Clinical Trials of Adjuvant Trastuzumab

Randomized trial data from the advanced disease setting demonstrate that in women with HER2-overexpressing breast cancer, the combination of trastuzumab and chemotherapy — using either doxorubicin/cyclophosphamide or paclitaxel — results in improved progression-free and overall survival compared to the same chemotherapy given without trastuzumab. These encouraging results have led to a new generation of adjuvant trials evaluating a variety of chemotherapeutic regimens combined with trastuzumab. While no efficacy endpoints have been met, closely evaluated cardiac monitoring has not yet revealed dysfunction that would preclude continuing these trials. Almost all clinical research leaders currently advocate using adjuvant trastuzumab only in a clinical trial setting.

PHASE III CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Status	Target accrual	Eligibility	Randomization	Primary endpoint	Key issues
BCIRG-006	Closed*	3,150	N+ or high-risk N-HER2+ (FISH+)	AC x 4 → docetaxel 100 mg/m² q3wk x 4 AC x 4 → docetaxel 100 mg/m²‡§ q3wk x 4 + H qwk x 12 → H q3wk† remainder of one year Carboplatin + docetaxel 75 mg/m²‡ q3wk x 6 + H qwk x 12 → H q3wk† remainder of one year	Disease-free survival§	Nonanthracycline/ H combination H in combination with chemotherapy
NSABP-B-31	Open	2,700	N+ HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel q3wk‡ x 4 AC x 4 → paclitaxel q3wk‡ x 4 + H qwk x 52	CHF-rate Overall survival	Combined analysis with N9831 Every three-week or weekly taxane with concurrent H
NCCTG-N9831	Open	3,300	N+ or high-risk N-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	Cardiac tolerability Disease-free survival	Combined analysis with B-31 Weekly taxane with concurrent or sequential H Effect of three-month delay between doxorubicin and H on cardiotoxicity
BIG-01-01, HERA	Closed	4,482	N+ or N- HER2+ (IHC 3+ or FISH+) Any chemo + XRT	H q3wk†‡ x 12 months H q3wk†‡ x 24 months Observation	Disease-free survival§	Duration of H Value of H versus no H following adjuvant chemo

N = node; H = trastuzumab (Herceptin®)

* Enrollment completed March 2004; interim analysis is planned for the first quarter of 2006.

† Every 3 weeks at 6 mg/kg

‡ Protocol amended to allow weekly or every three-week H

§ BCIRG-006 will evaluate pathologic and molecular markers predictive of efficacy, the value of cardiac biochemical and genetic markers for cardiac events, and the correlation between the shed HER2 extracellular domain and relapse. Cardiac monitoring is comparable to NSABP-B-31 and NCCTG-N9831. Two out of three planned interim cardiac safety analyses have been completed and passed the review of the Data Monitoring Committee without safety concerns.

‖ Three interim cardiac safety analyses identified no safety concerns.

SOURCES: NCI Physician Data Query, January 2005.

Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7.

ASSESSMENT OF TRASTUZUMAB-ASSOCIATED CARDIAC EVENTS: NSABP-B-31 TREATMENT AND MUGA SCHEDULE

	Cardiac events (CE)
	4.28%
	minus 0.78%
Cardiotoxicity uniquely attributable to trastuzumab (ARM 1 CE - ARM 2 CE)	= 3.5% CI, 1.6-5.3%

Protocol-defined acceptance of <4% congestive heart failure in anticipation of 25% reduction in death and reversible cardiac effects from trastuzumab; LVEF declines requiring cessation of trastuzumab were reversible in the vast majority of patients; therefore, trial accrual continued.

DERIVED FROM: Geyer CE Jr. Presentation. San Antonio Breast Cancer Symposium, 2003.

SELECT PUBLICATIONS

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STATUS OF THE ADJUVANT TRASTUZUMAB TRIALS

NSABP-B-31 has accrued nearly 2,000 patients, but it has been the slowest of the trials to accrue, in part because it had the every three-week paclitaxel regimen, which was somewhat of a barrier until we allowed the weekly regimens. Additionally, B-31 is a two-arm rather than a three-arm trial. In the other trials, patients had a two-out-of-three chance of receiving trastuzumab, whereas patients in our trial had a one-out-of-two chance. The HERA and BCIRG-006 studies have finished accruing patients, and the N9831 US Intergroup trial is within eight to 12 months of completing accrual. At our current rate, B-31 would require another two and a half years to complete accrual. We are optimistic about the possibility of combining N9831 and B-31 for a joint analysis, which will substantially accelerate the reporting time. We are close to having our first interim analysis of B-31; the analysis is based on deaths because survival was our primary endpoint.

— Charles E Geyer Jr, MD

CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

I predict we will see a five to seven percent reduction in recurrence at five years and an impact on disease-free survival in the adjuvant trastuzumab trials. The adjuvant trials are limited to patients with node-positive or high-risk, node-negative disease because the expected benefit must outweigh the known three to five percent short-term risk of cardiotoxicity associated with trastuzumab.

The most common trial design is AC followed by a taxane with or without trastuzumab. BCIRG-006 includes a carboplatin in combination with docetaxel arm because of the synergy seen *in vitro* and the possibility that omitting the anthracycline may mitigate cardiotoxicity. These studies have approximately 3,000 to 5,000 patients and are designed to detect small variations in outcome — approximately a five percent difference in recurrence and possibly a two percent survival benefit.

The adjuvant trials are evaluating one year of trastuzumab therapy, except for the European HERA study that randomly assigns patients to observation versus one year or two years of trastuzumab. The natural history of breast cancer suggests that longer-term biological therapy is more beneficial, so I believe more than one year of trastuzumab will be necessary for optimal effect.

— Debu Tripathy, MD

BCIRG-006 ADJUVANT TRASTUZUMAB TRIAL

For the first time in a large randomized adjuvant study of patients with HER2-positive tumors, a non anthracycline-containing synergistic combination will be put to the test in a carefully selected patient population. All patients must have FISH-positive disease; I think the trial will define the standard of care for the adjuvant treatment of patients with HER2-positive breast cancer. The other important component of this trial is safety. It doesn't appear that cardiac safety is going to be a major issue in the adjuvant trastuzumab trials.

— Mark D Pegram, MD

CARDIAC SAFETY ANALYSIS IN NSABP-B-31

"… a 3.5 percent increase in cardiac events among patients receiving AC followed by Herceptin and Taxol compared to AC followed by Taxol alone was identified.

"The increase in cardiac events was within protocol limits, justifying continuation of accrual. Abnormal LV function and symptoms, if present, improved with cessation of Herceptin in the vast majority of patients. A peak decline in median LVEF of 3 percent was noted when patients had received six months of Herceptin.

"Clearly, additional follow-up will be needed to fully define the short and long term cardiac events of Herceptin in this setting. And these results support continued accrual into ongoing adjuvant trials, but indicate use as adjuvant therapy outside of clinical trial would clearly be premature."

— Geyer Jr CE. Presentation. San Antonio Breast Cancer Symposium, 2003.