Genentech
BIONCOLOGY™

August 2005

IMPORTANT DRUG WARNING

Dear Healthcare Provider:

Genentech, Inc. wishes to inform you of updated **cardiotoxicity** information related to the use of HERCEPTIN® (trastuzumab), obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study (B-31), a randomized, Phase III trial that was conducted in 2043 women with operable, HER2 overexpressing breast cancer (IHC 3+ or FISH+). This study demonstrated a significant increase in cardiotoxicity in patients who were randomized to the HERCEPTIN-containing arm as compared to patients who received chemotherapy alone.

A preliminary analysis of the safety data from Study NSABP B-31 was presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in May 2005, during the presentation of a joint analysis of Study NSABP B-31 and the North Central Cancer Treatment Group (NCCTG) study (N9831). Study NSABP B-31 was intended, in part, to characterize cardiotoxicity associated with HERCEPTIN use and to assess the value of serial cardiac monitoring during HERCEPTIN therapy as a predictor of cardiotoxicity and as an aid to early identification of cardiac toxicity.

Study NSABP B-31 evaluated the addition of HERCEPTIN to standard adjuvant chemotherapy. The chemotherapy regimen consisted of four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of paclitaxel every 3 weeks; patients were randomized to receive 1 year of HERCEPTIN, at the approved dose and schedule, during and following paclitaxel (Arm 2) or to paclitaxel alone (Arm 1). Patients in this study were required to have a baseline assessment of cardiac function with either multigated acquisition scan (MUGA) or echocardiogram and to have follow-up assessments at the completion of AC and at 6, 9, and 18 months after the initiation of paclitaxel with or without HERCEPTIN. Eligible patients had a left ventricular ejection fraction (LVEF) measurement at baseline (prior to any therapy) that was within normal limits and no history of or active cardiac disease, including cardiomyopathy, congestive heart failure, prior myocardial infarction, or arrhythmia.

Prior to initiation of HERCEPTIN (Arm 2), LVEF measurements were required to be at or above the radiology facility's lower limit of normal (LLN) and be no more than 15 points below baseline measurements. For patients randomized to Arm 2 with asymptomatic decrease in LVEF, the following table lists the guidelines that were employed for dose modification of HERCEPTIN:

Dose Modification Guidelines for HERCEPTIN in Study NSABP B-31

Relationship of LVEF to LLN	Absolute Decrease		
	<10%	10%–15%	≥16%
Within normal limits	Continue	Continue	Hold[a]
1%–5% below LLN	Continue	Hold[a]	Hold[a]
≥6% below LLN	Continue[a]	Hold[a]	Hold[a]

LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

[a]Repeat LVEF assessment after 4 weeks. If criteria for continuation were met, HERCEPTIN was resumed. If two consecutive holds or total of three holds occurred, HERCEPTIN was discontinued.

HERCEPTIN was permanently discontinued in patients with symptomatic cardiac toxicity. In the event that HERCEPTIN administration was withheld or discontinued because of cardiotoxicity, paclitaxel was administered at the investigator's discretion.

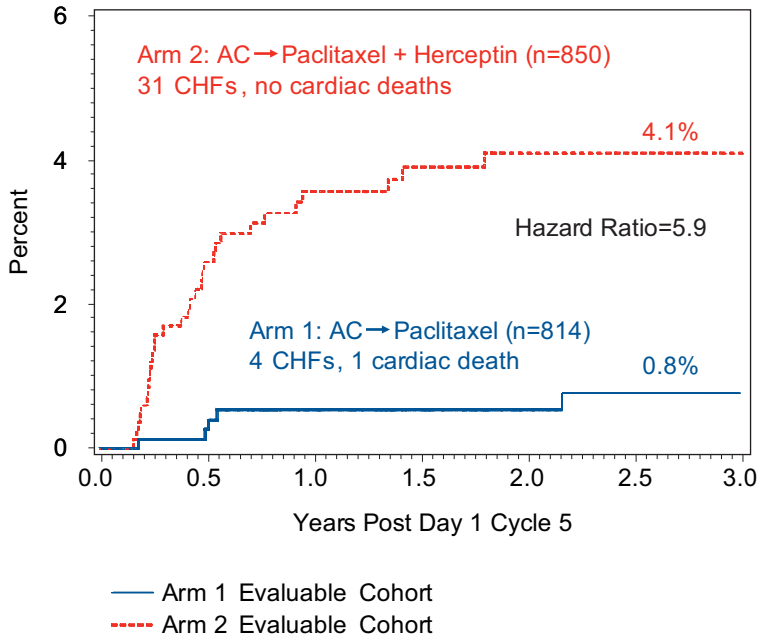
A total of 1019 patients were randomized to the HERCEPTIN-containing arm (Arm 2). Based on preliminary data and analyses through April 2005, 6.8% of patients were unable to initiate HERCEPTIN per the protocol because of decreased LVEF or symptoms of cardiac toxicity experienced during the AC portion of therapy. Among the evaluable patients who had adequate cardiac function and initiated HERCEPTIN, 30.5% required at least one dose delay because of asymptomatic decrease in LVEF or cardiac symptoms. In 18.6% of patients, HERCEPTIN was discontinued prior to the completion of 1 year of therapy because of asymptomatic decrease in LVEF (14.3%) and symptomatic cardiac dysfunction/other cardiac toxicity (4.3%). In addition, a statistically significant increase in the 3-year cumulative incidence of New York Heart Association Class III and IV congestive heart failure and cardiac death was observed in patients who received the HERCEPTIN-containing regimen (4.1%) compared with control (0.8%). There were no cardiac deaths observed in patients who received the HERCEPTIN-containing regimen and 1 cardiac death was observed in the control arm. Final analysis of the cardiac safety data collected in Studies NSABP B-31 and NCCTG N9831 is ongoing.

1 DNA Way, South San Francisco, CA 94080-4990
(650) 225-1000

Genentech
BIOONCOLOGY™

The following plot presents the time course for the development of these events in the evaluable cohort.

Cumulative Incidence of Cardiac Events in the Evaluable Cohort



Years Post Day 1 Cycle 5	Cum Inc Arm 1 (%)	Cum Inc Arm 2 (%)	Number at Risk
0.5	0.3	2.6	1466
1.0	0.5	3.6	1200
1.5	0.5	3.9	979
2.0	0.5	4.1	773
2.5	0.8	4.1	593
3.0	0.8	4.1	402

Cycle 5 Day 1 represents the start of paclitaxel or paclitaxel + HERCEPTIN.

Risk factors for cardiac dysfunction will be analyzed with data from both the NSABP B-31 and NCCTG N9831 trials, when available. A preliminary exploratory analysis performed by NSABP investigators suggests that age and LVEF following AC chemotherapy may identify patients at greatest risk for symptomatic cardiac dysfunction.

The current HERCEPTIN Package Insert is enclosed for your reference. HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression. It should be noted that HERCEPTIN is not indicated for any other patients, including those with newly diagnosed, operable breast cancer.

Should you need any further information on HERCEPTIN-related cardiotoxicity, please contact our Medical Communication Department at 1-800-821-8590 or at the "Contact Us" section of the Genentech corporate website (http://www.gene.com/gene/contact/).

Healthcare professionals should report any serious adverse events suspected to be associated with the use of HERCEPTIN to Genentech at 1-888-835-2555. Alternately, this information may also be reported to the FDA's MedWatch reporting system by telephone (1-800-FDA-1088), facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/), or mailed, using the MedWatch form FDA 3500 to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

Hal Barron, M.D.
Senior Vice President, Development
Chief Medical Officer
Genentech, Inc.

1 DNA Way, South San Francisco, CA 94080-4990
(650) 225-1000