Adjuvant Trastuzumab Clinical Trial Results

At the 2005 ASCO meeting, practice-changing results from several adjuvant trastuzumab trials — NCCTG-N9831, NSABP-B-31 and HERA — were presented. The combined analysis of NCCTG-N9831 and NSABP-B-31 demonstrated that the addition of trastuzumab to AC → paclitaxel significantly improved disease-free and overall survival in women with HER2-positive breast cancer. Data were also presented from the HERA trial (updated in San Antonio) which demonstrated that adjuvant trastuzumab could improve disease-free survival when started after a variety of chemotherapy regimens. At the San Antonio meeting, data were also presented from BCIRG 006 in which adjuvant trastuzumab was found again to significantly improve disease-free survival with both AC → docetaxel and a nonanthracycline-containing chemotherapy regimen of carboplatin plus docetaxel. These four landmark studies will be followed by a new generation of adjuvant trials, and one issue of great interest — as in HER2-negative disease — will be the potential role of bevacizumab.

PHASE III CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Target accrual	Eligibility	Randomization	Primary endpoint
BCIRG 006	3,150	Node-positive or high-risk node-negative HER2+ (FISH+)	AC x 4 → docetaxel 100 mg/m^2 q3wk x 4 AC x 4 → docetaxel 100 mg/m^2 q3wk x 4 + H qwk x 12 → H q3wk remainder of 1y Carboplatin + docetaxel 75 mg/m^2 q3wk x 6 + H qwk x 12 → H q3wk remainder of 1y Note: H 4 mg/kg LD → 2 mg/kg during chemo (after chemo, 6 mg/kg q3wk)	Disease-free survival
NSABP-B-31	2,700	Node-positive HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel q3wk* x 4 AC x 4 → paclitaxel q3wk* x 4 + H qwk x 52 Note: H 4 mg/kg LD → 2 mg/kg qwk x 51	CHF rate Overall survival
NCCTG-N9831	3,300	Node-positive or high-risk node-negative HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 52 AC x 4 → paclitaxel qwk x 12 + H qwk x 52 Note: H 4 mg/kg LD → 2 mg/kg qwk x 51	Cardiac tolerability Disease-free survival
BIG-01-01, HERA	4,482	Node-positive or node-negative HER2+ (IHC 3+ or FISH+) Any chemo + XRT	H q3wk x 12 months H q3wk x 24 months Observation Note: H 8 mg/kg LD → 6 mg/kg q3wk x 1y	Disease-free survival

H = trastuzumab; chemo = chemotherapy; LD = loading dose; CHF = congestive heart failure; * protocol amended to allow weekly or every three-week paclitaxel

SOURCES: NCI Physician Data Query, December 2005; Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7; Nabholtz JM et al. *Clin Breast Cancer* 2002;3(Suppl 2):75-9.

BCIRG 006 INTERIM EFFICACY ANALYSIS (N = 3,222)

	Median follow-up	AC-docetaxel/trastuzumab	Docetaxel/carboplatin/trastuzumab
Hazard ratios for disease-free survival relative to AC-docetaxel	23 months	0.49 [95% CI: 0.37-0.65] $p < 0.0001$	0.61 [95% CI: 0.47-0.79] $p = 0.0002$

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

COMBINED ANALYSIS OF NSABP-B-31/NCCTG-N9831 EFFICACY DATA

Parameters	AC → paclitaxel (n = 1,679)	AC → paclitaxel with trastuzumab (n = 1,672)	Hazard ratio [95% CI]	*p*-value*
Disease-free survival			0.48 [0.39-0.59]	< 0.0001
Three-year disease-free survival	75.4%	87.1%		
Four-year disease-free survival	67.1%	85.3%		
Time to first distant recurrence			0.47 [0.37-0.61]	< 0.0001
Three years from randomization	81.5%	90.4%		
Four years from randomization	73.7%	89.7%		
Overall survival			0.67 [0.48-0.93]	0.015
Three years from randomization	91.7%	94.3%		
Four years from randomization	86.6%	91.4%		

* All *p*-values were two sided.

SOURCE: Romond EH et al. *N Engl J Med* 2005;353:1673-84.

FIRST RESULTS OF HERA: TRASTUZUMAB FOR ONE VERSUS TWO YEARS VERSUS PLACEBO AFTER CHEMOTHERAPY FOR HER2-POSITIVE BREAST CANCER

Efficacy endpoint (one-year median follow-up)	Placebo (n = 1,693)	Trastuzumab for one year (n = 1,694)	Hazard ratio [95% CI]	*p*-value
Two-year disease-free survival	77.4%	85.8%	0.54 [0.43-0.67]	<0.0001
Distant recurrence-free survival	82.8%	90.6%	0.49 [0.38-0.63]	<0.0001
Overall survival	95.1%	96.0%	0.76 [0.47-1.23]	0.26

SOURCES: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72; Gelber RD et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

SELECT PUBLICATIONS

Baselga J et al. **Future options with trastuzumab for primary systemic and adjuvant therapy.** *Semin Oncol* 2004;31(5 Suppl 10):51-7.

Gelber RD on behalf of the HERA Study Team. **Trastuzumab (Herceptin) following adjuvant chemotherapy significantly improves disease-free survival in HER2-positive early breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

Nabholtz JM et al. **HER-2 positive breast cancer: Update on Breast Cancer International Research Group trials.** *Clin Breast Cancer* 2002;3(Suppl 2):75-9.

Perez EA et al. **NCCTG N9831 May 2005 update.** Presentation. ASCO 2005;Abstract 556.

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353:1659-72.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353:1673-84.

Slamon D et al. **Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2-positive early breast cancer patients: First interim efficacy analysis.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

Spicer J et al. **Adjuvant trastuzumab for HER2-positive breast cancer.** *Lancet* 2005;366(9486):634.

COMBINED ANALYSIS: NSABP-B-31 AND NCCTG-N9831

Our conclusions for high-risk HER2-positive breast cancer: Trastuzumab, when given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at three years by 52 percent. This benefit should change the standard of care. The benefit was present and of similar magnitude in virtually all subsets of patients analyzed. There is not, however, statistical power to establish efficacy in the node-negative subset. The addition of trastuzumab reduced the probability of developing distant recurrence by 53 percent at three years, and the hazard of developing distant metastases appears, thus far, to decrease over time. Early results at a median follow-up of two years show a statistically significant survival advantage with a relative risk reduction of 33 percent.

— Edward H Romond, MD et al. Presentation. ASCO 2005.

INITIAL RESULTS OF BCIRG 006

In a three-arm trial with 300 events, we recognize that we're walking a fine line here, but still, both arms crossed their efficacy boundaries. The relevant question will be: How does the TCH arm, the nonanthracycline arm, look relative to the anthracycline-containing arm? The risk reduction in the TCH arm is 0.39, and the risk reduction in the ACTH arm is 0.51, almost identical to what was seen in the trials reported at ASCO for that type of combination. That's based on very few event differences between the two arms. We need to wait until the data mature, and it won't take a long period of time. Physicians should basically do what they feel most comfortable with at this point. If they feel more comfortable with the ACTH data, they should go with that arm, recognizing that those patients will have to be watched very closely for cardiotoxicity.

— Dennis J Slamon, MD, PhD.
Breast Cancer Update: ***Special NSABP Edition 2005***

REDUCTION IN DISTANT DISEASE RECURRENCE

In the joint analysis of NCCTG-N9831 and NSABP-B-31, the hazard rates for distant disease recurrence in patients who received trastuzumab appeared to improve with time. It's still too early to analyze these data because few patients in either trial are four years out; however, the distant disease-free survival curve appears to plateau in the trastuzumab arm. If that's the case, it's astonishing. We've never seen a true plateau in any adjuvant trial. When we examine disease-free survival curves like this, we need to ignore a fair amount of the right side of the curve because there are so few numbers, but if that is maintained it will be exciting.

— George W Sledge Jr, MD. **Breast Cancer Update** ***2005 (6)***

ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE DISEASE

I have trepidation about using adjuvant trastuzumab in patients with node-negative disease and tumors under one centimeter. If the patient's tumor is ER-negative, the threshold to treat with trastuzumab is lower. On the other hand, for those with ER-positive disease, I would probably want to do an Onco*type* DX™ assay because I believe that is a reliable method to determine risk and would really be helpful. If it's a high-risk tumor, I would add trastuzumab to that regimen.

— Norman Wolmark, MD.
Breast Cancer Update: ***Special NSABP Edition 2005***

In the HERA trial, node-negative patients were allowed to enter if their tumor size was greater than one centimeter. It was the only criterion. We didn't require other aggressive features such as high proliferation or the absence of hormone receptors. It was purely based on pathological size. I don't see why these women would not derive a substantial benefit with trastuzumab and provided these women are well informed about cardiotoxicity risk, and are not elderly, we are discussing the possibility of adjuvant trastuzumab with them.

— Martine J Piccart-Gebhart, MD, PhD.
(Interview, December 2005)