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RESEARCH**

APPLICATION NUMBER:

125409Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 8, 2012
DDOP Clinical Team Leader	Patricia Cortazar, M.D.
BLA	125409
Applicant	Genentech, Inc
Date of Submission	December 6, 2011
PDUFA Goal Date	June 8, 2012
Proprietary Name / Established (USAN) names	Perjeta/ Pertuzumab
Dosage forms / Strength	420 mg per 14 mL (30mg/mL) single-use vial
Proposed Indication(s)	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
Recommended:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers/ Team Leaders
Regulatory Project Manager	Amy Tilley/Alice Kacuba
Medical Officer Reviewers	Gideon Blumenthal, M.D. (efficacy) Nancy Scher, M.D. (safety)
Statistical Review	Somesh Chattopadhyay/ Shenghui Tang
Pharmacology Toxicology Review	Kimberly Ringgold/ Anne Pilaro
CMC Review/DMA	Kathryn King (Traditional Elements)/Wendy Weinberg Laurie Graham (Quality by Design)/Barb Rellahan
Microbiology Review (BMAB)	Bo Chi (Drug Substance)/Patricia Hughes Colleen Thomas (Drug Product)/Patricia Hughes
Clinical Pharmacology Review	Pengfei Song/ Qi Liu
CDRH	Kevin Lorick/ Rena Philip
DDMAC	Marybeth Toscano/ Karen Rulli
OSI	Robert Young/Janice Pohlman
OSE/DMEPA Consult	Jibril Abdus-Samad/Todd Bridges
Maternal Health Team Consult	Melissa Tassinari/Lisa Mathis

Introduction

Genentech, Inc. submitted an original biologic licensing application (BLA) to support marketing approval of Perjeta (pertuzumab) 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. This document summarizes the reviews and conclusions of each review discipline.

The demonstration of a 6.1 month improvement in progression free survival was highly persuasive and statistically robust. A preliminary analysis suggests an improvement in overall survival. The effect on progression free survival was consistent across relevant subgroups and was supported by evidence of anti-tumor activity with significant improvement in objective tumor responses in the major efficacy study and in the neoadjuvant supportive study.

The toxicity profile of pertuzumab, when added to trastuzumab and docetaxel, was acceptable; major toxicities are transient (diarrhea, rash, and mucositis) and reversible myelotoxicity. There was no additive cardiac toxicity with the addition of pertuzumab to docetaxel and trastuzumab; and the incidence of cardiotoxicity was lower in the pertuzumab treatment arm.

1. Background

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).

Preclinical mouse models show 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 is also observed after tumor progression on trastuzumab monotherapy. Pre-clinical data suggests that the enhanced antitumor activity is mainly due to the differing but complimentary mechanisms of action of trastuzumab and pertuzumab, such as inhibition of HER2 dimerization and prevention of p95HER2 formation.

The initial IND application for this product (IND 9900) was submitted by Genentech, Inc in June 2001. The development program in support of pertuzumab registration was discussed with FDA at a Pre-IND meeting (3 May 2001), an End-of-Phase 2 meeting (17 April 2007), a Type C teleconference regarding revisions to the Phase 3 protocol and statistical analysis plan (5 November 2007), a Type C teleconference regarding content and format of the BLA (24 May 2011) and a pre-BLA meeting (30 September 2011).

April 17, 2007: 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.
- Genentech: Agreed to provide a detailed plan for evaluation of patients with NCI CTC Grade ≥ 2 cardiotoxicity. FDA stated that the 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.

November 5, 2007: Summary of Meeting Minutes Type C meeting to discuss the registration trial and SAP.

- FDA stated that 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.
- The 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 and Genentech agreed to sampling anti-pertuzumab antibodies at baseline, before the second pertuzumab dose, every 3 cycles, and at study discontinuation.

September 2011: Type B pre-BLA meeting.

- FDA stated that 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.
- The final OS analysis is planned late in 2013 at 385 events. Genentech was to provide by November, 2011, a proposal for conducting an additional OS analysis, should FDA request this.

2. CMC/Device

Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic, gentamicin. Gentamicin is not detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa. PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

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

(b) (4)

- 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 (b) (4). In addition, surviving thaws showed (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 telecons (1-2 per week) with Genentech 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. Within the context of the June 8th PDUFA deadline, discussions have focused on the type of data needed to address our concerns, and the time frame within which the data could be provided. This was approached with the initial understanding that the problem was limited to the working cell bank thaw and (b) (4).

- In April, Genentech agreed to a three-pronged action plan recommended by the FDA, as follows:
 - Extended characterization of drug substance derived from the current campaign (to mitigate risks to product quality associated (b) (4) and productivity)
 - Development of a new working cell bank (based on the possibility that the root cause for (b) (4) productivity is due to instability of the current working cell bank; this could be a PMR)
 - 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.

- (b) (4)
(b) (4)
(b) (4)

- The continued failures at multiple stages 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. (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 Genentech has a validated process and can consistently manufacture pertuzumab with product quality characteristics comparable to that used in their clinical trials. Given the ongoing failures with the current working cell bank, Genentech has not yet demonstrated a consistent process that would ensure continued supply of commercial material.



3. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer, Dr. Ringgold, and the supervisory reviewers, Drs. Pilaro and Leighton state that there are no outstanding clinical pharmacology issues that preclude approval and that no additional pharmacology/toxicology studies are needed.

The application was supported by pharmacology studies conducted in human tumor xenograft models, safety pharmacology studies. Two in vivo safety studies that supported this submission were the single dose PK and tolerability and the 6-month (Q weekly dosing x 26 weeks) repeat-dose toxicity studies in cynomolgus monkeys. Pertuzumab appeared to be well-tolerated in monkeys. In the pertuzumab single dose toxicity study, there were no treatment-related effects or abnormal clinical signs reported, other than a mild reactivity at the injection site. In a multiple dose toxicology study, the primary toxicities observed were diarrhea and elevations in blood urea nitrogen without a clear dose-relationship in either incidence or severity.

Cardiac toxicity is well known treatment related toxicity with trastuzumab. However, there were no remarkable treatment-related effects on electrocardiograms, heart rate, blood pressure or troponin levels in monkeys during the 6-month, repeat-dose toxicity study with pertuzumab, given weekly at doses of 15, 50, or 150 mg/kg/dose.

As documented in Dr. Ringgold's review, the EFD study demonstrated that pertuzumab resulted in fetal lethality in cynomolgus monkeys treated with loading doses approximately 0.2 to 2 fold greater than the exposure at the recommended human dose by AUC. These malformations included impaired renal development, paw hyper-extension/ hyper-flexion, microtia, small lungs, thin walls in the ventricular regions of the heart, fused caudal and sacral vertebra, and supernumerary lumbar 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.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewer (Pengfei Song) and team leader (Qi Liu) concluded that there are no outstanding clinical pharmacology issues that preclude approval.

The dose and schedule chosen for the major efficacy trial, was based on the results of Phase 1 studies (TOC2297 and JO17076) that demonstrated Pertuzumab 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. The target serum concentrations were achieved by the

loading dose of 840 mg and a 420 mg maintenance dose every three weeks regimen. The steady-state concentrations of pertuzumab were reached after the first maintenance dose. The population PK analysis did not identify age, race, gender, or mild/moderate renal impairment as significant covariates on the PK of pertuzumab. Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomized trial.

No dedicated renal impairment trial for pertuzumab has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200). No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available.

No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

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.

The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in the randomized trial. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

5. Clinical Microbiology

The FDA CMC Micro reviewers, Drs. Bo Chi, Colleen Thomas and the supervisory reviewer, Dr. Patricia Hughes, recommend Pertuzumab approval from a product quality microbiology perspective with three PMRs.

The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

The CMC microbiology issues resolved are related to the microbial control of the pertuzumab manufacturing process. Information in the BLA was clarified and updated, which includes location of (b) (4), in-process bioburden and endotoxin limits, and (b) (4) hold times. New (b) (4) bioburden sampling points were also added to the (b) (4).

The issues that will be resolved through PMRs include the (b) (4) the requalification of bioburden test. The three corresponding PMRs are provided below:

1. Revalidate the hold time for non-sterile cell culture media with a (b) (4) bioburden acceptance criterion that demonstrates microbial control during the hold period. In addition, test three different lots of raw materials in the re-validation runs. The information and results of the revalidation study will be submitted in a CBE-30 by December 31, 2013.
2. Conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of (b) (4) the screening of raw materials for (b) (4) bioburden and endotoxin, the (b) (4) non-sterile media hold time and temperature (b) (4) and the expanded use of (b) (4). The risk assessment summary and action plan will be submitted in a CBE-30 by March 31, 2013.
3. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL test sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). The summary data will be provided in a CBE0 by December 31, 2012.

6. Clinical/Statistical- Efficacy

This BLA is primarily supported 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.” Two additional supportive clinical studies were submitted by the applicant: NEOSPHERE (Study TOC4129g), a 4 arm trial neoadjuvant and BO17929, a single arm Phase 2 study.

Table 1 Studies submitted to support the BLA (from the clinical review)

Protocol	Study Design	Treatment Arms	N	Primary	Status
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				EP	
CLEOPATRA WO20698/ TOC4129g	Phase 3 trial in first line HER2+ MBC	Pertuzumab + Trastuzumab + Docetaxel Versus Placebo + Trastuzumab + Docetaxel	808	PFS	Ongoing Full report for primary analysis submitted
Neosphere WO20697	Phase 2 Neoadj trial in HER2+ early BC	Pertuzumab Trastuzumab Docetaxel	417	pCR	Ongoing Full report for primary analysis submitted
BO17929	Phase 2 trial in HER2+ MBC prior trastuzumab	Pertuzumab + Trastuzumab	95	ORR, CBR	Ongoing Full report for primary analysis submitted

CLEOPATRA (U.S. study number TOC4129g; world study number WO20698):

The original protocol was finalized on September 2007 and was amendment three times:

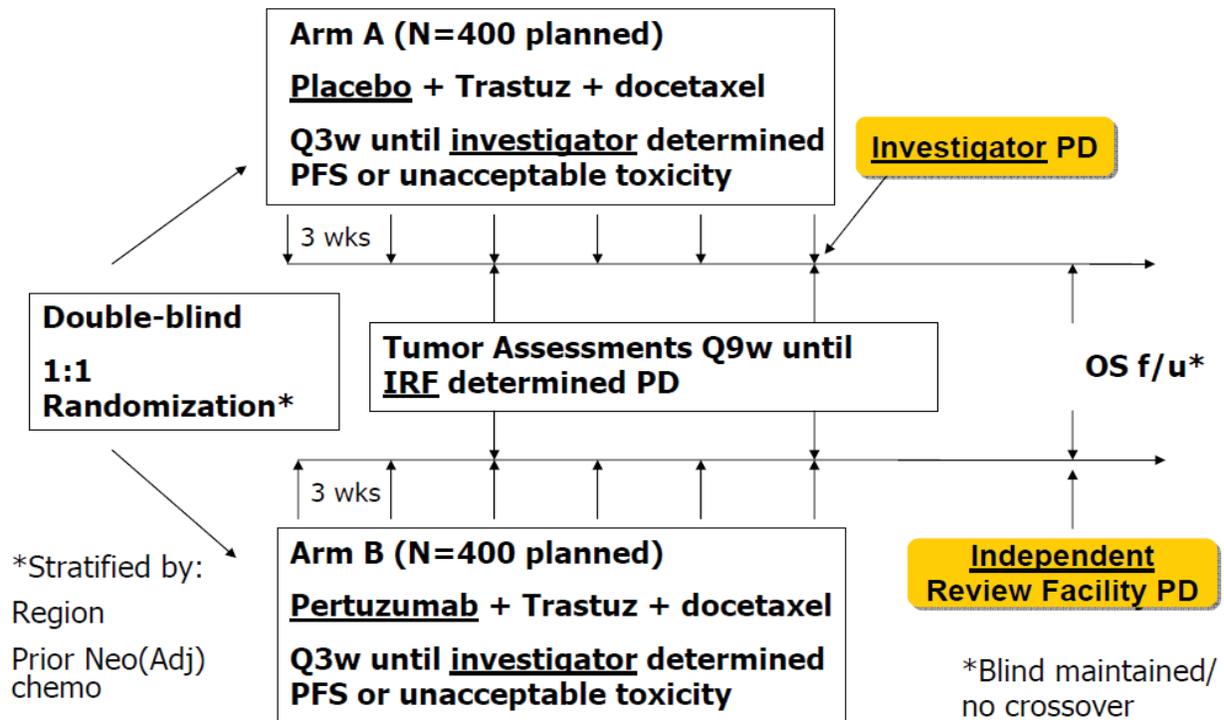
- **September 2007 (Protocol Version A):** In response to EMA and FDA comments, in the original protocol the sponsor increased the sample size from 600 to 800 to power for OS.
- **December 2007 (Protocol Version B):** In response to FDA recommendations; included the collection of LVEF historic values during and after adjuvant trastuzumab adjuvant treatment, LVEF assessments were added during follow-up and surveillance for Anti pertuzumab antibodies was increased.
- **June 23, 2009 (Protocol Version C):** 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 updated contraceptive requirements to align with ICH M3 guidelines.

Study Design:

The randomized trial was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. Key eligibility criteria included confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease. Breast tumor specimens were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were eligible if they had not been treated previously with chemotherapy and/or biologic therapy (including approved or investigational tyrosine kinase/ HER inhibitors or vaccines) for their metastatic disease. Patients were allowed prior adjuvant hormonal therapy and one line of hormonal therapy for metastatic disease. Baseline LVEF was required to be $\geq 50\%$. Patients were randomized 1:1 to receive placebo plus trastuzumab and docetaxel or pertuzumab plus trastuzumab and docetaxel. Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. Randomization was stratified by prior treatment

(prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia).

Figure 1 Study Design (from the clinical review)



Pertuzumab was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks thereafter. Patients were treated with Pertuzumab and trastuzumab until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was given as an initial dose of 75 mg/m² by intravenous infusion every 3 weeks for at least 6 cycles. The docetaxel dose could be escalated to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated.

The primary endpoint of the randomized trial was progression-free survival (PFS) as assessed by an independent review facility (IRF). PFS was defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment. 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 included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR) and duration of response.

As stated in the clinical review, Cleopatra is a well-designed trial with 'real time' PFS analysis by independent review facility. If the investigator determined progressive disease (PD) but the independent review facility (IRF) disagreed, patients were to continue with every 9 week tumor assessments until IRF determined progressive disease. In addition, once progressive disease was determined, the blind was maintained without cross-over. This trial design reduced informative censoring and reduced confounding variables in the PFS and OS analyses.

Statistical Analysis Plan:

The statistical analysis plan specified 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.

In order to detect a 33% improvement in median PFS (10.5 months in the control arm vs. 14 months in the experimental arm) or a hazard ratio of 0.75 at a two-sided significance level of 0.05 with 80% power and 1:1 randomization, a total of 381 IRF-assessed PFS events (corresponding to approximately 448 investigator assessed PFS events) were required.

No interim analysis of PFS was planned. An interim efficacy analysis of OS was planned and conducted at the time of the final PFS analysis. A Lan-DeMets alpha-spending function with an O'Brien-Fleming stopping boundary was used for the interim analysis of OS. The alpha for the interim OS analysis with cut-off date May 13, 2011 was 0.0012.

CLEOPATRA Efficacy Results:

The trial randomized 808 patients, 402 to the pertuzumab arm and 406 to the placebo arm, comprising the ITT population. The safety analysis excluded two patients in each arm that did not receive any study treatments. Patients were recruited at 204 centers in 25 countries. The study recruited patients from 25 countries. Approximately 37.9% patients were from Europe, 31.3% from Asia and 14.4% from the US. Majority of the patients were White (59.4%) and Asian (32.3%). The mean and median age of patients at randomization was 53.49 and 54 years, respectively, with an overall age range of 22 to 89 years. Approximately 16% of patients were elderly. Baseline demographics and treatment characteristics were well balanced between treatment arms with a slight imbalance in ECOG performance status that did not bias study results. Most of the patients (78%) had visceral disease and a small number (11%) had non measurable disease.

Approximately 47% of the patients previously received adjuvant or neo-adjuvant therapy including a small number of patients (11%) who received prior 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. Forty eight percent of the patients were hormone receptor positive (HR+) and only half of them (52%) received adjuvant hormonal therapy. and 78% had visceral disease at baseline.

PFS Results:

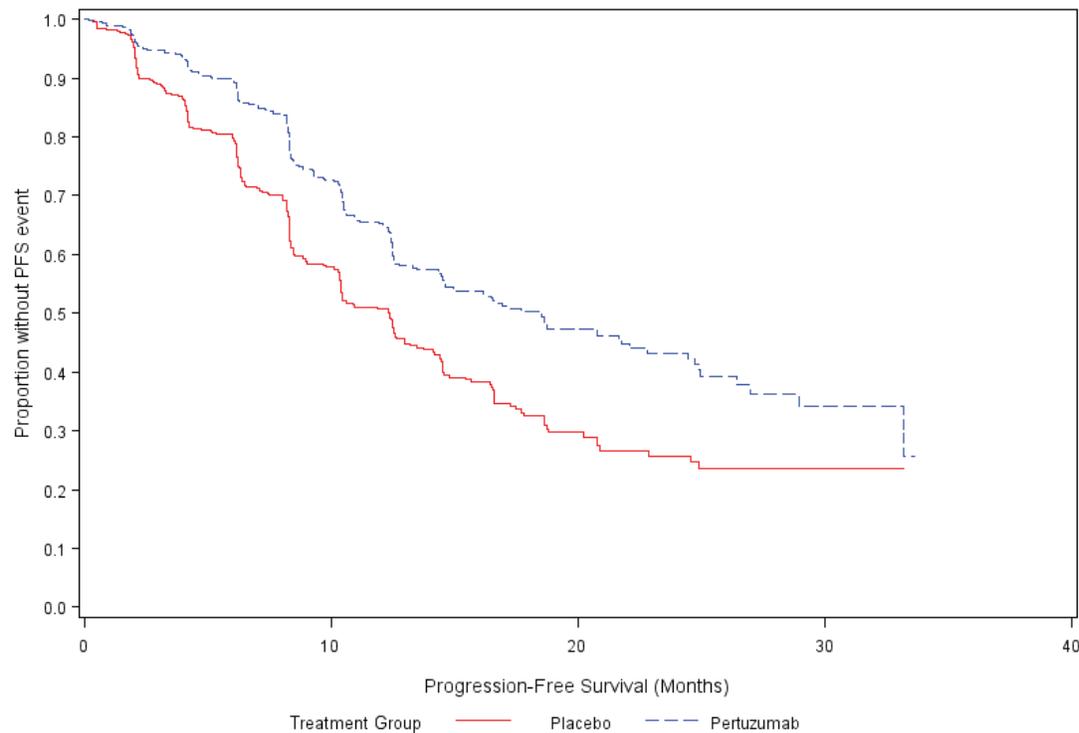
At the data cut-off date of May 13, 2011, 433 IRF-confirmed PFS events had occurred; 242 (60%) in the placebo arm. The CLEOPATRA trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab-treated group compared with the placebo-treated group [hazard ratio (HR) = 0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the pertuzumab-treated group vs. 12.4 months in the placebo-treated group) (Table 2 and Figure 2). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

Table 2 Summary of Efficacy from the Randomized Trial

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)				
No. of patients with an event	191 (47.5%)	242 (59.6%)	0.62	< 0.0001
Median months	18.5	12.4	(0.51, 0.75)	
Overall Survival (interim analysis)				
No. of patients with an event	69 (17.2%)	96 (23.6%)	0.64	0.0053*
Objective Response Rate (ORR)			(0.47, 0.88)	
No. of patients analyzed	343	336		
Objective response (CR + PR)	275 (80.2%)	233 (69.3%)		
Complete response (CR)	19 (5.5%)	14 (4.2%)		
Partial Response (PR)	256 (74.6%)	219 (65.2%)		
Median Duration of Response (months)	20.2	12.5		

Figure 2 Kaplan-Meier Plot of PFS in the ITT Population Based on IRF Assessment



PFS in Subgroups of Interest:

Dr Blumenthal looked at PFS in specific subgroups of interest. Patients who received prior (neo)adjuvant trastuzumab, patients who were HR+, patients with non visceral disease, black patients, and patients who received prior neoadjuvant or adjuvant systemic therapy. 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. 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. There was no apparent benefit in patients with non-visceral disease.

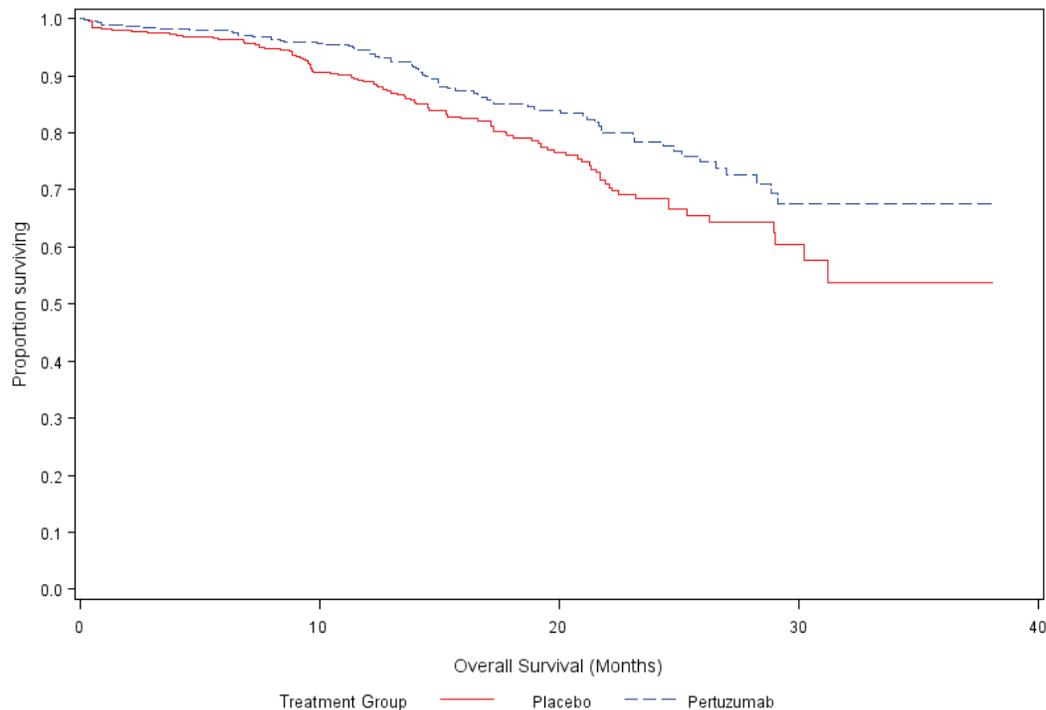
Table 3 WO20698 IRF-PFS analysis in sub-groups of interest (Reviewer Table)

IRF-PFS analysis in sub-groups of interest	HR (95% CI)	<u>Placebo</u> + T + D Median PFS	<u>Pertuzumab</u> + 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

OS Results:

At the May 2011 cut-off, a planned interim OS analysis was performed, comprising 43% of the events planned at the final analysis. At the time of the planned interim analysis, 165 patients had died; 96 deaths (24%) on the placebo arm compared to 69 deaths (17%) on pertuzumab arm. 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 2 and Figure 3). There was no statistically significant difference between treatment arms with respect to OS (log-rank test stratified by prior treatment status and region, nominal two-sided p-value 0.0053). The p-value did not cross the O'Brien-Fleming boundary (0.0012).

Figure 3 Kaplan-Meier Plot of OS in the ITT Population at the Interim Analysis



Objective Response Rate:

Pertuzumab improved ORR is consistent with the PFS and interim OS results. The IRF assessed objective response rate was 69% in the placebo arm and 80% in the pertuzumab arm. The ORR by investigator assessment was 68% placebo and 77% pertuzumab, respectively.

SUPPORTIVE STUDIES

Neosphere (WO20697):

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.

Study BO17929:

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.

7. Safety

The safety database for pertuzumab was adequate to characterize the safety of this product for the proposed indication. 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.

The most common adverse reactions (> 30%) seen with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%). The safety data from study WO20698 are provided in the table below.

Table 4 Body System/Adverse Reactions PERJETA

Body System/Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407		Placebo + trastuzumab + docetaxel n=397	
	Frequency rate %		Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3

Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5
Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5
Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab. In study WO20698, pertuzumab in combination with trastuzumab and docetaxel was not associated with an increased incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel. Left ventricular dysfunction occurred in 4.4% of patients in the pertuzumab-treated group and 8.3% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1.0% of patients in the pertuzumab-treated group and 1.8% of patients in the placebo-treated group.

Infusion Associated Reactions, Hypersensitivity Reactions/Anaphylaxis

Pertuzumab has been associated with infusion and hypersensitivity reactions. In study WO20698, an infusion reaction was defined as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The overall frequency of infusion reactions was 13.0% in the pertuzumab-treated group and 9.8% in the placebo-treated group, with the majority being mild or moderate. The most common infusion reactions were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. The overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the pertuzumab-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the pertuzumab-treated group and 2.5% in the placebo-treated group. Overall, 4 patients in pertuzumab-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

Deaths

In study WO20698, there were 8 deaths in the pertuzumab arm and 10 in the placebo arm within 30 days of study treatment. One subject randomized to each treatment arm, died prior to institution of study therapy. Most 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.

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”. 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.

8. Advisory Committee Meeting



There were no controversial issues identified by the review team that would have benefitted from an advisory committee discussion.

9. Pediatrics

Pertuzumab has not been studied in children.

The review for Pertuzumab was conducted by the PeRC PREA Subcommittee on February 22, 2012. The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population, which is indicated for the treatment of patients with 1st line HER2-positive metastatic breast cancer. The PeRC agreed with the Division to grant a full waiver for this indication.

10. Other Relevant Regulatory Issues

The patent exclusivity has not been determined at the time of this review. This determination will need to be taken to the CDER Exclusivity Board after the BIC discussion. This decision and process will set precedent for biologic reference product exclusivity so there is a need to have agreement from involved parties.

The OSI inspected three of the highest accruing sites, two in South Korea, and one in Brazil. The inspectional findings revealed no significant deviations that would preclude the use of the clinical data provided in support of this BLA.

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).

There were no financial conflicts of interest identified by any investigator as defined in 21 CFR 54.2(a), (b), and (f).

11. Labeling

There were extensive internal labeling discussions with all review disciplines. The rationale for rejection of labeling recommendations by DDMAC reviewers were verbally provided at these meetings.

Key clinical labeling recommendations included:

Labeling changes to address the potential for embryo-fetal toxicity:

- Add a ‘boxed warning’ regarding embryo-fetal harm.

WARNING: EMBRYO-FETAL TOXICITY

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.6)

- Warnings and Precautions: Added a new section on Embryo-Fetal Toxicity.
- Pregnancy Category D was added.
- Patient Counseling Information: included a section advising females of reproductive potential.

Febrile Neutropenia in Asians:

- In section 6.1, add data regarding the increased incidence of febrile neutropenia in Asian patients.

Additional efficacy information:

- Section 14.1, added 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.
- Section 14.1, added the subgroup PFS data on prior neo/adjuvant trastuzumab, hormone receptor positive and negative patients, and patients with non-visceral disease.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend that this BLA be approved for the following indication:

“PERJETA is a HER2/neu receptor 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”

- Risk Benefit Assessment

The current recommendation for full approval is based on a statistically significant and clinically meaningful, 6.1 month improvement in median progression-free survival (PFS) observed in patients receiving pertuzumab compared to those receiving placebo [HR 0.62 (95% CI: 0.51, 0.75; $p < 0.0001$)]. The large magnitude of PFS improvement is robust based on the consistency of the finding across relevant subgroups supported by patient demographics and tumor prognostic characteristics. Efficacy is supported by evidence of anti-tumor activity with a large

objective tumor response (80%) and an early analysis of OS suggests an improvement in OS. At the time of PFS analysis, a planned interim analysis for OS showed an improvement in OS [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053]. However, the HR and p-value for the interim analysis of OS did not meet the pre-defined stopping boundary (HR < 0.603, p < 0.0012).

The pertuzumab PFS benefit was preserved in the subgroup of patients (11%) who had prior adjuvant trastuzumab (HR=0.62, 95% CI: 0.35, 1.07). Most patients in the United States are diagnosed with early breast cancer and are treated with adjuvant trastuzumab-based therapy for HER2+ disease. Therefore, the study results appear applicable to the United States population.

Additionally, efficacy results from the pivotal study are further supported by two Phase 2 studies: NEOSPHERE and BO17929. In NEOSPHERE (randomized study), the observed 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 BO17929 (single-arm study), in trastuzumab-resistant HER2+ MBC, the ORR of combination trastuzumab and pertuzumab was 24% compared to an ORR of 3% with pertuzumab monotherapy, and an ORR of 18% with the combination of trastuzumab and pertuzumab, in patients progressing on both antibodies.

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.

Regarding CMC issues, the review team is concerned about [REDACTED] (b) (4) problems which could affect Genentech's ability to manufacture pertuzumab, and their ability to continue to supply pertuzumab after it is launched. The Office of Manufacturing and Product Quality in CDER's Office of Compliance has recommended that we withhold approval of BLA 125409 (May 31, 2012 memorandum from Shawn Gould). Qualification lots of pertuzumab were successfully manufactured in 2010, and based on the Sponsor's estimates, a [REDACTED] (b) (4) supply exists for patients.

We have consulted with CDER's Office of Compliance regarding the inspectional findings of OMPQ. Ilisa Bernstein, Acting Director of the Office of Compliance, has reported that the problems observed during the 2012 campaign were not observed during the inspection with respect to the 2010 campaign. She further reported that there were no observations made during the 2012 inspection that would lead us to believe there were any significant issues with the 2010 campaign. In addition, she reported the previous GMP surveillance inspection of this manufacturing facility was conducted by FDA's San Francisco District Office in June 2010. No form FDA 483 was issued, and the inspection was classified as no action indicated (NAI).

The Agency generally requires that the validation of the manufacturing process for a drug product be fully complete before approval of an application. In this case, we are taking the unusual step of approving only pertuzumab that contains drug substance from Genentech's 2010 campaign prior to completion of the full demonstration of process validation for all pertuzumab manufacturing. We are approving this application in this manner based on: (1) our determination

that product from the 2010 campaign meets all applicable requirements with respect to safety, purity, and potency; (2) that the (b)(4) problems in the 2012 campaign were not observed with the 2010 campaign, and no other significant issues were observed with respect to the 2010 campaign, and the facility received an NAI in 2010; (3) the applicant's commitment to undertake several steps to expeditiously resolve the (b)(4) problem; (4) the applicant's commitment to reduce and mitigate the risk of a drug shortage; and (5) our clinical determination that a compelling exigent public health need outweighs the risk of a future interruption in the drug's availability. The 6.1 month improvement in median PFS shown in the CLEOPATRA study suggests a meaningful clinical benefit to patients. Pertuzumab is the first dual antiHER2 therapy to be approved for the treatment of first line metastatic breast cancer, and we would not like to delay its availability to patients pending resolution of CMC issues pertaining to production after the 2010 campaign. The marketing of additional production campaigns, including the 2012 campaign that experienced the (b)(4) problems, will be subject to further approval.

Steps to ensure a consistent drug supply and manufacturing process are (b)(4)

[REDACTED]

In conclusion, pertuzumab when added to trastuzumab and docetaxel in front-line HER2+ MBC (the first dual antiHER2 therapy in first-line metastatic breast cancer), demonstrates a favorable risk-benefit profile.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
The clinical review team believes that a REMS is not required for this product for the requested indication. When administered in accordance with product labeling, it is anticipated that the risks of Pertuzumab will be tolerable and manageable. There are no unusual risks which required training to assure safe use, given that this therapy is generally prescribed and administered only by healthcare professionals with specific training and experience in medical oncology and use of agents with similar toxicities.
- **Recommendation for other Postmarketing Requirements and Commitments**

Post-Marketing Requirement Under Section 505(o) of the FD&C Act

1. Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-

containing regimen within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

The timetable you submitted on May 16, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2012
Final Protocol Submission:	08/2012
Interim Report #1:	08/2013
Interim Report #2:	08/2014
Interim Report #3:	08/2015
Interim Report #4:	08/2016
Interim Report #5:	08/2017
Interim Report #6:	08/2018
Interim Report #7:	08/2019
Interim Report #8:	08/2020
Interim Report #9:	08/2021
Interim Report #10:	08/2022
Study Completion:	08/2022
Final Report Submission:	08/2023

Rationale for required PMR:

Animal studies suggest that exposure to pertuzumab during pregnancy can result in oligohydramnios, delayed renal development, and embryo-fetal death. There are 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.

Post-Marketing Commitments

2. Provide a plan for responding to potential pertuzumab shortages. The plan should address your proposed response to a potential or actual shortage situation if inventory falls below a six month supply, if attempts to re-establish the pertuzumab manufacturing process are unsuccessful, and/or if demand is greater than anticipated. The plan should include proposed communications to the press, health care professionals, and patients and a description of how these communications will be disseminated. In addition, you must propose a mechanism for ensuring that patients who are already receiving pertuzumab can continue to be treated according to the agreed-upon package insert.

The timetable you submitted on June 8, 2012, states that you will complete this plan according to the following schedule:

Draft Plan Submission:	07/2012
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Final Plan Submission: 09/2012

Rationale for PMC:

The sponsor needs a plan for responding to potential pertuzumab shortage if attempts to re establish the pertuzumab manufacturing process are unsuccessful or if demand is greater than anticipated.

3. Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. The stressed stability testing must be performed prior to release of drug substance arising from thaws #4 and #6 to support comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, one lot of drug substance and drug product arising from both thaws #4 and #6 must be placed on real time stability monitoring. Provide a root cause analysis relating to poor cell growth and viability of the Q1/Q2 2012 pertuzumab campaign. Submit the results of the stressed stability study and a root cause analysis in the Interim Report. Submit the Interim and Final Reports as Prior Approval Supplements (PAS).

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Interim Report:	09/2012
Study Completion:	10/2014
Final Report:	12/2014

Rationale for PMC:

Cell growth characteristics can alter product quality attributes. To support comparability of these batches of drug substance to those from the 2010 manufacturing campaign, (b) (4) from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign should be assessed in (b) (4) stability studies.

4. Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Drug substance testing that is part of this qualification must include standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4), ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the 2012 MCB campaign must be placed into the annual drug substance and drug product stability programs. Perform concurrent release of process performance qualification (PPQ) batches as per FDA guidance for industry Process Validation: General Principles and Practices. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this

study and submit monthly independent reports between now and approval of the first PAS. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2012
Final Report Submission:	02/2013

Rationale for PMC:

The pre-approval inspection of the Vacaville drug substance manufacturing site showed that the Sponsor is no longer able to consistently manufacture pertuzumab drug substance from working cell bank (WCB) (b) (4). Additional investigations showed consistent failures in the (b) (4) and subsequent propagation from WCB (b) (4). Those cultures that did survive exhibited (b) (4). The root cause of the cell culture failures is unknown. Production of monoclonal antibodies from cell cultures with (b) (4) can result in product with different quality attributes, which can impact product efficacy and safety. Product quality attributes can be managed by maintaining the manufacturing process in a state of control. Data provide by sponsor to date are not consistent with a validated commercial process. The Sponsor is working on 3 concurrent plans to resolve the cell growth issues associated with manufacturing: 1) manufacturing from the MCB (PMC #3); 2) developing a new WCB and manufacturing from this new WCB (PMC #4); and 3) manufacturing using a modified process from WCBs including (b) (4) (PMC #5). Process validation data are required for drug substance generated by each of these strategies.

5. Conduct a process validation study to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced from the new WCB must include analysis of the percent G0-F, ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the new WCB campaign must be placed into the annual drug substance and drug product stability programs. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	09/2014
Final Report Submission:	10/2014

Rationale for PMC:

In order to assure that new manufacturing processes (MCB, new WCB and modified WCB) are able to deliver consistent product with comparable strength, quality, purity and potency to that which was used in the Phase III clinical studies, it is necessary for the sponsor to perform process performance qualification. In addition, to ensure sufficient future cell bank stocks, a new working cell bank must also be developed.

6. Conduct process validation studies to support manufacture of pertuzumab from Working Cell Banks by a modified process (b) (4) in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced by the (b) (4) process must include analysis of the pertuzumab glycosylation profile, (b) (4), ADCC activity, and purity by non-reduced CE-SDS. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	10/2015
Final Report Submission:	11/2015

Rationale for PMC:

As described above, in order to assure that new manufacturing processes, it is necessary for the Sponsor to perform process performance qualification.

7. Conduct stability studies of the MCB at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Interim Report 1:	06/2016
Interim Report 2:	06/2020
Interim Report 3:	06/2024
Interim Report 4:	06/2028
Final Report Submission:	06/2032

Rationale for PMC:

The MCB is a critical source material for ensuring the availability of a continued supply of pertuzumab. Currently, stability testing of the MCB is required once every 10 years.

However, data pointing towards instability of pertuzumab WCB (b) (4) have raised concerns about the stability of this cell line. In order to ensure a continued source material from which to generate future pertuzumab WCBs, a protocol ensuring more frequent MCB stability testing should be submitted. Given the criticality of this source material to future supply of commercial product, this should be a PMR and not a PMC.

8. Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/ 2014
Final Report Submission:	03/2015

Rationale for PMC:

An assessment of release and stability specifications requires long-term data. This is a standard post-approval assessment that needs to be performed as part of the life cycle approach to manufacturing.

9. Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	07/2013
Final Report Submission:	09/2013

10. Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab (b) (4) and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. The control strategy must be updated to include ADCC activity and the drug substance release specifications must be updated to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, the (b) (4) manufacturing process will need to be updated to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	02/2013
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Final Report Submission: 03/2013

Rationale for PMC:

The proposed control strategy for pertuzumab does not include ADCC activity, which is potentially relevant to both the safety and efficacy of the product. Drug substance release testing will need to be revised to provide sufficient control of ADCC activity. In addition, as (b) (4) operations appear to be critical in controlling (b) (4), and this attribute is tightly linked to ADCC activity, the (b) (4) manufacturing process will need to be updated to include parameters, and their ranges, required to meet the revised drug substance specifications for ADCC activity.

11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2012
Study Completion:	12/2012
Final Report Submission:	02/2013

Rationale for PMC:

The data in the submission for this testing was performed using cells from reduced scale models. Because of concerns regarding the models not being representative of the commercial process, it was determined that this testing would need to be done on cells from the commercial scale process.

12. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). Submit the Final Report as a Changes Being Effected-0 (CBE-0).

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Study Completion:	07/2012
Final Report Submission:	12/2012

Rationale for PMC:

The requalification studies of the bioburden test need to use product samples generated at the next product campaign. The bioburden test was qualified using (b) (4) instead of USP strains. In addition, the sample volumes used in the qualification study were

not what is used in routine testing. The bioburden test needs to be requalified using the USP strains and correct sample volumes.

13. To evaluate the risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	08/2013
Final Report Submission:	12/2013

Rationale for PMC:

The validation studies of non-sterile cell culture media hold time need to be conducted during the next product campaign. (b) (4)

(b) (4) The non-sterile cell culture media hold time needs to be revalidated to demonstrate adequate microbial control.

14. To evaluate the risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of discontinuing the (b) (4), the screening of raw materials for (b) (4) bioburden and endotoxin, (b) (4) the non-sterile media hold time and temperature (b) (4) and the expanded use of (b) (4). Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Final Report Submission:	03/2013

Rationale for PMC:

The firm needs to analyze long-term data and possibly conduct studies to provide input to the risk assessment. (b) (4)

15. Conduct a clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive

metastatic breast cancer population. Study MO27775 (PERTAIN) as designed will be completed to fulfill this post-marketing commitment.

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2012
Trial Completion:	09/2016
Final Report Submission:	03/2017

Rationale for PMC:

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.

16. Submit the final overall survival (OS) analysis of trial WO20698/TOC4129g as defined in your protocol and Statistical Analysis Plan (SAP).

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2012
Trial Completion:	12/2013
Final Report Submission:	05/2014

Rationale for PMC:

The final results of this study will provide more complete information on the efficacy of pertuzumab in the indication population.

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/s/

PATRICIA CORTAZAR
06/08/2012