CLINICAL UPDATE

Brand Name	Herceptin®
Generic Name	trastuzumab
Drug Manufacturer	Genentech, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength

FDA APPROVAL DATE

August 05, 2020

LAUNCH DATE

February 16, 2022

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Biologic License Application (BLA): 103792

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Herceptin® is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin®.

MECHANISMS OF ACTION

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Herceptin® has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin® is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, Herceptin® -mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing 677 cancer cells compared with cancer cells that do not overexpress HER2.

DOSAGE FORM(S) AND STRENGTH(S)

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution.
- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution.

CLINICAL UPDATE

DOSE & ADMINISTRATION

For intravenous (IV) infusion only. Do not administer as an IV push or bolus.
Do not substitute Herceptin® (trastuzumab) for or with ado-trastuzumab emtansine.
Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency

Adjuvant Treatment of HER2-Overexpressing Breast Cancer
Administer at either:

- Initial dose of 4 mg/kg over 90-minute IV infusion, then 2 mg/kg over 30-minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin®, administer 6 mg/kg as an IV infusion over 30−90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30−90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer

- Initial dose of 4 mg/kg as a 90-minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30-minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

EFFICACY

Adjuvant Breast Cancer

The safety and efficacy of Herceptin® in women receiving adjuvant chemotherapy for HER2 750 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, 751 open-label, clinical trials (Studies 1 and 2).

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by 757 IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1).

A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin® arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel + Herceptin® arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of 49 years (range, 22−80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4% 782 Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 783 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or 784 PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy 785 evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin® arm.

Study 3 was designed to compare one and two years of three-weekly Herceptin® treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of Herceptin® treatment or two years of Herceptin® treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin® was administered

with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or N2, or known N3 or M1 breast cancer were not eligible.

Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies 1 + 2[a]				
AC→TH (n = 1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) 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]	261[b]		418[c]	
Study 3[f]				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p< 0.0001[g]	31	0.75 p = NS[h]
Chemo→ Observation (n = 1693)	219		40	
Study 4[i]				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p=0.0006[e,j]	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p< 0.0001[e,i]	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

[a] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

[b] Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC→TH arm.

[c] Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC→TH arm).

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

[e] stratified log-rank test.

[f] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year Herceptin treatment arm.

[g] log-rank test.

[h] NS = non-significant.

[i] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

[j] A two-sided alpha level of 0.025 for each comparison.

Metastatic Breast Cancer

The safety and efficacy of Herceptin® in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease.

Study 5: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] $\chi 2$-test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+).

Treatment Effects in Study 5 as a Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk[b] for Time to Disease Progression (95% CI)	Relative Risk[b] for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)[a]	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (–)[a]	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (–)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (–)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

[a] FISH testing results were available for 451 of the 469 patients enrolled on study.
[b] The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 6)

Herceptin® was studied as a single agent in a multicentre, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin® at 2 mg/kg IV. The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. mplete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

Metastatic Gastric Cancer

The safety and efficacy of Herceptin® in in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin® in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%). On the Herceptin® - containing arm, Herceptin® was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m2 Day 1 every 3 weeks for 6 cycles as a 2-hour IV infusion. On both study arms, capecitabine was administered at 1000 mg/m2 dose orally twice daily (total daily dose 2000 mg/m2) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m2 /day from Day 1 through Day 5 every three weeks for 6 cycles. The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91%

had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy. The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13.

Study 7: Overall Survival in ITT Population

	FC Arm N = 296		FC + H Arm N = 298
Definitive (Second Interim) Overall Survival			
No. Deaths (%)	184 (62.2%)		167 (56.0%)
Median	11.0		13.5
95% CI (mos.)	(9.4, 12.5)		(11.7, 15.7)
Hazard Ratio		0.73	
95% CI		(0.60, 0.91)	
p-value*, two-sided		0.0038	
Updated Overall Survival			
No. Deaths (%)	227 (76.7%)		221 (74.2%)
Median	11.7		13.1
95% CI (mos.)	(10.3, 13.0)		(11.9, 15.1)
Hazard Ratio		0.80	
95% CI		(0.67, 0.97)	

* Comparing with the nominal significance level of 0.0193.