CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s051

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	9/30/13
From	Robert L. Justice, M.D., M.S. Anthony J. Murgo, M.D., M.S.
Subject	Signatory Authority Summary Review
NDA/BLA # **Supplement #**	BLA 125409/51
Applicant Name	Genentech, Inc.
Date of Submission	April 30, 2013
PDUFA Goal Date	October 31, 2013
Proprietary Name / **Established (USAN) Name**	PERJETA Injection/ pertuzumab
Dosage Forms / Strength	420 mg/14 mL (30 mg/mL) single-use vial
Proposed Indication(s)	PERJETA is indicated for use 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. 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.
Action/Recommended Action for NME:	*Accelerated Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Laleh Amiri-Kordestani, Suparna Wedam
Statistical Review	Lijun Zhang, Shenghui Tang, Rajeshwari Sridhara
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	Pengfei Song, Kevin M Krudys, Qi Liu
OPDP	Marybeth Toscano
OSI	Lauren Iacono-Connors, Janice Pohlman, Susan D. Thompson
CDTL Review	Patricia Cortazar

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). This sBLA for a new indication for pertuzumab was submitted on April 30, 2013, and received on May 1, 2013. The PDUFA date is October 31, 2013. The originally proposed indication was for "neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin."

Pertuzumab was given regular approval on June 8, 2012, 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. The approval was based on the results of Study 1 (CLEOPATRA), a randomized trial comparing pertuzumab plus trastuzumab and docetaxel to placebo plus trasuzumab and docetaxel. The study demonstrated a statistically and clinically significant improvement in IRF-assessed PFS favoring the pertuzumab arm [HR=0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] resulting in an increase in median PFS of 6.1 months (18.5 months vs. 12.4 months). At the first interim OS analysis, the results were not mature and did not meet the pre-specified stopping boundary for statistical significance.

The second interim analysis of OS from the CLEOPATRA trial demonstrated a clinically and statistically significant improvement in OS [HR=0.66 (95% CI: 0.52, 398 0.84), p=0.0008]. A sBLA supplement incorporating the results of this analysis into labeling was approved on April 12, 2013.

This review will summarize the designs and efficacy and safety data from the trials supporting accelerated approval of the new indication, the recommendations of each review discipline, the risk benefit assessment, the regulatory implications of this approval, and the post-marketing requirements and commitments.

2. Background

As noted in the Clinical Review, there are currently no drugs approved in the U.S. for the indication of neoadjuvant treatment of HER2+ breast cancer but regimens used in the adjuvant setting are often used in the neoadjuvant setting. These include AC (doxorubicin and cyclophosphamide) or FEC (fluorouracil, epirubicin, and cyclophosphamide) plus a taxane (paclitaxel or docetaxel) plus trastuzumab. TCH is a non-anthracycline regimen consisting of docetaxel plus carboplatin, plus trastuzumab.

In May 2012, the Agency released a draft guidance titled "Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval." In March 2013, the Agency had a workshop related to drug development and approval for neoadjuvant treatment of breast cancer. In the CTNeoBC pooled analysis, pCR was informative at an individual patient level, but the analysis could not establish whether an increase in pCR rate between treatment groups predicts for the superiority of one regimen over another in terms of EFS or OS (i.e., is an established surrogate endpoint for clinical benefit). However, for multiple reasons, this analysis does not preclude the use of pCR as a surrogate endpoint that is reasonably likely to predict clinical benefit for the purpose of accelerated approval. Confirmation of clinical benefit would be required for continued marketing.

3. CMC/Device

N/A

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Pharmacometrics

Clinical Pharmacology and Pharmacometrics reviewed an updated population PK analysis that suggested that pertuzumab exposure in patients with early breast cancer in the NEOSPHERE trial was similar to exposure in other historical patient types, including first-line metastatic breast cancer. In addition, no significant exposure-response relationship was identified between predicted pertuzumab trough serum concentration and the probability of pCR response. The review team concluded that the efficacy supplement is acceptable from a clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology/pharmacometrics review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The design and results of the NEOSPHERE (Study 2) and TRYPHAENA (Study 3) trials are summarized in the following excerpts from the agreed-upon labeling.

Study 2
Study 2 was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0).

Demographics were well balanced (median age was 49 – 50 years old, the majority were Caucasian (71%) and all were female. Overall, 7% of patients had inflammatory cancer, 32% had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive).

The efficacy results are summarized in Table 5. Statistically significant improvements in pCR rates by both the study and FDA-preferred definitions were observed in patients receiving PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 5 Summary of Efficacy from Study 2

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)
Hormone 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]
Hormone 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=PERJETA, H=trastuzumab
CI=Confidence Interval
[1] ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)
[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 hormone receptor status. The patient did not achieve a pCR.

Study 3
An additional phase 2 neoadjuvant study was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients were randomly allocated 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 PERJETA and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with PERJETA, or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in combination with PERJETA. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 3 cycles. In the PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles. Following surgery all patients received trastuzumab to complete 1 year of therapy, which was administered intravenously every 3 weeks.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (76%)) and all were female. Overall 6% of patients had inflammatory cancer, 25% had locally advanced cancer and 69% had operable cancer, with approximately half the patients in each treatment group having ER-positive and/or PgR-positive disease.

The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%, 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

The Statistical Review and Evaluation provided the following conclusions and recommendations:

This is the first marketing application using pCR as the primary efficacy endpoint for neoadjuvant treatment of breast cancer. For efficacy evaluation, the applicant submitted results from a multicenter, phase 2, randomized, open-labeled clinical study (NEOSPHERE) which assessed efficacy of the addition of pertuzumab to trastuzumab and docetaxel in the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2cm in diameter). The addition of pertuzumab showed a statistically significant improvement on pCR rates per different definitions. Results of long term clinical endpoints, EFS and DFS, were not mature at this time. The benefit of pertuzumab on long term clinical outcomes is going to be evaluated in the confirmatory study, APHINITY.

In this disease setting, pCR is not an established surrogate endpoint of long term benefit yet. It is not clear whether the observed 17.8% improvement on pCR will be

translated into long term clinical benefit. However, the approvability of this sBLA should be considered in the context of that pertuzumab has demonstrated benefit in a more refractory population, metastatic breast cancer, on both PFS and OS (study CLEOPATRA). The judgment on the approvability is deferred to the clinical review team.

I concur that pCR is not yet an established surrogate endpoint for full approval and that it is not yet known whether the approximately 18% improvement in pCR rate in the pertuzumab arm will translate into long-term clinical benefit, such as an improvement in EFS. However, based on the results of Study 1 (CLEOPATRA study) in the first-line treatment of metastatic breast cancer, there is less risk to granting accelerated approval pending confirmation of clinical benefit than there would be without that data.

8. Safety

The safety results from Study 2 and 3 are summarized in the following excerpts from the Adverse Reactions and Warnings and Precautions sections of the agreed-upon labeling.

In Study 2, the most common adverse reactions seen with PERJETA in combination with trastuzumab and docetaxel administered for 4 cycles were similar to those seen in the PERJETA-treated group in Study 1. The most common adverse reactions (> 30%) were alopecia, neutropenia, diarrhea, and nausea. The most common NCI – CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In this group, one patient permanently discontinued neoadjuvant treatment due to an adverse event. Table 2 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in Study 2.

Table 2 Summary of Adverse Reactions Occurring in ≥ 10% in the Neoadjuvant Setting for Patients Receiving PERJETA in Study 2

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=108 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27.1	0.0	26.2	0.9	12.0	0.0	25.5	1.1
Asthenia	17.8	0.0	20.6	1.9	2.8	0.0	16.0	2.1
Edema peripheral	10.3	0.0	2.8	0.0	0.9	0.0	5.3	0.0
Mucosal inflammation	21.5	0.0	26.2	1.9	2.8	0.0	25.5	0.0

Pyrexia	10.3	0.0	16.8	0.0	8.3	0.0	8.5	0.0
Skin and subcutaneous tissue disorders								
Alopecia	66.4	0.0	65.4	0.0	2.8	0.0	67.0	0.0
Rash	21.5	1.9	26.2	0.9	11.1	0.0	28.7	1.1
Gastrointestinal disorders								
Diarrhea	33.6	3.7	45.8	5.6	27.8	0.0	54.3	4.3
Nausea	36.4	0.0	39.3	0.0	13.9	0.0	36.2	1.1
Vomiting	12.1	0.0	13.1	0.0	4.6	0.0	16.0	2.1
Stomatitis	7.5	0.0	17.8	0.0	4.6	0.0	9.6	0.0
Blood and lymphatic system disorders								
Neutropenia	63.6	58.9	50.5	44.9	0.9	0.9	64.9	57.4
Leukopenia	21.5	11.2	9.3	4.7	0.0	0.0	13.8	8.5
Nervous system disorders								
Headache	11.2	0.0	11.2	0.0	13.9	0.0	12.8	0.0
Dysgeusia	10.3	0.0	15.0	0.0	4.6	0.0	7.4	0.0
Peripheral Sensory Neuropathy	12.1	0.9	8.4	0.9	1.9	0.0	10.6	0.0
Musculoskeletal and connective tissue disorders								
Myalgia	22.4	0.0	22.4	0.0	9.3	0.0	21.3	0.0
Arthralgia	8.4	0.0	10.3	0.0	4.6	0.0	9.6	0.0
Metabolism and nutrition disorders								
Decreased appetite	6.5	0.0	14.0	0.0	1.9	0.0	14.9	0.0
Psychiatric disorders								
Insomnia	11.2	0.0	8.4	0.0	3.7	0.0	8.5	0.0

In Study 3, when PERJETA was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, leukopenia, febrile neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting.

Similarly, when PERJETA was administered in combination with docetaxel, carboplatin, and trastuzumab (TCH) for 6 cycles, the most common adverse reactions (> 30%) were diarrhea, alopecia, neutropenia, nausea, fatigue, vomiting, anemia, and thrombocytopenia. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, anemia, leukopenia, diarrhea,

thrombocytopenia, vomiting, fatigue, ALT increased, hypokalemia, and hypersensitivity.

The rates of adverse events resulting in permanent discontinuation of any component of neoadjuvant treatment were 6.7% for patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC and 7.9% for patients receiving PERJETA in combination with TCH. Table 3 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in Study 3.

Table 3 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in Study 3

Body System/Adverse Reactions	**PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel** **n=72** **Frequency rate %**		**PERJETA + trastuzumab + docetaxel following FEC** **n=75** **Frequency rate %**		**PERJETA + TCH** **n=76** **Frequency rate %**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
General disorders and administration site conditions						
Fatigue	36.1	0.0	36.0	0.0	42.1	3.9
Asthenia	9.7	0.0	14.7	1.3	13.2	1.3
Edema peripheral	11.1	0.0	4.0	0.0	9.2	0.0
Mucosal inflammation	23.6	0.0	20.0	0.0	17.1	1.3
Pyrexia	16.7	0.0	9.3	0.0	15.8	0.0
Skin and subcutaneous tissue disorders						
Alopecia	48.6	0.0	52.0	0.0	55.3	0.0
Rash	19.4	0.0	10.7	0.0	21.1	1.3
Dry skin	5.6	0.0	9.3	0.0	10.5	0.0
Palmar-Plantar Erythrodysaesthesia Syndrome	6.9	0.0	10.7	0.0	7.9	0.0

Gastrointestinal disorders						
Diarrhea	61.1	4.2	61.3	5.3	72.4	11.8
Dyspepsia	25.0	1.4	8	0.0	22.4	0.0
Nausea	52.8	0.0	53.3	2.7	44.7	0.0
Vomiting	40.3	0.0	36.0	2.7	39.5	5.3
Constipation	18.1	0.0	22.7	0.0	15.8	0.0
Stomatitis	13.9	0.0	17.3	0.0	11.8	0.0
Blood and lymphatic system disorders						
Neutropenia	51.4	47.2	46.7	42.7	48.7	46.1
Anemia	19.4	1.4	9.3	4.0	38.2	17.1
Leukopenia	22.2	19.4	16.0	12.0	17.1	11.8
Febrile neutropenia	18.1	18.1	9.3	9.3	17.1	17.1
Thrombocytopenia	6.9	0.0	1.3	0.0	30.3	11.8
Immune system disorders						
Hypersensitivity	9.7	2.8	1.3	0.0	11.8	2.6
Nervous system disorders						
Neuropathy peripheral	5.6	0.0	1.3	0.0	10.5	0.0
Headache	22.2	0.0	14.7	0.0	17.1	0.0
Dysgeusia	11.1	0.0	13.3	0.0	21.1	0.0
Dizziness	8.3	0.0	8.0	1.3	15.8	0.0
Musculoskeletal and connective tissue disorders						
Myalgia	16.7	0.0	10.7	1.3	10.5	0.0
Arthralgia	11.1	0.0	12.0	0.0	6.6	0.0
Respiratory, thoracic, and mediastinal disorders						
Cough	9.7	0.0	5.3	0.0	11.8	0.0
Dyspnea	12.5	0.0	8.0	2.7	10.5	1.3
Epistaxis	11.1	0.0	10.7	0.0	15.8	1.3
Oropharyngeal pain	8.3	0.0	6.7	0.0	11.8	0.0
Metabolism and nutrition disorders						
Decreased appetite	20.8	0.0	10.7	0.0	21.1	0.0
Eye disorders						
Lacrimation	12.5	0.0	5.3	0.0	7.9	0.0

increased						
Psychiatric disorders						
Insomnia	11.1	0.0	13.3	0.0	21.1	0.0
Investigations						
ALT increased	6.9	0.0	2.7	0.0	10.5	3.9

FEC=5-fluorouracil, epirubicin, cyclophosphamide, TCH=docetaxel, carboplatin, trastuzumab

Section 5.2 of Warnings and Precautions already states that decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. In Study 1, for patients with MBC, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel. However, the section was revised to include the following new information from Study 2 and Study 3.

> In patients receiving neoadjuvant treatment in Study 2, the incidence of LVSD was higher in the PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An increased incidence of LVEF declines was observed in patients treated with PERJETA in combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 1.9% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 8.4% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in the other 3 arms. LVEF recovered to ≥ 50% in all patients.
>
> In patients receiving neoadjuvant PERJETA in Study 3, in the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 6.9% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 10.5% of patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in 4.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1.3% of patients treated with PERJETA in combination with TCH, and none of the patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel. LVEF recovered to ≥ 50% in all but one patient.

As a result of this new information, the following was added to the boxed warning.

> **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.**

9. Advisory Committee Meeting

This application was discussed at the Oncologic Drugs Advisory Committee (ODAC) meeting held on September 12, 2013. The ODAC voted 13 "Yes", 0 "No" and 1 "Abstain" to the question "Has Perjeta demonstrated a favorable benefit to risk evaluation for the neoadjuvant treatment of early breast cancer?" A summary of the ODAC discussion is included in the CDTL review.

10. Pediatrics

The pediatric study requirement for this application was waived because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

11. Other Relevant Regulatory Issues

Three clinical sites were chosen for inspection based on enrollment of large numbers of study subjects. The Clinical Inspection Summary noted some regulatory violations but stated that that they were unlikely to importantly impact primary safety and efficacy analyses. The OSI conclusion was that "The overall data for Study WO20697 (NEOSPHERE) in support of this application may be considered reliable based on available information."

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: no changes
- Physician labeling: The major labeling issues that were discussed and resolved were the precise wording of the indication, the addition of limitations of use, the boxed warning, and the inclusion of information about some of the neoadjuvant regimens used Study 3.
- Carton and immediate container labels: no changes
- Patient labeling/Medication guide: N/A

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: accelerated approval

- Risk Benefit Assessment

I concur with the risk benefit assessments in the Clinical and CDTL reviews. Although pCR has not been shown to be an established surrogate for clinical benefit for regular approval, for the purpose of accelerated approval it is still reasonably likely to predict clinical benefit in the setting of large improvements in pCR rates between treatment arms. Whether an approximately 18% improvement in pCR rate is large enough to translate into an improvement in EFS or DFS remains to be seen. However, the initial approval of this drug was based on a large improvement in PFS in the first-line treatment of metastatic breast cancer followed by demonstration of a large improvement in OS at the second interim analysis. This is a unique circumstance and should not be considered to be setting a precedent for the magnitude of pCR rate needed to support accelerated approval (which may vary by drug) or for future accelerated approvals of neoadjuvant therapies based solely on similarly sized randomized trials. In addition, the confirmatory trial (APHINITY) is a large randomized adjuvant trial that has fully accrued providing reassurance that the question regarding clinical benefit will be answered relatively quickly.

The safety profile of pertuzumab is acceptable for the treatment of women at high risk for recurrence of their breast cancer. In the neoadjuvant studies, the most common (>30%) adverse reactions for the pertuzumab, trastuzumab and docetaxel combination were alopecia, diarrhea, and neutropenia. The most common adverse reactions for the regimen of 3 cycles of pertuzumab, trastuzumab, and docetaxel followed by 3 cycles of FEC were fatigue, alopecia, diarrhea, nausea, vomiting, and neutropenia. Finally, the most common adverse reactions for the TCH regimen were fatigue, alopecia, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. However, there was a clear increase in left ventricular dysfunction in the pertuzumab arm in Study 2 as well as all arms of Study 3. At the present time most of the cases of cardiac dysfunction are asymptomatic and reversible. However, further study of the safety of pertuzumab in combination with anthracycline regimens likely to be used in the U.S. and careful monitoring of LVEF are essential. There is currently insufficient information to support the safety of using pertuzumab in a doxorubicin-containing regimen.

The benefit to patients for granting accelerated approval to pertuzumab for this indication is that more patients who are at high risk for disease recurrence may be cured. The risk to patients is that they are exposed to increased toxicity without certainty that clinical benefit will ultimately be demonstrated. Given the prior data with pertuzumab in the first-line metastatic setting and the fact that the confirmatory study has already completed accrual, these risks are outweighed by the potential benefit.

- Recommendation for Postmarketing Risk Management Activities

  Postmarketing surveillance

- Recommendation for Postmarketing Requirements and Commitments

  The postmarketing requirement for verifying and describing clinical benefit under the accelerated approval regulations (21 CFR 601.41) is listed below.

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

Final Protocol Submission:	10/13
Trial Completion:	11/16
Final Report Submission:	05/17

The postmarketing requirement under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) is based on new safety information of an increased rate of left ventricular dysfunction with the addition of PERJETA (pertuzumab) treatment in the NEOSPHERE and TRYPHAENA studies. Although most of the cases of cardiac dysfunction were asymptomatic and reversible, the cardiac safety of PERJETA (pertuzumab) needs to be further evaluated when combined with chemotherapy regimens that are commonly used in the U.S. because of the potential for additive or synergistic cardiac toxicity.

2. 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.

Final Protocol Submission:	01/14
Trial Completion:	08/16
Final Report Submission:	02/17

The following are postmarketing commitments:

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

Final Protocol Submission:	10/13
Trial Completion:	11/14
Final Report Submission:	03/15

4. 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.

Final Protocol Submission:	01/14
Study Completion:	08/16
Final Report Submission:	08/17

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/s/

ROBERT L JUSTICE
09/30/2013

ANTHONY J MURGO
09/30/2013