CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 27, 2014
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BLA Supplement#	103792/S-5311
Applicant	Genentech, Inc.
Date of Submission	November 25, 2013
PDUFA Goal Date	May 28, 2014
Review Completion Date	February 27, 2014
Proprietary Name / Established (USAN) names	Herceptin® (Trastuzumab)
Dosage forms / Strength	Herceptin® (Trastuzumab) 1 vial containing 440 mg trastuzumab • Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks
Proposed Indication(s)	Adjuvant Treatment of HER2 Overexpressing Breast Cancer
Recommended:	*PMCs #1 and #3 fullfilled*

1. Introduction and Background

Herceptin is a HER2/neu receptor antagonist approved for the following indications:

- Adjuvant Breast Cancer:
  Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer
  - as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
  - with docetaxel and carboplatin
  - as a single agent following multi-modality anthracycline based therapy.
- Metastatic Breast Cancer:
  Herceptin is indicated:
  - In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
  - As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.
- Metastatic Gastric Cancer:
  Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

The November 2006 approval for the adjuvant indication was based on the Disease-Free Survival (DFS) results from the joint analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study B-31 and the North Central Cancer Treatment Group (NCCTG) Study N9831.

The current submission addresses the following Postmarketing Commitments (PMCs) which are subject to reporting of 21 CFR 601.70:

PMC# 1: To provide a final study report at the time of the final analysis of overall survival (analysis based on 710 deaths) in accordance with the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The final study report should include the primary datasets and programs for generation of analyses and all subset analyses for the final analysis of overall survival and an updated analysis of disease-free survival, including
exploratory analyses in subgroups based on the timing and type of hormonal treatment administered to patients.

PMC#3: To provide interim cardiac safety updates on an annual basis beginning on 30 September 2006, as the first cutoff date and ending with a final comprehensive cardiac safety analysis report submitted by 30 September 2012. Each annual cardiac safety update will include a detailed narrative summary of each new clinical event with associated radiologic reports and laboratory findings for all patients enrolled as of the termination of study enrollment in April 2005. The first annual cardiac safety update will be submitted by 28 April 2007. The final comprehensive cardiac safety analysis will be included in the final study report based on 710 deaths. In addition, the final comprehensive study report will contain primary datasets for the intent-to-treat (ITT) population and summary analyses that include, but are not limited to, the analyses described in the statistical analysis plan of April 2005.

This submission provides the updated report of efficacy from the protocol-specified preplanned final Overall Survival (OS) analysis and the final cardiac safety analysis of results from Studies NSABP B31 and NCCTG N9831 in fulfillment of PMCs #1 and #3.

The 8.3-year follow-up data from this joint NSABP B-31 and NCCTG N9831 analysis encompasses the mature OS results which continue to support the superiority of trastuzumab therapy in the adjuvant setting with no new safety signals. At 8.3 years of median follow-up [AC→TH], the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74) and the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis indicates that the OS benefit was consistent across several subgroups (age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy).

We recommend fulfillment of both PMCs #1 and #3. FDA will update the label accordingly. Herceptin continues to demonstrate a favorable benefit risk assessment for the adjuvant treatment of patients with HER2 overexpressing breast cancer.

2. CMC/Device

There was no new CMC information submitted with this submission.

3. Nonclinical Pharmacology/Toxicology

There was no new nonclinical pharmacology/toxicology information submitted with this submission.

4. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology/biopharmaceutics information submitted with this submission.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

Specific details on the study designs are found in the review of the 2006 adjuvant approval. This application jointly analyzed two randomized Phase 3 studies: The National Surgical Adjuvant Breast and Bowel Cancer Project (NSABP) Study B-31 and the North Central Cancer Treatment Group (NCCTG) Study N9831. There were extensive discussions on the plan for a combined analysis of data from the two studies in order to get an earlier assessment of the efficacy of Herceptin for adjuvant treatment, and the FDA agreed with this joint analysis plan prior to the first planned analysis of either study. The studies were considered amenable for a joint analysis given that both contained comparable control and treatment arms and although the population in the studies differed slightly, both high-risk node-negative and node-positive patients are of high risk of recurrence and death.

The following study arms were joined:

- Arm 1 of NSABP B-31 and Arm A of NCCTG N9831 which contained AC→T doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) as the control arm
- Arm 2 of NSABP B-31 and Arm C of NCCTG N9831 which contained AC→TH doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) plus herceptin for one year beginning with T

Arm B (sequential therapy) from the NCCTG N9831 trial was not joined because this treatment arm was not comparable to the treatment arms included in Study NSABP B31 and it would have been invalid to pool and analyze this data.

The ITT population from the joint study population included 4063 patients at the protocol-specified final overall survival analysis; 2031 patients received Herceptin with median treatment duration of 51 weeks. Similar demographic and baseline characteristics were reported. The median age was 49 years (range 24-80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian. The primary endpoint of the joint analysis of the studies was DFS and safety with a secondary endpoint of OS. DFS was measured from the time of randomization until recurrence of local, regional, or distant breast cancer, development of a contralateral breast cancer or other second primary cancer, or death from any cause. Patients who did not experience any DFS events were censored at the time of their last visit. OS was measured from the time of randomization until death from any cause. Patients not reported as deceased were censored at the time of their last visit. The joint study was set to have a final OS analysis at a protocol-specified number of deaths that occurred on June 30th, 2012 with 707 deaths.

The section below shows the 2-year follow-up and 8.3-year follow-up efficacy data (Table # 1).

2-year follow-up efficacy data:
The 2006 approval was based on the results of a planned interim analysis. The joint analysis demonstrated that the addition of Herceptin to adjuvant chemotherapy had a statistically significant improvement in DFS at 2.0 years of follow up. The ITT population included 3752 patients; 1872 patients received Herceptin and 133 (7.1%) experienced a DFS event compared to 261 (13.9%) of the 1880 patients not receiving Herceptin. The hazard ratio for the addition of Herceptin to chemotherapy relative to chemotherapy alone was 0.48 (95% CI 0.39, 0.59; $p<0.0001$). OS analysis at this time was not mature, as not enough OS events occurred. These DFS results supported the initial approval of Herceptin in the adjuvant setting.

8.3-year follow-up efficacy data:
The updated efficacy data, after a median follow up of 8.3 years, continues to show herceptin clinical benefit.

Disease Free Survival:
At 8.3 years of median follow-up 1161 patients in the ITT population experienced a DFS event, 479 from the Herceptin arm and 682 from the control arm. Of note 24.8% of patients in the chemotherapy alone arm crossed over to receive some Herceptin. The hazard ratio for the Herceptin containing arm compared to the chemotherapy alone arm was 0.61 (95% CI 0.54, 0.69; log-rank p-value <0.0001). These results are consistent with the DFS findings at 2.0 years of median follow-up and remain statistically significant in demonstrating a benefit of the addition of Herceptin to the chemotherapy regimen in this setting. An absolute benefit of 11.2% (95% CI 8.3%, 14.2 %) was demonstrated with the DFS estimated at 74.2% in the AC→TH arm and 62.9% in the AC→T arm.

Table 1 Studies 1 and 2 Efiicacy Data

	DFS events	DFS Hazard ratio (95% CI) p value	Deaths (OS events)	OS Hazard ratio p value
Studies 1 + 2[a] 2.0 years of follow-up				
AC→TH (n =1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) p< 0.0001[e]	62[c]	0.67[c,d] p= NS
AC→T (n = 1880)[b] (n = 2032)[c]	261[b]		92[c]	
Studies 1 + 2[a] 8.3 years of follow-up				
AC→TH (n =1872)[b] (n = 2031)[c]	682	0.61 (0.54, 0.69) p< 0.0001[e]	289[c]	0.64[c,d] (0.55, 0.74) p< 0.0001[e]
AC→T (n = 1880)[b] (n = 2032)[c]	479		418[c]	

CI □ confidence interval.

aStudies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC□T) or paclitaxel plus Herceptin (AC□TH).

bEfficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC□TH arm.

cEfficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC□TH arm).

dHazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

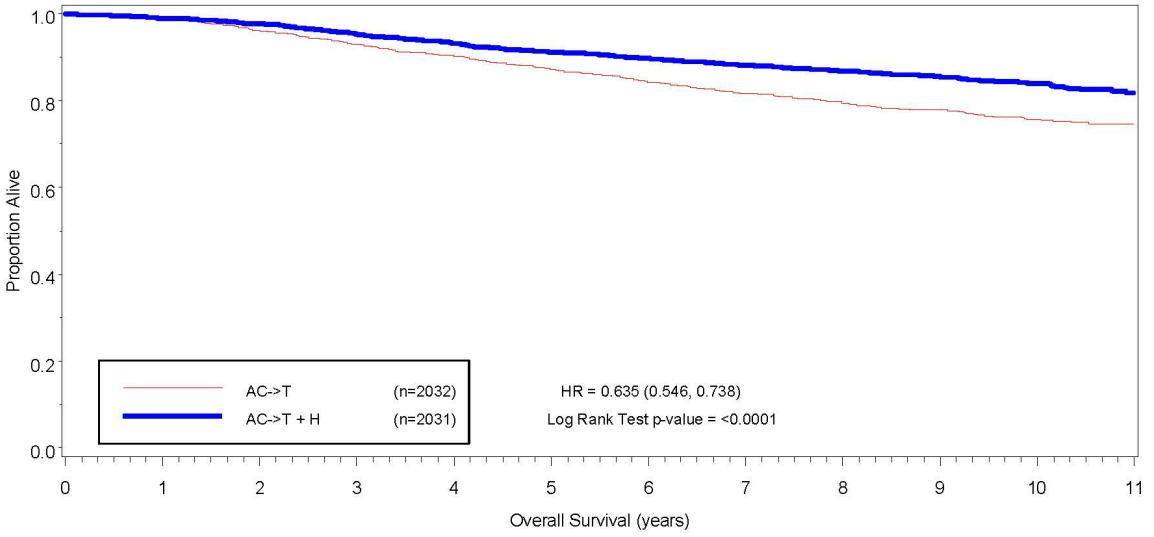
estratified log rank test.

Survival:

Genentech submitted the final OS analysis for the joint NSABP B-31 and NCCTG N9831 trials. At the time of the current analysis with a follow-up of 8.3 years, there were 707 deaths with 289 deaths in the AC→TH arm and 418 deaths in the AC→T arm. The hazard ratio for Herceptin arm relative to the chemotherapy alone arm was 0.64 (95% CI 0.55, 0.74; p<0.0001). At 8.3 years of follow-up the OS rate was estimated to be 86.9% in the Herceptin arm and 79.4% in the chemotherapy alone arm yielding an absolute benefit of 7.4% (95% CI 4.9%, 10%). Table 1 and Figure 1 summarize the OS joint analysis results.The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and

grade, and surgery/radiation therapy, was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n=2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n=1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n=2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n=1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤2 cm (n=1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size >2 cm (n=2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

Figure 1 Duration of Overall Survival in Patients with



Number at risk

AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

A=doxorubicin; C=cyclophosphamide; H=Herceptin; T=paclitaxel;
An event was defined as death from any cause at any time during the study.
Kaplan-Meier estimates are shown.
The strata were study, intended paclitaxel schedule, number of positive nodes and hormone receptor status.
Source: Biostatistics(tabbycat) pgm(/immuno/her2/abcjoint/finalos/programs/g_dur) output (g_dur_os_itt)
Database(Data Received in 2013)
Joint Analysis Final Overall Survival : Generated 17JUL13 13:33 Page 1 of 1
Datasets (pateff)

7. Summary of Safety Findings

The sponsor submitted updated safety data which indicates the safety profile of Herceptin is consistent with the previous analyses, clinical study reports and addendum (2/4/2006 and 7/23/2008).. Although NSABP B-31 and NCCTG N9831 were analyzed jointly for this supplement, the adverse events (AEs) were recorded differently and thus AE safety data submitted was for individual studies. In addition, patients who received Herceptin at any point for added adjuvant therapy after chemotherapy treatment (regardless of if they were randomized to Arm 1, 2, A, or C) were analyzed as a separate sequential arm (AC→T→H).

The clinical review team reviewed the cardiac death patient narratives and verified the sponsor assessments. While the percentage of cardiovascular events is increased from prior reports so are the events in the chemotherapy alone arm and the difference remains similar, as does the comparison to other Herceptin cardiac data. FDA also examined and verified the numbers of reversibility of cardiac toxicity after discontinuation of Herceptin and concurred that the majority of events occurred within the first 15 months after Herceptin therapy with most CHF events being reversible. The per patient incidence of new onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow up of 2.0 years in the AC TH arm. This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC TH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

8. Conclusions

This submission provides the updated report of efficacy from the protocol-specified preplanned final OS analysis and the final cardiac safety analysis of results from Studies NSABP B31 and NCCTG N9831 in fulfillment of PMCs #1 and #3. The long term safety and efficacy data from the joint trials clearly demonstrate clinical benefit with no new safety signals associated with Herceptin in the adjuvant treatment of HER2 overexpressing breast cancer.

9. Recommendations/Risk Benefit Assessment

We recommend fulfillment of both PMCs #1 and #3. FDA will update the label accordingly. Herceptin continues to demonstrate a favorable benefit risk assessment for the adjuvant treatment of patients with HER2 overexpressing breast cancer.

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/s/

PATRICIA CORTAZAR
02/28/2014