First FDA Approval of Dual Anti-HER2 Regimen: Pertuzumab in Combination with Trastuzumab and Docetaxel for HER2-positive Metastatic Breast Cancer

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Abstract:

On June 8, 2012, the U.S. Food and Drug Administration approved pertuzumab (Perjeta®, Genentech) for use in combination with trastuzumab (Herceptin®, Genentech) 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. Approval was based on the results of a randomized, double-blind, placebo-controlled trial conducted in 808 patients with HER2-positive MBC. Patients were randomized (1:1) to receive pertuzumab (n=402) or placebo (n=406) in combination with trastuzumab and docetaxel. The primary endpoint was progression-free survival (PFS), and a key secondary endpoint was overall survival (OS). A statistically significant improvement in PFS (difference in medians of 6.1 months) was observed in patients receiving pertuzumab [HR 0.62 (95% CI: 0.51, 0.75), p< 0.0001]. A planned interim analysis suggested an improvement in OS [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053] but the HR and p-value did not cross the stopping boundary. Common adverse reactions (>30%) observed in patients on the pertuzumab arm included diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. No additive cardiac toxicity was observed. Significant manufacturing issues were identified during the review. Based on substantial evidence of efficacy for pertuzumab in MBC and the compelling public health need, FDA did not delay availability to patients pending final resolution of all manufacturing concerns. Therefore, FDA approved pertuzumab but limited its approval to lots not affected by manufacturing problems. The Applicant agreed to multiple manufacturing and testing post-marketing commitments under third-party oversight to resolve manufacturing issues.
Introduction:

Metastatic breast cancer (MBC) is a serious and life-threatening condition, causing 39,250 deaths in the U.S. in 2011[1]. The HER2/neu receptor is over-expressed in 15-30% of MBC and is associated with a poor prognosis and an aggressive phenotype. With the incorporation of trastuzumab-based therapy for the treatment of early breast cancer [2,3,4] and for MBC [5], the prognosis of HER2-positive breast cancer has improved. However, new therapies are needed to prolong life, substantially delay disease progression, and alleviate cancer-related symptoms.

Pertuzumab is administered in conjunction with trastuzumab, another IgG1κ humanized antibody. Both antibodies target the HER2 receptor extracellular domain (ECD). Trastuzumab binds to subdomain IV of the HER2 ECD, whereas pertuzumab binds to subdomain II [6]. HER2 is one of four members of the human EGFR family which also includes EGFR (HER1), HER3 and HER4. HER signaling is known to contribute to neoplastic cell growth, malignant transformation and resistance to chemotherapy [7,8]. As a proposed primary mechanism of action, pertuzumab blocks heterodimerization of HER2 with other members of the family and diminishes resultant ligand activated signaling. In contrast, trastuzumab disrupts ligand independent HER2 activity and associated downstream signaling. As would be expected of IgG1κ antibodies, both pertuzumab and trastuzumab can also mediate antibody dependent cell-mediated cytotoxicity (ADCC) [6,7].
Prior to approval of the pertuzumab Biologic License Application (BLA), there were two drugs available in the U.S. for the treatment of HER2-positive MBC (*Table 1*).

Trastuzumab was approved for first-line MBC in 1998 in combination with paclitaxel based on a time to progression (TTP) endpoint, and later demonstrated improved overall survival (OS). Trastuzumab was also granted a refractory MBC indication based on objective response rates (ORR) in a single-arm trial. In 2007, the FDA approved lapatinib (Tykerb®, GSK), a tyrosine kinase inhibitor, in combination with capecitabine for refractory HER2-positive MBC based on TTP.

**Chemistry and Manufacturing** [9]

Pertuzumab is produced using recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line. During the pre-approval inspection of the drug substance manufacturing facility, it became apparent that a high failure rate of the working cell bank (WCB) thaw and subsequent propagation of the cells used to manufacture pertuzumab was being experienced in the ongoing Q1/Q2 2012 manufacturing campaign. This indicated that the process was not in a state of control during this manufacturing campaign and was suggestive of WCB instability. The failure rates observed were inconsistent with previous pertuzumab manufacturing experience at the same facility in 2010 and with other antibodies manufactured at the facility. Based on these growth issues, the major concern was whether the Applicant could consistently manufacture pertuzumab with product quality characteristics comparable to that used in their clinical trials [9].
An investigation into the cell growth issues was ongoing at the time of the FDA inspection and frequent teleconferences were held with the Applicant subsequent to the inspection. Following discussions with FDA, the Applicant initiated three concurrent plans to address these concerns: 1) confirmation of stability and manufacturing of pertuzumab from the Master Cell Bank; 2) development of a new WCB; and 3) extended characterization of drug substance produced in the Q1/Q2 campaign of 2012 to evaluate product quality [9].

In view of the cell growth failures observed upon thaw and subsequent propagation of the WCB, FDA determined that the Applicant did not, in 2012, have a consistent process that would ensure continued supply of commercial material. However, qualification lots of pertuzumab were manufactured in 2010 by a consistent process and the Applicant estimated that adequate supply of these lots existed for patients. Lots from the 2010 campaign met all applicable requirements with respect to product safety, purity and potency and there were no GMP or process consistency issues associated with these lots. Therefore, only drug product from the 2010 manufacturing campaign was approved for marketing. To address issues regarding future supply, the FDA approval letter outlined post-marketing commitments to ensure a consistent pertuzumab manufacturing process. Some of the post-marketing commitments were to be performed under third party oversight. The marketing of pertuzumab generated in campaigns other than the 2010 campaign is subject to successful fulfillment of these post-marketing commitments [9].
Pharmacology and Toxicology

Nonclinical studies in support of the BLA application investigated the pharmacology, pharmacokinetics, and toxicology of pertuzumab. The antitumor activity of pertuzumab was studied in multiple tumor xenograft models, including one model that is resistant to trastuzumab; tumor growth in this model was inhibited by pertuzumab, but not by trastuzumab treatment. *In vitro* and *in vivo* studies showed that although pertuzumab and trastuzumab as single agents could significantly inhibit the growth of HER2 overexpressing tumor cells, the combination of both agents had greater anti-tumor activity when compared to the single agent effects.

The cynomolgus monkey was the appropriate model for nonclinical evaluation since the amino acid homology of human and monkey ErbB2 is 99% and binding affinities for pertuzumab were comparable. The toxicological profile of pertuzumab in monkeys suggests that it is well-tolerated, with toxicities limited to diarrhea. Despite the clinical evidence of cardiovascular toxicity observed with trastuzumab treatment, safety pharmacology and general toxicology testing did not reveal any remarkable cardiovascular findings in cynomolgus monkeys treated with pertuzumab up to 6 months.

Administration of pertuzumab by intravenous (I.V.) injection to monkeys during gestation was associated with fetal lethality and embryo-fetal effects including oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal hypoplasia consistent with delayed renal development. Various external, visceral and skeletal abnormalities were also observed and were generally considered to be
secondary to intrauterine restriction resulting from the oligohydramnios. Ratios of fetal to maternal pertuzumab exposure levels were comparable, indicating that pertuzumab did cross the placenta, resulting in significant fetal exposure. Thus, administration of pertuzumab during pregnancy is expected to pose a risk to the human fetus. Because this risk is likely outweighed by the potential for clinical benefit, pertuzumab was designated pregnancy category D.

**Clinical Pharmacology**

Pertuzumab demonstrated linear pharmacokinetics (PK) at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With the approved I.V. dosing regimen (an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter), the steady-state concentration of pertuzumab was reached after the first maintenance dose. Population PK analysis suggested no PK differences based on age or gender. No PK differences were observed between Japanese and non-Japanese populations. No dose adjustments based on body weight or baseline albumin level are needed.

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel. Dose adjustments of pertuzumab are not needed in patients with mild or moderate renal impairment. No large changes in the mean QT interval (i.e., greater than 20 ms) were detected for the approved dosing regimen.
Anti-therapeutic antibodies (ATAs) to pertuzumab were detected in patients, but no known association with hypersensitivity reactions or anaphylaxis was determined, and the benefit of pertuzumab treatment seemed to be preserved within both ATA-positive and ATA-negative subgroups.

**Clinical Studies**

The BLA was supported by results from a randomized, phase 3, multinational, multicenter, double-blind, placebo-controlled study (Cleopatra/WO20698) [10]. Patients with MBC were required to have HER2 positive disease, defined as 3+ by immunohistochemistry or $\geq 2.0$ amplification by FISH, determined at a central laboratory. Those patients who received prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months prior to trial enrollment. Patients were randomized 1:1 to receive either pertuzumab by I.V. infusion (840 mg initial dose, 420 mg every three weeks thereafter) or matched placebo as an add-on to the standard-of-care: trastuzumab (8 mg/kg initial I.V. dose, 6 mg/kg I.V. every three weeks thereafter) and docetaxel (75 mg/m$^2$ I.V. every three weeks for at least six cycles, with the option of dose escalation to 100 mg/m$^2$).

In addition to the Phase 3 trial, two supportive clinical trials were submitted and reviewed: Neosphere/TOC 4129g (a four-arm randomized phase 2 trial in neoadjuvant early breast cancer) [11] and BO17929 (a single-arm phase 2 study in refractory disease) [12].
Endpoints in the Phase 3 trial

The primary endpoint for the phase 3 trial was PFS based on tumor assessments by an independent review facility (IRF). The study featured a ‘real time’ PFS analysis by the IRF. If the investigator determined progressive disease (PD) but the IRF disagreed, patients would continue with every 9 week tumor assessments until the IRF determined PD. In addition, once PD was determined, the blind was maintained without cross-over. This design reduced informative censoring and confounding variables in the PFS and OS analyses. Secondary endpoints in the phase 3 trial included OS, PFS based on investigator assessment, ORR, and safety.

The study was designed to have 80% power to detect a 33% improvement in median PFS (14 months on the pertuzumab-treatment arm and 10.5 months on the placebo-treatment arm, corresponding to a hazard ratio of 0.75) at a 2-sided alpha of 0.05. The planned sample size was 800, with 381 planned PFS events. For OS, the study was designed to have 80% power to detect a 33% increase in median survival (48 months on the pertuzumab-treatment arm and 36 months on the placebo-treatment arm, corresponding to a hazard ratio of 0.75) at a two-sided alpha of 0.05. One interim analysis for OS was planned at the time of final PFS analysis with Lan-Demets alpha spending based on the O’Brien-Fleming boundary. PFS and OS were compared between treatment arms by log-rank test stratified by prior treatment status and region.
Patient Baseline Characteristics in the Phase 3 trial

In the phase 3 trial, 808 patients were randomized, 402 to the pertuzumab treatment arm and 406 to the placebo treatment arm. Overall baseline demographic and tumor characteristics were balanced between treatment arms. The median age was 54, 59% of patients were White, 32% of patients were Asian, and 78% had visceral metastases. Approximately 47% of patients previously received adjuvant or neoadjuvant therapy, including a small number of patients (11%) who received prior trastuzumab. Forty-eight percent of patients were hormone receptor positive, of whom roughly half (52%) received adjuvant hormonal therapy.

Efficacy Results in the Phase 3 trial

In May 2011, the pre-specified number of PFS events occurred, demonstrating a statistically significant prolongation of IRF PFS in the pertuzumab arm [Hazard Ratio (HR)=0.62 (95% CI: 0.51, 0.75), p<0.0001] as shown in Figure 1. The median PFS was 18.5 months in the pertuzumab arm and 12.4 months in the placebo arm.

At the final PFS analysis, a planned interim OS analysis was performed, comprising 43% of events planned at the final OS analysis. This interim analysis indicated an OS advantage for the patients allocated to pertuzumab [HR=0.64 (95% CI: 0.47, 0.88), p=0.0053]. However, the HR and p-value for the interim analysis of OS did not meet the pre-defined stopping boundary.
During the pertuzumab review, FDA evaluated efficacy in various subgroups of interest. Importantly, in the subset of patients who received prior trastuzumab in the adjuvant setting (which best reflects the U.S. population in which most patients are diagnosed with early breast cancer), the PFS benefit of pertuzumab was maintained [HR=0.62 (95% CI: 0.35, 1.07)]. The pertuzumab PFS benefit in patients with hormone receptor-positive MBC [HR=0.72 (95% CI: 0.55, 0.95)] and in patients with disease confined to non-visceral metastasis [HR=0.96 (95% CI: 0.61, 1.52)] appeared to be less compared to the benefit observed in the overall population.

**Safety in the Phase 3 trial**

In the phase 3 trial, patients were to be treated with docetaxel in combination with trastuzumab and either pertuzumab or placebo for a minimum of 6 cycles, in the absence of unacceptable toxicity or disease progression. Trastuzumab and pertuzumab/placebo were to be continued until progression.

The safety population consists of 397 patients on the placebo treatment arm and 407 on the pertuzumab treatment arm. The median duration of study treatment was 18.1 months in the pertuzumab-treated group and 11.8 months in the placebo-treated group.

**Table 2** summarizes the safety overview. Adverse events >5% more common in the pertuzumab-treated group included mucosal inflammation, rash, dry skin, diarrhea, and febrile neutropenia. Grade 3-4 adverse events > 2% more common in the pertuzumab-
treatment group included diarrhea, neutropenia, and febrile neutropenia. Among Asian patients, the incidence of febrile neutropenia was particularly high in the pertuzumab-treated group (26%) compared to the placebo-treated group (12%). These differences were not explained by differences in supportive care between regions or higher doses of or higher exposure to docetaxel. There were no differences in rates of left ventricular systolic dysfunction between treatment arms.

Discussion

The pertuzumab BLA marks the first time FDA approved a molecularly targeted monoclonal antibody to be used in combination with another monoclonal antibody. In its decision, the Agency considered the large magnitude of PFS improvement (6.1 month difference in medians), the consistency of findings across relevant subgroups, the interim OS analysis favoring the pertuzumab arm (which on a subsequent analysis demonstrated statistical significance) [13], and the supportive evidence of high antitumor response (80% ORR) in the phase 3 trial as well as in the two supportive phase 2 trials.

An exploratory analysis of subgroups in the phase 3 trial revealed less efficacy in the hormone receptor-positive subgroup compared to the overall population. This was consistent with results in the neoadjuvant randomized phase 2 trial [11], in which rates of pathologic complete response were lower in patients with hormone receptor-positive disease as compared to patients with hormone receptor-negative disease. Therefore, the Applicant agreed as a post-marketing commitment to submit the results of a randomized phase 2 study [14] testing whether the addition of pertuzumab to the combination of
trastuzumab and an aromatase inhibitor can enhance anti-tumor activity in HER2-positive, hormone receptor-positive MBC.

The safety of pertuzumab in combination with trastuzumab and docetaxel was acceptable, with no evidence of additive cardiac toxicity in the phase 3 trial. This was in contrast to findings from early clinical development, which suggested that pertuzumab might increase the cardiotoxicity of trastuzumab [15]. Trials in neoadjuvant and adjuvant breast cancer will further clarify the cardiac risk in a treatment-naive, early breast cancer population.

The cell growth problems associated with pertuzumab manufacturing identified during the 2012 pre-approval inspection of the drug substance manufacturing facility proved to be a critical issue during BLA review. FDA requires demonstration of a consistent manufacturing process prior to approval of a BLA. In this case, FDA took the unusual step of approving only product containing drug substance manufactured during the Applicant’s 2010 manufacturing campaign, which was produced using a consistent process and of which an adequate supply existed. Marketing of product produced from future manufacturing campaigns, including that produced during the Q1/Q2 2012 campaign, would be subject to further approval.

It was FDA’s determination that a compelling exigent public health need outweighed the risk of future interruption in the drug supply to patients. The justification for approving the pertuzumab application to allow only release of the 2010 lots was based on: (1)
FDA’s determination that product from the 2010 campaign met all applicable requirements with respect to safety, purity, and potency; (2) the cell expansion problems of the Q1/Q2 2012 campaign were not observed with the 2010 campaign; (3) a consistent and controlled process was in place at the time of the 2010 manufacturing campaign; (4) the Applicant’s commitment to undertake several steps to resolve expeditiously the cell expansion problem and (5) the Applicant’s commitment to reduce and mitigate the risk of a drug shortage. At the time of approval, the manufacturer agreed to several post-marketing commitments that would be performed under third-party oversight to address the process consistency concerns and allow approval of a viable commercial process.

In summary, the approval of the pertuzumab BLA marked the licensing of the first dual anti-HER2 regimen for treatment of breast cancer in the United States. This represents another significant advance in the treatment of HER2-positive breast cancer, which began with the approval of trastuzumab for MBC in 1998. The safety and efficacy of pertuzumab in early breast cancer is currently being tested in a large phase 3 adjuvant trial [16].
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14 ClinicalTrials.gov Identifier: NCT01491737. A Study of Pertuzumab with Trastuzumab Plus an Aromatase Inhibitor in Patients with Hormone Receptor-Positive, Metastatic, HER2-positive Breast Cancer.


16 ClinicalTrials.gov Identifier: NCT01358877. A Study of Pertuzumab in Addition to Chemotherapy and Herceptin (Trastuzumab) as Adjuvant Therapy in Patients with HER2-Positive Primary Breast Cancer.

Figure Captions:
Fig 1. Kaplan Meier curve of Progression Free Survival (PFS) by independent review facility by treatment arm (pertuzumab plus trastuzumab plus docetaxel) versus (placebo plus trastuzumab plus docetaxel)
**Table 1: FDA Approvals for HER2-directed Agents in MBC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Indication</th>
<th>N</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (+ paclitaxel)</td>
<td>1998</td>
<td>HER2+ MBC</td>
<td>469</td>
<td>Chemotherapy: • Doxorubicin/ Cyclophosphamide or • Paclitaxel</td>
<td>TTP: HR 0.53, median Δ 2.7 mo combined; 4.2 mo paclitaxel subgroup. Later demonstrated OS: HR 0.80; median Δ 4.8 mo</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1998</td>
<td>HER2+ MBC patients who received ≥ 1 chemotherapy regimen for MBC</td>
<td>222</td>
<td>N/A</td>
<td>ORR: 14% in single arm study</td>
</tr>
<tr>
<td>Lapatinib (+ capecitabine)</td>
<td>2007</td>
<td>HER2+ MBC after failure of anthracycline, taxane, trastuzumab</td>
<td>399</td>
<td>Capecitabine</td>
<td>TTP: IRC HR 0.57, median Δ 2 mo; INV HR 0.72, median Δ 1.2 mo</td>
</tr>
<tr>
<td>Lapatinib (+ letrozole)</td>
<td>2010</td>
<td>Postmenopausal women with HR+, HER2+ MBC for whom hormonal therapy is indicated</td>
<td>219</td>
<td>Letrozole + placebo</td>
<td>PFS: HR 0.71, median Δ 5 mo</td>
</tr>
</tbody>
</table>

MBC = Metastatic Breast Cancer; HR+ = Hormone Receptor Positive; TTP = Time to Progression; Δ = change, OS = Overall Survival; ORR = Objective Response Rate; IRC = Independent Radiologic Charter; INV = Investigator
### Table 2: Adverse Reactions Occurring >5% Difference Between Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>Placebo + trastuzumab + docetaxel n=397</th>
<th>Pertuzumab + trastuzumab + docetaxel n=407</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 – 4 %</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>30.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.9</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>24.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4.3</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>24.9</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>7.3</td>
</tr>
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</table>
Figure 1:

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 406</th>
<th>Pertuzumab N = 402</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (%)</td>
<td>242 (60)</td>
<td>191 (48)</td>
</tr>
<tr>
<td>Disease progression (%)</td>
<td>226 (56)</td>
<td>180 (45)</td>
</tr>
<tr>
<td>Death within 18 weeks (%)</td>
<td>16 (4)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Censored (%)</td>
<td>164 (40)</td>
<td>211 (52)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>12.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Hazard ratio (stratified)</td>
<td>0.62 (0.51 to 0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p-value (log rank)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo + T + D

Pertuzumab + T + D

Disease progression (%)
Death within 18 weeks (%)
Censored (%)
Median PFS (months)
Hazard ratio (stratified)
p-value (log rank)

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