CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s051

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 25, 2013
DDOP Clinical Team Leader	Patricia Cortazar, M.D.
BLA	s125409/51
Applicant	Genentech, Inc
Date of Submission	April 30, 2013
PDUFA Goal Date	October 31, 2013
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 as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer
Recommended:	*Accelerated Approval*

Material Reviewed/Consulted	Names of discipline reviewers/ Team Leaders
Regulatory Project Manager	Amy Tilley/Alice Kacuba
Medical Officer Reviewers	Laleh Amiri-Kordestani, M.D. (efficacy) Suparna Wedam, M.D. (safety)
Statistical Review	Lijun Zhang/ Shenghui Tang
Clinical Pharmacology Review	Pengfei Song/ Qi Liu Kevin Krudys
OPDP	Marybeth Toscano/ Jessica Cleck-Derenick
OSI	Lauren Iacono-Connor/Janice Pohlman

Introduction

Genentech, Inc. submitted a supplemental biologic licensing application (BLA) to support marketing approval of Perjeta® (pertuzumab) in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival. This document summarizes the reviews and conclusions of each review discipline.

Currently there are no FDA approved agents for the preoperative (neoadjuvant) treatment of early breast cancer. This is the first application for a breast cancer neoadjuvant indication.

The review team recommends accelerated approval of this supplement based on a favorable benefit-risk profile for pertuzumab when added to trastuzumab and docetaxel as part of a neoadjuvant regimen in HER2-positive, locally advanced, inflammatory or early breast cancer.

The current recommendation for accelerated approval is based on the totality of the pertuzumab data and the unique features in this application. In the main neoadjuvant trial (NEOSPHERE) that supports this application, a demonstration of a statistically significant improvement in pCR rate was observed in patients receiving pertuzumab plus trastuzumab and docetaxel (39.3% pCR rate) compared to those receiving trastuzumab plus docetaxel (21.5% pCR rate). This difference of 17.8% was statistically significant (adjusted p-value = 0.0063, Cochran-Mantel-Haenszel test). The demonstration of an improvement in pathological complete response (pCR) rate in the NEOSPHERE trial is also supported by the pCR data from the TRYPHAENA trial. Most importantly, pertuzumab is an active agent already approved for the treatment of HER2-positive metastatic breast cancer, with a highly significant and clinically robust improvement in overall survival, which may exceed 10 months, and a statistically significant and substantial improvement in PFS. In addition, the toxicity profile of pertuzumab, when added to trastuzumab and docetaxel, was acceptable; major toxicities are transient (diarrhea, nausea, and mucositis) and reversible myelotoxicity. There was an increased rate of LVEF decline observed in the neoadjuvant studies with the addition of pertuzumab but it was mostly reversible.

No data are available demonstrating improvement in event-free survival or overall survival with pertuzumab treatment in the early breast cancer setting. Therefore, continued approval for this indication will be contingent upon demonstration of improvement in disease-free survival in the confirmatory trial (APHINITY), which is currently fully accrued.

1. Background

Pertuzumab is a monoclonal antibody that targets the extracellular domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab was approved in June 2012 and is indicated for use 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.

On June 8, 2012, FDA approved pertuzumab (PERJETA®) 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. (See Clinical Section for details on the CLEOPATRA Trial)[5].

Neoadjuvant Breast Cancer Treatment

New agents to treat breast cancer have historically been approved first in the metastatic setting, with approval for use in early-stage breast cancer following many years later based upon the results of large randomized adjuvant trials with prolonged follow-up. Neoadjuvant trials, in which systemic therapy is delivered prior to definitive breast cancer surgery, permit rapid assessment of drug efficacy and could expedite development and approval of treatments for early-breast cancer.

Despite advances in systemic therapy of breast cancer, there remains a need to expedite drug development and approval of highly effective therapies for patients with high-risk early-stage breast cancer. To improve the current drug development paradigm and to expedite approvals of treatments for early-stage breast cancer, the FDA decided to open a regulatory pathway for approval of agents in the neoadjuvant breast cancer setting. To learn about the endpoint that could support approval in neoadjuvant breast cancer, the FDA established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). Using primary source data from nearly 12,000 patients enrolled in neoadjuvant randomized controlled trials with pCR clearly defined and at least 5 years of follow-up available, FDA performed a pooled-analysis to assess the relationship between pCR and long-term outcome [1]. In addition, the FDA published a Draft Guidance for Industry, outlining a pathway for future neoadjuvant breast cancer trials intending to use pathological complete response (pCR) to support accelerated approval [2,3]. These issues were also extensively discussed on March 22, 2013, at the "Innovations in Breast Cancer Drug Development – Neoadjuvant Breast Cancer Workshop"[4].

2. CMC/Device

The pertuzumab manufacturing process is described in Genentech's BLA 125409 (see prior BLA review for details).

3. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology information was submitted with this sBLA.

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. Genentech submitted new PK data from the NEOSPHERE trial and the results of an exposure response analysis. The population PK analysis results suggested no PK differences based on age, ethnicity or disease status (neoadjuvant compared to the metastatic population from the CLEOPATRA trial).

5. Clinical/Statistical- Efficacy

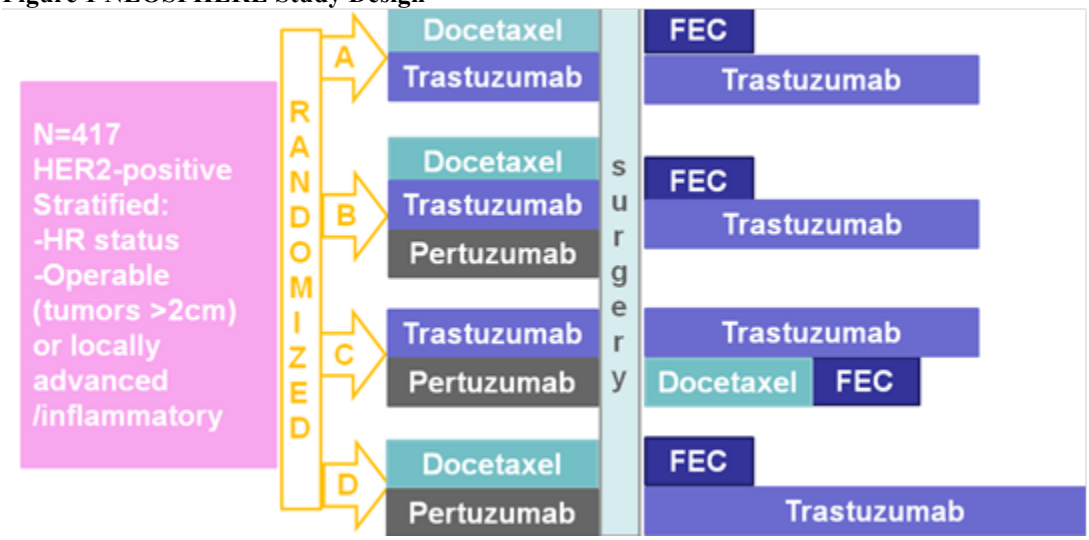
This BLA is primarily supported by results from a single industry-sponsored study, NEOSPHERE (WO20697), entitled:
"A randomized, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer"

Two additional supportive clinical studies were submitted by the applicant: TRYPHAENA (BO22280), a 3-arm neoadjuvant trial and CLEOPATRA (WO20698), a Phase 3 trial in first line HER2-positive metastatic breast cancer that supported the initial approval of pertuzumab.

Study Design:

The main study supporting this efficacy supplement is NEOSPHERE (WO20697), a multicenter, randomized trial designed to evaluate four neoadjuvant regimens in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d). Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery: trastuzumab plus docetaxel, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel (Figure 1). The main comparison for this sBLA review is trastuzumab plus docetaxel (control) vs. pertuzumab plus trastuzumab and docetaxel (experimental). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. The primary endpoint of the study was pathological complete response (pCR) rate defined as absence of invasive cancer in the breast (ypT0/is).

Figure 1 NEOSPHERE Study Design



FEC=5-FU, epirubicin, and cyclophosphamide

Pertuzumab was administered by intravenous (IV) infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks for a total of 4 cycles. Following surgery, all patients received 3 cycles of FEC given IV every 3 weeks and trastuzumab administered IV every 3 weeks to complete 1 year of therapy.

The NEOSPHERE study efficacy results are summarized in Table 1. Statistically significant improvements in pCR rates were observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 1: Summary of Efficacy from NEOSPHERE

Endpoint/Study Population	H + T	Ptz + H + T	Ptz + H	Ptz + T
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n (%) [95% CI][2]	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)
Hormonal receptor-positive subgroup	**N=50**	**N=50**	**N=51[4]**	**N=46**
pCR[1], n (%) [95% CI] 2	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormonal receptor-negative subgroup	**N=57**	**N=57**	**N=55[4]**	**N=50**
pCR[1], n (%) [95% CI] [2]	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13(26.0%) [14.6, 40.3]

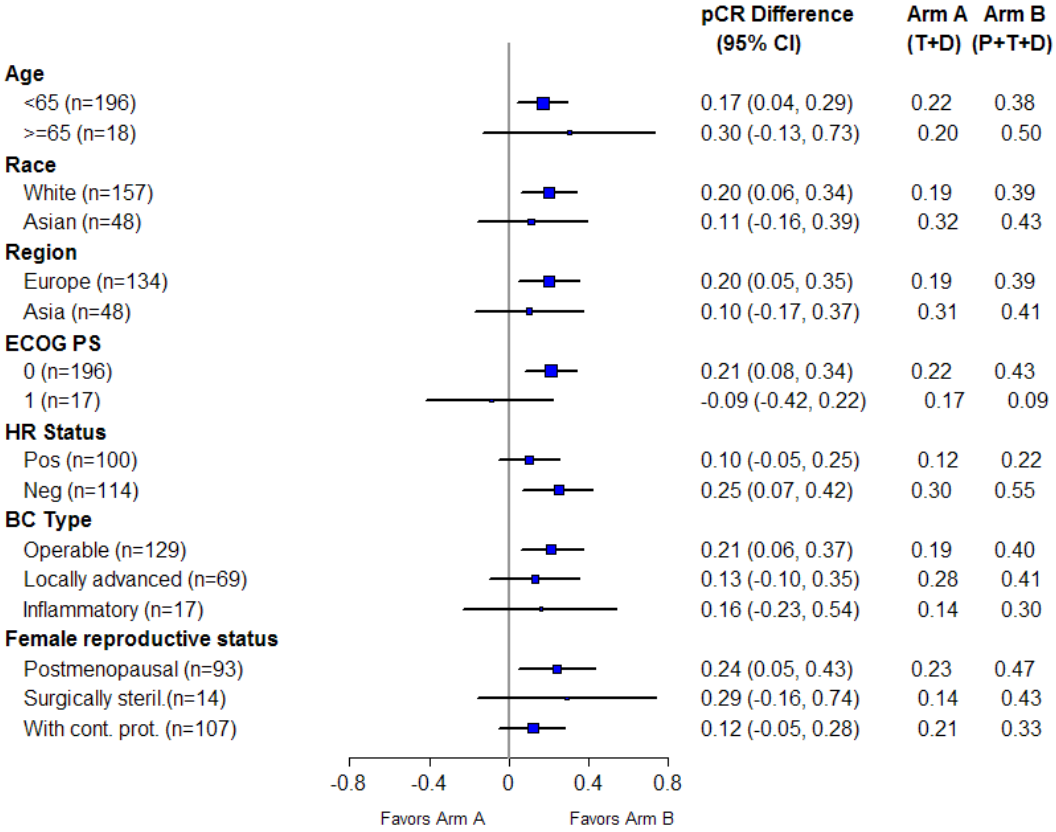
T=docetaxel, Ptz=pertuzumab, H=trastuzumab, CI=Confidence Interval

[1] ypT0/isypN0, [2] 95% CI for one sample binomial using Pearson-Clopper method. [3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment

[4] One patient had unknown hormonal receptor status. The patient did not achieve a pCR.

Consistent improvements in pCR rates were observed across several patient subgroups including age, race, geographic region, breast cancer type (operable, locally advanced and inflammatory) and hormone-receptor status. The pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors. This finding is consistent with the results from several trials (CLEOPATRA, EMILIA, NEOALTTO) including the CTNeoBC meta-analysis, in which patients with HER2-positive/hormone-receptor-positive tumors do not appear to benefit to the same extent as patients with HER2-positive/hormone-receptor-negative tumors. Pre-clinical models have demonstrated continued cross-talk between the estrogen and HER2 receptors. Therefore, the therapeutic benefit of concurrent blocking of the HER2 and estrogen receptors in patients with HER2-positive/hormone-receptor-positive breast cancer to improve outcomes needs to be addressed in future trials

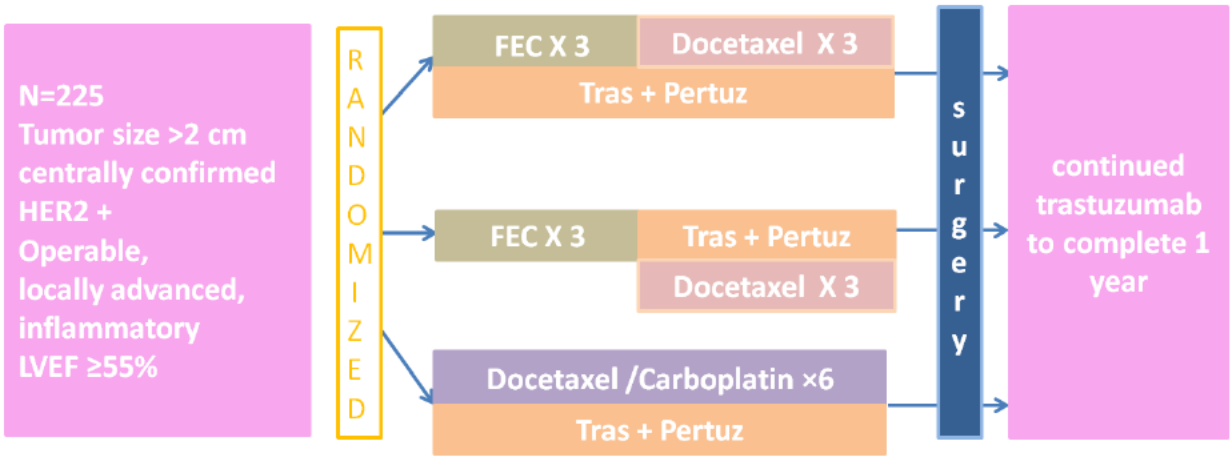
Figure 2 NEOSPHERE Forest plot pCR (ypT0/is ypN0) (From FDA Statistical Reviewer Dr. Zhang)



Neoadjuvant Supportive Trial: TRYPHAENA (BO22280)

TRYPHAENA (BO22280) is a randomized Phase 2 study conducted in 225 patients with HER2-positive, locally advanced, operable, or inflammatory (T2-4d) breast cancer (Figure 3). Patients were randomized to receive 1 of 3 neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with pertuzumab and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, or 6 cycles of TCH in combination with pertuzumab. The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. Secondary endpoints were pCR rate in the breast (ypT0/is), DFS, PFS, and OS.

Figure 3 TRYPHAENA Study Design



FEC=5-FU, epirubicin, and cyclophosphamide; tras=trastuzumab; Pertuz=Pertuzumab

Higher pCR rates were observed in the 3 pertuzumab treatment arms compared to the NEOSPHERE trial possibly due to the incorporation of the anthracycline regimen preoperatively. The results were consistent using the two pCR definitions (ypT0/is and ypT0/isypN0) (Table 2 Summary of Efficacy from TRYPHAENA (FDA table)). Similar to the NEOSPHERE study results, the pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 2 Summary of Efficacy from TRYPHAENA (FDA table)

	FEC x 3→T x 3 Ptz + H x 6	FEC x 3→T x 3 + Ptz+H x 3	TCH x 6 + Ptz x 6
	N= 73	**N= 75**	**N= 77**
pCR[1], n (%) **95% CI**	45 (61.6%) [49.5, 72.8]	43 (57.3%) [45.4, 68.7]	51 (66.2%) [54.6, 76.6]
pCR[2] , n (%) **95% CI**	41 (56.2%) [44.1, 67.8]	41 (54.7%) [42.7, 66.2]	49 (63.6%) [51.9, 74.3]

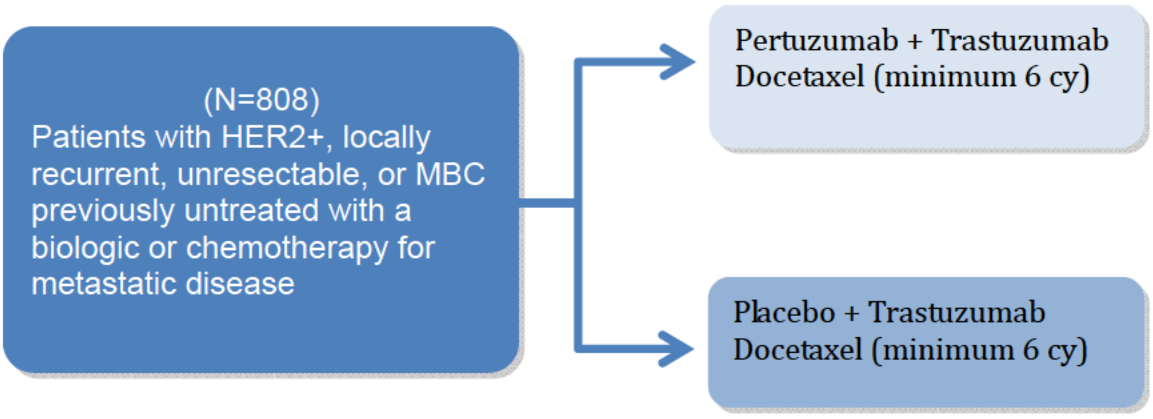
FEC=5-fluorouracil, epirubicin, cyclophosphamide, T= docetaxel, Ptz= Pertuzumab, H= trastuzumab, TCH=docetaxel, carboplatin, trastuzumab , CI=Confidence Interval

[1] ypT0/is, [2] ypT0/isypN0, 95% CI for one sample binomial using Pearson-Clopper method.

Metastatic Breast Cancer Supportive Trial: CLEOPATRA (WO20698)

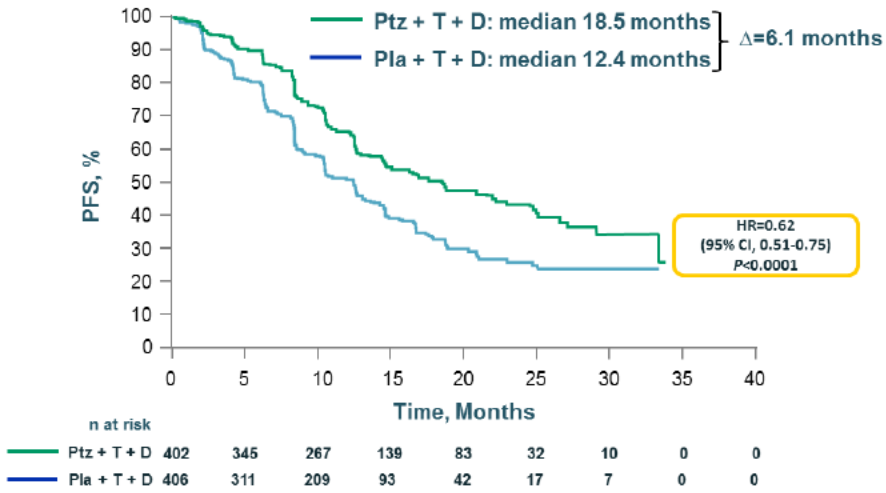
CLEOPATRA (Wo20698/TOC4129g) is a randomized, double-blind, placebo-controlled, multicenter trial in patients with HER2-positive metastatic breast cancer. The trial enrolled 808 patients who were randomly allocated (1:1) to receive pertuzumab in combination with trastuzumab and docetaxel (n=402) or placebo in combination with trastuzumab and docetaxel (n=406) (Figure 4).

Figure 4 CLEOPATRA Study Design



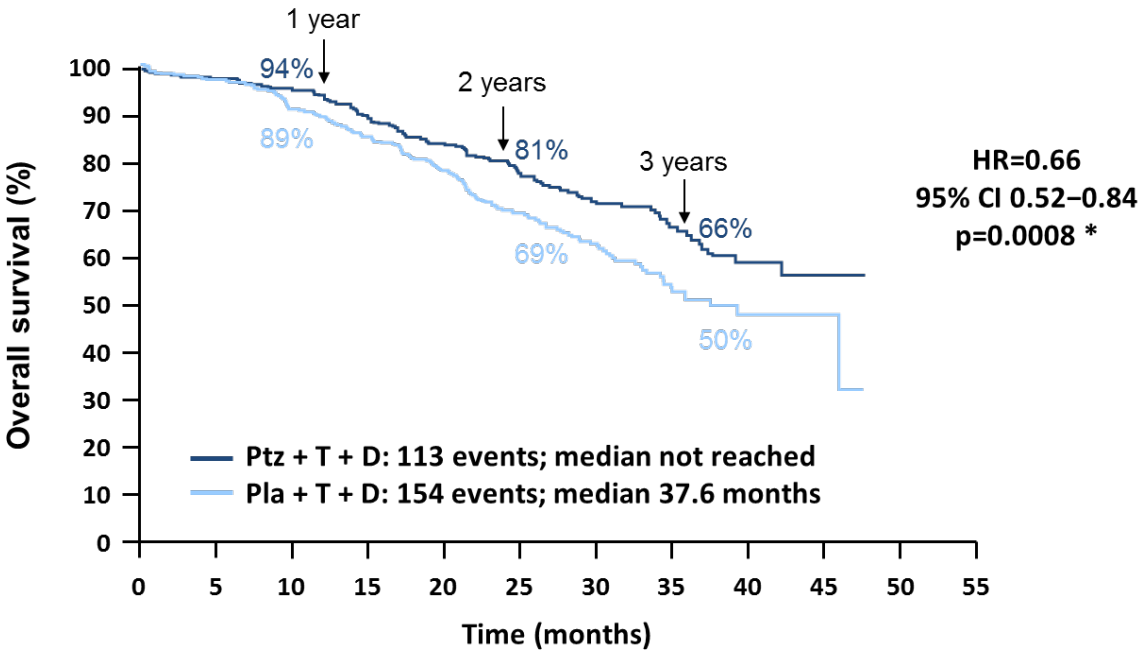
The basis of the initial approval was a statistically and clinically significant 6.1 month improvement in progression-free survival (PFS) in patients receiving pertuzumab compared to those receiving placebo [HR 0.62 (95% CI: 0.51, 0.75; p< 0.0001, log-rank test)] (Figure 4). The median PFS was 18.5 and 12.4 months for patients on the pertuzumab and placebo arms, respectively. At the time of PFS analysis, a planned interim analysis for overall survival (OS) was performed. The first interim OS analysis showed a trend towards improved survival with pertuzumab [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053]. At the second interim analysis, the stopping boundary for statistical significance (p<0.0138) was crossed. Thus, the pertuzumab treatment arm demonstrated superiority in overall survival [HR=0.66, 95% CI (0.52, 0.84) p=0.0008] (Figure 5).

Figure 5: Kaplan-Meier Curve of IRF-Assessed PFS for CLEOPATRA



Baselga J. et al [6]

Figure 6: Kaplan-Meier Curve of Overall Survival for CLEOPATRA



Swain SM et al [7]

6. Safety

Safety data from the two neoadjuvant trials, NEOSPHERE (WO20697) and TRYPHAENA (BO22280), the first-line metastatic trial, CLEOPATRA (WO20698) and 12 additional studies for a total of 2100 patients constitute the safety database for this application. 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.

The safety profile of pertuzumab in the two neoadjuvant trials is very similar to that seen in the metastatic breast cancer setting (CLEOPATRA) with no new safety signals. The main difference with the metastatic trial is the increase in cardiotoxicity with the addition of pertuzumab (compared with placebo) to trastuzumab and docetaxel in the neoadjuvant trials. The addition of pertuzumab did increase the incidence of diarrhea, nausea, mucosal inflammation, and rash but these appear to be clinically manageable. As seen in the metastatic breast cancer setting, increased toxicity (neutropenia) was again observed in the Asian population. This increase in toxicity appears to be due to docetaxel. In this curative intent setting, treatment was delivered as planned in the majority of patients. Key safety findings are summarized as follows:

Deaths
In the neoadjuvant trials, there were 14 deaths, 13 occurred in the post-treatment follow-up period and were attributed to disease progression. Only one death in the pertuzumab arm occurred during the neoadjuvant period and was due to fulminant hepatitis. The study steering committee attributed the death to docetaxel, which is a known hepatotoxic agent and has a label box warning. Currently, over 10,000 patients have been exposed to pertuzumab and there is no signal of hepatotoxicity.

Left Ventricular Dysfunction
The addition of pertuzumab led to an increased incidence of all cardiac events including left ventricular dysfunction (Table 5). Discontinuation due to cardiac toxicity was low and all cases of left ventricular dysfunction in NEOSPHERE eventually recovered to LVEF >50%. All but two cases of left ventricular dysfunction in TRYPHAENA eventually recovered to LVEF >50%.

Most cases of left ventricular dysfunction in the NEOSHERE and TRYPHAENA studies were asymptomatic LVEF declines of >10% with a decrease to less than 50%. Although it appears that the cardiac safety is similar in the 3 study arms, the TRYPHAENA study is small and we believe there are insufficient safety data to support concomitant administration of an anthracycline and pertuzumab. It should be noted that cardiac events in the CLEOPATRA Trial (metastatic breast cancer) were not increased in the pertuzumab arm. An additional safety trial should be conducted to address the cardiac safety of preoperative administration of an anthracycline regimen with pertuzumab plus trastuzumab in the neoadjuvant setting.

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	H+T	Ptz + H + T	Ptz + H	Ptz + T
NEOADJUVANT PERIOD	**N= 107**	**N= 107**	**N= 108**	**N= 94**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	**N= 103**	**N= 102**	**N= 94**	**N= 88**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	5 (5.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD	**N= 97**	**N= 99**	**N= 96**	**N= 86**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	0	3 (3.0%)	1 (1.0%)	2 (2.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
TOTAL # Patients with Cardiac Event	**N= 2**	**N= 9**	**N= 2**	**N= 7**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	2 (1.9%)	9 (8.4%)	1 (0.9%)	7 (7.4%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0

T=docetaxel, Ptz=pertuzumab, H=trastuzumab

Table 4: Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC x 3→T x 3 Ptz + H x 6	FEC x 3→T x 3 + Ptz+H x 3	TCH x 6 + Ptz x 6
NEOADJUVANT PERIOD	**N= 72**	**N= 75**	**N= 76**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	4 (5.6%)	1 (1.3%)	2 (2.6%)
Symptomatic LV Dysfunction (CHF)	0	2 (2.7%)	0
ADJUVANT PERIOD	**N= 68**	**N= 65**	**N= 67**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	3 (4.4%)	5 (7.7%)	2 (3.0%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (1.5%)
FOLLOW-UP PERIOD	**N= 70**	**N= 75**	**N= 74**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	1 (1.4%)	2 (2.7%)	2 (2.7%)
Symptomatic LV Dysfunction (CHF)	0	1 (1.3%)	0
TOTAL # Patients with Cardiac Event	**N= 5**	**N= 9**	**N= 7**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	5 (6.9%)	6 (8.0%)	6 (7.9%)
Symptomatic LV Dysfunction (CHF)	0	3 (4%)	1 (1.3%)

FEC=5-fluorouracil, epirubicin, cyclophosphamide; T=docetaxel; Ptz= Pertuzumab; H=trastuzumab; TCH=docetaxel, carboplatin, trastuzumab

7. Main Issues with this Application

a) Neoadjuvant trials require less time to assess the endpoint of pCR and differences in pCR can be detected with a smaller sample size than is required to detect differences in DFS/OS in post-operative adjuvant trials. However, conducting trials in the neoadjuvant setting early in drug development leads to a concern that patients with a curable disease may be exposed to unknown rare and late toxicities. Therefore, for a given application, the advantages of the neoadjuvant accelerated approval pathway should outweigh these concerns. The current sBLA for Perjeta® has supportive efficacy and safety data from the CLEOPATRA Phase 3 trial in the metastatic setting, which included a significant improvement in overall survival and an acceptable toxicity profile. The two neoadjuvant trials, NEOSPHERE (WO20697) and TRYPHAENA (BO22280), also support the safety profile of pertuzumab for the treatment of women with HER2-positive early-breast

cancer. The safety profile in the NEOSPHERE trial is similar to that seen in the metastatic breast cancer setting (CLEOPATRA Trial) with no new safety signals. The addition of pertuzumab in the neoadjuvant trials led to an increased incidence of all cardiac events including left ventricular dysfunction. It should be noted that cardiac events in the CLEOPATRA Trial were not increased in the pertuzumab arm. Genentech plans to submit additional safety data from the ongoing and fully accrued Phase 3 adjuvant trial (APHINITY BO25126). An additional safety trial should be conducted to address the cardiac safety of preoperative administration of an anthracycline regimen with pertuzumab plus trastuzumab in the neoadjuvant setting.

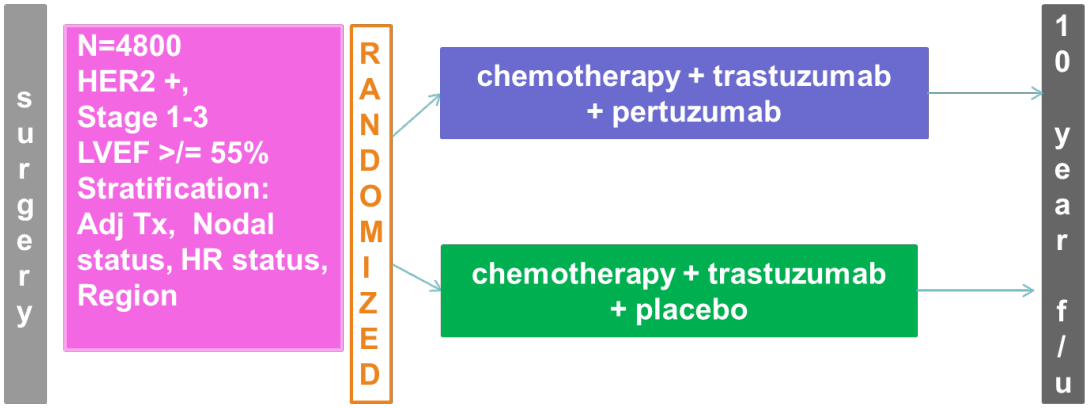
b) Pathological complete response has been proposed as a surrogate endpoint for predicting long-term clinical benefit in endpoints such as disease-free survival (DFS), event-free survival (EFS) and overall survival (OS). Among the 11,955 patients in the CTNeoBC meta-analysis, individual patients who attained a pCR were found to have improved EFS and OS. This association of pCR with EFS and OS is greater in patients with aggressive tumor subtypes (HER2–positive and triple-negative tumors) compared to less aggressive tumor subtypes. However, this pooled-analysis found that while pCR has clear prognostic value for individual patients, an association between pCR and long-term outcome could not be confirmed at a trial level. The pooled-analysis was unable to demonstrate that pCR is an established surrogate for EFS or OS, possibly because of the small improvements in pCR rates in most of the trials. However, FDA believes that with larger improvements in pCR rates with more effective treatments, pCR is a surrogate endpoint that is reasonably likely to predict clinical benefit and plans to open a regulatory pathway for accelerated approval of neoadjuvant treatments.

   An accelerated approval is subject to a postmarketing requirement to study the drug further to confirm clinical benefit. Since there is uncertainty regarding the ultimate long-term efficacy and safety of drugs approved under this pathway, long-term follow-up with confirmation of clinical benefit will be required. As noted above, this regulatory approach has some benefits and risks. The potential benefits include allowing the use of a non-validated surrogate endpoint that can be assessed earlier than EFS or OS to permit earlier approval of highly effective agents for patients with an unmet medical need. The risks include approving an agent that ultimately does not demonstrate clinical benefit and, in the interim, exposing patients to the toxicity of therapy. We recognize that this is a trade-off to provide earlier availability of promising anti-cancer agents. To justify the risks of this pathway, enrollment to neoadjuvant trials intended to support accelerated approval should be restricted to patients with high-risk early breast cancer.

   In this case, the HER2-positive early breast cancer population is considered to be at sufficient risk of relapse to qualify for this regulatory pathway. The regulatory risks of this new pathway are reduced in this application because we already have strong supportive evidence of efficacy in the metastatic setting and a well characterized toxicity profile.

c) Genentech plans to submit efficacy and safety data from the ongoing and fully accrued Phase 3 study APHINITY (BO25126) that is investigating pertuzumab in the adjuvant setting, with a primary outcome measure of invasive disease-free survival (IDFS). The final analysis of IDFS from this study could permit confirmation of the clinical benefit of pertuzumab observed in the neoadjuvant setting to support conversion of accelerated approval to regular approval for the proposed indication.

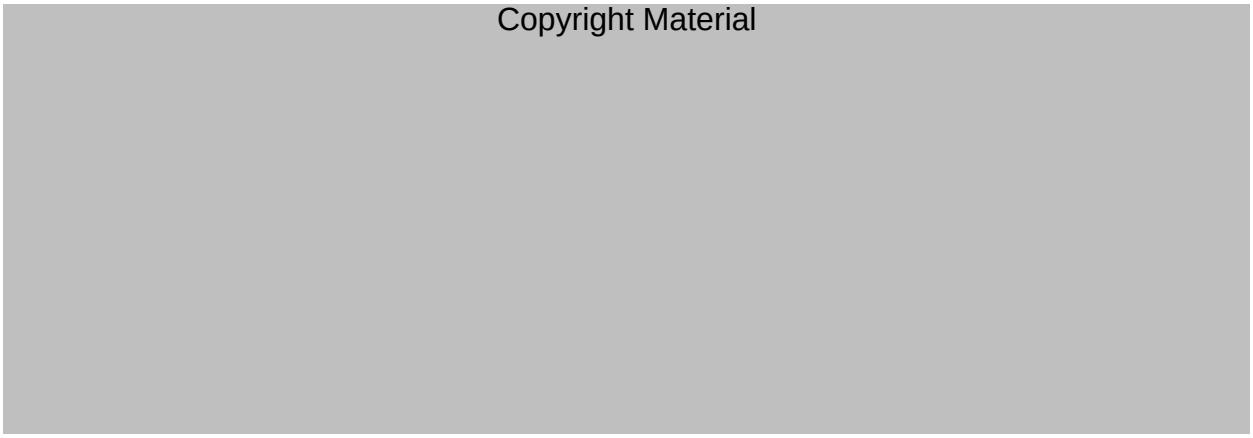
Figure 7 Confirmatory Trial (APHINITY)



d) While pCR has been proven to be informative at a patient level, indicating a more favorable prognosis for those with complete eradication of invasive tumor by preoperative therapy, the CTNeoBC meta-analysis could not establish the magnitude of improvement in pCR rates necessary to predict the superiority of one regimen over another in terms of EFS or OS. As a consequence, it is uncertain whether the 17.8% difference in pCR rates demonstrated in the NEOSPHERE study will be associated with improved long-term outcome (EFS, DFS or OS) in the confirmatory trial. However, in a similar patient population, the NOAH Trial demonstrated that patients treated with preoperative chemotherapy plus trastuzumab had a 19% absolute difference in pCR rate compared to patients treated with the same regimen of preoperative chemotherapy alone. The 5-year EFS and OS from the NOAH trial [8] showed an improved long-term outcome in patients treated with neoadjuvant chemotherapy plus trastuzumab followed by 1-year of adjuvant trastuzumab (Figure 8). The addition of trastuzumab to adjuvant chemotherapy has also shown to result in a substantial improvement in DFS in 4 large adjuvant trials and OS improvement in a metastatic trial (**Error! Reference source not found.**). Whether or not a similar improvement in pCR rates (17.8%) in the NEOSPHERE trial will be accompanied by an IDFS improvement in the confirmatory trial (APHINITY) remains to be seen. However, in the CLEOPATRA trial, the use of pertuzumab in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer who had not received prior anti-HER2 therapy or chemotherapy for metastatic disease, demonstrated an unprecedented improvement in median progression-free survival [HR 0.62 (95% CI: 0.51, 0.75; p< 0.0001, log-rank

test)] and an overall survival improvement at the second interim analysis [HR = 0.66, 95% CI (0.52, 0.84) p = 0.0008].

Figure 8 NOAH Trial: 5-yr EFS/OS



Gianni: ASCO 2013 [8]

e) Although pCR has been the most commonly used endpoint in neoadjuvant trials, it has been variably defined, which has made interpretation of data from neoadjuvant trials challenging. The primary endpoint of the NEOSPHERE study was pCR rate in the breast (ypT0/is). In the CTNeoBC meta-analysis, we found the eradication of tumor from both the breast and lymph nodes (ypT0/isypN0) better predicted for EFS and OS compared with eradication of tumor from the breast alone (ypT0/is). Consequently, the FDA-preferred definition of pCR is the absence of invasive cancer in the breast and nodes (ypT0/isypN0). FDA analysis of the NEOSPHERE study showed statistically significant improvements in pCR rates by both the study and FDA-preferred definitions in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel (Table 5).

Table 5 NEOSPHERE Efficacy Results Using Two Pathological Complete Response Definitions

	pCR (ypT0/isypN0)		pCR (ypT0/is)	
	Arm A H+T	Arm B Ptz+H+T	Arm A H+T	Arm B Ptz+H+T
	N=107	N=107	N=107	N=107
pCR, n (%)	23 (21.5%)	42 (39.3%)	31 (29.0%)	49 (45.8%)
95% CI	14.1, 30.5	30.0, 49.2	20.6, 38.5	36.1, 55.7
Difference of pCR Rates	17.8% (5.7%, 29.9%)		16.8% (4.1%, 29.6%)	
p-value*	0.0063		0.0141	

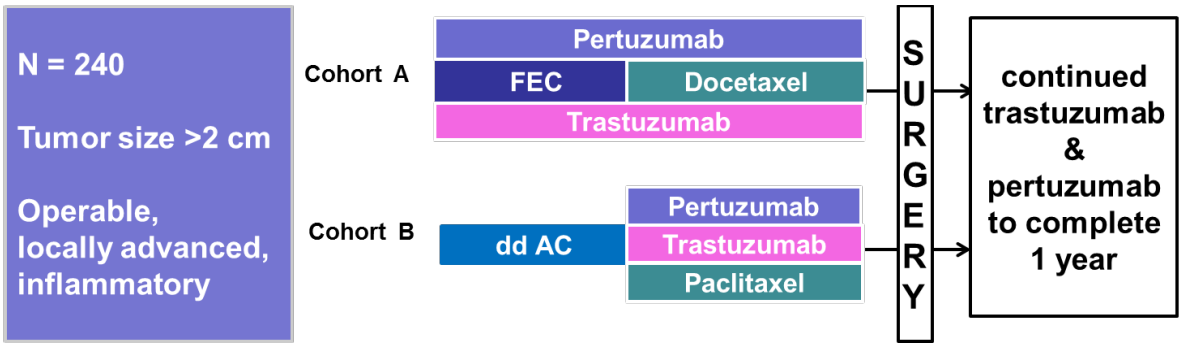
T=docetaxel, Ptz=pertuzumab, H=trastuzumab
* with Simes corr. for CMH test
ypT0/isypN0 = Absence of invasive cancer in the breast and axillary nodes; DCIS allowed,
ypT0/is = Absence of invasive cancer in the breast and DCIS allowed; regardless of nodal involvement

f) A very important issue with this application is how to put the NEOSPHERE study results into clinical practice context. The anthracycline regimen (FEC) in the NEOSPHERE study was given after surgery is not widely used in the U.S. and is not FDA-approved for use in combination with trastuzumab. At the current time, there is insufficient cardiac safety information to recommend concomitant administration of an anthracycline regimen with pertuzumab.

The main rationale for giving the anthracycline regimen after surgery in neoadjuvant trials conducted with regulatory intent is to better isolate the treatment effect of the experimental agent. As seen with the TRYPHAENA study, the combination of an anthracycline regimen (FEC), taxane and dual anti-HER2 therapy resulted in higher pCR rates (57% to 66%) compared to the NEOSPHERE study (39%), where the anthracycline regimen (FEC) was given after surgery. It is possible that higher pCR rates will translate into better clinical outcomes. However, for trials conducted with regulatory intent, it will be difficult to demonstrate a significant absolute difference in pCR rates between treatment arms when the control arm already has a high pCR rate. Therefore, the administration of anthracycline regimens following surgery may facilitate the detection of pCR differences, but may make the study results difficult to translate to the current standard of care.

Consequently, the Agency discussed with Genentech the need for a larger trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens more commonly used in the US, when administered in combination with neoadjuvant pertuzumab and trastuzumab. The following trial is a FDAAA PMR.

Figure 9 PMR Cardiac Safety Trial



8. Advisory Committee Meeting

This application was presented at the ODAC meeting on September 12, 2013. ODAC voted 13 to 0, with one abstention, that pertuzumab demonstrated a favorable benefit to risk profile for the neoadjuvant treatment of early breast cancer. In summary FDA and ODAC members stated that they considered the pertuzumab application was favorable based on the totality of the evidence. This evidence included:

- Strong supportive evidence of efficacy in the metastatic setting from the CLEOPATRA trial, which showed a highly significant and clinical robust improvement on overall survival, which may exceed 10 months.
- The NEOSPHERE trial isolates the effect of pertuzumab with an improvement in pathological complete response rate supported by efficacy data from the TRYPHAENA trial.
- The confirmatory trial (APHINITY) is fully accrued and results will be available in 2016.
- Evidence that trastuzumab, a similar agent, can improve disease-free survival.
- A large database reflecting extensive exposure of patients to pertuzumab in a variety of breast cancer settings, with an acceptable safety profile.

A summary of the minutes from the discussion at ODAC regarding this application are as follows:

Many committee members described their consideration of this benefit to risk evaluation as being primarily based on the "totality of evidence," including the significant amount of data from the use of pertuzumab in the metastatic setting. Several members expressed some lack of confidence in the results of the NEOSPHERE study when taken alone, but an understanding of safety and efficacy in the metastatic setting helped to contribute to the comfort when interpreting the study results from the neoadjuvant setting. Some members of the committee cited this reasoning in suggesting that the results from NEOSPHERE should not be used as precedent for approval in this area of treatment, and instead should be viewed as a unique situation due to the robust overall clinical development of this product.

In evaluating the NEOSPHERE study, members cited several issues which create challenges in applying the results to clinical practice. Many members talked about the problems of pCR as an endpoint, and uncertainty over whether this translates to long term clinical benefit for patients. Several committee members were unsure on the appropriate chemotherapy regimen to use with

this targeted therapy. One member described uncertainty about the appropriate duration of treatment as well. Additional concerns that were highlighted by members included cardiac toxicities, the need for appropriate patient selection, the small size of the trial, and the lack of patients from the United States.

Many members of the committee explained that the completion of enrollment for the APHINITY confirmatory trial increased the comfort with the accelerated approval of pertuzumab. ODAC members described this as a "well-designed" study, and expressed hope that this trial would ultimately support the clinical benefit of this product. Several members went further to encourage the sponsor – in the event that the confirmatory trial does not support the clinical benefit of pertuzumab after its accelerated approval – to voluntarily withdraw the indication at that time.

The committee member who abstained cited the "black and white" nature of the question, and a feeling that the issue was "gray" instead. This member detailed a feeling that it is "okay to go ahead" in this area, but that careful monitoring is necessary.

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 OSI inspected three of the highest accruing sites: Site 116798 (Dr. Luca Gianni, Milano, Italy), Site 116801 (Dr. Tadeusz Pienkowski, Warszawa, Poland), and Site 116814 (Dr. Ana Lluch Hernandez, Valencia, Spain). 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. Key clinical labeling recommendations included:

Changes to the proposed indication were added to state the lack of long-term efficacy.

> "This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival"

Limitations of use were included to address the following safety issues:

- The safety of PERJETA in combination with doxorubicin-containing regimens has not been established.
- The safety of PERJETA administered for greater than 6 cycles for early breast cancer has not been established.

Labeling changes to address the potential for cardiac toxicity:

- Add a 'boxed warning' regarding the risk of cardiomyopathy.

WARNING: CARDIOMYOPATHY

Cardiomyopathy

PERJETA administration can result in subclinical and clinical cardiac failure. Evaluate left ventricular function in all patients prior to and during treatment with PERJETA. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.2, 6.1)

Changes to the Dosage and Administration section were included to clarify the treatment of pertuzumab with different regimens. Since there are insufficient safety data to support concomitant administration of an anthracycline and pertuzumab, the concomitant administration of FEC and pertuzumab plus trastuzumab regimen is not recommended.

PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer *[see Clinical Studies (14.2)]*:

- For 4 cycles in combination with trastuzumab and docetaxel, preoperatively followed by 3 cycles of postoperative fluorouracil, epirubicin, and cyclophosphamide (FEC) as given in Study 2
- For 3 cycles in combination with trastuzumab and docetaxel as sequential therapy following 3 cycles of preoperative FEC as given in Study 3
- For 6 cycles in combination with docetaxel, carboplatin and trastuzumab (TCH) (escalation of docetaxel above 75 mg/m^2 is not recommended) as given in Study 3

Following surgery, patients should continue to receive trastuzumab to complete 1 year of treatment. There is insufficient evidence to recommend continued use of PERJETA for greater than 6 cycles for early breast cancer. There is insufficient evidence to recommend concomitant

administration of an anthracycline with PERJETA, and there are no safety data to support sequential use of doxorubicin with PERJETA.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend that this BLA be approved under the accelerated approval regulations, 21 CFR 601.41, for the following indication:

"for the use of pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer"

- Risk Benefit Assessment

There are benefits and risks associated with the accelerated approval process. However, the regulatory risks are reduced in the pertuzumab application. The current recommendation for accelerated approval is based on the totality of the pertuzumab data and the unique features in this application. The demonstration of an improvement in pathological complete response (pCR) rate in the NEOSPHERE trial is also supported by the pCR data from the TRYPHAENA trial. Most importantly, pertuzumab is a highly active agent already approved for the treatment of HER2-positive metastatic breast cancer, with a highly significant and clinically robust improvement in overall survival, which may exceed 10 months and a statistically significant and substantial improvement in PFS. In addition, the toxicity of pertuzumab is well characterized and acceptable.

No data are available demonstrating improvement in event-free survival or overall survival with pertuzumab treatment in the early breast cancer setting. Therefore, continued approval for this indication will be contingent upon demonstration of improvement in disease-free survival in the confirmatory trial (APHINITY), which is currently fully accrued.

It is important to point out that although an 18% improvement in pCR rate may be acceptable for the pertuzumab application, due to its unique strengths. We are not setting a precedent that an 18% improvement in pCR rates will result in a neoadjuvant approval. The magnitude of pCR improvement necessary for a product approval of a neoadjuvant indication will be unique to each product and will depend upon the benefit risk assessment and the supportive data.

In the safety analysis of the neoadjuvant trials, there was 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.

In conclusion, pertuzumab when added to trastuzumab and docetaxel, for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) and as part of a complete treatment regimen for early breast cancer, demonstrates a favorable risk-benefit profile. The benefit of

introducing a potentially curative agent for this patient population with high-risk early-breast cancer outweighs the potential risks.

- 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

PMR 1 Description:	Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP).

PMR Schedule Milestones:	Final Protocol Submission:	10/2013
	Trial Completion:	11/2016
	Final Report Submission:	05/2017

Rationale for required PMR:
Genentech proposes to use the ongoing APHINITY trial as the confirmatory trial to support the conversion from accelerated approval to regular approval for pertuzumab in the neo-adjuvant setting. This adjuvant trial is a randomized controlled trial in 4800 women with HER2-positive early breast cancer designed to demonstrate the superiority of adjuvant pertuzumab plus trastuzumab in combination with standard chemotherapy compared to placebo pertuzumab plus trastuzumab and standard chemotherapy with regard to the primary endpoint disease-free survival from invasive breast cancer. This trial will also provide information to better characterize the overall toxicity profile of pertuzumab in the early breast cancer population.

PMR 2 Description:	Conduct a clinical trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer.

PMR Schedule Milestones:	Final Protocol Submission:	01/2014
	Trial Completion:	08/2016
	Final Report Submission:	02/2017

Rationale for required PMR:
The NEOSPHERE and TRYPHAENA trials showed an increase rate of left ventricular dysfunction with the addition of pertuzumab treatment. Most cases of cardiac dysfunction were asymptomatic and reversible; however, the cardiac safety profile of pertuzumab and trastuzumab in combination with chemotherapy regimens commonly used in the USA needs to be evaluated. This is of particular importance due to the longer life expectancy in the early breast cancer population as compared to the metastatic breast cancer population. This PMR trial will evaluate the cardiac and overall safety of two different neoadjuvant pertuzumab and anthracycline-containing regimens using a parallel two cohort trial design.

Post-Marketing Commitments

PMC 3 Description:	Submit the final event-free survival (EFS) analysis of trial WO20697 (NEOSPHERE).

PMC Schedule Milestones:	Final Protocol Submission:	10/2013
	Trial Completion:	11/2014
	Final Report Submission:	03/2015

Rationale for PMC:
The final event-free survival (EFS) results of trial WO20697 (NEOSPHERE) will, if significant, provide support for the pathological complete response (pCR) result favoring the pertuzumab treatment arm in the NEOSPHERE trial.

PMC 4 Description:	Conduct a study of pretreatment molecular subtyping of tumors from patients treated in the postmarketing cardiac safety trial (PMR#2) and submit an exploratory analysis of the relationship of pathological complete response with the different tumor subtypes.

PMC Schedule Milestones:	Final Protocol Submission:	01/2014
	Study/Trial Completion:	08/2016
	Final Report Submission:	08/2017

Rationale for PMC:
HER2-positive breast cancer is very heterogeneous. Data from prior trials in which patients with different HER2-positive tumor subtypes were enrolled suggest differing sensitivities to HER2 targeted agents depending on the tumor molecular subtype.. This may impact the pathological complete response (pCR) endpoint. Pretreatment molecular subtyping of HER2+ tumors will assist the clinician in identifying patients who are at higher risk of failing to attain a pCR with pertuzumab combination therapies and who are at higher risk of relapse and death despite therapy with pertuzumab containing regimens. In addition, information about tumor molecular subtyping and sensitivity to HER2 targeted therapies will provide information for the selection of patients to be included in future trials using HER2+ directed agents.

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