CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	June 8, 2012
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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:	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers/ Team Leaders**
Regulatory Project Manager	Amy Tilley/Alice Kacuba
Division Director	Robert Justice, MD, MS
CDTL	Patricia Cortazar, MD
Medical Officer Reviewers	Gideon Blumenthal, MD (efficacy) Nancy Scher, MD (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

1. Introduction

Genentech submitted an original biologic license 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.

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).

The clinical trial supporting this BLA is a single Phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (US study number TOC4129g, CLEOPATRA). Two additional supportive Phase 2 trials (NEOSPHERE and BO17929) were submitted by the applicant.

CLEOPATRA demonstrated a 6.1 month improvement in progression free survival (PFS), and an early analysis of survival suggests a potential improvement in overall survival. The effect on PFS was consistent across relevant subgroups and 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 were transient (diarrhea, rash, and mucositis) and reversible myelotoxicity. No additive cardiac toxicity with the addition of pertuzumab to docetaxel and trastuzumab was observed; and the incidence of cardiotoxicity was lower in the pertuzumab treatment arm.

2. CMC

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.

The pertuzumab manufacturing process includes a standard cell culture process (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 during the 2012 manufacturing campaign. 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 telecons (1-2 per week) with Genentech to gain an understanding of the scope, impact and potential for resolution of the observed failure rate of the 2012 working cell bank thaw. Review issues have focused on impact to product quality and process consistency. Discussions have focused on data required to address FDA concerns, and the time frame of data submission. This was approached with the initial understanding that the problem was limited to the 2012 working cell bank thaw and (b) (4).

In April 2012, Genentech agreed to a three-pronged action plan recommended by the FDA, as follows:

- Extended characterization of drug substance derived from the 2012 campaign (to evaluate risks to product quality associated with (b) (4) 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)
- Confirm stability of the master cell bank. This is a critical source material, as it is the origin of all future working cell banks; if both the master cell banks and the working cell banks are not stable, there could be no future source of pertuzumab.

(b) (4)

The initial and continued major concern is whether Genentech 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. However, qualification lots of pertuzumab were successfully manufactured in 2010, and based on the sponsor's estimates, a (b) (4) supply (derived from a 2010 production) exists for patients.

3. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology reviewers have concluded that there are no outstanding clinical pharmacology issues that preclude approval and that no additional pharmacology/toxicology studies are needed to support approval.

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 repeat-dose toxicity studies in cynomolgus monkeys. Pertuzumab appeared to be well-tolerated in monkeys. In the pertuzumab single dose toxicity study, no treatment-related effects or abnormal clinical signs were 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.

There were no remarkable cardiotoxicity treatment-related effects in monkeys during the 6-month, repeat-dose toxicity study with pertuzumab.

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. 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 lumber vertebra. 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 postmarketing pregnancy registry to collect clinical data on oligohydramnios risk.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewers 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 linear PK for pertuzumab at doses ranging from 2 to 25 mg/kg with a half-life of about 18 days. A maximum tolerated dose was not identified. 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 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 and moderate renal impairment were similar to those in

patients with normal renal function. No dose adjustment can be recommended for patients with severe renal impairment 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 recommend pertuzumab approval from a product quality microbiology perspective with three PMCs. See action letter for PMCs.

The BLA is not recommended for unrestricted 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 issues that will be resolved through PMCs include the (b) (4) the requalification of bioburden test.

6. Clinical/Statistical- Efficacy

This BLA is primarily supported by results from a single Phase 3 (N=808), randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (CLEOPATRA, US study number TOC4129g).

Two additional supportive clinical studies were also submitted: NEOSPHERE/Study TOC4129g (a 4 arm trial in neoadjuvant setting) 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 EP	Status
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 Efficacy Results:

The trial randomized 808 patients, 402 to the pertuzumab arm and 406 to the placebo arm, comprising the ITT population. 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 neoadjuvant 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:

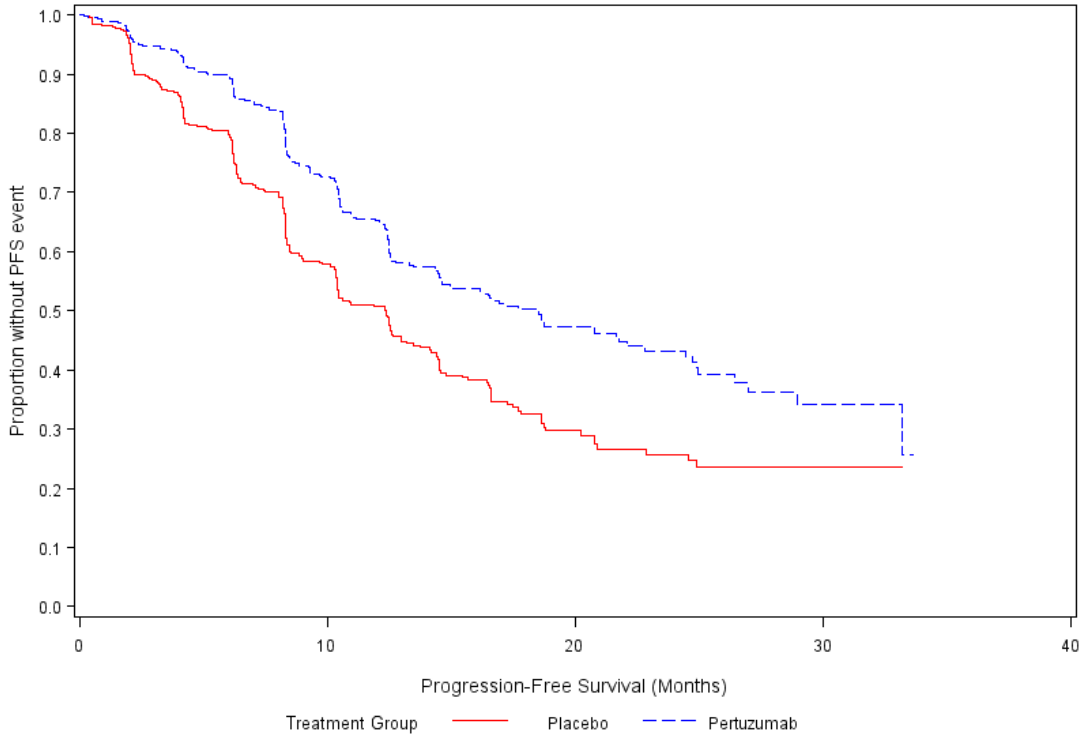
The CLEOPATRA trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab-treated group compared with the placebo-treated group [hazard ratio (HR) = 0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the pertuzumab-treated group vs. 12.4 months in the placebo-treated group) (Table 2 and Figure 2).

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 (0.47, 0.88)	0.0053*
Objective Response Rate (ORR)				
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 1 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 neoadjuvant 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. There was no apparent benefit in patients with non-visceral disease.

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

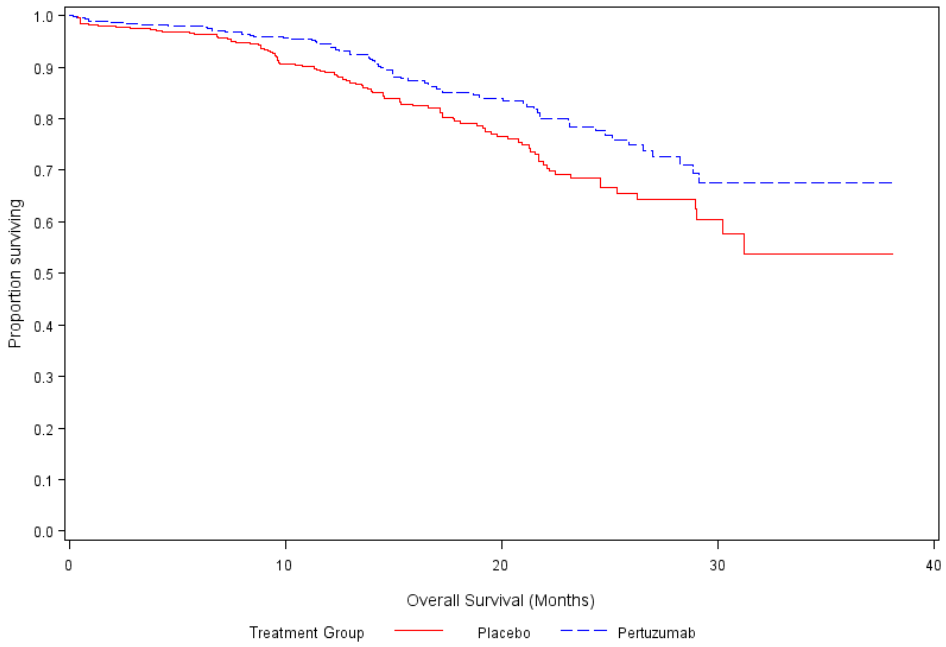
IRF-PFS analysis in sub-groups of interest	HR (95% CI)	Placebo + T + D Median PFS	Pertuzumab + T + D Median PFS
ITT n=808	0.62 (0.51;0.75)	12.4 months	18.5 months
HR+ n=388	0.72 (0.55;0.95)	14.4 months	17.2 months
Prior trastuzumab n=88	0.62 (0.35;1.07)	10.4 months	16.9 months
Black n=30	0.64 (0.23;1.79)	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

OS Results:

An early analysis of OS suggests a potential improvement in 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. 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 ($p \leq 0.0012$) (Table 2 and Figure 3).

Figure 2 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 tolerable in light of pertuzumab's benefits. 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%).

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.

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 clinical 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. The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population. The PeRC agreed with the Division to grant a full waiver for this indication.

10. Labeling

Labeling addressed the potential for embryo-fetal toxicity as described below:

- 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.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.

- Risk Benefit Assessment

The current recommendation for 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 a potential improvement in OS. At the time of PFS analysis, a planned interim analysis for OS showed a potential 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 $\leq$ 0.603, p $\leq$ 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 tolerable considering the benefits of pertuzumab.

This application will be granted regular approval, rather than accelerated approval, because the 6.1 month magnitude of improvement in median PFS, the primary endpoint in the CLEOPATRA trial, is considered a direct clinical benefit to patients. Furthermore, these findings are robust with an early analysis showing a potential improvement in overall survival, and we do not have concerns about the design or conduct of the CLEOPATRA trial.

Regarding CMC issues, the review team is concerned about the (b) (4) problems that occurred in the 2012 campaign, 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, (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 drug product 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. This is the first dual antiHER2 therapy (pertuzumab, trastuzumab, docetaxel) 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 outlined in the post-marketing requirement and commitments that the company has agreed to undertake. These include 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. Genentech has agreed that the drug shortage plan will include communications to healthcare providers and patients, and it also will include a mechanism for ensuring that patients who are already receiving pertuzumab can continue to be treated according to the product label. Specific postmarketing requirements include conducting process validation studies under third party oversight to support further manufacture of pertuzumab.

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. In addition, review staff including Dr. Robert Justice, Dr. Patricia Cortazar, Dr. Gideon Blumenthal, and Dr. Nancy Scher recommend approval of this application, and I concur with their recommendation. This application will be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter for Postmarketing Requirements and Commitments.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
06/08/2012

RICHARD PAZDUR
06/08/2012