12.5 months in the placebo arm and 20.2 months on the pertuzumab arm.

Time to Symptom Progression:
Only female patients completed the FACT-B questionnaire and thus 806 patients were included in the analysis populations (404 placebo; 402 pertuzumab). Questionnaires were to be completed every 3 cycles. The sponsor reports at least 75% compliance of completion of the FACT-B questionnaire beyond the first year in both treatment groups.

Symptom progression according to FACT-B was defined as a decrease from baseline in TOI-PFB score of $\geq$ 5 points. TOI-PFB is a composite score of physical well-being, functional well-being, and additional concerns subscale. There were 229 (57%) placebo arm patients and 239 (60%) pertuzumab-treated patients experiencing symptom progression based on the TOI-PFB. The median time to symptom progression was 18.3 weeks in the placebo arm versus 18.4 weeks in the pertuzumab arm, with a HR of 0.97 (0.81,1.16).

***Reviewer Comment**: This is a blinded study so bias is less of an issue, but it is questionable whether the FACT-B questionnaire has content validity and whether the long interval between questionnaire administration was adequately sensitive to detect differences in symptom deterioration between treatment arms. These assessments are considered exploratory. Future breast cancer registration trials with PRO endpoints should have early discussion with FDA SEALD.*

6.1.7 WO20698 Exploratory Endpoints

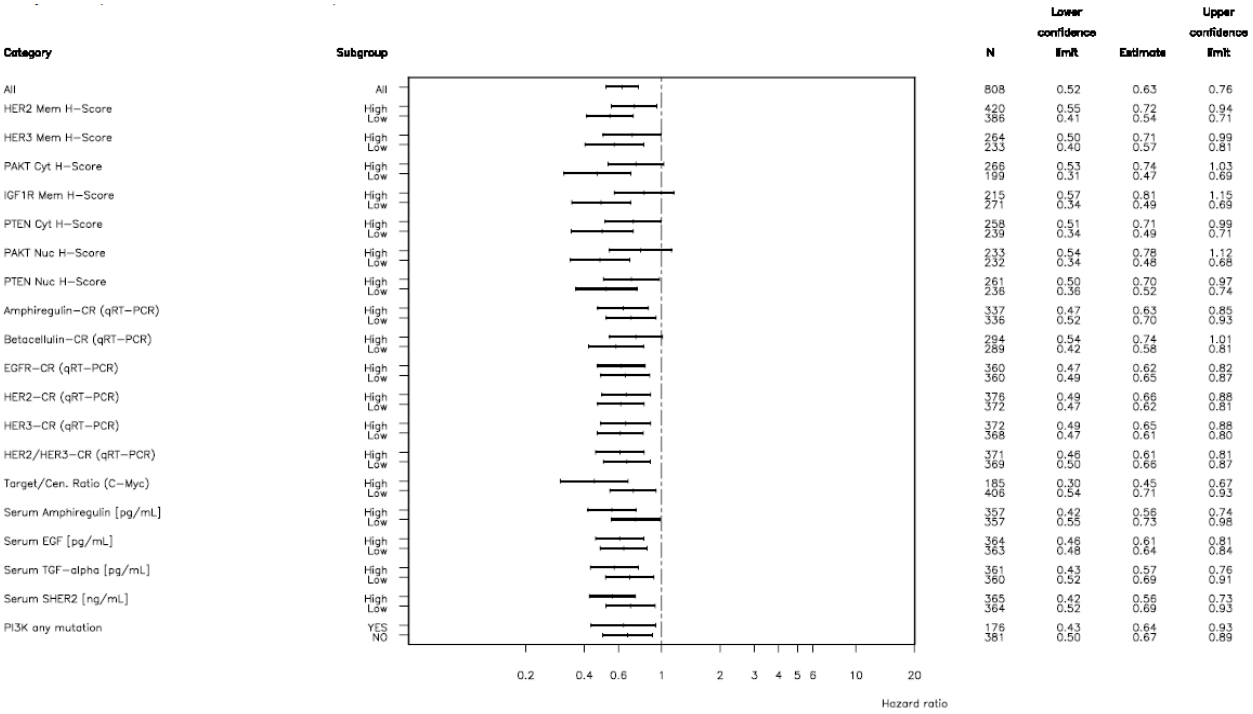
The sponsor collected a number of exploratory biomarkers in both the tumor, serum and germline DNA and rates of sample acquisition were relatively high (Table 20). An analysis of biomarker subgroups (low vs. high) did not appear to differentiate a subgroup with a markedly better or worse PFS result with the addition of pertuzumab (Figure 12). The sponsor reported that 32% of the tumor samples analyzed had a PIK3CA mutation.

Table 20: WO20698 Biomarker Samples Collected (Reviewer Table)

Analysis	% Sample Acquisition
IHC/FISH	
HER2 IHC	99.8%
HER3 IHC	62%
IGF1R IHC	60%
PTEN IHC	62%
pAKT IHC	58%
c-myc FISH	73%
qRT-PCR	
Amphiregulin	83%
Betacellulin	72%
EGFR	89%
HER2	93%
HER3	92%
HER2/HER3	92%
Serum	
Amphiregulin	88%
EGF	90%
Shed HER2 (HER2 ECD)	89%
TGFa	89%
DNA	
PIK3CA	84%
FCGR2A	88%
FCGR2B	84%
FCGR3A	91%

Source: CSR Section 3.3

Figure 12: WO20698 PFS by exploratory biomarker subgroups (Applicant Figure)

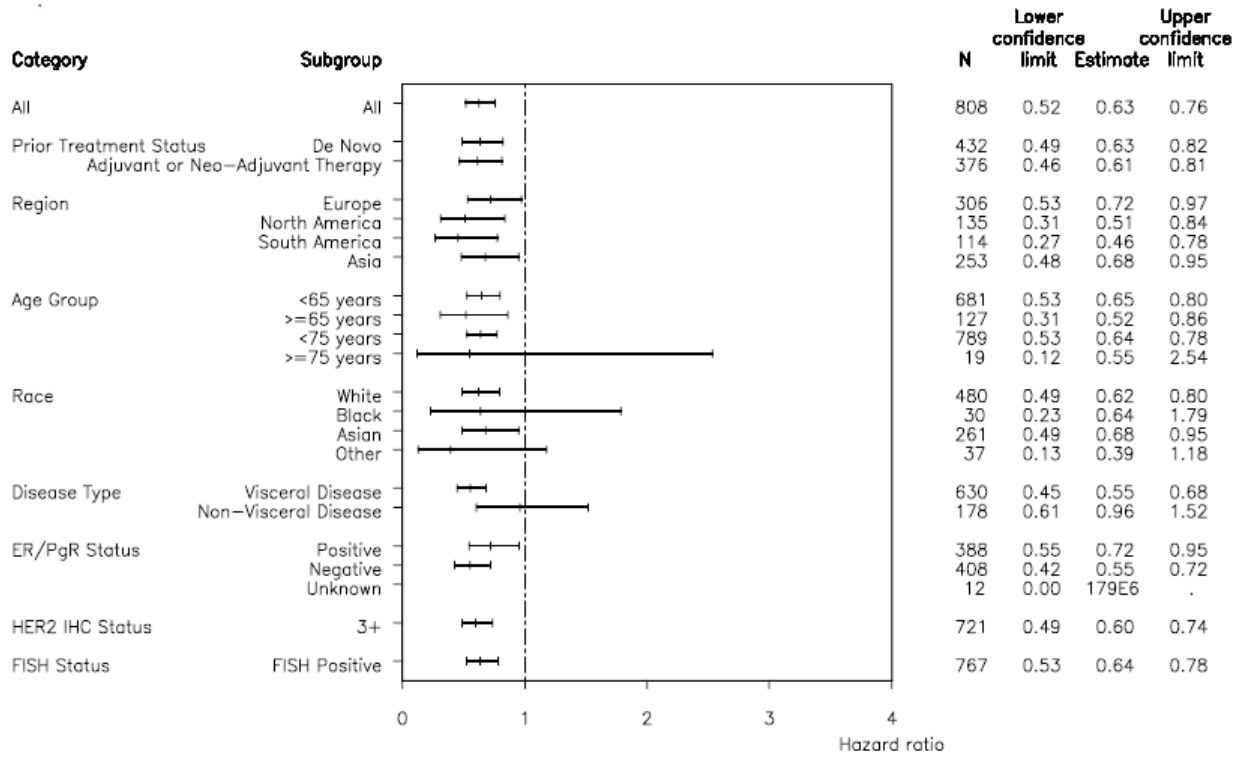


Source: CSR section 3.3

6.1.8 WO20698 Subpopulations

The IRF-assessed PFS tended to favor the pertuzumab arm on all the covariates pre-specified in the statistical analysis plan (Figure 13).

Figure 13: WO20698 Forest Plot unstratified IRF-PFS (Applicant Figure)



Source: CSR Figure 9

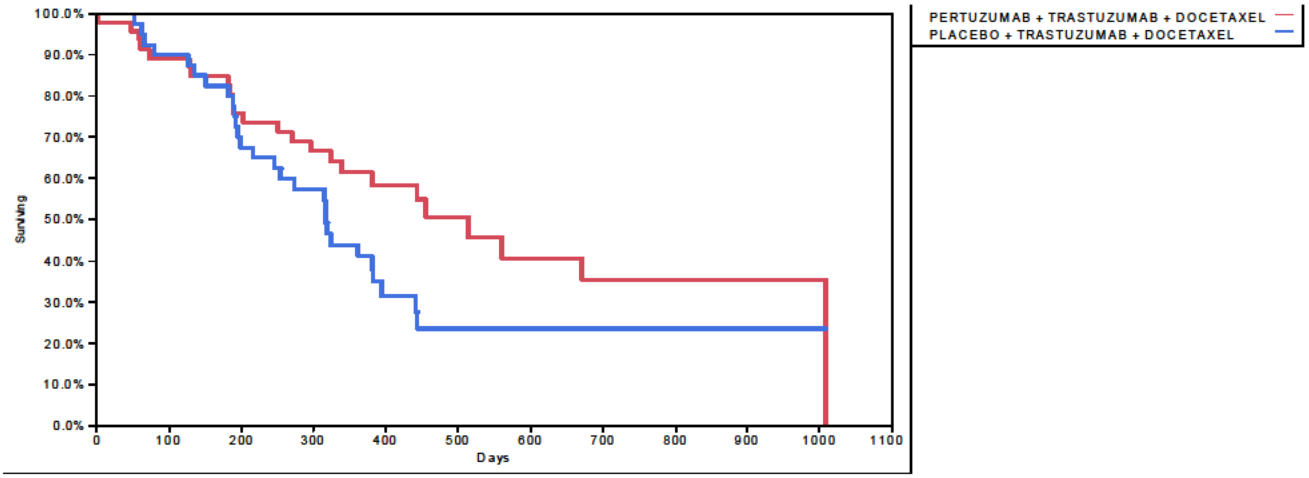
Reviewer Comment: *All major subgroups assessed tend to favor pertuzumab arm, demonstrating the internal consistency of the treatment effect and robustness of the PFS results. The benefit in the HR+ population is less than that observed in the ITT population, and there does not appear to be any benefit in patients with non-visceral disease. The 'Black' subgroup has wide confidence intervals, owing to the small numbers of this sub-population enrolled on the study.*

Subgroups of Interest:
This reviewer looked at specific subgroups in greater detail (Table 21):
Patients who received prior (neo)adjuvant trastuzumab (Figure 14), patients who were HR+ (Figure 15), patients with non visceral disease (Figure 16), black patients, and patients who received prior neoadjuvant or adjuvant systemic therapy.

Table 21: WO20698 IRF-PFS analysis in sub-groups of interest (Reviewer Table)

IRF-PFS analysis in sub-groups of interest	HR (95% CI)	Placebo + T + D Median PFS	Pertuzumab + T + D Median PFS
ITT n=808	0.62 (0.51;0.75)	12.4 months	18.5 months
HR+ n=388	0.72 (0.55;0.95)	14.4 months	17.2 months
Prior trastuzumab n=88	0.62 (0.35;1.07)	10.4 months	16.9 months
Black n=30	0.64 (0.23;1.79)	12.5 months	10.3 months
Non visceral disease n=178	0.96 (0.61;1.52)	17.3 months	20.7 months
Prior neo/adjuvant therapy n=376	0.61 (0.46;0.81)	12.4 months	18.6 months

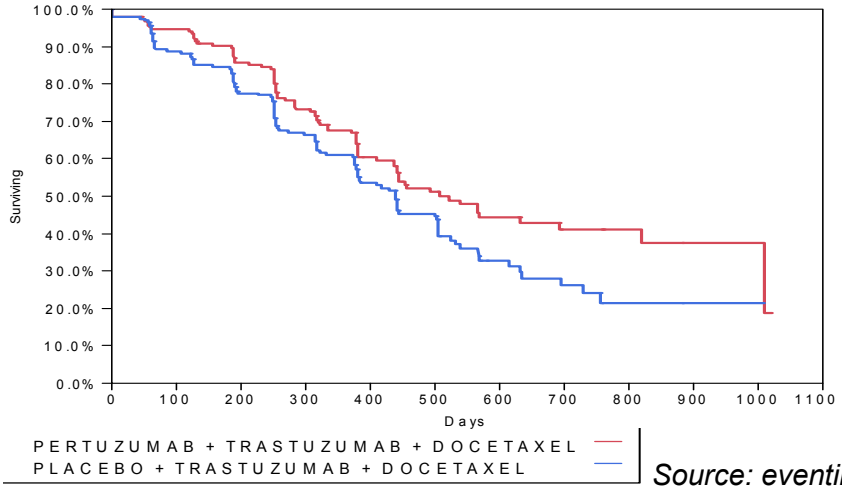
Figure 14: KM curve prior adjuvant trastuzumab (n=88) IRF-PFS (Reviewer Figure)



Source: eventirf.xpt

***Reviewer Comment**: The treatment effect was preserved in patients receiving prior trastuzumab. This was a key review issue as this most accurately reflects the majority of U.S. patients, who typically present with early breast cancer and are treated with adjuvant trastuzumab-based regimens.*

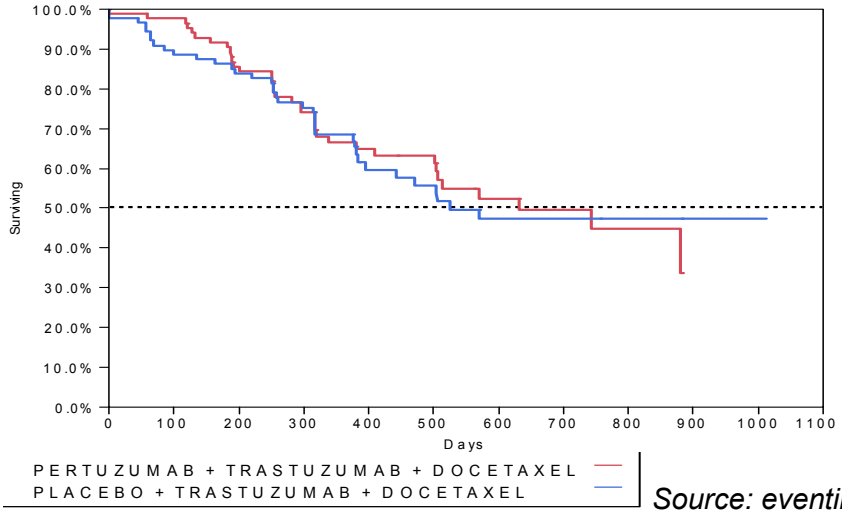
Figure 15: KM Curve in HR+ patients (n=388) IRF-PFS (Reviewer Figure)



Source: eventirf.xpt

Reviewer Comment: *Although there was a treatment effect with pertuzumab in HR+ patients, it was less than in the overall population. An interesting hypothesis would be whether the addition of hormonal therapy to this regimen would increase efficacy in this patient population.*

Figure 16: KM Curve non visceral patients (n=178) IRF-PFS (Reviewer Figure)



Source: eventirf.xpt

Reviewer Comment: *No apparent benefit in patients with non-visceral disease. Approximately 52% of patients with non-visceral disease were HR+.*

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Clinical Pharmacology Review by Dr Pengfei Song

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.11 Supportive Neoadjuvant Study Results

Phase 2b Neoadjuvant Results (Neosphere/ WO20697)

See section 5.3.2 for study design.

Disposition: From December 17, 2007 to December 22, 2009 (primary analysis cut-off), a total of 603 patients were screened, of whom 417 patients were randomized [107 to Arm A (trastuzumab + docetaxel), 107 to Arm B (trastuzumab + docetaxel + pertuzumab), 107 to Arm C (trastuzumab + pertuzumab) and 96 to Arm D (pertuzumab + docetaxel) across 59 centers in 16 countries.

Demographics: The study population was primarily Caucasian with a median age of 49-50. Approximately half of patients were HR negative. The majority of patients had either operable (61%) or locally advanced breast cancer (32%) at baseline (Table 22).

Table 22: WO20697 Summary of patient characteristics (Reviewer Table)

Characteristics	Total (n=417)	Trastuz + Docetaxel (N=107)	Trastuz + Pertuz + Docetaxel (N=107)	Trastuz + Pertuz (N=107)	Pertuz + Docetaxel (N=96)
Female	100%	100%	100%	100%	100%
Median Age	49.8 (22 – 80)	50.9 (32 -74)	49.6 (28 – 77)	49.7 (22 – 80)	48.9 (27 – 70)
Caucasian	71.2%	74.8%	72%	73.8%	63.5%
Black	1.4%	0%	1.9%	0.9%	3.1%
Asian	4.6%	1.9%	4.7%	4.7%	7.3%
Postmenopausal	43.9%	44.9%	42.1%	46.7%	41.7%
ECOG PS 0	88.5%	94.3%	89.7%	86%	83.3%
HR+	52.6%	53.3%	53.3%	51.9%	52.1%
Inflammatory	7%	6.5%	9.3%	6.5%	5.2%
Locally Advanced	32.1%	33.6%	29.9%	32.7%	32.3%
Operable	60.9%	59.8%	60.7%	60.7%	62.5%

Efficacy results:

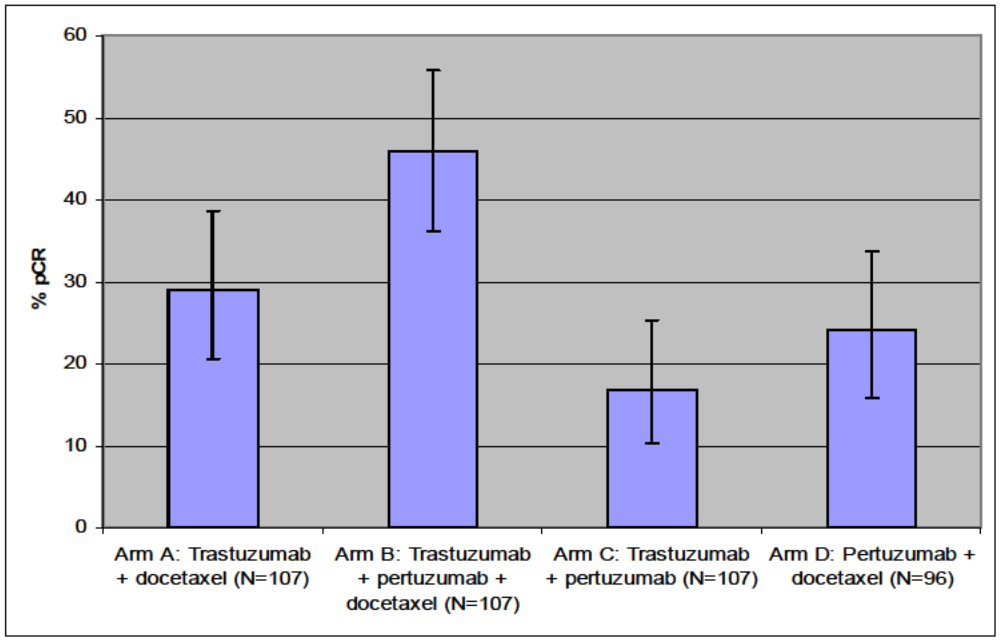
The combination of pertuzumab and trastuzumab plus docetaxel (Arm B) significantly improved pCR rates over trastuzumab plus docetaxel (Arm A), 46% versus 29% (Table 23, Figure 17). The combination of pertuzumab and docetaxel (Arm D) also had activity, with a pCR rate of 24%. The dual antibody/ no chemotherapy regimen of Trastuzumab + Pertuzumab (Arm C) had a 17% pCR rates, with less toxicity. However, 7.5% of patients assigned to Arm C progressed through neoadjuvant therapy. In contrast, no patients progressed through Arm A, 1% of patients progressed through Arm B, and 2% of patients progressed through Arm D. Figure 18 presents pCR results by Hormone Receptor Status.

Table 23: WO20697 Summary of pCR results (Reviewer Table)

	A: Trastuz + Docetaxel (N=107)	B: Trastuz + Pertuz + Docetaxel (N=107)	C: Trastuzumab + Pertuzumab (N=107)	D: Pertuzumab + Docetaxel (N=96)
pCR (%) (95% CI)	31 (29%) (21-39)	49 (46%) (36-56)	18 (17%) (10-25)	23 (24%) (16-34)
p-value*		0.0141 (vs. arm A)	0.0198 (vs. arm A)	0.0030 (vs. Arm B)

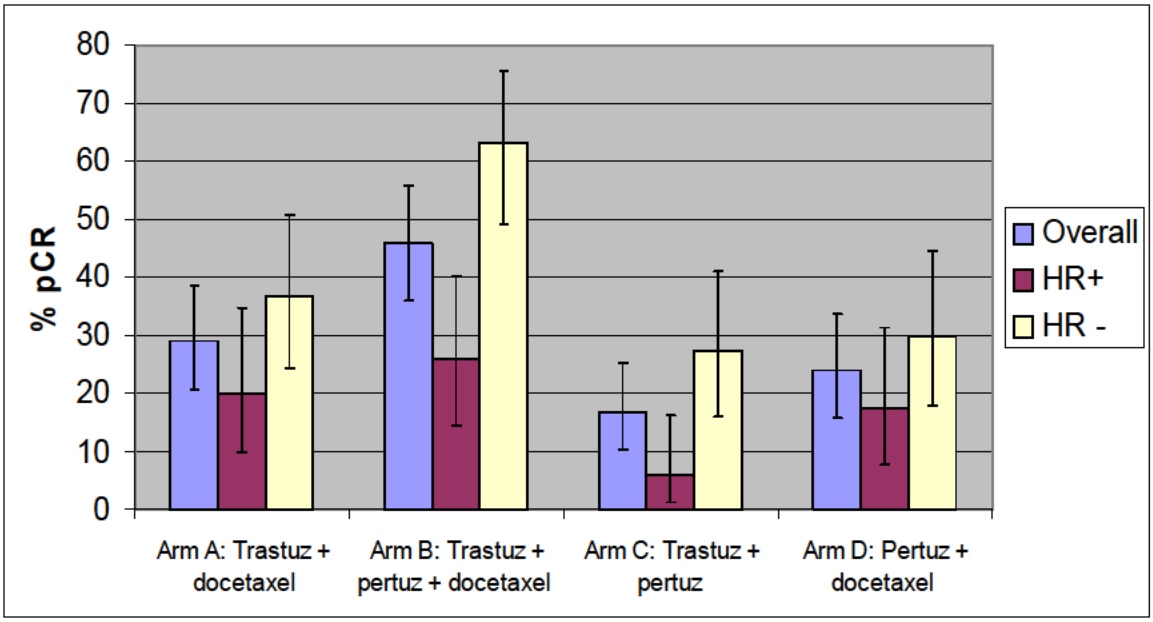
*Simes correction for Cochran-Mantel-Haenszel test

Figure 17: WO20697 pCR results (Reviewer Figure)



Reviewer Comment: *Arm B, the triple therapy with trastuzumab + pertuzumab + docetaxel, had the highest pCR rate. This isolates the relative contribution and additive benefit of pertuzumab to this combination regimen, which was also used in the pivotal study in the metastatic setting. The mature DFS data from NEOSHPHERE/WO20697 is pending. Other studies (such as NOAH[12]) in HER2+ neoadjuvant BC suggest that pCR rates correlate with long term outcomes, both at the patient level and across therapeutic arms of a randomized study.*

Figure 18: WO20697 pCR results by Hormone Receptor Status (Reviewer Figure)



***Reviewer Comment**: Similar to the pivotal phase 3 trial, it appears that HR negative patients derive the most benefit from the addition of pertuzumab to trastuzumab and docetaxel. To further study the subgroup of HR+ patients, we have requested a PMC to study pertuzumab along with hormonal therapy in postmenopausal HR+, HER2+ MBC.*

6.1.12 Supportive Metastatic Phase 2b Study Results (BO17929)

Results single arm phase 2b BO17929 in HER2+ MBC who progressed on trastuzumab-based regimen as last treatment for metastatic disease

Disposition: The trial is on-ongoing. The trial started May 2006. Primary data cut (cohorts 1 and 2) was February 2008. Cohort 3 data cut was November 2010. Sixty-six patients from 16 centers in 5 countries (UK, Canada, Italy, Spain and France) with MBC were recruited to Cohorts 1 and 2 and treated. For Cohort 3, 51 patients were screened, of whom 29 were recruited across 13 centers in four countries. Of these 29 patients who received at least one cycle of pertuzumab, 17 went on to receive dual agent pertuzumab + trastuzumab after they had documented progression on pertuzumab alone.

Demographics: In Cohorts 1 and 2, all patients were female and 91% were Caucasian. The median age was 54 (range 25 – 85). The majority of patients (80%) were ECOG PS 0 at screening. Half of the patients were ER + and 29% were PgR+. By IHC, 79%

of patients were HER2 3+. All patients received trastuzumab prior to enrollment as their last treatment for metastatic disease as per inclusion criteria.

Results: ORR is presented in Table 24.

Table 24: Objective Response Rates in BO17929 (Reviewer Table)

	Cohorts 1 + 2[a] Pertuzumab + Trastuzumab N=66	**Cohort 3[b]** Pertuzumab alone N=29	**Cohort 3[c]** Pertuzumab + Trastuzumab re-challenge N=17
ORR (%)	16 (24.2%)	1 (3.4%)	3 (17.6%)

[a] Simon 2 stage optimal design
[b] progressed on trastuzumab, pertuzumab naive
[c] progressed on trastuzumab and pertuzumab

Reviewer Comment: *Supportive evidence that the combination of pertuzumab and trastuzumab has activity (24% ORR) in trastuzumab-resistant MBC, consistent with mouse xenograft models. Also notable that single agent pertuzumab has minimal activity (ORR 3.4%) in trastuzumab-resistant MBC but re-introduction of the combination has greater than additive activity (17.6% ORR) in double-resistant patients.*

7 Review of Safety

Safety Summary

Data from the randomized trial WO20698 and the supportive trials demonstrate no unexpected toxicities. Pertuzumab was administered in combination with trastuzumab and docetaxel with acceptable toxicity. There was no increase in cardiotoxicity with the addition of pertuzumab (compared with placebo) to trastuzumab and docetaxel. The addition of pertuzumab did increase the incidence of diarrhea, rash, mucosal inflammation, neutropenia and febrile neutropenia, but these appear to be clinically manageable. The higher incidence of febrile neutropenia observed in Asians in both treatment arms of study WO20698, and especially in the pertuzumab treatment arm, is not explained.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The claim for efficacy and safety for the application is based on the phase 3 trial WO20698/TOC412g (CLEOPATRA), with supportive data from a randomized phase 2 trial (WO20697/NEOSPHERE) in patients with HER2+ early breast cancer (EBC) and the single-arm phase 2 trial (BO17929) in patients with HER2+ metastatic breast cancer (MBC). Safety data are provided from an additional 11 trials, including phase 1 and phase 2 trials of single-agent pertuzumab or combination therapy in a variety of malignancies, and a phase 1a dose escalation study (TOC2297g). Preliminary summary results are provided (ISS section 5.10.1) from study BO22280 (Tryphaena), a randomized, phase 2, neoadjuvant trial in patients with inflammatory or HER2+ EBC treated with pertuzumab + trastuzumab and sequential or concomitant anthracycline or non-anthracycline drugs.

Key features of studies WO20698, WO20697and BO17929 are summarized in the table in Section 5.1. Details of trial design for the 3 trials are discussed in section 5.3. Efficacy results are presented in section 6.

The major focus of the safety review (contained in section 7) is the data from the phase 3 trial WO20698/TOC412g (CLEOPATRA). Study WO20698 contains an associated sub-study to evaluate QT interval, pharmacokinetics and drug-drug interactions. The sub-study results have been reviewed by the IRT/QT team. Reference will be made to the WO20697/NEOSPHERE and BO17929 phase 2 studies, and to any signals from the ISS, which includes data from 14 trials, as appropriate.

7.1.2 Categorization of Adverse Events

Safety coding appears generally appropriate. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) v. 14 thesaurus terms. AEs were summarized by MedDRA primary system organ class (PSOC) and preferred term (PT). The Roche Drug Thesaurus was used to code and classify medications.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The 17 clinical trials submitted to the BLA provide safety data from more than 1400 subjects exposed to pertuzumab. The database includes:

- 514 patients treated with pertuzumab in combination with trastuzumab and docetaxel
- 191 patients treated with pertuzumab in combination with trastuzumab

- 386 patients exposed to pertuzumab monotherapy in phase 2 trials with fixed doses of 420 mg or 1050 mg
- 321 patients exposed in phase 1 dose escalation studies or phase 2 studies in combination with other agents.

The applicant integrated safety data from 14 of the 17 studies into a single safety database. The 3 studies not integrated were a single agent phase 1 trial in solid tumors, a single agent extension protocol, and NCI-06-C-0035. The NCI trial is a phase 2 study combining pertuzumab with trastuzumab in HER2+ MBC for which Roche does not hold the database. The extension protocol enrolled only 3 subjects. Accessibility to the phase 1 trial data was limited because verbatim terms had not yet been translated from Japanese.

Across all studies, the applicant reported no evidence that pertuzumab exacerbates the cardiac toxicity of trastuzumab. The larger safety base did not demonstrate unexpected toxicities compared with the findings in the pivotal trial and two supportive phase 2 studies. Diarrhea and rash were the AEs most frequently observed with single-agent pertuzumab. Across the studies, the most commonly reported AEs were gastrointestinal toxicities, fatigue, alopecia, neutropenia and rash.

7.2 Adequacy of Safety Assessments

The safety assessments for study WO20698 (CLEOPATRA), the phase 3, randomized, controlled trial in metastatic breast cancer, are adequate. There was particular attention to assessment of cardiac adverse events (AEs), due to the known cardiac effects of trastuzumab and concern that the combination of pertuzumab with trastuzumab might increase cardiac toxicity. A dedicated CRF page was utilized to collect cardiac-specific AEs. Left Ventricular Ejection Fraction (LVEF) and ECG's were performed every 9 weeks during treatment, then every 6 months x 1 year, then yearly for 3 years. A Cardiac Review Committee was constituted to adjudicate possible symptomatic left ventricular dysfunction (LVSD) and suspected cardiac deaths.

A dedicated sub-study was conducted as part of study WO20698, with the objectives of describing the effect of pertuzumab on the QTc interval, and ECG parameters for heart rate, QT interval, PR interval, and QRS duration. (See the separate review of the sub-study by the CDER IRT-QT team, Dr. Jiang Liu.)

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In trial WO20698 patients were to be treated with docetaxel in combination with trastuzumab and either pertuzumab or placebo for a minimum of 6 cycles, in the absence of unacceptable toxicity or disease progression. Trastuzumab and pertuzumab/placebo were to be continued until progression. Docetaxel could be continued longer than 6 cycles at the discretion of the investigator, and the dose of docetaxel could be escalated after the first cycle from 75 mg/m^2 to 100 mg/m^2. Docetaxel was discontinued before the other study drugs in 255 patients (64.2%) in the placebo arm and 298 pts (73.2%) in the pertuzumab arm. A similar number of patients in each treatment arm was discontinued from docetaxel early for an adverse event, 90 (23%) in the placebo arm and 97 (24%) in the pertuzumab arm.

Table 25 summarizes patient exposure to study treatment in Trial WO20698.

Table 25: Exposure to Study Treatment WO20698 (Reviewer Table)

	Placebo + T + D n=397	Pertuzumab + T + D n=407
Time on any Study Treatment (median), months	11.8	18.1
Docetaxel Dose Intensity (median), mg/m^2/week	24.8	24.6
Docetaxel # of cycles, median (range)	8 (1-41)	8 (1-35)
Pertuzumab/placebo # of cycles, median (range)	15 (1-50)	18 (1-56)
Trastuzumab # of cycles, median (range)	15 (1-50)	18 (1-56)

Patients in the pertuzumab arm remained on study longer than patients in the placebo arm. The docetaxel dose intensity was comparable for the 2 treatment arms. The median number of docetaxel cycles was the same for both treatment arms. At the time of the clinical data cut-off, the median number of cycles of pertuzumab/placebo + trastuzumab administered was 18.0 for the pertuzumab arm and 15.0 for the placebo arm. The median dose of pertuzumab per cycle was 443 mg. The median dose of trastuzumab per cycle was 404 mg in the placebo arm and 400 mg in the pertuzumab arm.

Demographic information is provided in section 6.1.4 of this review for patients in trial WO20698 and the key supportive trials.

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate. Exposure during pregnancy to Herceptin (trastuzumab), an approved anti-HER2 drug, is associated with oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Oligohydramnios is related to the pharmacologic mechanism of action, inhibition of HER2, the same target as pertuzumab. An embryo-fetal developmental toxicity study in cynomolgus monkeys demonstrated that administration of pertuzumab during organogenesis is associated with oligohydramnios, delayed renal development, and embryo-fetal deaths.

7.2.4 Routine Clinical Testing

Subjects in study WO20698 were required to have baseline evaluations, which included a complete medical history and physical examination, ECOG performance status, chest X-ray, and 12-lead ECG within 28 days of starting treatment. LVEF (left ventricular ejection fraction) by echocardiogram or MUGA could be performed a maximum of 42 days before randomization. Baseline laboratory studies required within 7 days of starting treatment included hematology, biochemistry, coagulation (INR and aPTT or PTT). These tests were to be repeated prior to each cycle of therapy and hematology assessment was also to be done day 8 of each treatment cycle. Serum pregnancy test was to be documented to be negative for women of childbearing potential (WCBP) at baseline, and urine pregnancy test was to be conducted every 3 months until 6 months after treatment discontinuation. (Serum antibodies to pertuzumab were to be collected at baseline and every 9 weeks from the date of randomization until treatment discontinuation.) A variable window of 3 days was deemed acceptable for all visits and safety assessments (a 7 day window was permitted for documentation of death).

LVEF assessments and ECG's were to be conducted every 9 weeks from the date of randomization (study treatment to start within 3 days of randomization) until treatment discontinuation. LVEF assessments were to continue every 6 months for the first year, then annually for up to 3 years following treatment discontinuation. Patients who were discontinued from therapy due to decreased LVEF were required to have assessments as clinically indicated, but not less frequently than every 3 months, until the LVEF returned to ≥ 50%, or 1 year after the treatment discontinuation visit. Then assessments were required annually for up to 3 years after the treatment discontinuation visit.

Safety analyses in study WO20698 included:

- Incidence and severity of Adverse Events (AEs) and serious adverse events (SAEs). Progression of underlying malignancy and hospitalization solely for

progressive disease were not to be reported as AEs or SAEs. AEs and SAEs were to be graded according to NCI-CTCAE version 3.0.

- Incidence of symptomatic left ventricular systolic dysfunction (congestive heart failure) and asymptomatic left ventricular systolic dysfunction (LVSD). Symptomatic LVSD was to be reported as an SAE (CHF) and graded according to both NCI and New York Heart Association (NYHA) criteria. Occurrence of CHF within 3 years of study drug was to be reported.
- Sequential measurements of left ventricular ejection fraction (LVEF).
- Laboratory test abnormalities.

Patients assigned to participate in the QT sub-study were required to have more frequent ECGs for correlation with PK parameters. The plan was to enroll at least 50 ECG-evaluable patients and 40 PK-evaluable patients to the sub-study.

Reviewer comment: *The planned safety assessments and analyses for study WO20698 are appropriate.*

For study WO20697 (NEOSPHERE), the randomized phase 2 trial in HER2+ EBC, reporting requirements for cardiac dysfunction were similar, except reporting of CHF (as an SAE) was only required for 2 years after completion of study medication. In study BO17929, the single-arm phase 2 trial in HER2+ MBC, reporting of cardiac events was similar to the requirements of WO20698.

7.2.5 Metabolic, Clearance, and Interaction Workup

Since pertuzumab is an antibody of high molecular weight, traditional *in vitro* drug metabolism and interactions studies were not conducted during development. Although no specific drug-drug interaction (DDI) studies were conducted, pertuzumab has been tested clinically with a variety of anti-cancer agents and does not alter the PK of docetaxel, gemcitabine, capecitabine or erlotinib. In the PK/QT sub-study of the phase 3 trial, WO20698, there was no evidence for a DDI between pertuzumab and docetaxel or trastuzumab. As an antibody, pertuzumab is not cleared by hepatic metabolism, nor is dose adjustment needed for renal impairment.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The drugs currently approved in the US that block HER2 are both associated with decrease in LVEF. Lapatinib (Tykerb) is a small molecule that inhibits the intracellular domains of HER2 and EGFR. Trastuzumab (Herceptin), like pertuzumab, is a recombinant humanized monoclonal antibody that selectively binds to the extracellular domain of HER2. The trastuzumab label contains a boxed warning of risk of cardiomyopathy, infusion reactions, pulmonary reactions, and embryo-fetal toxicity. The

Warning and Precautions section additionally references exacerbation of chemotherapy-induced grade 3-4 neutropenia and febrile neutropenia, without increase in septic death compared with patients receiving myelosuppressive chemotherapy without trastuzumab. Lapatinib carries a boxed warning for hepatotoxicity and the Warning and Precautions section of the label additionally references decreased left ventricular ejection fraction, diarrhea, interstitial lung disease and QT prolongation. (QT prolongation was observed in an uncontrolled dose escalation trial in advanced cancer.)

In the phase 3 randomized control trial, study WO20698, the applicant prospectively defined "adverse events to monitor" based on the known profile of pertuzumab and related drugs. The events to monitor prospectively defined by the applicant include:

- Cardiac events
  - Asymptomatic LVSD assessed by the investigator
  - Cardiac events adjudicated by the CRC
- Diarrhea
- Rash
- Leukopenia, neutropenia, febrile neutropenia
- Leukopenic infection, febrile neutropenic infection
- Interstitial lung disease
- Hypersensitivity/anaphylaxis
- Hepatic disorders
- Cardiac dysfunction/SAEs suggestive of CHF
- QT prolongation.

Several of the prospectively defined adverse events to monitor are discussed in section 7.3.5 of this review (Submission Specific Primary Safety Concerns). Cardiac events and Febrile neutropenia and related concerns are discussed in section 7.3.4 (Significant Adverse Events). QT prolongation is discussed in section 7.4.5.

Reviewer comment: *The sponsor did appropriate analyses to evaluate for potential adverse events observed for other drugs that block HER2 and for treatments utilizing docetaxel in combination.*

To better characterize the incidence of infusion reactions attributable to pertuzumab, on day 1 of cycle 1 pertuzumab alone (or placebo alone) was administered, and trastuzumab and docetaxel were administered on day 2. For subsequent cycles, all therapy was administered on day 1.

The sponsor also characterized adverse events by treatment phase, distinguishing AEs that started during the docetaxel treatment period, or after discontinuation of docetaxel, or AEs reported during the post-treatment period. The applicant defined the post-treatment period as the period > 42 days after discontinuation of study medication. The WO20698 protocol specified that the following AEs were to be reported during the post-treatment period:

- Cardiac events for up to one year (regardless of causality or seriousness)
- Treatment-related SAEs for up to one year
- Symptomatic LVSD for up to 3 years (regardless of causality).

7.3 Major Safety Results

Table 26 provides a safety overview for study WO20698, details of which will be described further in subsequent sections of the review. There were 406 patients randomized into the placebo + trastuzumab + docetaxel (+T+D) treatment arm and 402 into the pertuzumab + T +D treatment arm. The safety population consists of 397 patients in the placebo treatment arm and 407 in the pertuzumab treatment arm. Eight patients randomized to receive placebo received at least one dose of pertuzumab and were analyzed for safety purposes with the pertuzumab treatment arm. One patient who was randomized to receive pertuzumab received placebo instead each cycle, and was analyzed in the placebo arm for safety.

Table 26: Safety Overview for Trial WO20698 (Reviewer Table)

	Placebo + T + D n=397	Pertuzumab + T + D n=407
Deaths within 30 days of study treatment	10 (2.5%)	8 (2.0%)
All study drugs discontinued for AEs	21 (5.3%)	25 (6.1%)
Any study drug discontinued for AEs	110 (27.7%)	119 (29.2%)
Patients with Non-fatal SAEs	104 (26.2%)	140 (34.4%)
Patients with AEs (%)	391 (98.5%)	406 (99.8%)

7.3.1 Deaths

WO20698
In the phase 3 randomized control trial, study WO20698, there were 8 deaths in the pertuzumab arm and 10 in the placebo arm within 30 days of study treatment. Table 27 shows the causes of death in the safety population. (One subject randomized to each treatment arm, died prior to institution of study therapy.)

Table 27: Deaths within 30 Days of Therapy WO20698 (Reviewer Table)

Cause of Death	Placebo + T + D n=397	Pertuzumab + T + D n=407
Progressive Disease	1	2
Intestinal Perforation	2	1
Myocardial Infarction/ Cerebro-vascular Accident	2/1	0
Sepsis/ Pneumonia	2	1
Febrile Neutropenia	0	2
Hepatic Failure	1	0
GI bleed	1	0
Miscellaneous	0	2
TOTAL	10 (2.5%)	8 (2.0%)

The applicant provided narratives for these patients, which were reviewed. A brief synopsis is provided for some of the deaths of particular interest.

- #8222 (pertuzumab): The patient died of intestinal perforation, presenting on study day 650 with intestinal obstruction due to newly diagnosed colon cancer, and had sepsis as a contributory cause of death.
- #6895 (placebo): This patient presented on study day 7 with perforation of a sigmoid diverticulum.
- #9816 (placebo): The patient presented on study day 10 with intestinal perforation, associated with neutropenic sepsis, and possibly due to typhilitis.
- #9564 (pertuzumab): This patient presented with bilateral pneumonia on study day 6 and died the same day.
- #8740 (placebo): This Asian patient from Japan was hospitalized on day 10 with fever, neutropenia and pneumonia and died the same day.
- #8435 (placebo): The patient developed sepsis on study day 201, with a high white blood count, and died on study day 209. The last doses of trastuzumab

and placebo were administered on study day 199, and the last dose of docetaxel had been administered on study day 180.

- #7215 (pertuzumab): A new pleural effusion and pulmonary mass were identified for this Asian patient from the Philippines just before study day 1, followed by progressive dyspnea. On day 7, she had grade 4 febrile neutropenia (absolute neutrophil count 0.9 x 10^9/L, temperature 39.2C). Cause of death was classified as febrile neutropenia, although by day 11, the day of death, pneumonia was diagnosed, and the neutrophil count had just returned to normal.

- #8185 (pertuzumab): The patient was hospitalized with febrile neutropenia grade 4 on study day 9. Despite antibiotics, the patient progressed to sepsis by study day 13, subsequently developed respiratory failure and died on study day 28 with multi-organ failure.

- #9609 (placebo): This patient, with metastatic disease to the liver, died of hepatic failure. She had baseline elevated (grade 4) AST, ALT, and bilirubin, in violation of study eligibility.

Reviewer comment: *There were several early cycle deaths in both treatment arms in which neutropenic infection was etiologic or contributory. This is consistent with the known adverse event profile of docetaxel and may be attributable to docetaxel. No AEs of febrile neutropenia were reported in patients following discontinuation of docetaxel therapy.*

As of the time of the original data cut off, May 13, 2011, 94/397 (23.7%) patients in the placebo treatment arm had died and 69/407 (17.0%) in the pertuzumab study arm. The most frequent cause of death was progressive disease, with 81 (20.4%) subjects in the placebo arm dying of progressive disease and 57 (14.0%) in the pertuzumab arm.

7.3.2 Nonfatal Serious Adverse Events

WO20698
Progression of underlying malignancy and hospitalization solely for progressive disease were not reported as Serious Adverse Events (SAEs) or AEs. SAEs and AEs and were graded according to NCI-CTCAE version 3.0.

The incidence of patients with SAEs was higher in the pertuzumab treatment arm (34.4%) than in the placebo treatment arm (26.2%). The most commonly reported SAEs in both treatment arms were Blood and Lymphatic System Disorders, occurring in 10.6% of patients in the placebo arm and 16% of patients in the pertuzumab arm. This difference was mainly due to a higher incidence of febrile neutropenia in the pertuzumab arm (11.3% of patients) compared with the placebo group (5.0% of patients). The increase in febrile neutropenia was more notable in the Asian population

(see sections 7.3.4 and 7.5.3 for discussion). The next most frequently reported class of SAEs was infections and infestations, 10.8% of patients in the pertuzumab arm and 7.3% of patients in the placebo arm. The incidence of type of infection by preferred term was < 2% of patients in each treatment arm of this category. Table 28 summarizes the non-fatal SAEs occurring in at least 2% of patients in each treatment arm, by preferred term.

Table 28: Serious Adverse Events (non-Fatal) in ≥ 2% of Patients in Either Treatment Arm WO20698 (Reviewer Table)

Body System/ Serious Adverse Event (SAE)	**Placebo + T + D** N=397 (%)	**Pertuzumab + T + D** N=407 (%)
Any SAE	104 (26.2)	149 (34.4)
Blood & Lymphatic System Disorders	42 (10.6)	65 (16.0)
Febrile Neutropenia	20 (5.0)	46 (11.3)
Neutropenia	19 (4.8)	18 (4.4)
Gastrointestinal Disorders (GI)	17 (4.3)	18 (4.4)
Diarrhea	5 (1.3)	11 (2.7)

More patients in the pertuzumab treatment arm experienced non-fatal SAEs due to diarrhea than in the placebo arm, although the overall incidence of patients experiencing GI SAEs was similar in the treatment arms. The incidence of patients with at least one cardiac SAE was 3.3% in the placebo arm and 1.2% in the pertuzumab arm, with 7 patients (1.8%) and 4 patients (1.0%), respectively experiencing SAE (investigator-assessed symptomatic) left ventricular dysfunction. (See section 7.3.4 for discussion of cardiac SAEs and AEs.)

7.3.3 Dropouts and/or Discontinuations

WO20698

Patients were permitted to continue on study therapy with placebo/pertuzumab + trastuzumab if docetaxel was discontinued prematurely for adverse events believed attributable to that drug. (The protocol-specified duration of therapy with docetaxel was a minimum of 6 cycles.) If placebo/pertuzumab *or* trastuzumab were discontinued for adverse events, patients were to be withdrawn from all study treatment. There were 21 patients (5.3%) in the placebo arm who discontinued all study treatment due to adverse events and 25 patients (6.1%) in the pertuzumab arm. AEs led to discontinuation of docetaxel only in 92 (23.2%) of patients in the placebo treatment arm and 96 (23.6%) of patients in the pertuzumab arm.

Reviewer comment: *The incidence of subjects discontinued from any (docetaxel) or all study treatment due to AEs was similar in the treatment arms. More subjects were discontinued from therapy due to AEs associated with docetaxel. Although Asian patients experienced an increased incidence of febrile neutropenia compared with other*

subjects (see sections 7.3.4 and 7.5.3), there was no observed increase in treatment withdrawal for this population.

For patients discontinued from all study therapy due to AEs, many of the AEs causing discontinuation were cardiac disorders, occurring in 10 patients (2.5%) in the placebo arm and 8 (2.0%) in the pertuzumab arm. Most of these cardiac events were left ventricular dysfunction (LVD), occurring in 8 patients in the placebo arm and 6 patients in the pertuzumab arm. (See section 7.3.4 for further discussion.) The next largest category was Immune system disorders, with discontinuations due to hypersensitivity or drug hypersensitivity for 2 patients in the placebo arm and 3 patients in the pertuzumab arm. An additional patient in the pertuzumab arm discontinued due to an anaphylactic reaction.

Table 29 summarizes the adverse events occurring in at least 2% of patients in either treatment arm, and leading to discontinuation of docetaxel only (from CSR data listing pages 3083-3087).

Table 29: Adverse Events in ≥ 2% of Patients in Either Treatment Arm WO20698 Leading to Discontinuation of Docetaxel Only (Reviewer Table)

Body System/ Adverse Event (AE)	**Placebo + T + D** N=397 (%)	**Pertuzumab + T + D** N=407 (%)
Patients with any AE	92 (23.2)	96 (23.6)
General Disorders and Administration	36 (9.1)	31 (7.6)
Edema, Peripheral and Generalized	26 (6.5)	19 (4.7)
Fatigue	8 (2.0)	9 (2.2)
Nervous System Disorders	17 (4.3)	23 (5.7)
Peripheral Neuropathy	16 (4.0)	20 (4.9)
Blood and Lymphatic System Disorders	11 (2.8)	13 (3.2)
Neutropenia and Leukopenia	8 (2.0)	8 (2.0)
Febrile Neutropenia	0	4 (1.0)

In addition to the 8 patients in each treatment arm that discontinued docetaxel due to neutropenia/leukopenia, an additional 4 subjects in the pertuzumab arm discontinued for febrile neutropenia.

Study drug dose modifications or interruptions due to adverse events occurred in 60% of patients in the pertuzumab arm and in 53% of patients in the placebo arm. The most common causes for dose modifications (>5% either treatment arm) were neutropenia (11.3% each arm), febrile neutropenia (7.6% pertuzumab vs. 5% placebo), and diarrhea (5.4% pertuzumab vs. 1.8% placebo). More subjects required dose modifications for left ventricular dysfunction in the placebo arm than in the pertuzumab arm (2.5% vs. 1.0%).

7.3.4 Significant Adverse Events

This section summarizes data from study WO20698 pertaining to 2 very significant categories of adverse events (AEs) for the pertuzumab application, cardiac events and febrile neutropenia, along with related issues. The applicant pre-specified the following related "AEs to monitor":

- Cardiac events
  - Asymptomatic LVSD assessed by the investigator
  - Cardiac events adjudicated by the CRC
- Cardiac dysfunction/SAEs suggestive of CHF
- Leukopenia, neutropenia, febrile neutropenia
- Leukopenic infection, febrile neutropenic infection.

(See section 7.3.5 for other categories of applicant pre-specified "AEs to monitor."

7.3.4.1 Cardiac events and cardiac SAEs

See section 7.2 and 7.2.4 for additional discussion of study-required testing and safety analyses for study WO20698. Cardiac AEs and cardiac SAEs thought to be unrelated to treatment were required to be reported for up to 12 months after last administration of study drugs. Cardiac SAEs believed to be related were to be reported at *any time,* regardless of time elapsed, even if the study were closed. Cardiac AEs and SAEs were to be followed until resolution, stabilization or death, for the later date of up to 1 year post-treatment or post-onset. Asymptomatic left ventricular systolic dysfunction (LVSD) requiring treatment or discontinuation was to be reported for up to 12 months after last administration of study drug, with follow-up as for cardiac AEs/SAEs, or until the end of survival follow-up for the study. Symptomatic LVSD, related or unrelated, was to be reported as an SAE for up to 3 years after last drug administration and followed until survival follow-up completes.

Pre-specified decreases in left ventricular ejection fraction (LVEF) and symptoms consistent with congestive heart failure were to be reported as asymptomatic or symptomatic LVSD, respectively. Investigators were to report symptomatic LVSD as an SAE and grade the event by NYHA as well as NCI-CTCAE v. 3.0 criteria.

Asymptomatic decreases in LVEF were not reportable as AEs *per se,* unless one of the following criteria was met:

- An asymptomatic decrease in LVEF to a value of ≥ 10 percentage points below baseline and < 50% absolute value.
- An asymptomatic decrease in LVEF requiring treatment or discontinuation of study treatment (reported as a Non-Serious Event of Special Interest)>

Study WO20698 provided for a dedicated cardiac Review Committee (CRC). Patients were selected for review based on reports of AEs consistent with symptomatic LVSD

(congestive heart failure, CHF), treatment with cardiac drugs, reports of studies including echocardiograms, MUGA scans, Chest X-ray, ECGs. Based on their evaluation, the CRC was to assign subjects to the following categories:

- Symptomatic LVSD (fatal or non-fatal)
- Probable cardiac death
- Non-LVSD cardiac death (death due to myocardial infarction or documented arrhythmia).

Table 30 summarizes the major LVSD results assessed by investigators and the CRC during the overall study treatment period.

Table 30: Overview of Left Ventricular Dysfunction during Treatment Period of Trial WO20698 (Reviewer Table)

Events to Monitor	Placebo + T + D N=397 (%)	Pertuzumab + T + D N=407 (%)
Symptomatic LVSD by CRC	4 (1.0%)	4 (1.0%)
NYHA class III-IV	0 (0%)	3 (0.7%)
[1]Symptomatic LVSD by Investigator	7 (1.8%)	4 (1.0%)
NYHA class III-IV	4 (1.0%)	3 (0.7%)
Left ventricular dysfunction (preferred term)	33 (8.3%)	18 (4.4%)
NCI-CTCAE grade ≥ 3	11 (2.8%)	5 (1.2%)

[1]Reported as SAE (congestive heart failure)

The incidence of investigator identified symptomatic LVSD (CHF), reported as an SAE, was higher in the placebo arm than the pertuzumab arm (1.8% vs. 1.0%). The CRC adjudicated incidence was 1.0% in both treatment arms. Left ventricular dysfunction (LVD) was a preferred term in dataset AE and the most common cardiac AE. It was reported in 8.3% of patients in the placebo arm and 4.4% of patients in the pertuzumab arm. LVD included subjects with investigator-assessed symptomatic LVSD and those who had a fall in LVEF that met the pre-defined criteria. Table 31 shows the LVEF results during the treatment period for trial WO20698.

Table 31: LVEF Results during Treatment Period of Trial WO20698 (Reviewer Table)

	Placebo + T + D N=397 (%)	Pertuzumab + T + D N=407 (%)	Total N=804 (%)
Protocol-defined[1] significant decrease in LVEF	25 (6.3%)	16 (3.9%)	41 (5.1%)
No baseline EF	3 (0.8%)	2 (0.5%)	5 (0.6%)
No follow-up EF	17 (4.3%)	13 (3.2%)	30 (3.7%)

[1] Absolute value < 50% and fall ≥ 10 from baseline.
Source: Dataset lvefext.xpt

***Reviewer comment**: There was a high degree of compliance with obtaining required assessments of LVEF in both arms of the trial. Almost all patients had baseline assessments, and the number of patients who had follow-up LVEF testing over time by cycle (through at least cycle 12) was comparable for the treatment arms.*

By the time of the data cut-off, 8 of 11 symptomatic LVSD events had resolved (5 in placebo and 3 in the pertuzumab arm) and there had been no related deaths.

***Reviewer comment**: The applicant indicated that there were "serious audit findings related to the process of CRC adjudication, especially in the management of data flow to and from the committee." The applicant advises reviewing the CRC data "with caution." However, for the important SAE of symptomatic LVSD, the incidence is low overall, with similar results determined by the investigators and the CRC. The CRC determined that there were 3 probable cardiac deaths in the placebo arm and 2 in the pertuzumab arm. Trial WO20698 demonstrates no evidence of additive cardiac toxicity with the addition of pertuzumab to docetaxel and trastuzumab. This conclusion should not be affected by any applicant-reported irregularities in the CRC adjudication process.*

(See section 7.5.2, Time Dependency for AEs)

7.3.4.2 Leukopenia, neutropenia, febrile neutropenia, febrile neutropenic infection.

WO20698
Table 32 shows the number of patients by treatment arm that experienced leukopenia, neutropenia and febrile neutropenia.

Table 32: Leukopenia and Related Adverse Events WO20698 (Reviewer Table)

Adverse Event	Placebo + T + D N=397 (%)	Pertuzumab + T + D N=407 (%)
Leukopenia Grades All Grades	81 (20.4%)	74 (18.2%)
Leukopenia Grade 3-4	58 (14.6)	50 (12.3)
Neutropenia Grades All Grades	197 (49.6)	215 (52.8)
Neutropenia Grade 3-4	182 (45.8)	199(48.9)
Febrile Neutropenia All Grades *	30 (7.6)	56 (13.8)
Febrile Neutropenia Grade 3-4	29 (7.3%)	53 (13.0%)

* Includes fatal events, 1 AE in placebo group, 2 AEs in pertuzumab group

The incidence was higher for patients in the pertuzumab arm for neutropenia (48.9% vs. 45.8%) and especially for febrile neutropenia (13.8% vs. 7.6%) compared with the placebo arm. The incidence of leukopenia was higher for patients in the placebo treatment arm (14.6% vs. 12.3%) compared with the pertuzumab treatment arm. Study drug dose modification for leukopenic events was required in 19.4% of patients in the pertuzumab arm and 17.1% of patients in the placebo arm. Similar percentages of patients received colony-stimulating factor in the placebo arm (26.4%) and in the

pertuzumab arm (28.1%). The incidence of leukopenic infections was higher in the pertuzumab arm (12.5% of patients vs. 9.8%) as was the incidence of febrile neutropenic infections higher in the pertuzumab arm (3.4% vs. 0.8% of patients) compared with the placebo arm. The incidence of leukopenic infections grade ≥ 3 was also higher in the pertuzumab arm (4.7% vs. 2.3%) than the placebo arm. There were 2 febrile neutropenic deaths in the pertuzumab treatment group and 1 febrile neutropenic death in the placebo group.

In WO20698, the incidence of febrile neutropenia was increased in Asian patients compared with other races and other regions. This has not been explained. (See section 7.5.3)

Key Supportive Trials
In single-arm phase 2 study BO17929, in which the treatment regimen consisted of pertuzumab +trastuzumab, and no docetaxel was administered, leukopenia-related events were not observed. In trial #WO20697 (Neosphere), the randomized phase 2b, neoadjuvant trial in patients with HER2+ early breast cancer, the incidences of grade ≥ 3 febrile neutropenia and neutropenia, respectively, were 0 and 0.9% for the 108 patients in the treatment arm consisting of pertuzumab +trastuzumab and no docetaxel. By contrast, for the patients in the pertuzumab +trastuzumab + docetaxel arm of trial WO20697, the incidences of grade ≥ 3 febrile neutropenia and neutropenia, respectively, were 8.4% and 44.9%.

Reviewer comment: *The marked decrease (to absence) of grade ≥ 3 neutropenia and febrile neutropenia, in the treatment arms which omit docetaxel in the 2 major supportive trials, is strong evidence that neutropenic-related events in the phase 3 trial, WO20698 (Cleopatra) are related to docetaxel, at least to a significant degree.*

7.3.5 Submission Specific Primary Safety Concerns

This section will summarize the information from the application that pertains to these additional “adverse events to monitor” for trial WO20698 pre-specified by the applicant and based on the known pertuzumab safety profile or mechanism of action. (See section 7.3.4 for discussion of cardiac and febrile neutropenia concerns.)

- Diarrhea
- Rash
- Interstitial lung disease.
- Hypersensitivity/anaphylaxis
- Hepatic disorders

7.3.5.1 Diarrhea

In trial WO20698, more patients experienced diarrhea in the pertuzumab arm than in the placebo arm (66.8% vs. 46.3%). The incidence of grade ≥ 3 AEs was higher in the

pertuzumab arm than the placebo arm (7.9% of patients vs. 5.0%). Most episodes of diarrhea occurred in the first three treatment cycles, with the most severe episodes in the first 2 cycles. More patients were treated for diarrhea in the pertuzumab arm.

Key supportive trials
In the single-arm phase 2 trial, BO17929, in which patients were treated with pertuzumab and then dual agent pertuzumab +trastuzumab after progression, 56.6% of patients experienced diarrhea. In the 4-arm neoadjuvant trial, WO20697 (Neosphere), the treatment arm with pertuzumab +trastuzumab alone had a lower incidence of diarrhea (27.8%) than the other treatment arms, which all included docetaxel. The incidence of grade ≥ 3 diarrhea in the pertuzumab +trastuzumab arm was 0%, compared with the pertuzumab +trastuzumab + docetaxel arm (5.6%), the pertuzumab + docetaxel arm (4.3%), and the docetaxel +trastuzumab arm (3.7%).

7.3.5.2 Rash

Skin rash was reported in more patients in the pertuzumab arm than in the placebo arm (45.2% vs. 36.0%) in trial WO20698. The incidence of grade 3 AEs was higher in the pertuzumab arm than the placebo arm (2.7% of patients vs. 1.3%). No patients in the placebo arm discontinued docetaxel only for rash compared with 8 patients in the pertuzumab arm (2.0%). Most AEs of rash occurred during the first two treatment cycles.

7.3.5.3 Interstitial lung disease

In trial WO20698, the reported incidence of interstitial lung disease (ILD) was 2.2% in the pertuzumab arm and 1.5% in the placebo arm, with a low incidence of grade ≥ 3 ILD in both arms (0.7% vs. 0.5%, respectively).

Supportive safety database
In all pertuzumab-exposed patients (> 1400), the incidence of ILD was 1.1% (16 AEs).

7.3.5.4 Hypersensitivity/anaphylaxis

In trial WO20698, the incidence of hypersensitivity/anaphylaxis reactions was 9.1% in the placebo group and 10.8% in the pertuzumab group, with grade 3-4 AEs occurring in 2.5% of the placebo group and 2% of the pertuzumab group. Six patients, 2 in the placebo group and 4 in the pertuzumab group were reported to have anaphylaxis. Two of these events were considered SAEs. The onset was on day 22 for patient 9560 in the placebo group and required dose modification of docetaxel. For patient 8012 in the pertuzumab group, onset was on day 2 with resolution but the patient was withdrawn from study medication. For cycle 1, pertuzumab was given alone on day 1, and trastuzumab and docetaxel were given day 2.

Infusion reactions occurred on day 1 of cycle 1 in 9.8% of placebo patients and 13.0% of pertuzumab patients. Infusion reactions were defined as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction, or cytokine release syndrome which occurred during an infusion or on the same days as the infusion.

7.3.5.6 Hepatic disorders

WO20698

The incidence of hepatic disorders was similar in the 2 treatment arms, 10.1 % of patients in the placebo arm vs. 9.6% of patients in the pertuzumab arm. Grade ≥ 3 events were also similar, 1.3% of patients in the placebo arm vs. 1.7% of patients in the pertuzumab arm. The most common category of hepatic events in both treatment arms was Investigations (6.8% placebo arm vs. 6.4% of patients in the pertuzumab arm). Increased alanine aminotransferase was the most common event in both treatment arms (3.0% placebo vs. 3.7% pertuzumab arm). One patient in the placebo arm (#9609) was hospitalized for neutropenia and died of hepatic failure on study day 10. She had liver metastases and markedly elevated baseline liver function tests (LFT's), in violation of study eligibility. Four patients in the pertuzumab arm were reported to have toxic hepatitis (preferred term), which led to discontinuation of docetaxel.

- Patient 8178 had liver metastases and mild LFT elevations at baseline with normal bilirubin. Grade 1-3 elevations in ALT and AST occurred intermittently, with treatment delays cycle 4, 13, and 14. As of the data cut-off, the patient had received 29 cycles of pertuzumab and trastuzumab, with normal ALT/AST after discontinuation of docetaxel.
- Patient 9525 had baseline LFT elevations and liver metastases. On day 22 she was reported to have grade 3 hepatitis. After resolution, docetaxel was to be discontinued, but it was restarted in error at cycle 5 (at an increased dose of 100 mg/m^2). Patient subsequently experienced grade 2 toxic hepatitis. Eventually pertuzumab and trastuzumab were resumed, and the patient received cycle 32 as of the time of data cut-off, with acceptable LFTs.
- Patient 9930 experienced grade 4 "toxic hepatitis" on day 22. She had known liver metastases. Bilirubin was normal, ALT elevated to 9.6 x ULN, AST 22 x ULN, alkaline phosphatase 9.7 x ULN. Docetaxel was discontinued. Subsequently the patient completed 7 cycles of therapy, but was then lost to follow-up.
- Patient 9477 was reported to have grade 2 toxic hepatitis, resulting in a treatment delay at cycle 6 for 21 days. Subsequently docetaxel was discontinued and the patient continued remaining study drugs through cycle 36.

Reviewer comment: *The ability of these patients to continue long term therapy with pertuzumab and trastuzumab after discontinuation of docetaxel, supports that docetaxel contributed significantly to the hepatotoxicity of the combination regimen.*

A single patient in trial WO20698 was found to meet criteria for Hy's Law (for drug-induced liver injury). However, this patient, #5940, was in the placebo treatment arm and did not receive pertuzumab. Hy's law was defined as:

- AST and/or ALT > 3 X ULN and total bilirubin > 2x ULN, with alkaline phosphatase < 2 x ULN.

To fulfill criteria for Hy's Law, there should be no alternative cause for hepatic dysfunction. This patient was receiving docetaxel (and was in the placebo group).

Supportive safety database

Three hepatic deaths occurred during treatment in the key supporting studies. The 2 deaths in study BO17929 were considered related to progressive disease and unrelated to therapy. A death (patient #116963/1747) due to fulminant hepatitis was reported in trial WO20697, the randomized neoadjuvant phase 2 trial. This 69 year-old woman was randomized to receive pertuzumab +trastuzumab +docetaxel. Baseline LFTs were normal. Two days after treatment cycle 4, she became symptomatic, was hospitalized (in Brazil) and was found to have elevations in AST/ALT (3520 U/L and 1920 U/L) and bilirubin (value not reported). She died on study day 69. The patient had a history of type 2 diabetes, hypertension, and obesity. Chronic medications included enalapril. The patient was dosed initially with docetaxel 169 mg (75 mg/m^2), but the dose was increased to 225 mg (100 mg/m^2) for cycles 3 and 4. No information is available regarding serum alkaline phosphatase or hepatitis serologies.

Reviewer comment: *If the fulminant hepatitis death is drug related, docetaxel is more suspect than other concomitant therapy. Overall, pertuzumab does not appear to be significantly hepatotoxic.*

In the safety database for pertuzumab (more than 1400 patients), the overall incidence of hepatic disorders was 9.8%. No other cases suggestive of Hy's law were reported.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

WO20698

Table 33 shows common adverse events with an incidence of at least 10% in the pertuzumab treatment arm for all grades, and the incidence of grade 3-4 events. The table is taken from the sponsor's proposed labeling, and the data are consistent with dataset "AE" from the CSR.

Table 33: Common Adverse Events (Grade 1-4) WO20698 (Applicant Table)

System Organ Class/ Preferred Term	Placebo + T + D n=397		Pertuzumab + T + D n=407	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	36.8	3.3	37.6	2.2
Asthenia	30.2	1.5	26.0	2.5
Edema peripheral	30.0	0.8	23.1	0.5
Mucosal inflammation	19.9	1.0	27.8	1.5
Pyrexia	17.9	0.5	18.7	1.2
Skin and subcutaneous tissue disorders				
Alopecia	60.5	0.3	60.9	0.0
Rash	24.2	0.8	33.7	0.7
Nail disorder	22.9	0.3	22.9	1.2
Pruritus	10.1	0.0	14.0	0.0
Dry skin	4.3	0.0	10.6	0.0
Gastrointestinal disorders				
Diarrhea	46.3	5.0	66.8	7.9
Nausea	41.6	0.5	42.3	1.2
Vomiting	23.9	1.5	24.1	1.5
Constipation	24.9	1.0	15.0	0.0
Stomatitis	15.4	0.3	18.9	0.5
Blood and lymphatic system disorders				
Neutropenia	49.6	45.8	52.8	48.9
Anemia	18.9	3.5	23.1	2.5
Leukopenia	20.4	14.6	18.2	12.3
Febrile neutropenia	7.6	7.3	13.8	13.0
Nervous system disorders				
Neuropathy peripheral	33.8	2.0	32.4	3.2
Headache	16.9	0.5	20.9	1.2
Dysgeusia	15.6	0.0	18.4	0.0
Dizziness	12.1	0.0	12.5	0.5
Musculoskeletal and connective tissue disorders				
Myalgia	23.9	0.8	22.9	1.0
Arthralgia	16.1	0.8	15.5	0.2
Infections and infestations				
Upper respiratory tract infection	13.4	0.0	16.7	0.7
Nasopharyngitis	12.8	0.3	11.8	0.0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	15.6	2.0	14.0	1.0
Metabolism and nutrition disorders				
Decreased appetite	26.4	1.5	29.2	1.7
Eye disorders				
Lacrimation increased	13.9	0.0	14.0	0.0
Psychiatric disorders				
Insomnia	13.4	0.0	13.3	0.0

The most frequently reported treatment emergent adverse events (TEAEs) in WO20698 occurring in ≥ 30% of patients in the pertuzumab treatment arm were diarrhea, alopecia, neutropenia, nausea, fatigue, and rash. AEs (all grades) for which the incidence in the pertuzumab treatment arm was ≥ 5% more than the incidence in the placebo arm include diarrhea (66.8% vs. 46.3%), rash (33.7% vs. 24.2%), mucosal inflammation (27.8% vs.19.9%), febrile neutropenia (13.8% vs. 7.6%), and dry skin (10.6% vs. 4.3%). AEs for which the incidence in the placebo group was ≥ 5% more than the incidence in the pertuzumab group include constipation (25% vs.15%) and peripheral edema (30% vs. 23%).

Reviewer comment: *The findings are consistent with the expected safety profiles of the study drugs. The incidence for all grades of mucosal inflammation (General Disorders) was 27.8% and 19.9%, respectively, in the pertuzumab and placebo arms. The incidence of stomatitis (Gastrointestinal Disorders) was 18.9% and 15.4%, respectively. Since there is a large overlap of the categories, comparing verbatim and preferred terms for these AEs, the incidence of stomatitis (oral mucosal inflammation) is underestimated.*

The most common grade 3-4 AEs ≥ 2% in study WO20698 were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia and fatigue. The grade 3-4 AEs for which there was a ≥ 2% difference between arms, and the incidence was higher for the pertuzumab arm, include neutropenia (48.9% vs. 45.8%), febrile neutropenia (13.8% vs. 7.6%), and diarrhea (7.9% vs. 5.0%). The incidence of leukopenia was higher in the placebo treatment arm (14.6% vs. 12.3%).

Integrated safety database
The most common adverse events ≥ 20% in patients treated with fixed therapeutic doses of single-agent pertuzumab alone (n=386) were diarrhea 57.3%, fatigue 31.6%, nausea 30.8%, vomiting 22.3%, and decreased appetite 21.2%. The incidence of rash was 15.8%. The incidence of ejection fraction decreased was 13.0%. The incidence of pruritus, stomatitis, and pyrexia were each 7%. These data are from the integrated safety database from applicant table 34, ISS of the CSR from study WO20698.

(See section 7.3.4 for discussion of cardiac events and febrile neutropenia. See section 7.3.5 for discussion of other applicant predefined “other adverse events to monitor” in study WO20698.)

7.4.2 Laboratory Findings

Laboratory parameters were required to be monitored on days 1 and 8 of each treatment cycle WO20698. The most common changes in laboratory parameters from baseline were for hematology parameters. The incidence of grade 3-4 neutropenia post-baseline was similar in the two treatment arms, 86.6% of patients in the placebo arm vs. 86.0% of patients in the pertuzumab arm, and was due to docetaxel therapy in both treatment arms. Shifts from baseline for biochemistry values were similar in the

two treatment arms or favored the pertuzumab arm with the exception that increase in SGPT to grade 3 occurred in 3 patients (<1%) in the placebo arm vs. 11 patients (2.7%) in the pertuzumab arm.

7.4.3 Vital Signs

In trial WO20698, mean, median and changes from baseline in temperature, supine diastolic and systolic blood pressure and pulse rate were compared. There were no clinically meaningful differences between treatment arms for these parameters.

7.4.4 Electrocardiograms (ECGs)

In the QT sub-study of the pivotal trial, WO20698, ECG findings were evaluated from Holter monitoring. The sponsor also summarized ECG findings of investigator assessments based on routine ECGs conducted at the study site. Most abnormalities were seen on one or two tracings, and some subjects had baseline abnormalities. Table 34 summarizes abnormalities not present at baseline.

Table 34: ECG Abnormalities Not Present at Baseline WO20698 (Applicant table)

Main Post-baseline ECG abnormality (based on Investigator comment for abnormal ECGs)	No. of patients	
	Pla+T+D N = 397	Ptz+T+D N = 407
QT prolongation	4	4
First degree AV block	3	5
Bundle branch & fascicular blocks	3	4
Atrial fibrillation	5	1
Atrial enlargement	2	0
Myocardial infarction & ischemia*	3	7
Repolarization abnormalities	3	3
Axis deviation	1	0
Non-specific ST, T wave and other abnormalities	3	7
Pericarditis, pericardial effusions & low voltage complexes	3	0
Left ventricular hypertrophy	1	2
Ventricular arrhythmias	1	2
Miscellaneous & multiple abnormalities	2	5
No clear information	1	3
Total	35	43

Derived from l_vs03_phys
*including old or indeterminate changes

Source: CSR section 3.5.5.1.1 (sponsor table 81)

Reviewer comment: *This summary information, abstracted from routinely conducted, periodic ECG's does not suggest a safety signal. Nor were there signals from the ECG data of the patients who were evaluated in the QT sub-study of trial WO20698.*

7.4.5 Special Safety Studies/Clinical Trials

A dedicated sub-study was conducted as part of study WO20698, with the objectives of describing the effect of pertuzumab on the QTc interval, and ECG parameters for heart rate, QT interval, PR interval, and QRS duration. There was no clinically relevant effect of pertuzumab on the QT interval at the proposed therapeutic dose, and there was no exposure-response relationship within the range of concentrations in the study. (See the separate review of the sub-study by the CDER IRT-QT team, Dr. Jiang Liu and colleagues.)

7.4.6 Immunogenicity

In the pivotal trial, WO20698, the incidence of anti-therapeutic antibody (ATA) positivity was 6.2% for the placebo arm and 2.8% for the pertuzumab treatment arm. The assay does not differentiate ATA to pertuzumab from ATA to trastuzumab, and there is possible interference in the assay from HER2 shed antigen. Seven of the 23 patients in the placebo arm who were positive for ATA had pre-existing antibodies at baseline, although they had not previously been treated with pertuzumab or trastuzumab. One of 11 patients positive for ATA in the pertuzumab treatment arm tested positive at baseline. The impact on PK of ATA is unknown due to very limited PK data in ATA-positive patients (1 pertuzumab arm patient, 3 control arm patients). Immunogenicity-related hypersensitivity reactions did not appear to occur in patients that were ATA-positive. Although ATA appear to impact efficacy negatively, the efficacy advantage for ORR and PFS was preserved for pertuzumab in both the ATA-negative and ATA-positive subgroups. (See the separate Clinical Pharmacology review of Dr. Pengfei Song for details.)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In single agent studies of pertuzumab (ISS database), the applicant found no strong association for AE incidence and dose for fixed doses of pertuzumab 420 mg and 1050 mg. However in selected studies in the safety database that randomized patients or treated patients in sequential cohorts with high and low dose, the incidences of skin disorders (preferred term: stomatitis) and diarrhea were slightly higher with high vs. low dose pertuzumab.

7.5.2 Time Dependency for Adverse Events

The applicant conducted an analysis of (cardiac) mean LVEF over time in trial WO20698. The mean LVEF by cycle remained stable in both treatment arms. However, the incidence of significant decline in LVEF was low overall. The incidence of LVEF decline of at least 10 percentage points to an absolute value below 50% was 6.6% in the placebo arm and 3.8% in the pertuzumab arm. LVEF decline below 40% was observed in only 6 patients, 3 in each arm. The time to first decrease in LVEF to an absolute value below 50% with a decline of ≥ 10% from baseline was similar for the 2 treatment arms (by visual inspection of Kaplan-Meier curves).

7.5.3 Drug-Demographic Interactions

Since almost all of the patients in the WO20698 trial and major supportive trials were female, an analysis of AEs by gender could not be conducted based on data from these trials. (See section 6.1.4 for details of patient demographic information.) In trial WO20698, patients younger than age 65, particularly those in the pertuzumab arm, were more likely to experience febrile neutropenia than patients age ≥ 65. The incidence of diarrhea was higher for patients age ≥ 65 than for younger patients for both treatment arms. The incidence of diarrhea grade ≥ 3 is highest for older patients treated with pertuzumab. Table 35 compares the incidence of important AEs occurring in patients age < 65 vs. age ≥ 65 by treatment arm.

Table 35: Adverse Events by Age Group and Treatment WO20698 (Reviewer Table)

Age in Years	Age < 65 N=678 (84.3%)		Age ≥ 65 N=126 (15.7%)	
	Placebo +D+T N=332	Pertuz[1] +D+T N=346	Placebo +D+T N=65	Pertuz[1] +D+T N=61
Any AE	327 (98.5)	345 (99.7)	64 (98.5)	61 (100)
Grade ≥ 3	241 (72.6)	255 (73.7)	48 (73.8)	47 (77.0)
Leukopenia ≥ grade 3	183 (55.1)	206 (59.5)	28 (43.1)	31 (50.8)
Leukopenic Infection	37 (11.1)	43 (12.4)	2 (3.1)	8 (13.1)
Grade ≥ 3	9 (2.7)	16 (4.6)	0	3 (4.9)
Febrile Neutropenia	26 (7.8)	51 (14.7)	4 (6.2)	5 (8.2)
Febrile Neut. Infection	3 (0.9)	13 (3.8)	0	1 (1.6)
Diarrhea	149 (44.9)	229 (66.2)	35 (53.8)	43 (70.5)
Grade ≥ 3	16 (4.8)	23 (6.6)	4 (6.2)	9 (14.8)
Symptomatic LVSD[2]	4 (1.2)	3 (0.9)	0	1 (1.6)
LVEF decline[3] (only)	17 (5.1)	12 (3.5)	5 (7.7)	1 (1.6)

1Pertuzumab +Docetaxel+Trastuzumab

2Left ventricular systolic dysfunction

3Left ventricular ejection fraction (protocol-defined decline)

From ISS Table 135 and CSR Table 42 (WO20698)

For both age groups, the incidence of symptomatic LVSD was low. For both age groups, the incidence of protocol-defined decline in LVEF (section 7.3.4.1) was higher in the placebo treatment arms. The incidence of LVEF decline was lowest for patient in the pertuzumab-treated arm of the older age group.

Reviewer comment: *Comparisons between age groups should be made with caution due to the small number of patients in the older age subgroups.*

Adverse Events by Race in WO20698

Table 36 shows the racial distribution of subjects for Trial WO20698.

Table 36: Racial Representation in Trial WO20698 by Treatment Arm (Reviewer Table)

Race	Total N=804 (100%)	Placebo + T + D N=397 (%)	Pertuzumab + T + D N=407 (%)
Caucasian (White)	476 (59.2)	227 (57.2)	249 (61.2)
Asian	261 (32.5)	133 (33.5)	128 (31.4)
Black	30 (3.7)	20 (5.0)	10 (2.5)
Other	37 (4.6)	17 (4.3)	20 (4.9)

In trial WO20698, most patients were Caucasian. The incidence of Asian patients was next highest. Few patients were Black or "other." The distribution of Caucasians and Asians across the treatment arms was similar, with 4% more Caucasians in the pertuzumab group and 2.1% more Asian patients in the placebo group. Table 37 summarizes selected adverse events by treatment arm and race for Caucasian and Asian subjects who represent 59.2 % and 32.5%, respectively, of patients in trial WO20698.

Table 37: AEs by Race and Treatment Arm WO20698 (Reviewer Table)

	Caucasian		Asian	
	Placebo +D+T N=227 (%)	Pertuz[1] +D+T N=249 (%)	Placebo +D+T N=133 (%)	Pertuz[1] +D+T N=128 (%)
Any AE	224 (98.7)	248 (99.6)	132 (99.2)	128 (100)
AE ≥ grade 3	165 (72.7)	177 (71.1)	98 (73.7)	104 (81.3)
Any SAE	51 (22.5)	70 (28.1)	36 (27.1)	59 (46.1)
Leukopenia ≥ grade 3	118 (52.0)	132 (53.0)	76 (57.1)	89 (69.5)
Leukopenic Infection	21 (9.3)	30 (12.0)	14 (10.5)	18 (14.1)
Grade ≥ 3	5 (2.2)	9 (3.6)	2 (1.5)	9 (7.0)
Neutropenia Grade 4	134 (59)	137 (55)	97 (73)	92 (72)
Febrile Neutropenia	14 (6.2)	20 (8.0)	15 (11.3)	33 (25.8)
Febrile Neut. Infection	3 (1.3)	6 (2.4)	0	7 (5.5)
Diarrhea	96 (42.3)	152 (61.0)	67 (50.4)	94 (73.4)
Grade ≥ 3	5 (2.2)	18 (7.2)	11 (8.3)	14 (10.9)
CHF or LVEF[2] decline	16 (7.0)	9 (3.6)	5 (3.8)	5 (3.9)

1Pertuzumab +Docetaxel+Trastuzumab

2Congestive Heart Failure (Symptomatic LVSD) or protocol-defined LVEF decline

From ISS Table 139 and CSR Table 43 (WO20698) and eCTD #0017

The incidence of any AE grade ≥ 3 or any SAE was higher for Asians in the pertuzumab treatment arm compared with the placebo arm and compared with either treatment arm for Caucasians. The incidence of grade 4 neutropenia was higher for Asians in both treatment arms compared with Caucasians (and Blacks). The incidence of febrile neutropenia was higher for Asians compared with Caucasians for both treatment arms and was higher for Asians in the pertuzumab arm compared with Caucasians treated with pertuzumab (25.8 vs. 8.0%). For the trial, overall, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (13.8%% of patients) compared with the placebo-treated group (7.6% of patients). Although Asian patients experienced an increased incidence of febrile neutropenia compared with other subjects, there was no observed increase in treatment withdrawal for this population or deaths due to AEs.

The incidence of diarrhea was higher for patients of the Asian race compared with Caucasians and was highest for Asians in the pertuzumab treatment arm. The incidence of mucosal inflammation + stomatitis (not listed in the table above), was also higher for Asians than Caucasians, particularly in the pertuzumab arm (60% vs. 40%, respectively).

Reviewer comment: *From the safety database, diarrhea and mucositis are part of the known toxicity profile of pertuzumab. However, the incidence of leukopenic events is low in single-agent studies and the docetaxel-free regimens of the key supporting trials. The much higher incidence of febrile neutropenia for Asians in the pertuzumab*

treatment arm compared with placebo (25.8% vs. 11.3%) in trial WO20698, does suggest that the addition of pertuzumab may be contributory.

Adverse Events by Geographic Region
In trial WO20698, the highest accrual by region was from Asia, 32% of patients (see section 6.1.4). The incidence of febrile neutropenia for patients from the geographic region of Asia was also increased in both treatment arms compared with the incidence for other geographic regions. For Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26% of patients) compared with the placebo-treated group (12% of patients). The incidence of febrile neutropenia in the trial, overall, was 13.8% of patients the pertuzumab group and 7.6% of patients in the placebo group.

Reviewer comment*: Grade 4 neutropenia is increased in Asians (see Table 37) compared with Caucasians and Blacks in trial WO20698. Febrile neutropenia is increased in (ethnic and geographic region) Asian patients in both treatment arms, but especially in the pertuzumab treatment arm. The applicant provided an analysis which suggested that differences in supportive care (between regions) do not explain the increase in febrile neutropenia. Asian patients were not more dose-escalated with respect to docetaxel (from 75 mg/m^2 to 100 mg/m^2, as permitted in the protocol) than other patients. The applicant suggests that the explanation relates to the lower weight/surface area/BMI of Asian patients, which would result in higher exposure to docetaxel. The applicant suggests this theory is supported by a higher incidence of mucositis and diarrhea in both treatment arms for Asian patients. FDA Clinical Pharmacology reviewers are not in agreement with this theory that smaller size explains the increased toxicity, since dosing of docetaxel is adjusted for surface area. (See Dr. Pengfei Song's separate review.)*

(See section 7.3.4.2 for additional discussion of febrile neutropenia in trial WO20698 and the key supportive trials.)

7.5.4 Drug-Disease Interactions

Since pertuzumab is not cleared by the kidneys or metabolized by cytochrome P450 isoenzymes, drug-disease interactions are not anticipated for co-morbidities.

7.5.5 Drug-Drug Interactions

There was no evidence of drug-drug interactions occurring between pertuzumab and trastuzumab or docetaxel, as assessed in the 37-patient (QT/PK) sub-study of the randomized phase 3 trial, WO2698, or based on population PK analysis. The applicant indicates that during development, pertuzumab was found not to alter the PK of docetaxel, gemcitabine, capecitabine, or erlotinib. Since pertuzumab is not cleared by the kidneys or metabolized by cytochrome P450 isoenzymes, drug-drug interactions were not anticipated.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The carcinogenic potential of pertuzumab has not been evaluated in long-term studies in animals.

7.6.2 Human Reproduction and Pregnancy Data

Administration of pertuzumab to cynomolgus monkeys during organogenesis was associated with oligohydramnios, delayed renal development, and embryo-fetal death. Two patients in the phase 3 trial (WO20698), who were randomized to the pertuzumab arm, were reported to have SAEs of "abortion" for which Narratives were submitted. A third patient, #164950/8832, in the placebo arm, had a positive pregnancy test at cycle 8, but was not reported as an AE, and no narrative was provided. No information was available regarding the fetuses of any of the subjects. The 2 patients with narratives who were treated with pertuzumab were:

- #121040/8295: This subject had a spontaneous abortion on Study Day 37, Dec. 16, 2009, which delayed administration of cycle 2 until study day 44. The pregnancy test had been negative prior to cycle 1, but was positive on day 23 (Dec. 2, 2009). The last menstrual period (LMP) was Oct. 22 and the date of conception was estimated as Nov. 9. The spontaneous abortion was considered possibly related to trastuzumab and docetaxel.
- #121220/9577: This subject had an induced abortion on Study Day 500, (b) (6) On Study Day 494, the patient was administered pertuzumab (cycle 22). However, before trastuzumab could be administered, the pregnancy test was found to be positive (performed unscheduled, at the patient's request). LMP was Dec. 31, 2010, and the estimated date of conception was Jan. 15, 2011. After an induced abortion, the patient continued with therapy (cycle 23) on Feb. 24, 2011.

Two patients became pregnant during study WO2067 (randomized phase 2, NEOSPHERE, in early breast cancer). Both patients were randomized to arm C of the trial (pertuzumab + trastuzumab).

- Patient 2512 received cycle 4 of neoadjuvant therapy on Jan. 21, 2009 (study day 62). Following a positive pregnancy test, she had a therapeutic abortion on (b) (6) (study day 85). The date of conception was thought to be (b) (6) one day after cycle 3 of treatment with pertuzumab and trastuzumab.
- Patient 1722 was confirmed to be pregnant on Jan. 19, 2010 (study day 215), during cycle 9 of study treatment. The last dose of pertuzumab was given Aug. 21, 2009 (day 64), during cycle 4. Conception is estimated to have occurred in (b) (6) Docetaxel was given Dec. 16, 2009 (study day 181, cycle 8). Cycle

9, consisting of trastuzumab and FEC, was given Jan. 6, 2010 (study day 202). Treatment was subsequently discontinued, and a healthy baby was born (b) (6)

7.6.3 Pediatrics and Assessment of Effects on Growth

Pertuzumab has not been studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdoses have not been reported for pertuzumab. There is no abuse potential and withdrawal considerations are not relevant.

7.7 Additional Submissions / Safety Issues

The 90-day safety update was submitted March 8, 2012 (eCTD #010). It included safety information beyond the original data cut-off date of May 13, 2011, through Nov. 7, 2011. The update consisted of information from the randomized phase 3 trial, study WO 20698 (Cleopatra), including updates of:

- Datasets
- Safety data analyses
- Patient narratives and CRF's.

The 90-day safety update provided no new safety signals.

8 Postmarket Experience

Pertuzumab is not marketed in the US or other jurisdiction.

9 Appendices

9.1 Advisory Committee Meeting

No advisory committee meeting was held for this BLA.

9.2 Labeling Recommendations

There were extensive internal labeling discussions with all review disciplines. Key clinical labeling recommendations included:

- Add a 'boxed warning' regarding embryo-fetal harm.
- In section 6.1, add data regarding the increased incidence of febrile neutropenia in Asian patients.
- In section 14.1, add data on percent of patients who received prior neo/adjuvant trastuzumab, percent of subjects who were hormone receptor positive, percent of hormone receptor positive patients who received adjuvant hormonal therapy, and percent of hormone receptor positive patients who received hormonal therapy for metastatic disease.
- In section 14.1, add the subgroup PFS data on prior neo/adjuvant trastuzumab, hormone receptor positive and negative patients, and patients with non-visceral disease.

9.3 Literature Review/References

[1] US Food and Drug Administration Commissioner Statement: FDA commissioner removes breast cancer indication from Avastin label. http://www.fda.gov/NewsEvents/Newsroom/UCM279485.
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