CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s0051

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	BLA 125,409/ 51
Drug Name:	PERJETA®
Indication(s):	Patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter)
Applicant:	Genentech
Date(s):	Submission Date: 1 May 2013
	PDUFA Due Date: 31 October 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Lijun Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Oncology Products 1 (HFD-150)
Clinical Team:	Laleh Amiri Kordestani, M.D.
	Suparna Wedam, M.D.
	Patricia Cortazar, M.D., Team Leader
Project Manager:	Amy Tilley

Keywords: Pathologic Complete Response, Cochran–Mantel–Haenszel test, Neoadjuvant breast cancer

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Pertuzumab (Perjeta) was approved in 2012 for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease, in combination with trastuzumab and docetaxel. In this supplemental Biologic License Application (sBLA), the applicant seeks an accelerated approval of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (> 2cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin.

The pivotal phase 2 study WO 20697 (NEOSPHERE) was a multicenter, randomized, open-label trial comparing the efficacy and safety of four treatments (Arm A: trastuzumab plus docetaxel; Arm B: trastuzumab plus docetaxel plus pertuzumab; Arm C: trastuzumab plus pertuzumab; Arm D: pertuzumab and docetaxel) in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer. The primary efficacy endpoint was pathological complete response (pCR) rate in the breast (ypT0/is), defined as no invasive cancer in the breast. The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes regardless of DCIS (ypT0/isypN0).

A statistically significant improvement in pCR rate per the FDA-preferred definition was observed in patients randomized to Arm B to receive pertuzumab plus trastuzumab and docetaxel (n=107) compared to patients randomized to Arm A to receive trastuzumab plus docetaxel (n=107), with an increase in pCR rate of 17.8% (95% CI: 5.7%, 29.9%; adjusted p-value: 0.0063). A similar improvement was also observed using the pCR rate per the definition pre-specified in the protocol (ypT0/is). Long term clinical endpoints including event-free survival (EFS) and disease-free survival (DFS) will be analyzed after 5-year follow-up. Only limited data of long term clinical endpoints are available in the current submission.

This sBLA is the first application in the neoadjuvant breast cancer disease setting and the first application using pCR rate as the primary efficacy endpoint. At the current time, pCR is not an established surrogate endpoint of long term benefit in this disease setting, and it is not clear whether the observed 17.8% improvement in pCR will translate into long term clinical benefit. However, the approvability of this sBLA should be considered in the context that pertuzumab has demonstrated benefit in a more refractory population, metastatic breast cancer, on both progression-free survival (PFS) and overall survival (OS) (study CLEOPATRA). The judgment on the approvability is deferred to the clinical review team.

This application was discussed at the Oncologic Drug 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?”

2. INTRODUCTION

2.1 Overview

Pertuzumab in combination with trastuzumab and docetaxel has been approved for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2

therapy or chemotherapy for metastatic disease in 2012 based on a benefit in PFS (HR=0.62; 95% CI: 0.51, 0.75). At a subsequent interim OS analysis after approval, a statistically significant improvement in OS (HR=0.66; 95% CI: 0.52, 0.84) was observed in the same trial.

The current sBLA submission is based primarily on two phase 2 studies: WO 20697 (NEOSPHERE) and BO 22280 (TRYPHAENA) (Table 1). Study NEOSPHERE was 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". The protocol amendments are summarized in Table 2. The primary endpoint was pCR rate in the breast (ypT0/is, no invasive tumor in the breast). Study TRYPHAENA was entitled "A randomized, multicenter, multinational phase II study to evaluate pertuzumab in combination with trastuzumab, given either concomitantly or sequentially with standard anthracycline-based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positve breast cancer". The primary endpoint of study TRYPHAENA was the tolerability of neoadjuvant treatment, and pCR rate in the breast (ypT0/is) was a secondary endpoint. With all the three treatment arms in study TRYPHAENA containing pertuzumab, the efficacy effect of pertuzumab could not be isolated. Therefore, this review focused on study NEOSPHERE for efficacy evaluation.

Table 1: Overview of Studies Supporting the sBLA Indication

Study No.	**Population, Phase and Study Design**	**Treatment arms (number of randomized patients)**	**Enrollment period** **Geographic region: n of centers**
WO 20697 (NEOSPHERE)	Phase 2, open-label, 4-arm, randomized study in chemotherapy naïve patients with early stage HER2+ breast cancer whose primary tumors were >2cm and who were scheduled to receive neoadjuvant therapy	Arm A: Trastuzumab + Docetaxel (n=107) Arm B: Pertuzumab + Trastuzumab + Docetaxel (n=107) Arm C: Pertuzumab + Trastuzumab (n=107) Arm D: Pertuzumab + Docetaxel (n=96)	December 2007 - September 2009 59 centers in 16 countries North America: 5 (Canada: 4; Mexico: 1) South America: 10 Europe: 35 Asia: 8 Other: 1
BO 22280 (TRYPHAENA)	Phase 2, open label, 3-arm, randomized study in patients with HER2+ breast cancer which was early stage, and >2cm in diameter, or locally advanced or inflammatory.	Arm A: FEC + Trastuzumab + Pertuzumab followed by Docetaxel + Trastuzumab + Pertuzumab (n=73) Arm B:FEC followed by Docetaxel + Trastuzumab + Pertuzumab (n=75) Arm C: TCH+pertuzumab (n=77)	December 2009 – January 2011 44 centers in 19 countries North America: 6 (Canada) South America: 2 Europe: 28 Asia: 4 Other: 4

Table 2. History of Study NEOSPHERE Protocol Amendments

Protocol Amendment	Date	Major Amendments
Version B	December 4, 2007	▪ Addition of a fourth treatment arm (arm D) ▪ Increasing sample size to 400 ▪ Amendment of efficacy endpoints, hypothesis testing and analyses to reflect addition of arm D.
Version C	December 11, 2008	▪ Correction of tumor-node-metastasis (TNM) classes used to classify patients' disease for the stratification groups: operable, locally advanced, or inflammatory cancer (see Table 3).
Version D	June 27, 2009	▪ Updates to: the definition of post-menopausal women, the contraceptive requirements for women of child bearing potential, and the pregnancy testing scheduling ▪ Clarification of clinical response definition

Table 3. Definition of Breast Cancer Type by TNM Staging

Breast cancer type	Protocol Version	
	Original Protocol and Amendment B	Amendments C and D
Operable	T2-3a, N0-1, M0	T2-3, N0-1, M0
Locally advanced	T3b-4c or N2 or N3, M0	T2-3, N2 or N3, M0; or T4a-c, any N, M0
Inflammatory	T4d, any N, M0	T4d, any N, M0

This sBLA submission seeks an accelerated approval of pertuzumab. Since an accelerated approval requires confirmation of benefit, the applicant is conducting a confirmatory study, APHINITY, which is currently ongoing with enrollment completed. APHINITY (BIG-4-11/BO25126/TOC4939g) is a randomized, double-blind, placebo-controlled two-arm phase 3 study of adjuvant trastuzumab and chemotherapy plus pertuzumab or placebo, in patients with primary operable breast cancer. APHINITY was designed to demonstrate the superiority of adjuvant pertuzumab and trastuzumab with standard treatment compared with placebo and trastuzumab with standard treatment, in early-stage HER2-positive breast cancer. The primary endpoint of the APHINITY study was invasive disease-free survival (iDFS), excluding second, non-breast malignancies. Analysis of iDFS is intended to directly demonstrate the long term clinical benefit of adding pertuzumab to an adjuvant trastuzumab/chemotherapy regimen in patients with HER2- positive early breast cancer. Positive results from the APHINITY study in the adjuvant setting would confirm the benefit of adding pertuzumab in the neoadjuvant setting and support conversion from an accelerated approval of pertuzumab to a full approval. The analysis of iDFS will be performed once 379 iDFS events occurring, that is expected to be in 2016. The design of the adjuvant confirmatory is summarized in Table 4.

Table 4. Study Design of the Confirmatory Study: APHINITY

Study No.	**Population, Phase and Study Design**	**Treatment arms (number of planned patients)**	**Primary Endpoint and Statistical design**
BO 25126 (APHINITY)	A randomized, double-blind, placebo-controlled two-arm Phase 3 study of adjuvant trastuzumab and chemotherapy plus pertuzumab or placebo, in patients with primary operable breast cancer	Arm A: Chemo+Trastuzumab +Pertuzumab (n=2400) Arm B: Chemo+Trastuzumab +Placebo (n=2400)	iDFS 379 iDFS events needed to have 80% power to detect a HR of 0.75 (3-yr iDFS 89.2% vs. 91.8%)

In the tables and figures of this review, "H+D" represents the trastuzumab plus docetaxel arm, "P+H+D" represents the pertuzumab plus trastuzumab plus docetaxel arm, "P+H" represents the pertuzumab plus trastuzumab arm, and "P+D" represents the pertuzumab plus docetaxel arm.

Reviewer's comments

- *In study NEOSPHERE, before the protocol Amendment B being effective, 29 patients have been randomized to one of the three arms under the original protocol. A sensitivity analysis for the primary endpoint has been performed by excluding the 29 patients enrolled before*

the activation Amendment B from the analysis population. The results are consistent with the primary findings in the ITT population. See Table 11 for details.

- *In study NEOSPHERE, before protocol Amendment C being effective, 149 pts have been randomized using the old definition of TNM stage. Though the definition used was different in the 149 patients, the final classification of tumor subtype was the same as that per the corrected TNM staging definition. Therefore, the correction of TNM staging definition had no impact on the values of breast cancer type.*

2.2 Data Sources

Electronic submission including protocols, statistical analysis plan, and study reports for this sBLA submission is located on network with network path: \\cber-fs3\M\eCTD_Submissions\STN125409\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mbc\5351-stud-rep-contr\wo20697. Analysis and raw datasets are located at \\cber-fs3\M\eCTD_Submissions\STN125409\0112\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Overall Study Design

Study NEOSPHERE was a phase 2 open-label, multicenter, multinational, randomized study to evaluate the efficacy and safety of neoadjuvant treatment of trastuzumab plus docetaxel (Arm A: H+D) versus trastuzumab plus pertuzumab plus docetaxel (Arm B: H+P+D) as versus trastuzumab plus pertuzumab (Arm C: H+P) in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer. In addition, the activity of pertuzumab plus docetaxel (Arm D: P+D) was evaluated compared to that of trastuzumab plus pertuzumab plus docetaxel (Arm B: H+P+D).

Study used a dynamic randomization method to randomly allocate patients to one of the four treatment arm. The randomization procedure considered the following two prognostic factors:

- Breast cancer type (operable defined as T2-3, N0-1, M0; locally advanced defined as T2-3, N2-3, M0, or T4a-c, any N, M0; inflammatory defined as T4d, any N, M0)
- Estrogen and Progesterone status (at least one positive; both negative)

All patients were treated every three weeks for four cycles and then underwent breast surgery.

The primary efficacy endpoint of this study was pCR rate in the breast (ypT0/is), defined as absence of invasive neoplastic cells on microscopic examination of the tumor remnants at

surgery. The pathological complete response status was evaluated after 4 cycles of neoadjuvant treatment and surgery or withdrawn from the study whichever occurred sooner.

Post surgery, patients in Arms A, B and D would have received three cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) from Cycle 5-7, and patients in Arm C would have received four cycles of docetaxel followed by three cycles of FEC. All patients would have received trastuzumab every three weeks for one year (from Cycle 5 to 17 for patients on Arms A, B and C and from Cycles 5 to 21 for patients on Arm D). After completion of post-operative chemotherapy, patients would have received radiotherapy as per local clinical standard and those patients whose tumors were estrogen-receptor positive would have received hormone manipulation as per local clinical standard. In summary, all patients would have received equivalent cumulative doses of the chemotherapeutic agents and trastuzumab (although the timing would differ); all patients would have received the same overall therapy, with the exception of Arm A patients who would not receive any pertuzumab. See Figure 1 for details.

Patients whose neoadjuvant study treatment was discontinued prior to surgery would have been managed as per local practice. Patients, whose adjuvant (post-operative) chemotherapy was discontinued due to standard chemotherapy related intolerable toxicity, would have continued with trastuzumab until they have received a total of 17 cycles of treatment. After completion of the study treatment, patients would be followed up for PFS until disease progression or until five years after randomization of the last patient, whichever is earlier.

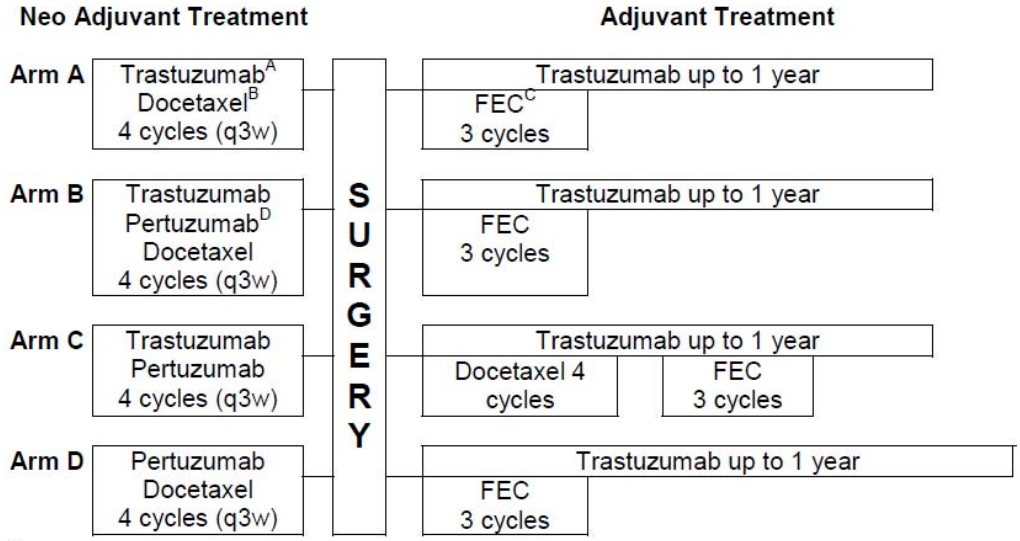


Figure 1. Overall Study Design

[Source: CSR Figure 1]

Reviewer's comments

- *Although the study had 4 arms, and 3-pair comparisons were planned, the focus of this review is on the comparison between Arm B and Arm A to isolate the effect of pertuzumab in the combination therapy.*
- *This study used a dynamic randomization method to assign patients randomly to the four treatment arm. The "range method" proposed by Pocock and Simon [1] was followed in the dynamic randomization. In general, dynamic randomization is that the allocation of a new patient depends on the prognostic factor status of patients who have already been enrolled into the study. The purpose of dynamic randomization is to achieve balance between treatment arms with respect to pre-specified prognostic factors. However, if the analysis method does not take the randomization procedure into account, the type I error rate may not be well controlled, as demonstrated in literature. Therefore, a re-randomization test based on the same study randomization procedure is needed to confirm the results from the primary analysis. The applicant has performed and submitted the re-randomization test results per the FDA's request. Results are summarized in Section 3.2.4.1.*

3.2.1.2 Schedule of Assessments

Baseline total tumor burden was assessed within a maximum of 4 weeks before first dose of study drug treatment. The baseline breast tumor had to be > 2 cm and measured by mammography and clinical breast examination (CBE). A tumor response assessment was also required after completion of all pre-operative treatment cycles. During pre- operative treatment (cycle 1 - 4), tumor response was measured using CBE at every treatment cycle. The same techniques were to be used for evaluating the target lesion for all assessments throughout the treatment period.

Pathological complete response status was evaluated using microscopic examination of the tumor remnants after surgery following primary systemic therapy. All response rates were assessed locally and were not independently reviewed.

If there was suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment was performed. If the lesion showed clear signs of progression (clinical increase of the primary tumor or evidence of metastasis in the pre-operative setting (cycles 1 - 4)) the patient was immediately removed from study treatment and provided with the local standard of care, such as second-line cytotoxic regimen, surgery and or radiotherapy.

3.2.1.3 Efficacy Endpoints

Primary endpoints:

- pCR

Secondary endpoints:

- Best tumor response during neoadjuvant period
- Time to first clinical response during neoadjuvant period
- Clinical response at the last assessment in neoadjuvant period

- Breast conserving surgery rate
- Progressive disease (PD) rate
- Progression-free survival (PFS)
- Disease-free survival (DFS)

A **pCR** was defined as absence of invasive neoplastic cells on microscopic examination of the tumor remnants at surgery. Evaluation of pCR was planned after neo-adjuvant treatment (scheduled to be four cycles) and surgery, or withdrawal from the study whichever occurs first. Patients whose pCR assessment was missing or invalid were counted as not achieving a pCR.

Clinical response rate was defined as the proportion of patients who achieved a clinical response during cycles 1-4 (pre-surgery). Clinical response was defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) per local practice based on RECIST 1.0.

Time to clinical response was defined as the time from the date of first dose received to the date of assessment of clinical response.

Breast conserving surgery rate was defined as the proportion of patients who achieved breast conserving surgery where mastectomy was planned. Patients with inflammatory breast cancer were excluded from the analysis, as these patients received mastectomy irrespective of their response to neoadjuvant treatment.

Progressive disease rate was defined as the percentage of patients with progressive disease during neoadjuvant period.

PFS was defined as the time from the date of randomization to the first documentation of progressive disease or death. Patients who were withdrawn from study follow-up (alive) or continue without documented progression and for whom there exists eCRF evidence that evaluations have been made, would be censored at the date of the last assessment when the patient was known to be free from progressive disease.

DFS, only for patients who underwent surgery (patients who did not undergo surgery were excluded), was defined as the time from surgery date to the first documentation of progressive disease or death after the date of primary surgery. Any evidence of contralateral disease in-situ was not considered as a disease progression. DFS was described separately in patients who achieved a pCR from those who did not. Patients who had surgery but did not achieve a pCR were censored at date of surgery. Patients who withdrew from the study without documented progression and for whom there was eCRF evidence that evaluations were made were censored at the date of the last assessment when the patient was known to be disease-free.

Reviewer's Comments

- *As recommended in the draft Guidance for Industry, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf), the FDA-preferred pCR definition is absence of tumor in both breast and lymph nodes regardless DCIS status (ypT0/is ypN0). Therefore, the review team performed analyses based on the pCR definition of ypT0/is ypN0.*

- *There was no alpha adjustment for multiple secondary endpoints pre-specified in the statistical analysis plan. Results of the secondary endpoints may not be included in labeling.*
- *PFS is an endpoint commonly used in the metastatic disease setting, which is not an appropriate endpoint to be used in the neoadjuvant disease setting as events in neoadjuvant studies include disease recurrence after surgery. Event free survival (EFS) is an endpoint that is appropriate to be used in neoadjuvant studies. The calculation of EFS starts from time of randomization, which is similar to the sponsor-defined PFS. Therefore, we will use the term "EFS" instead of "PFS" throughout the review.*
- *The study was not powered on DFS or EFS analysis, although an analysis is planned to be performed after 5-year follow-up since the last patient randomization.*

3.2.1.4 Sample Size Determination

The overall significance level for the study was controlled at two-sided 0.20, and the Simes multiplicity adjustment was used to account for three comparisons: Arm B versus Arm A; Arm C versus Arm A; Arm B versus Arm D. A total of 400 patients (approximately 100 patients per arm) were needed for this study to have 80% power to detect an absolute percentage increase of 15% (25% versus 40%) in pCR rate between arms for each of the three comparisons, at an two-sided alpha level of 0.20.

Reviewer's Comments

- *The study was not designed as a pivotal study to support regulatory efficacy claim originally, with the alpha level set as 2-sided 0.20. However, to align with the overall type I error rate level required for a registration pivotal trial, p-values from all tests will be evaluated against 2-sided alpha of 0.05.*
- *Simes method was used for multiplicity adjustment. As the adjustment was made to the CMH p-values rather than the alpha level of test, the p-values can also be interpreted at the conventional two-sided 0.05 alpha level. Simes adjustment method is illustrated below:*
  Step 1. Each p-value from CMH test multiplied by the number of comparisons (=3)
  Step 2. Then divided by its rank (1=lowest p-value, 3=highest p-value)
  Step 3. P-values then compared with the significance level pre-defined

3.2.1.5 Interim Analyses

There was no interim analysis planned for pCR or any secondary efficacy endpoints.

3.2.2 Statistical Methodologies

3.2.2.1 Efficacy Analysis Population

The intent-to-treat (ITT) population included all patients randomized into the study, regardless of whether they received any study medication. Patients were to be classified according to assigned treatment group, regardless of the actual treatment received. The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.

The per-protocol (PP) population was a subset of the ITT population. It excluded patients who were deemed to have any major protocol violations prior to the adjuvant phase of the study.

3.2.2.2 Efficacy Analysis Methods

The primary analysis of pCR rate in breast was performed within the ITT population. The pCR rates and the corresponding 95% confidence intervals (estimated by the Pearson-Clopper method) were summarized for each randomized arm. Approximate 95% confidence intervals for differences in pCR rates between pairs of treatment arms were obtained using the Hauck-Anderson method. Cochran-Mantel-Haenszel (CMH) testing was used to obtain p-values for stratified comparisons between pairs of treatment arms, with breast tumor type and hormone receptor status as the stratification factors. Simes multiplicity adjustments were applied to individual p-values, account for the three pair-wise treatment comparisons.

Tumor response data and progressive-disease rate during neo-adjuvant treatment were summarized by treatment arm with 95% confidence intervals calculated using the Pearson-Clopper method. All time-to-event endpoints were summarized using Kaplan-Meier approach.

3.2.3. Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patients Disposition

From 14 December 2007 until 23 September 2009, a total of 417 patients from 59 clinical sites in 16 countries were randomized. A total of 107, 107, 107, and 96 patients were randomized to arms A, B, C, and D, respectively; however, the number of patients who actually received treatment according to each arm was 107, 107, 108 and 94. As of the 22 December 2009 data cut-off date for the primary efficacy analysis, 154 patients have finished study adjuvant treatment. Twenty-nine and 16 patients withdrew from the study neoadjuvant treatment and adjuvant treatment, respectively. The detailed withdrawal reasons are listed in Table 5.

Table 5. Reasons of Withdrawal during Neoadjuvant Phase and Adjuvant Phase

Reasons of Withdrawals	Arm A H+D (N=107)	Arm B P+H+D (N=107)	Arm C P+H (N=108)	Arm D P+D (N=94)
Withdrawals from Neoadjuvant Treatment				
Death	0	1	0	0
Insufficient Therapeutic Response	0	1	7	1
Violation of Selection Criteria at Entry	1	2	1	1
Refused Treatment	1	1	4	0
Failure to Return	1	0	0	0
Other	1	0	0	0
Total	4 (3.7%)	5 (4.7%)	14 (13%)	6 (6.4%)
	Arm A H+D (N=99)	Arm B P+H+D (N=98)	Arm C P+H (N=92)	Arm D P+D (N=84)
Withdrawals from Adjuvant Treatment				
Adverse Events	0	2	1	0
Insufficient Therapeutic Response	1	2	0	3
Refused Treatment *	0	1	0	3
Failure to Return	1	0	1	0
Other	0	1	0	0
Total	2 (2.0%)	6 (6.1%)	2 (2.2%)	6 (7.1%)

Note: this summary is based on patients who truly received the assigned treatment in each arm
[Source CSR Tables 5 and 6]

At a later safety update (clinical cutoff date: 9 March 2012), a total of 60 patients had withdrawn from either the neoadjuvant or adjuvant treatment periods. The most common reason was "insufficient therapeutic response" which included progressive disease. Eleven patients (3 in Arm B, 4 in Arm C, and 4 in Arm D) withdrew prematurely from study treatment because of adverse events.

3.2.3.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics are presented in Tables 6 and 7. The median age of all randomized patients was 50 years old. Seventy-one percent (71%) were Caucasian, 23% were Asian, and only 1% were African-American. Arm D had less percentage of Caucasian patients (64%) compared to other arms. Eighty-nine percent (89%) patients had ECOG performance score (PS) of 0 at baseline, and arm A had more patients with ECOG PS 0 (94%) compared to other three arms. No patients were enrolled from the United States, and 28 patients (6.7%) were enrolled from North America. Overall 7% of patient had inflammatory cancer, 32% had locally advanced cancer and 61% had operable cancer. Forty-seven percent (47%) had hormone receptor positive tumors.

Table 6. Summary of Demographics Characteristics

	Overall (n=417)	**Arm A H+D (n=107)**	**Arm B P+H+D (n=107)**	**Arm C P+H (n=107)**	**Arm D P+D (n=96)**
Age (years)					
n	417	107	107	107	96
Median	50	50	50	49	49
Range	22-80	32-74	28-77	22-80	27-70
Race, n (%)					
Caucasian	297 (71.2%)	80 (74.8%)	77 (72.0%)	79 (73.8%)	61 (63.5%)
Asian	95 (22.8%)	25 (23.4%)	23 (21.5%)	22 (20.6%)	25 (26.0%)
Black	6 (1.4%)	0	2 (1.9%)	1 (0.9%)	3 (3.1%)
Other	19 (4.6%)	2 (1.9%)	5 (4.7%)	5 (4.7%)	7 (7.3%)
Region, n (%)					
Asia	95 (22.8%)	26 (24.3%)	22 (20.5%)	22 (20.5%)	25 (26.0%)
Europe	245 (58.8%)	63 (58.9%)	71 (66.4%)	62 (57.9%)	49 (51.0%)
North America	28 (6.7%)	5 (4.7%)	5 (4.7%)	10 (9.4%)	8 (8.3%)
South America	48 (11.5%)	12 (11.2%)	9 (8.4%)	13 (12.1%)	14 (14.6%)
Other	1 (0.2%)	1 (0.9%)	0	0	0
Female Reproductive Status					
Postmenopausal	183 (43.9%)	48 (44.9%)	45 (42.1%)	50 (46.7%)	40 (41.7%)
Surgically Steril.	27 (6.5%)	7 (6.5%)	7 (6.5%)	4 (3.7%)	9 (9.4%)
With Cont. Prot.	207 (49.6%)	52 (48.6%)	55 (51.4%)	53 (49.5%)	47 (49.0%)
ECOG PS					
0	368 (88.5%)	100 (94.3%)	96 (89.7%)	92 (86.0%)	80 (83.3%)
1	48 (11.5%)	6 (5.7%)	11 (10.3%)	15 (14.0%)	16 (16.7%)

[Source CSR Table 9]

Table 7. Summary of Baseline Disease Characteristics

	Overall (n=417)	Arm A H+D (n=107)	Arm B P+H+D (n=107)	Arm C P+H (n=107)	Arm D P+D (n=96)
Histological Tumor Grade					
Anaplastic	1 (0.2%)	0	0	1 (0.9%)	0
Poorly Differentiated	137 (32.9%)	31 (29.0%)	34 (31.8%)	38 (35.5%)	34 (35.4%)
Moderately Differentiated	123 (29.5%)	37 (34.6%)	33 (30.8%)	28 (26.2%)	25 (26.0%)
Well Differentiated	10 (2.4%)	1 (0.9%)	2 (1.9%)	3 (2.8%)	4 (4.2%)
NK	2 (0.5%)	0	0	1 (0.9%)	1 (1.0%)
Unknown	144 (34.5%)	38 (35.5%)	38 (35.5%)	36 (33.6%)	32 (33.3%)
Lymph node status					
N0	123 (29%)	32 (30%)	31 (29%)	32 (30%)	28 (29%)
N1	188 (45%)	48 (45%)	53 (50%)	46 (43%)	41 (43%)
N2	90 (22%)	22 (21%)	22 (21%)	24 (22%)	22 (23%)
N3	15 (4%)	5 (5%)	0	5 (5%)	5 (5%)
Unknown	1 (<1%)	0	1 (<1%)	0	0
ER Status					
Negative	230 (55.2%)	59 (55.1%)	61 (57.0%)	57 (53.3%)	53 (55.2%)
Positive	186 (44.6%)	48 (44.9%)	46 (43.0%)	49 (45.8%)	43 (44.8%)
Unknown	1 (0.2%)	0	0	1 (0.9%)	0
PR Status					
Negative	278 (66.7%)	75 (70.1%)	73 (68.2%)	64 (59.8%)	66 (68.8%)
Positive	138 (33.1%)	32 (29.9%)	34 (31.8%)	42 (39.3%)	30 (31.3%)
Unknown	1 (0.2%)	0	0	1 (0.9%)	0
Hormone Receptor Status					
ER- and PR-	219 (52.5%)	57 (53.3%)	57 (53.3%)	55 (51.4%)	50 (52.1%)
ER+ and/or PR+	197 (47.2%)	50 (46.7%)	50 (46.7%)	51 (47.7%)	46 (47.9%)
Unknown	1 (0.2%)	0	0	1 (0.9%)	0
Breast Cancer Type					
Inflammatory	29 (7.0%)	7 (6.5%)	10 (9.3%)	7 (6.5%)	5 (5.2%)
Locally Advanced	134 (32.1%)	36 (33.6%)	32 (29.9%)	35 (32.7%)	31 (32.3%)
Operable	254 (60.9%)	64 (59.8%)	65 (60.7%)	65 (60.7%)	60 (62.5%)
Her2 Status IHC/FISH Combined					
-/FISH Positive	6 (1.4%)	0	1 (0.9%)	2 (1.9%)	3 (3.1%)
IHC 2+/FISH Positive	31 (7.4%)	8 (7.5%)	6 (5.6%)	13 (12.1%)	4 (4.2%)
IHC 3+/-	324 (77.7%)	86 (80.4%)	87 (81.3%)	79 (73.8%)	72 (75.0%)
IHC 3+/FISH NK	3 (0.7%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0
IHC 3+/FISH Positive	53 (12.7%)	12 (11.2%)	12 (11.2%)	12 (11.2%)	17 (17.7%)

[Source CSR Table 10]

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was pCR rate per ypT0/is in the ITT population. The combination of P+H+D (Arm B) improved the pCR in breast rate compared to H+D (Arm A, simes adjusted p-value=0.0141), with an increase in pCR rate of 16.8% (29.0% in arm A versus 45.8% in arm B). The pCR results from all 4 treatment arms are summarized in Table 8. Twenty-five patients did not undergo the primary surgery and no pCR assessment was performed. All patients who have undergone primary surgery had a valid assessment of pCR. The reasons of not receiving primary surgery are summarized in Table 9. In the analyses of pCR, those 25 patients were considered as not achieving a pCR as pre-specified in the study protocol.

Table 8. Analysis Results of pCR in the Breast (ypT0/is) Rate

	Arm A H+D (n=107)	**Arm B** P+H+D (n=107)	**Arm C** P+H (n=107)	**Arm D** P+D (n=96)
pCR in the breast (ypT0/is)				
Number of Pts with pCR (%)	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)
95% CI[1]	20.6%, 38.5%	36.1%, 55.7%	10.3%, 25.3%	15.8%, 33.7%
Comparison Arms		B vs. A	C vs. A	D vs. B
Difference in pCR Rate[2]		16.8% (4.1%, 29.6%)	-12.2% (-23.3%, -1%)	-21.8% (-34.6%, -9.0%)
Ratio of pCR Rate		1.58 (1.10, 2.27)	0.58 (0.35, 0.97)	0.52 (0.35, 0.79)
Odds Ratio		2.16 (1.20, 3.88)	0.44 (0.22, 0.89)	0.35 (0.19, 0.66)
CMH[3] p-value		0.0094	0.0198	0.0010
Adjusted CMH p-value[4]		**0.0141**	**0.0198**	**0.0030**

[1] 95% CI for one sample binomial using Pearson-Clopper method
[2] Approximate 95% CI for difference of two rates using Hauck-Anderson method
[3] CMH test stratified by breast cancer type and hormone receptor status
[4] P-value from CMH test, with Simes multiplicity adjustment
[Source: CSR Table 15]

Table 9. Reasons of Not Receiving Surgery

	Arm A H+D (n=107)	**Arm B** P+H+D (n=107)	**Arm C** P+H (n=107)	**Arm D** P+D (n=96)
# of Patients Not Receiving Surgery	4	6	11	4
Reason				
PD during Neoadjuvant treatment	0	1	6[1]	2
Withdrew concent	1	0	3	1
Failure to return	1	0	0	0
AE/intercurrent illness	0	1	1	0
Violation of selection criteria at entry	2	2	1	1
Refused treatment	0	1	0	0
Death	0	1	0	0

[1] 2 more patients had disease progression during neoadjuvant in Arm C, however, they still underwent surgery.

Reviewer's comments

- *All pCR assessments were performed locally and there was no independent review.*

- *As recommended in the FDA's neoadjuvant breast cancer trial draft guidance, the FDA preferred definition of pCR is ypT0/is ypN0.*

  ypT0/is ypN0 is defined as absence of invasive cancer in the breast and lymph nodes, with DCIS allowed.

  The Sponsor has collected the information of axillary lymph node status and DCIS/LCIS status at the time of pCR assessments. Therefore, the review team was able to calculate pCR rates based on the FDA preferred pCR definition, with results summarized in Table 10. The pCR improvement by adding pertuzumab to transtuzumab plus docetaxel combination was 17.8% per definition of ypT0/is ypN0, which is similar to the improvement magnitude observed based on definition of ypT0/is. The simes-adjusted p-value was 0.0063 for the comparison between Arm B and Arm A.

- *With the concern that a CMH test may not able to control the overall type I error when the study used a dynamic randomization, the FDA requested the applicant to perform re-randomization test by considering the randomization procedure which has been applied to the study. The applicant performed two re-randomization tests (5,000 simulations each), with one based on prognostic factor values collected on the original IXRS database and the other based on the values from the final clinical database. There were a total of 45 patients with different values of the two prognostic factors between the original IXRS database and the final clinical database. The results of both re-randomization tests are consistent to those from the CMH tests, as shown in Table 10 for pCR defined as ypT0/is ypN0. Similar findings were observed using pCR definition of ypT0/is.*

Table 10. Analysis Results of pCR (ypT0/is ypN0) Rate

	Arm A H+D (n=107)	**Arm B** P+H+D (n=107)	**Arm C** P+H (n=107)	**Arm D** P+D (n=96)
pCR (ypT0/is ypN0)				
Number of Pts with pCR (%)	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)
95% CI[1]	14.1%, 30.5%	30.0%, 49.2%	5.9%, 18.8%	10.7%, 26.8%
Comparison Arms		B vs. A	C vs. A	D vs. B
Difference of pCR Rates[2]		17.8% (5.7%, 29.9%)	-10.3% (- 20.1%, -0.47%)	-21.5% (-33.5%, -9.6%)
Ratio of pCR Rates		1.83 (1.19, 2.81)	0.52 (0.27, 0.99)	0.45 (0.28, 0.74)
Odds Ratio		2.46 (1.30, 4.66)	0.40 (0.18, 0.89)	0.31 (0.15, 0.61)
CMH[3] p-value		0.0042	0.0223	0.0006
Adjusted CMH p-value[4]		0.0063	0.0223	0.0018
Adjusted unstratified P-value[4]		0.011	0.0635	0.0033
Adjusted re-randomization p-value (original IXRS data)[4]		0.0057	0.0176	0.0006
Adjusted re-randomization p-value (final clinical data)[4]		0.0036	0.0218	0.0006

[1] 95% CI for one sample binomial using Pearson-Clopper method
[2] Approximate 95% CI for difference of two rates using Hauck-Anderson method
[3] CMH test stratified by breast cancer type and hormone receptor status
[4] P-value with Simes multiplicity adjustment

- *To explore whether achieving a pCR is associated with a better prognosis at baseline, baseline characteristics were compared between patients who achieved a pCR and those who did not. This exploratory analysis was performed within patients who were randomized to*

Arm A and Arm B, and patients were pooled together from the two arms for the comparison of pCR vs. non-pCR. As shown in Table 11, the baseline characteristics are similar between patients who achieved a pCR and those who did not, except for hormone receptor status. A majority (74%) of patients who achieved a pCR were hormone receptor negative, while in patients who did not achieve a pCR, 44% were hormone receptor negative. Therefore, t*he distribution of baseline characteristics was further explored by hormone receptor status. As shown in Table 12, most of the baseline characteristics are comparable between hormone receptor positive and negative groups, except that fewer patients (22%) had locally advanced breast cancer in the hormone receptor positive group compared to negative group (40%).*

Table 11. Baseline Characteristics by pCR status

	pCR N=65	**Non-pCR** N=149
Age		
< 65	59 (91%)	137 (92%)
>= 65	6 (9%)	12 (8%)
Race, n (%)		
Caucasian	45 (69%)	112 (75%)
Asian	18 (28%)	30 (20%)
Black	1 (2%)	1 (<1%)
Other	1 (2%)	6 (4%)
Histological Tumor Grade		
Poorly Differentiated	21 (32%)	44 (30%)
Moderately Differentiated	22 (34%)	48 (32%)
Well Differentiated	0	3 (2%)
Unknown	22 (34%)	54 (36%)
Lymph node status		
N0	22 (34%)	41 (28%)
N1	25 (38%)	76 (51%)
N2	16 (25%)	28 (19%)
N3	2 (3%)	3 (2%)
Unknown	0	1 (<1%)
Hormone Receptor Status		
ER- and PR-	48 (74%)	66 (44%)
ER+ and/or PR+	17 (26%)	83 (56%)
Breast Cancer Type		
Inflammatory	4 (6%)	13 (9%)
Locally Advanced	23 (35%)	45 (30%)
Operable	38 (58%)	91 (61%)
Baseline ECOG PS		
0	63 (97%)	133 (89%)
1	2 (3%)	15 (10%)
Unknown	0	1 (<1%)

Table 12. Baseline Characteristics by Hormone Receptor Status

	HR-pos N=100	**HR-neg** N=114
Age		
< 65	91 (91%)	105 (92%)
>= 65	9 (9%)	9 (8%)
Race, n (%)		
Caucasian	72 (72%)	85 (75%)
Asian	25 (25%)	23 (20%)
Black	2 (2%)	0
Other	1 (1%)	6 (5%)
Histological Tumor Grade		
Poorly Differentiated	25 (25%)	40 (35%)
Moderately Differentiated	36 (36%)	34 (30%)
Well Differentiated	2 (2%)	1 (<1%)
Unknown	37 (37%)	39 (34%)
Lymph node status		
N0	32 (32%)	31 (27%)
N1	50 (50%)	51 (45%)
N2	17 (17%)	27 (23%)
N3	1 (1%)	4 (4%)
Unknown	0	1 (<1%)
Breast Cancer Type		
Inflammatory	10 (10%)	7 (6%)
Locally Advanced	22 (22%)	46 (40%)
Operable	68 (68%)	61 (54%)
Baseline ECOG PS		
0	91 (91%)	105 (92%)
1	8 (8%)	9 (8%)
Unknown	1 (1%)	0

Sensitivity analyses on pCR

All the following sensitivity analyses are based on pCR definition of ypT0/is ypN0. The pCR results in the per-protocol population, in patient subpopulation excluding patients enrolled under Protocol Version A (3-arm), and in the population excluding patients without pCR assessment, are presented in Table 13. The results are consistent with the primary findings in the ITT population.

Table 13. Results of pCR Analyses in Different Patient Populations

	Arm A H+D	Arm B P+H+D	Arm C P+H	Arm D P+D
Per-protocol population				
Total # of Pts	104	101	105	90
pCR, n (%)	23 (22.1%)	40 (39.6%)	11 (10.5%)	15 (16.7%)
95% CI[1]	14.6%, 31.3%	30.0%, 49.8%	5.4%, 18.0%	9.6%, 26.0%
Comparison		B vs. A	C vs. A	D vs. B
Difference in pCR		17.5%	-11.6%	-22.9%
(95% CI)[2]		(5.1%, 29.9%)	(-21.5%, -1.7%)	(-35.2%, -10.7%,)
Simes adjusted CMH p-value[3]		0.0068	0.014	0.0009
Excluding patients randomized under protocol version A				
Total # of Pts	99	98	99	96
pCR, n (%)	22 (22.2%)	40 (40.8%)	10 (10.1%)	17 (17.7%)
95% CI[1]	14.5%, 31.7%	31.0%, 51.2%	5.0%, 17.8%	10.7%, 26.8%
Comparison		B vs. A	C vs. A	D vs. B
Difference in pCR		18.6%	-12.1%	-23.1%
(95% CI) [2]		(5.9%, 31.3%)	(-22.2%, -2.0%)	(-35.5%, -10.7%)
Simes adjusted CMH p-value[3]		0.0059	0.0118	0.0006
Excluding patients whose pCR status not available				
Total # of Pts	103	101	96	92
pCR, n (%)	23 (22.3%)	42 (41.6%)	12 (12.5%)	17 (18.5%)
95% CI[1]	14.7%, 31.6%	31.9%, 50.0%	6.7%, 20.8%	11.2%, 27.9%
Comparison		B vs. A	C vs. A	D vs. B
Difference in pCR		19.3%	-9.8%	-23.1%
(95% CI) [2]		(6.7%, 31.8%)	(-20.2%, 0.6%)	(-35.6%, -10.6%)
Simes adjusted CMH p-value[3]		0.0035	0.0485	0.0012

[1] 95% CI for one sample binomial using Pearson-Clopper method
[2] Approximate 95% CI for difference of two rates using Hauck-Anderson method
[3] CMH test stratified by breast cancer type and hormone receptor status; P-value with Simes multiplicity adjustment

3.2.4.2 Secondary Efficacy Endpoints

Secondary endpoints of this phase 2 study included response rate, rate of breast-conserving surgery, progression disease rate, DFS, and EFS. There was no multiplicity adjustment pre-specified to control the overall type I error rate. The results of objective response rate, breast-conservative rate, and number of disease progression during neoadjuvant treatment are summarized in Table 14. Among patients (T2-3 stage) with planned mastectomy surgery, the percentage of patients who converted the surgery to conservation therapy after neoadjuvant therapy was comparable in Arms A and B (pertuzumab + trastuzumab + docetaxel vs. trastuzumab plus docetaxel).

As planned in the study protocol, DFS and EFS will be analyzed at 5 years post the last patient randomization; the current submission does not report results of DFS and EFS. As of the most recent cutoff date for safety evaluation, 9 March 2012, there were 9 deaths and 49 disease progressions/recurrences occurred, as listed in Table 15. Based on the available EFS and DFS data, this reviewer plotted Kaplan-Meier curves for EFS and DFS (overall and by pCR status) for descriptive purpose only (Figure 2).

Table 14. Results of Secondary Efficacy Endpoints

	Arm A (H+D) N=107	Arm B (P+H+D) N=107	Arm C (P+H) N=107	Arm D (P+D) N=96
Overall Response per CBE				
N	97	100	98	88
Responders[1], n	79	88	65	65
% (95% CI)[2]	81.4% (72.3%, 88.6%)	88.0% (80.0%, 93.6%)	66.3% (56.1%, 75.6%)	73.9% (63.4%, 82.7%)
Overall Response per X-ray/Mammography				
N	71	53	55	43
Responders[1], n	48	36	26	28
%(95% CI) [2]	67.6% (55.5%, 78.2%)	67.9% (53.7%, 80.1%)	47.3% (33.7%, 61.2%)	65.1% (49.1%, 79.0%)
PD During Neoadjuvant Period				
Progressive disease, n (%)	0	1 (0.9%)	8 (7.5%)	2 (2.1%)
Breast Conserving Surgery (BCS) in patients with T2-3 stage tumor				
# pts with mastectomy planned	62	56	62	60
BCS Achieved, n	14	13	12	19
%(95% CI) [2]	22.6% (12.9%, 35.0%)	23.2% (13.0%, 36.4%)	19.4% (10.4%, 31.4%)	31.7% (20.3%, 45.0%)

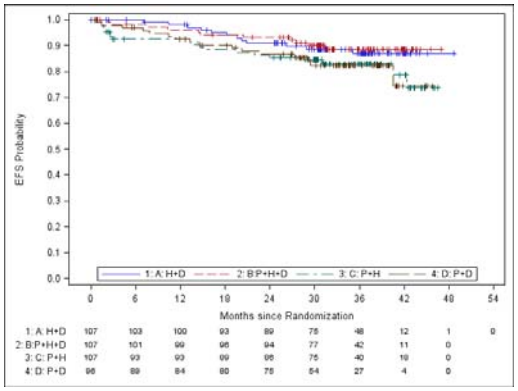
[1] Responders are defined as patients who achieved a CR or PR, and no confirmation assessment was required for CRs and PRs.
[2] 95% CI for one sample binomial using Pearson-Clopper method
[Source: CSR Tables 20, 23, and 25]

Table 15. Summary of Disease Progression and Death

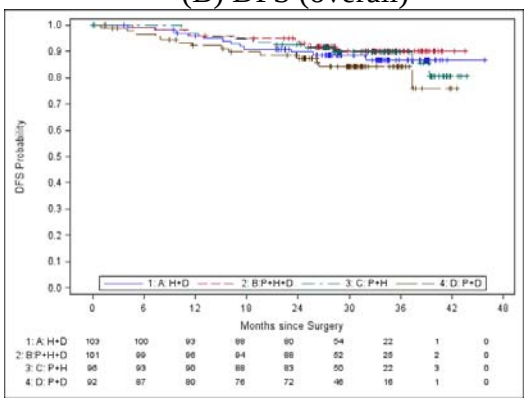
	Arm A (H+D) (n=107)	Arm B (P+H+D) (n=107)	Arm C (P+H) (n=107)	Arm D (H+D) (n=96)
Disease Progression/Death Since Randomization	12 (11.2%)	11 (10.3%)	19 (17.8%)	16 (16.7%)
Disease Recurrence/Death Post Surgery [1]	12 (11.2%)	9 (8.4%)	11 (10.3%)	14 (14.9%)
Death	2 (1.9%)	1 (0.9%)	1 (0.9%) [2]	5 (5.2%)

[1] Only patients who underwent surgery were included
[2] Death occurred during neoadjuvant period
Cutoff date: March 9, 2012
[Source: safety-update CSR Table 5]

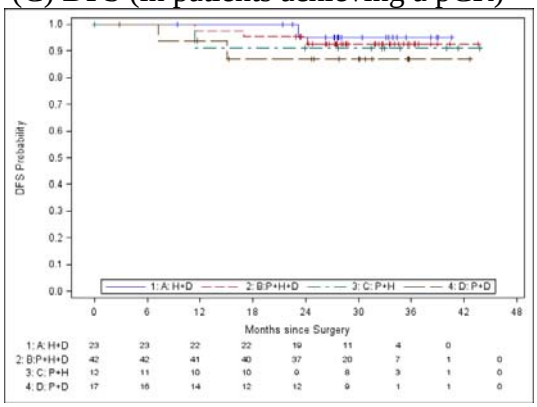
(A) EFS



(B) DFS (overall)



(C) DFS (in patients achieving a pCR)



(D) DFS (in patients not achieving a pCR)

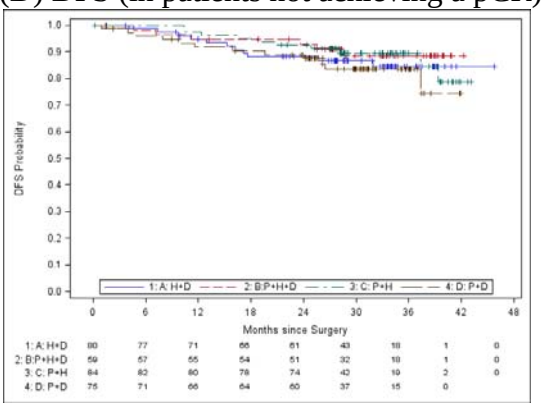


Figure 2. Kaplan-Meier Curves of EFS and DFS (Cutoff date: March 9, 2012)

Note: DFS analyses were performed within patients who underwent the primary surgery

3.2.4.3 Efficacy results from the supportive study TRYPHAENA

In this supportive study, 73, 75, and 77 patients were randomized to receive (1) FEC, trastuzumab and pertuzumab, followed by docetaxel, trastuzumab and pertuzumab, or (2) FEC followed by docetaxel, trastucuamb and pertuzumab, or (3) Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab, respectively. Pathologic complete response in the breast (ypT0/is) was one of the secondary endpoints. The results were consistent using the two pCR definitions (ypT0/is and ypT0/is ypN0), as shown in Table 16. With all the three treatment arms in study TRYPHAENA containing pertuzumab, the efficacy effect of pertuzumab could not be isolated. Higher pCR rates were observed in the 3 pertuzumab treatment arms compared to the NEOSPHERE study possibly due to the incorporation of the anthracycline regimen preoperatively.

Table 16. Summary of pCR Results in Study TRYPHAENA

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

FEC=5-fluorouracil, epirubicin, cyclophosphamide, D= docetaxel, P= 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.

3.2.5 Conclusions for Efficacy

The pivotal study NEOSPHERE has demonstrated a statistically significant improvement in pCR per the FDA-preferred definition , with a pCR rate of 39.3% in the pertuzumab + trastuzumab + docetaxel arm and 21.5% in the trastuzumab + docetaxel arm (a difference of 17.8% (95% CI: 5.7%, 29.9%); adjusted p-value: 0.0063). A similar magnitude of improvement was also observed using the applicant pre-specified pCR definition (ypT0/is). A re-randomization test which considered the actual dynamic randomization procedure used further confirmed the results from the primary analysis. Results of sensitivity analyses for pCR in different analysis populations were consistent with results in the ITT population. Analyses of DFS and EFS are planned to be performed after 5 years follow-up since the last patient randomization. Only limited data of DFS and EFS are available in the current sBLA submission.

3.3 Evaluation of Safety

Please refer to the clinical evaluations of this application for safety results and conclusions for safety.

3.4 Benefit-Risk Assessment

Please refer to clinical evaluations of this application for a benefit-risk evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 17 summarizes pCR rates by age, race and geographic region. Subgroup analysis by gender for this female-only study is not applicable. The subgroup analyses by age, race, and geographic region showed that the addition of pertuzumab improved pCR rate cross the subgroups, though the improvement magnitude is smaller in some subgroups, such as the subgroup of Asian patients. All pCR analyses were based on the definition of ypT0/is ypN0.

Table 17. Subgroup Analyses of pCR (ypT0/is ypN0) by Age, Race, and Region

	Arm A	Arm B	Arm C	Arm D
	H+D	P+H+D	P+H	P+D
Age				
< 65 years	21/97 (21.7%)	38/99 (38.4%)	11/99 (11.1%)	17/90 (18.9%)
≥ 65 years	2/10 (20%)	4/8 (50%)	1/7 (12.5%)	0/6
Race				
White	15/80 (18.8%)	30/77 (39.0%)	6/80 (7.6%)	5/61 (8.2%)
Black	0	1/ 2 (50%)	0/1	0/3
Asian	8/25 (32%)	10/23 (43.5%)	6/23 (26.1%)	9/25 (36%)
Other	0/2	1/5 (20%)	0/4	3/7 (42.9%)
Region				
Asia	8/26 (30.8%)	9/22 (40.9%)	6/22 (27.3%)	9/25 (36%)
Europe	12/63 (19.1%)	28/71 (39.4%)	4/62 (6.5%)	5/49 (10.2%)
North America	0/5	2/5 (40%)	0/10	1/8 (12.5%)
South America	2/12 (16.7%)	3/9 (33.3%)	2/13 (15.4%)	2/14 (14.3%)
Other	1/1 (100%)	0	0	0

4.2 Other Special/Subgroup Populations

Exploratory analyses of pCR by baseline ECOG PS level, hormone receptor status, breast cancer type, and female reproductive status are presented in Table 18. A forest plot further presents the differences in pCR between Arm B and Arm A in several subgroups (Figure 3). All pCR analyses were based on the definition of ypT0/is ypN0.

Table 18. Additional pCR (ypT0/is ypN0) Subgroup Analyses

	Arm A	Arm B	Arm C	Arm D
	H+D	P+H+D	P+H	P+D
Baseline ECOG				
0	22/100 (22%)	41/96 (42.7%)	10/92 (10.9%)	13/80 (16.3%)
1	1/6 (16.7%)	1/11 (9.1%)	2/15 (13.3%)	4/16 (25%)
Hormone Receptor Status				
ER+ or PR+	6/50 (12%)	11/50 (22%)	1/51 (2.0%)	4/46 (8.7%)
ER- and PR-	17/57 (29.8%)	31/57 (54.4%)	11/55 (20%)	13/50 (26%)
Breast Cancer Type				
Operable	12/64 (18.8%)	26/65 (40%)	9/65 (13.9%)	14/60 (23.3%)
Locally advanced	10/36 (27.8%)	13/33 (40.6%)	2/35 (5.7%)	2/31 (6.5%)
Inflammatory	1/7 (14.3%)	3/10 (30%)	1/7 (14.3%)	1/5 (20%)
Female reproductive status				
Postmenopausal	11/48 (22.9%)	21/45 (46.7%)	3/50 (6%)	5/40 (12.5%)
Surgically steril.	1/7 (14.3%)	3/7 (42.9%)	0/4	2/9 (22.2%)
With cont. prot.	11/55 (21.2%)	18/55 (32.7%)	9/53 (17%)	10/47 (21.3%)

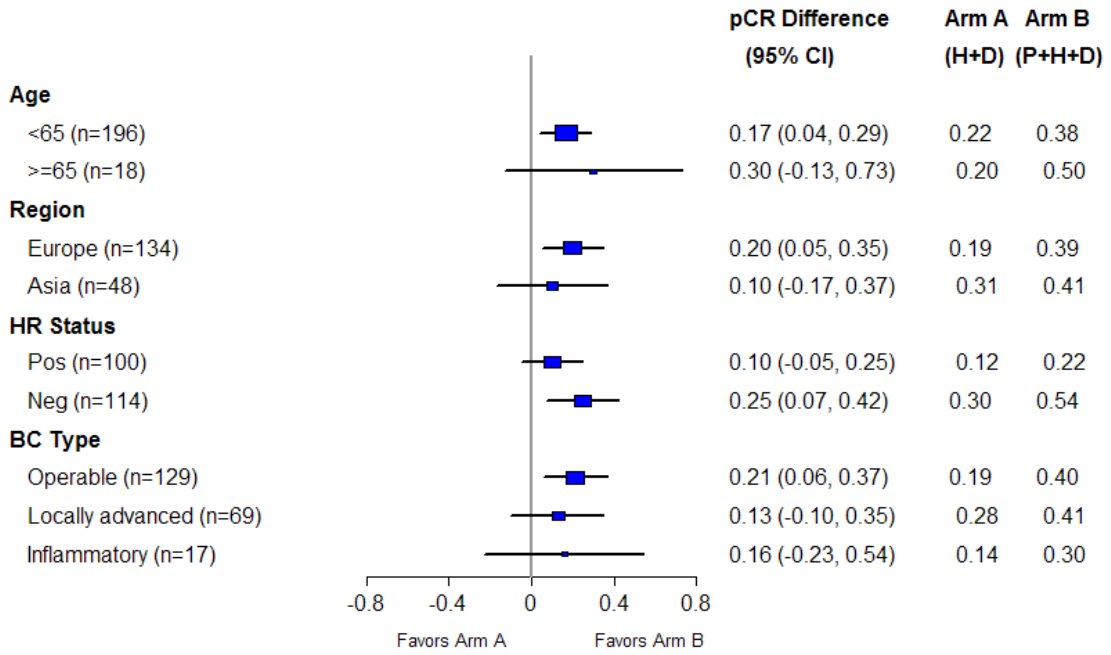


Figure 3. Forest Plot of the Difference in pCR Rates

In the subgroup patients with hormone receptor positive tumor, the absolute pCR rate in each arm and the magnitude of improvement in pCR between Arm B and Arm A are smaller, as compared to the results from the subgroup patients with hormone receptor negative tumor. Similar to the NEOSPHERE study results, in the supportive study TRYPHAENA, the pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors (see Table 19).

Table 19. Summary of pCR Results Based on Hormone Receptor Status

	NEOSPHERE		TRYPHAENA		
	H+D	**P+H+D**	**FEC+P+H/ P+H+D**	**FEC/ P+H +D**	**TCH+P**
Hormone receptor positive	N=50	N=50	N=39	N=35	N=40
pCR[1] %	12%	22%	41.0%	46%	48%
[95% CI]	[4.5, 24.3]	[11.5, 36.0]	[25.6, 57.9]	[28.8, 63.4]	[31.5, 63.9]
Hormone receptor negative	N=57	N=57	N=34	N=40	N=37
pCR[1] %	30%	54%	74%	63%	81%
[95% CI]	[18.4, 43.4]	[40.7, 67.6]	[55.6, 87.1]	[45.8, 77.3]	[64.8, 92.0]

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

Reviewer's comments:

As observed from both NEOSPHERE study and TRYPHAENA study, the absolute pCR rate in each arm and improvement in pCR rate by are smaller in the hormone receptor positive patients, as compared to the results from the subgroup patients with hormone receptor negative tumor. However, similar findings were observed in the registration trials of pertuzumab and T-DM1 (CLEOPATRA and EMILIA) for the treatment of patients with metastatic breast cancer

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The phase 2 pivotal study, NEOSPHERE, was not designed to support a regulatory efficacy claim originally, with the alpha level set as 2-sided 0.20. However, to align with the overall type I error rate level required for a registration trial, p-values from all tests were evaluated against 2-sided alpha of 0.05.

Study NEOSPHERE assigned patients randomly to one of four treatment arms using a dynamic randomization method. Although dynamic randomization may achieve better balance across arms for important prognostic factors and may improve study power, simulation studies show that if the analysis test does not take the randomization algorithm into account, type I error may mot be able to be controlled, either inflation or deflation. Therefore, a re-randomization test is needed to confirm the primary analysis results from a CMH test. Per the FDA's request, the applicant performed re-randomization tests and the results confirmed the primary findings from CMH tests.

In patients with hormone receptor positive tumors, the magnitude of pCR improvement is smaller, compared to that in the subgroup patients with hormone receptor negative tumors, i.e., 10% vs. 25%. However, similar findings in subgroups by hormone receptor status have been observed in the registration trials of pertuzumab and T-DM1 (CLEOPATRA and EMILIA) for the treatment of patients with metastatic breast cancer. In addition, in the confirmatory study, APHINITY, hormone receptor status has been used as a randomization stratification factor. Overall, this reviewer concluded that the effect magnitude difference observed does not have impact on the efficacy conclusions.

5.2 Collective Evidences

In the pivotal study for neoadjuvant treatment, NEOSPHERE, a statistically significant improvement in pCR rate was observed with the pertuzumab + trastuzumab + docetaxel combination over trastuzumab plus docetaxel. Using the FDA-preferred definition of pCR, ypT0/is ypN0, the improvement in pCR rate was 17.8% (95% CI: 5.7%, 29.9%; adjusted p-value: 0.0063), with a pCR rate of 39.3% in the pertuzumab + trastuzumab + docetaxel versus 21.5% in the trastuzumab + docetaxel arm. A similar magnitude of improvement in pCR using the study pre-specified definition, ypT0/is, was also observed: 16.8% (95% CI: 4.1%, 29.6%; adjusted p-value: 0.0141). Re-randomization tests considering the actual dynamic randomization procedure further confirmed the primary findings. Results of sensitivity analyses for pCR in different analysis populations were consistent with results in the ITT population.

In addition, pertuzumab in combination with trastuzumab and docetaxel has been approved for the treatment of patients with metastatic breast cancer, based on a PFS improvement (HR=0.62, 95% CI: 0.51, 0.75; p-value < 0.0001). In a post-marketing subsequent interim analysis of OS, addition of pertuzumab showed a statistically significant improvement on OS (HR=0.66, 95% CI: 0.52, 0.84; p-value = 0.0008).

This sBLA submission seeks an accelerated approval of pertuzumab. The confirmatory study, APHINITY, is currently ongoing with enrollment completed. Study APHINITY is a randomized, double-blind, placebo-controlled two-arm phase 3 study of adjuvant trastuzumab and chemotherapy plus pertuzumab or placebo, in patients with primary operable breast cancer. Analysis of the primary endpoint, iDFS, is intended to directly demonstrate the long term clinical benefit of adding pertuzumab to an adjuvant trastuzumab/chemotherapy regimen in patients with HER2- positive early breast cancer.

5.3 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.

5.4 Labeling Recommendations

We recommend that the labeling includes results of pCR using the FDA preferred definition (yoT0/is ypN0). Subgroup analysis results by hormone receptor status should also be presented due to the different magnitude of pCR improvement observed.

6. REFERENCES

1. Pocock, SJ. Simon, R. “Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial”. Biometrics, 31, pp 103-115, 1975

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: September 19, 2013

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:
Project Manager: Amy Tilley
Medical Officer: Laleh Amiri Kordestani, M.D., Suparna Wedam, M.D.
Medical Team Leader: Patricia Cortazar, M.D.
Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Statistical Team Leader: Shenghui Tang, Ph.D.
Biometrics Division Director: Rajeshwari Sridhara, Ph.D.
Lillian Patrician

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

/s/

LIJUN ZHANG
09/19/2013

SHENGHUI TANG
09/19/2013

RAJESHWARI SRIDHARA
09/19/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125409 **Applicant: Genentech** **Stamp Date: 05/01/2013**

Drug Name: Pertuzumab **NDA/BLA Type: Efficacy Supplement 001**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Gender not applicable (all females)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No interim analysis.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Lijun Zhang 5/28/2013

Reviewing Statistician Date

Shenghui Tang 5/28/2013

Supervisor/Team Leader Date

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

/s/

LIJUN ZHANG
05/31/2013

SHENGHUI TANG
05/31/2013