Clinical Trials of Adjuvant Trastuzumab

27TH ANNUAL San Antonio Breast Cancer Symposium 16

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 RANDOMIZED STUDY OF ADJUVANT AC AND DOCETAXEL WITH OR WITHOUT TRASTUZUMAB VERSUS TRASTUZUMAB, DOCETAXEL, AND EITHER CARBOPLATIN OR CISPLATIN

Protocol ID: BCIRG-006
Accrual: 3,150 patients (Closed)

Eligibility	Node-positive or high-risk node-negative HER2-overexpressing (FISH-positive) breast cancer
ARM 1	AC x 4 → docetaxel x 4
ARM 2	AC x 4 → docetaxel x 4 + H (qwk x 12 weeks) → H (qwk x 40 weeks)
ARM 3	(Docetaxel + C) x 6 + H (qwk x 18 weeks) → H (qwk x 34 weeks)

C = cisplatin or carboplatin; H = trastuzumab;
AC = doxorubicin/cyclophosphamide

Patients with ER- and or PR-positive disease receive oral tamoxifen for five years beginning three to four weeks after the completion of chemotherapy. Patients may undergo radiotherapy beginning three to eight weeks after completion of chemotherapy.

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF TRASTUZUMAB IN WOMEN WITH HER2-POSITIVE PRIMARY BREAST CANCER

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 4,482 patients (Open)

Eligibility	Node-negative or node-positive HER2-positive breast cancer
ARM 1	H q3wk x 1 y
ARM 2	H q3wk x 2 y
ARM 3	No H

H = trastuzumab

Previously treated with at least 3 months or 4 courses of approved neoadjuvant or adjuvant chemotherapy with or without radiotherapy. Concurrent systemic adjuvant hormonal therapy for patients with ER-positive disease is allowed.

Study Contact:
Martine J Piccart-Gebhart, MD, PhD, Chair
Breast International Group
Tel: 32-2-5413206

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

Protocol IDs: NCCTG-N9831, CLB-49909, E-N9831, SWOG-N9831
Projected Accrual: 3,300 patients (Open)

Eligibility	Node-positive or high-risk node-negative HER2-overexpressing breast cancer
ARM 1	AC x 4 → T qwk x 12
ARM 2	AC x 4 → T qwk x 12 → H qwk x 52
ARM 3	AC x 4 → (T + H) qwk x 12 → H qwk x 40

T = paclitaxel; H = trastuzumab; AC = doxorubicin/cyclophosphamide

All postmenopausal patients with ER/PR-positive disease receive tamoxifen or an aromatase inhibitor for five years. Patients may undergo radiotherapy at the completion of chemotherapy.

Study Contact:
Edith A Perez, MD, Chair
North Central Cancer Treatment Group
Tel: 904-953-7283

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF AC FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

Protocol ID: NSABP-B-31
Projected Accrual: 2,700 patients (Open)

Eligibility	HER2-positive, node-positive breast cancer
ARM 1	AC x 4 → paclitaxel q3wk x 4 or paclitaxel qwk x 12
ARM 2	AC x 4 → (paclitaxel q3wk x 4 or paclitaxel qwk x 12) + H (qwk x 1 y)

H = trastuzumab; AC = doxorubicin/cyclophosphamide

Patients with ER/PR-positive disease receive tamoxifen for five years. Lumpectomy patients undergo radiotherapy at completion of chemotherapy and concurrent with trastuzumab.

Study Contact:
Edward Romond, MD, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 859-323-8043

SOURCE: NCI Physician Data Query, October 2004.

N9831: EFFECT OF ADJUVANT AC ON LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH HER2-POSITIVE BREAST CANCER (n=1,458)

Reduction in LVEF	n (%)
Patients with >15%	37 (2.5)
Patients with ≤15% and LVEF below LLN	42 (2.9)
Patients with ≤15% and LVEF remains at or above LLN	745 (51.1)

LVEF= left ventricular ejection fraction (measured by MUGA or ECHO)
LLN = lower limit of normal

SOURCE: Perez EA et al. *J Clin Oncol* 2004;22(18):3700-4.

NSABP-B-31 CARDIAC SAFETY ANALYSIS

	AC → paclitaxel	AC → paclitaxel/ trastuzumab	Percent increase
Cardiac events/n (%)	4/510 (0.78%)	23/538 (4.28%)	3.50%

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

SELECT PUBLICATIONS

Geyer Jr CE et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** *Breast Cancer Res Treat* 2003;Abstract 23.

Gradishar WJ, O'Regan RM. **Progress in systemic adjuvant therapy of early-stage breast cancer**. *Int J Clin Oncol* 2003;8(4):239-47.

Hortobagyi GN, Perez EA. **Integration of trastuzumab into adjuvant systemic therapy of breast cancer: Ongoing and planned clinical trials.** *Semin Oncol* 2001;28(5 Suppl 16):41-6.

Jones AL, Leyland-Jones B. **Optimizing treatment of HER2-positive metastatic breast cancer**. *Semin Oncol* 2004;31(5 Suppl 10):29-34.

Nabholtz JM, Slamon D. **New adjuvant strategies for breast cancer: Meeting the challenge of integrating chemotherapy and trastuzumab (Herceptin).** *Semin Oncol* 2001;28(1 Suppl 3):1-12.

Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab**. *J Clin Oncol* 2004;22(2):322-9.

Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20(5):1215-21.

Slamon D, Pegram M. **Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials.** *Semin Oncol* 2001;28(1 Suppl 3):13-9.

Smith I. **Future directions in the adjuvant treatment of breast cancer: The role of trastuzumab.** *Ann Oncol* 2001;12(Suppl 1):75-9.

Sparano JA. **Cardiac toxicity of trastuzumab (Herceptin): Implications for the design of adjuvant trials.** *Semin Oncol* 2001;28(1 Suppl 3):20-7.

Tan AR, Swain SM. **Ongoing adjuvant trials with trastuzumab in breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):54-64.

Tan-Chiu E, Piccart M. **Moving forward: Herceptin in the adjuvant setting.** *Oncology* 2002;63(Suppl 1):57-63.

INTERGROUP 9831 TRIAL

N9831 is a randomized Phase III clinical trial building on several issues: (1) the relative importance of anthracyclines in the adjuvant management of patients with HER2-positive breast cancer, (2) the value of taxanes in patients eligible to receive adjuvant therapy, (3) the specific value of taxanes for patients with HER2-positive breast cancer, and (4) the value of weekly paclitaxel therapy for patients with breast cancer.

We were comforted by the data presented from CALGB-9741. That trial administered dose-dense chemotherapy with growth factor support once every two weeks, and in our trial we are using an even more dose-dense approach by administering paclitaxel on a weekly basis. The AC in our trial is still being given once every three weeks. Although we thought about potentially changing it to once every two weeks, we hypothesized that the advantage seen in CALGB-9741 may be due to the paclitaxel schedule. We also didn't want to introduce another factor that could impact cardiac toxicity.

— Edith A Perez, MD

HERA TRIAL OF ADJUVANT TRASTUZUMAB

The HERA trial is a relatively pragmatic study. Patients initially receive an approved adjuvant chemotherapy regimen, and then they are randomly assigned to trastuzumab monotherapy for either one or two years or no trastuzumab. It's my responsibility and that of Brian Leyland-Jones, who co-chairs the Trans-HERA Committee, to collect the tumor blocks from that trial and perform biomarker analyses.

— Mitchell Dowsett, PhD

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 very carefully selected patient population. All of the patients must have FISH-positive disease; therefore, 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

NSABP-B-31: ADJUVANT AC FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

After the NSABP designed the adjuvant trial B-31, the Intergroup designed a similar trial so that the data could be analyzed together. I think that's great because it will be a stronger analysis. I hope we'll see a benefit with trastuzumab, which has been a miracle drug in the metastatic setting. If this trial is positive, there will still be a lot of scheduling questions to be answered, such as, "How long do you really need trastuzumab and can it be administered every three weeks rather than weekly?"

— Sandra Swain, 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% was noted when patients had received 6 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."

— Charles E Geyer Jr, MD. Presentation. San Antonio Breast Cancer Symposium, 2003.