Adjuvant Trastuzumab Clinical Trial Results

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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/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, which demonstrated that adjuvant trastuzumab could improve disease-free survival when started after a variety of chemotherapy regimens. At this San Antonio meeting, data will be presented from BCIRG 006, in which adjuvant trastuzumab was found again to significantly improve disease-free survival, both with AC → docetaxel and a nonanthracycline-containing chemotherapy regimen of carboplatin plus docetaxel. These four landmark studies will now 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, October 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.

ADJUVANT CHEMOTHERAPY WITH OR WITHOUT TRASTUZUMAB: 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]	$p < 0.0001$
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]	$p < 0.0001$
Three years from randomization	81.5%	90.4%		
Four years from randomization	73.7%	89.7%		
Overall survival			0.67 [0.48-0.93]	$p = 0.015$
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 (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

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

BCIRG 006 INTERIM EFFICACY ANALYSIS: RISK OF RELAPSE RELATIVE TO AC → T (N = 3,222)

	Median follow-up	AC-docetaxel/trastuzumab	Docetaxel/carboplatin/trastuzumab
Relative reduction in risk of relapse	23 months	51% (95% CI: 35-63%)	39% (95% CI: 21-53%)

SOURCE: www.bcirg.org/Internet/Press+Releases, September 2005.

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.

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13.

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.

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

COMBINED ANALYSIS: NSABP-B-31/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.

HERA: TRASTUZUMAB FOR ONE YEAR OR PLACEBO

In conclusion, at one-year median follow-up, trastuzumab given every three weeks for one year following adjuvant chemotherapy significantly prolongs disease-free survival and relapse-free survival and significantly reduces the risk of distant metastasis. Trastuzumab's clinical benefits are independent of patients' baseline characteristics and type of adjuvant chemotherapy received. Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure, but clearly, longer follow-up is needed to better quantify this risk. All patients continue to be followed for long-term safety. Results regarding optimal trastuzumab duration, two years versus one year, should be available in 2008.

— Martine J Piccart-Gebhart, MD, PhD 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 still 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 Oncotype 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***