First FDA Approval of Neoadjuvant Therapy for Breast Cancer: Pertuzumab for the Treatment of Patients with HER2-Positive Breast Cancer

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Running Title: Pertuzumab Neoadjuvant Approval Summary

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
Abstract

On September 30, 2013, the FDA granted accelerated approval to pertuzumab (PERJETA, Genentech, Inc.) for use 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. The approval was based in part on a randomized multicenter trial in the indicated population that allocated 417 patients to neoadjuvant treatment with trastuzumab-docetaxel (TD), pertuzumab-trastuzumab-docetaxel (PTD), pertuzumab-trastuzumab, or pertuzumab-docetaxel. PTD was administered preoperatively every 3 weeks for 4 cycles. Following surgery patients received 3 cycles of fluorouracil, epirubicin, and cyclophosphamide every 3 weeks and trastuzumab every 3 weeks to complete 1 year of therapy. The pathological complete response (pCR) rates by the FDA-preferred definition [absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0)] were 39.3% and 21.5% in the PTD and the TD arms, respectively (p=0.0063). The most common adverse reactions with PTD were alopecia, diarrhea, nausea, and neutropenia. This approval was based on the totality of evidence, particularly improved survival in the metastatic breast cancer trial, and a fully accrued confirmatory trial.
Introduction

Although progress has been made in the treatment of breast cancer, it is still the second leading cause of cancer-related deaths among women. Amplification or overexpression of human epidermal growth factor receptor 2 (HER2), present in about 20% of all breast cancers, have historically been associated with a poor prognosis. After the trastuzumab approval for early breast cancer in 2006, the prognosis of patients with HER2-positive disease significantly improved; however, approximately one-third of these patients still relapse (1).

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the HER2 protein and blocks ligand-dependent heterodimerization of HER2 with other HER family members. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis. In addition, evidence suggests that pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (2, 3).

Pertuzumab was initially approved by the U.S. Food and Drug Administration (FDA) on June 8, 2012, for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease (4). The approval was based on a multicenter, randomized, double-blind, placebo-controlled trial (CLEOPATRA) in 808 patients with HER2-positive MBC (5). Patients were randomly allocated (1:1) to receive pertuzumab in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The improvement in progression-free survival (PFS) in the pertuzumab arm was statistically significant [HR, 0.62; 95% confidence interval (CI), 0.51–0.75; p< 0.0001, log-rank test]. Although the first planned interim analysis of survival did not cross the stopping boundary, the
second interim analysis demonstrated a statistically significant improvement in OS (HR, 0.66; 95% CI, 0.52-0.84; p=0.0008) (6).

In April 2013, the FDA received a supplemental Biologics License Application for the use of pertuzumab in the neoadjuvant setting. This was the first application for the neoadjuvant treatment of breast cancer and the FDA review is summarized below.

**Primary Trial**

The primary trial supporting this approval was a multicenter, randomized, open-label phase II trial (NEOSPHERE) that enrolled 417 patients from 59 centers in 16 countries (7). The study was designed to evaluate the pCR rate of 4 neoadjuvant regimens in patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) (Fig. 1A). Patients were randomly allocated to receive 1 of 4 regimens prior to surgery: trastuzumab plus docetaxel (TD), pertuzumab plus trastuzumab and docetaxel (PTD), pertuzumab plus trastuzumab (PT), or pertuzumab plus docetaxel (PD). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and hormone receptor status.

Treatment in the PTD arm included 4 preoperative cycles of pertuzumab, trastuzumab, and docetaxel administered by intravenous infusion (IV) every 3 weeks. Patients received an initial dose of pertuzumab 840 mg as a 60-minute infusion followed by 420 mg every 3 weeks. Trastuzumab was administered at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. Docetaxel was administered at an initial dose of 75 mg/m² but could be escalated to 100 mg/m² at the investigator’s discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m² (FEC) administered IV every 3 weeks and trastuzumab every 3
weeks to complete 1 year of therapy. The treatment regimen on the TD arm was identical except for the omission of pertuzumab.

The primary endpoint was pCR, defined as an absence of invasive neoplastic cells in the breast only (ypT0/is) on histopathological examination of the surgical specimen. The FDA-recognized definition of pCR is the absence of residual invasive cancer in the complete resected breast specimen and all sampled regional lymph nodes (ypT0/is ypN0), irrespective of the presence or absence of residual carcinoma in situ (7, 9, 9). The primary analysis was a comparison of pCR rates in the intent-to-treat (ITT) population using the Cochran-Mantel-Haenszel method. Using a one-sided alpha level of 0.1 with a sample size of 400 (100 per arm), the study had 80% power to detect an improvement in pCR rate from 25% to 40%. Key secondary endpoints included tumor response, breast conservation surgery rate, PFS, and disease-free survival (DFS). PFS was calculated from date of the randomization to the first documentation of progressive disease or death, and DFS was defined as the interval from the surgery date to the earliest occurrence of disease progression or death from any cause. For this application, the primary analysis of interest was the comparison of the PTD and TD arms.

Baseline characteristics were well balanced. All patients were female, median age was 50, 71% were Caucasian, 23% were Asian and 2% were Black. The majority of patients were enrolled in Europe, with no patients enrolled from the United States. Seven percent of patients had inflammatory breast cancer, 32% had locally advanced cancer, 70% had clinically involved lymph nodes, 61% had operable breast cancer, 47% had hormone-receptor-positive breast cancer, and all patients had HER2-positive disease.

Using the FDA definition, the pCR rates were 39.3% and 21.5% in the PTD and the TD arms, respectively (Table 1). The difference of 17.8% was statistically significant (adjusted
p=0.0063). A statistically significant improvement in pCR rate was also found using the study definition. 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).

**Supportive Trials**

The CLEOPATRA trial in MBC was reviewed with the original BLA (4). The TRYPHAENA trial was conducted in 225 patients with HER2-positive, locally advanced, operable, or inflammatory (T2-4d) breast cancer (10). Patients were randomly allocated to receive 1 of 3 neoadjuvant regimens prior to surgery: 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 docetaxel, carboplatin, and trastuzumab (TCH) in combination with pertuzumab (Fig. 1B). Doses and schedules were as reported. Although the primary endpoint of the study was cardiac safety, both the pCR and safety results were supportive of the approval.

The pCR (ypT0/is ypN0) rates were 56.2% (95% CI, 44.1-67.8) for patients treated with 3 cycles of FEC followed by 3 cycles of docetaxel, all in combination with pertuzumab and trastuzumab, 54.7% (95% CI, 42.7-66.2) for patients treated with 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, and 63.6% (95% CI, 51.9-74.3) for patients treated with 6 cycles of TCH in combination with pertuzumab. The pCR rates in each arm were lower in the subgroups of patients with hormone-receptor-positive tumors.

**Safety Results**
The primary comparison of safety was between the PTD and TD arms of the NEOSPHERE trial. Supplemental adverse reaction (AR) information was obtained from the TRYPHAENA and CLEOPATRA trials. As of the last data cutoff, there were 14 deaths on the NEOSPHERE trial and 10 deaths on the TRYPHAENA trial. There was one death due to fulminant hepatitis during the neoadjuvant treatment period on the PTD arm in the NEOSPHERE trial. The remaining 13 deaths were due to disease progression and occurred more than 30 days after the last dose of pertuzumab. In the TRYPHAENA trial, all deaths were due to disease progression and none occurred during the neoadjuvant period (11).

In the NEOSPHERE trial, the most common ARs (>30%) in the PTD arm were alopecia, diarrhea, nausea, and neutropenia. The most common (>2%) NCI-CTCAE (v3.0) Grade 3-4 ARs were neutropenia, febrile neutropenia, leukopenia and diarrhea. Discontinuation of neoadjuvant treatment due to ARs occurred in 1.9% of patients on the PTD arm and in no patients on the TD arm. Dose modifications or interruptions were similar in the two treatment arms. The majority of patients completed the planned neoadjuvant therapy, surgery and adjuvant FEC chemotherapy. Although more patients on the PTD arm than on the TD arm (17% vs. 8%) were unable to complete 1 year of trastuzumab therapy, most missed only one cycle (11).

While ARs in the NEOSPHERE and TRYPHAENA trials were similar, their frequency was higher in all the TRYPHAENA treatment arms, as all chemotherapy was given preoperatively. Grade 3-4 ARs (>2%) in the TRYPHAENA study included neutropenia, leukopenia, febrile neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting. Additional common ARs (>30%) with pertuzumab in combination with TCH included anemia and thrombocytopenia (11).

**Cardiac toxicity**

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**Cardiac toxicity**
Cardiac toxicity was of particular interest in both neoadjuvant studies. Left ventricular ejection fraction (LVEF) was assessed at baseline, every 6 weeks during the neoadjuvant period, after surgery, within 1 week prior to starting adjuvant therapy, every 3-4 cycles in the adjuvant period, at the end of treatment, and every 6 months for a total of 2 years. In the NEOSPHERE trial, the incidence of left ventricular dysfunction (LVD) was higher in the PTD arm than in the TD arm (8% vs. 2%). In the PTD arm the asymptomatic LVD rates during the neoadjuvant, adjuvant and follow-up periods were 3%, 6%, and 3%, respectively. The incidence of LVD in the TD arm was lower, 1% during the neoadjuvant and adjuvant periods with no cases during the follow-up period (Table 2). Symptomatic LVD occurred only in a patient treated with PT during the neoadjuvant period. In the TRYPHAENA trial, the highest rate of LVD and discontinuation due to cardiac ARs occurred in the sequential anthracycline, pertuzumab and trastuzumab treatment arm (Table 3). As of the last data cutoff, all patients on the NEOSPHERE trial and all but one patient on the TRYPHAENA trial had recovered their LVEF to >50% (11).

**Discussion**

Despite recent advances in the treatment of patients with early breast cancer (EBC), there are still patients at substantial risk of relapse and death, and expediting the development of effective new agents for these patients is an FDA priority. New agents to treat EBC have historically been developed and initially approved in the metastatic setting. Approvals for the adjuvant treatment of EBC have followed 8-10 years later and have been based on large randomized trials with prolonged follow-up for DFS or OS. An alternative approach to expedite drug approval is to develop new treatments in the neoadjuvant setting. The FDA published a draft guidance titled, “Guidance for Industry Pathologic Complete Response in Neoadjuvant Treatment of High Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval” (8).
Although pCR has been the most commonly used primary endpoint in neoadjuvant trials, the surrogacy of pCR for long-term outcomes has not been established. The FDA assembled an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) to evaluate the potential use of pCR as a regulatory endpoint for accelerated approval in high-risk EBC (9). The CTNeoBC pooled analysis found that individual patients who attain a pCR have a 64% reduction in the risk of death compared to patients with residual tumor at the time of surgery, confirming the prognostic value of pCR for use in clinical practice. However, the CTNeoBC pooled analysis found no association between the magnitude of difference in pCR rate between treatment arms and differences in long-term outcome. Potential explanations for this include the heterogeneity of the patient population, the overall low pCR rates in the CTNeoBC trials, and the lack of targeted therapies except for the NOAH trial. Randomized trials of targeted agents in more homogeneous tumor subtypes, with larger differences in pCR rates between treatment arms, may demonstrate a relationship between pCR and long-term outcome at a trial level. The pooled analysis could not validate pCR as an established surrogate endpoint for improved EFS and OS; however, given that individual patients who attain a pCR have substantial improvement in OS, for accelerated approval, an agent that produces a marked improvement in pCR rate may be reasonably likely to improve the long-term outcomes of EFS and/or OS.

Critical to the decision-making on this application was the comprehensive clinical development program for pertuzumab. In the NEOSPHERE trial, a statistically significant improvement in pCR rate was observed in patients receiving PTD compared to those receiving TD. In the TRYPHAENA study, high pCR rates were observed in all 3 pertuzumab-containing treatment arms. Importantly, the CLEOPATRA trial in first-line, HER2-positive MBC
demonstrated that addition of pertuzumab to docetaxel and trastuzumab significantly improved OS, potentially by more than one year \( \text{(Error! Reference source not found., 5)} \). In addition, the confirmatory adjuvant trial (APHINITY), comparing standard chemotherapy and trastuzumab plus one year of pertuzumab to chemotherapy and trastuzumab alone, was fully accrued with more than 4,800 patients at the time of accelerated approval. The first DFS results from this trial are anticipated in late 2016. The totality of the data, the robust development program, with a well-characterized efficacy and safety profile in approximately 10,000 patients who have received pertuzumab to date, and the fact that the confirmatory trial had already completed accrual, mitigated the risks of accelerated approval based upon pCR rate.

The short-term toxicity of neoadjuvant pertuzumab is similar to the known safety profile of the drug and appears to be manageable. However, the long-term safety of pertuzumab in an EBC setting is unknown. There was evidence of increased cardiac dysfunction with the addition of pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting. This is in contrast to the results from the CLEOPATRA trial in which the rate of LVEF decline was higher in the control arm. These differences may be due to the addition of an anthracycline in the neoadjuvant trials. In both neoadjuvant trials, most cases of LVD were asymptomatic and appeared reversible. Important information needed to better characterize the cardiac toxicity of pertuzumab in an EBC population will be gained from the APHINITY trial. Further information on cardiac safety will also be obtained from a postmarketing trial in which pertuzumab will be given in combination with two different anthracycline/taxane-based treatment regimens. However, based on the neoadjuvant trial results, a new BOXED WARNING regarding cardiomyopathy was added to pertuzumab’s labeling (12).
HER2-positive breast cancer is a heterogeneous tumor and different subtypes could have different sensitivities to HER2-targeted agents, potentially affecting the pCR rates (13). To address this issue the Applicant will conduct a study of pretreatment molecular subtyping to explore the relationship between pCR and tumor subtype.

This application was discussed at a meeting of the Oncologic Drugs Advisory Committee (ODAC) in September 2013. ODAC voted (13 yes, 0 no, 1 abstention) that pertuzumab demonstrated a favorable benefit to risk evaluation for the neoadjuvant treatment of EBC. Given the limited experience with pCR as a regulatory endpoint and uncertainty about the relationship between pCR rate and long-term outcome, the bar for approval in the neoadjuvant setting has been set high. The accelerated approval process assumes a risk that postmarketing trials may ultimately fail to confirm long-term clinical benefit. In this application the risk was considered to be acceptable. To minimize the risks to potentially curable patients, FDA will similarly evaluate development plans and applications for neoadjuvant drug approvals within the context of the totality of the efficacy and safety data for the drug and will require that the confirmatory trial be well underway at the time of accelerated approval (8). The goal is to balance the risks of approval versus the harm from delay in access to a practice-changing treatment for high-risk patients with breast cancer.

Acknowledgments

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References


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12. Drugs@FDA [database on the Internet]. Silver Spring (MD): FDA; 2013 - [cited 2014 Aug 18]. Label; ID: 3384285; [about 24 p.] Available from:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125409s051lbl.pdf Files updated daily.

Table 1. NEOSPHERE efficacy results

<table>
<thead>
<tr>
<th>Endpoint/ Population</th>
<th>Arm A TD</th>
<th>Arm B PTD</th>
<th>Arm C PT</th>
<th>Arm D PD</th>
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<td>C vs. A</td>
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<tr>
<td>Overall ITT</td>
<td>N=107</td>
<td>N=107</td>
<td>N=107</td>
<td>N=96</td>
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<tr>
<td>pCR (ypT0/is) (%)</td>
<td>31 (29.0%)</td>
<td>49 (45.8%)</td>
<td>18 (16.8%)</td>
<td>23 (24.0%)</td>
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<tr>
<td>95% CI</td>
<td>20.6%, 38.5%</td>
<td>36.1%, 55.7%</td>
<td>10.3%, 25.3%</td>
<td>15.8%, 33.7%</td>
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<td>Difference of Response (%) (95% CI)</td>
<td>16.80% (4.1%, 29.6%)</td>
<td>-12.20% (-23.3%, -1%)</td>
<td>21.80% (9.0%, 34.6%)</td>
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<tr>
<td>Adjusted CMH p-value</td>
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<td>0.0198</td>
<td>0.003</td>
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<tr>
<td>pCR (ypT0/is ypN0) (%)</td>
<td>23 (21.5%)</td>
<td>42 (39.3%)</td>
<td>12 (11.2%)</td>
<td>17 (17.7%)</td>
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<tr>
<td>95% CI</td>
<td>14.1, 30.5%</td>
<td>30.0, 49.2%</td>
<td>5.9, 18.8%</td>
<td>10.7, 26.8%</td>
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<tr>
<td>Difference of Response (%) (95% CI)</td>
<td>17.80% (5.7, 29.9%)</td>
<td>-10.30% (-20.1, -0.47%)</td>
<td>21.50% (9.6, 33.5%)</td>
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<td>pCR (ypT0/is ypN0) (%)</td>
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<td>11 (22.0%)</td>
<td>1 (2.0%)</td>
<td>4 (8.7%)</td>
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<td>95% CI</td>
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<td>11.5, 36.0%</td>
<td>0.1, 10.5%</td>
<td>2.4, 20.8%</td>
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<td>N=57</td>
<td>N=55</td>
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<tr>
<td>pCR (ypT0/is ypN0) (%)</td>
<td>17 (29.8%)</td>
<td>31 (54.4%)</td>
<td>11 (20.0%)</td>
<td>13 (26.0%)</td>
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<td>95% CI</td>
<td>18.4, 43.4%</td>
<td>40.7, 67.6%</td>
<td>10.4, 33.0%</td>
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TD = trastuzumab plus docetaxel; PTD = pertuzumab plus trastuzumab and docetaxel; PT = pertuzumab plus trastuzumab; PD = pertuzumab plus docetaxel; CI = Confidence interval; CMH: Cochran–Mantel–Haenszel; HR=hormone receptor; N=number; pCR= pathologic complete response
Table 2. Cardiac toxicity in NEOSPHERE (neoadjuvant, adjuvant, and follow-up periods)

<table>
<thead>
<tr>
<th></th>
<th>TD (N=107)</th>
<th>PTD (N=107)</th>
<th>PT (N=108)</th>
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<tr>
<td>LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%), asymptomatic</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
<td>0</td>
<td>1 (1%)</td>
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<tr>
<td>Symptomatic LV Dysfunction (CHF)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>ADJUVANT PERIOD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%), asymptomatic</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
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<td>5 (5%)</td>
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<tr>
<td>Symptomatic LV Dysfunction (CHF)</td>
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<td>0</td>
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<td>LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%), asymptomatic</td>
<td>0</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
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<tr>
<td>Symptomatic LV Dysfunction (CHF)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>TOTAL number of Patients with Cardiac Event</strong></td>
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<td>N= 2</td>
<td>N= 7</td>
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<td>LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%), asymptomatic</td>
<td>2 (2%)</td>
<td>9 (8%)</td>
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<td>Symptomatic LV Dysfunction (CHF)</td>
<td>0</td>
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<td>1 (1%)</td>
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TD = trastuzumab plus docetaxel; PTD pertuzumab plus trastuzumab and docetaxel; PT = pertuzumab plus trastuzumab; PD = pertuzumab plus docetaxel; LV = left ventricle, LVEF: left ventricular ejection fraction; CHF: congestive heart failure.
Table 3. Cardiac toxicity in TRYPHAENA (neoadjuvant, adjuvant, and follow-up periods)*

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<td>N= 72</td>
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<td>NEOADJUVANT PERIOD</td>
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<td>LVEF Decline ≥10% and drop to less than 50%, asymptomatic</td>
<td>4 (6%)</td>
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<td>Symptomatic LV Dysfunction (CHF)</td>
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<td>LVEF Decline ≥10% and drop to less than 50%, asymptomatic</td>
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<td>Symptomatic LV Dysfunction (CHF)</td>
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</tr>
<tr>
<td>Symptomatic LV Dysfunction (CHF)</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL # Patients with Cardiac Event</td>
<td>N= 5</td>
<td>N= 9</td>
<td>N= 7</td>
</tr>
<tr>
<td>LVEF Decline ≥10% and drop to less than 50%, asymptomatic</td>
<td>5 (7%)</td>
<td>6 (8%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Symptomatic LV Dysfunction (CHF)</td>
<td>0</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Two patients were randomized but did not receive treatment and are not included in the safety analysis.

FEC = fluorouracil plus epirubicin plus cyclophosphamide; D = docetaxel; PT = pertuzumab plus trastuzumab; TCH = docetaxel plus cyclophosphamide plus trastuzumab; LV = left ventricle, LVEF = left ventricular ejection fraction; CHF = congestive heart failure
**Figure 1.** NEOSPHERE and TRYPHAENA trials design. A, NEOSPHERE study design. B, TRYPHAENA study design.

FEC=5-FU, epirubicin, and cyclophosphamide
**Figure 1:**

### NEOSPHERE study design

- **Randomized**
  - **A**
    - $N = 417$
    - Tumor size $> 2$ cm
    - Operable, locally advanced, or inflammatory HER2-positive breast cancer
    - LVEF $\geq 55$
  - **Docetaxel**
  - **Trastuzumab**
  - **FEC**
  - **Surgery**
  - **Trastuzumab**

### TRYPHAENA study design

- **Randomized**
  - **B**
    - $N = 225$
    - Tumor size $> 2$ cm
    - Operable, locally advanced, or inflammatory HER2-positive breast cancer
    - LVEF $\geq 55$
  - **Pertuzumab**
  - **FEC x 3**
  - **Docetaxel x 3**
  - **Trastuzumab**
  - **Surgery**
  - **Continued trastuzumab to complete 1 year**
Clinical Cancer Research

First FDA Approval of Neoadjuvant Therapy for Breast Cancer: Pertuzumab for the Treatment of Patients with HER2-Positive Breast Cancer


Clin Cancer Res  Published OnlineFirst September 9, 2014.

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