Clinical Trials of Adjuvant Trastuzumab

Randomized trial data from the advanced disease setting demonstrate that in women with HER2-overexpressing breast cancers, 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 and schedules of trastuzumab administration.

PHASE III RANDOMIZED STUDY OF ADJUVANT DOXORUBICIN, CYCLOPHOSPHAMIDE, AND DOCETAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) VERSUS TRASTUZUMAB, DOCETAXEL, AND EITHER CARBOPLATIN OR CISPLATIN IN WOMEN WITH HER2-NEU-EXPRESSING NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE OPERABLE BREAST CANCER

Open Protocol

Protocol ID: BCIRG-006
Projected Accrual: 3,150 patients

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 (qw x 12 weeks) ➜ H (qw x 40 weeks)
ARM 3	(Docetaxel + C) x 6 + H (qw x 18 weeks) ➜ H (qw x 34 weeks)

C=cisplatin or carboplatin; H=trastuzumab

Study Contacts:
Linnea Chap, Chair. Tel: 310-825-5268
Jonsson Comprehensive Cancer Center, UCLA

SOURCE: NCI Physician Data Query, January 2003

PHASE III RANDOMIZED STUDY OF TRASTUZUMAB (HERCEPTIN®) IN WOMEN WITH HER2-POSITIVE PRIMARY BREAST CANCER — Open Protocol

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 3,192 patients

Eligibility	Node-negative or -positive, HER2-positive breast cancer previously treated with at least 3 months or 4 courses of approved neoadjuvant or adjuvant chemotherapy with or without radiotherapy
ARM 1	H q3w x 1 year
ARM 2	H q3w x 2 years
ARM 3	No H

H=trastuzumab

Study Contacts:
Martine J Piccart-Gebhart, Chair. Tel: 32-2-5413206
Breast International Group

Robert E Coleman, Chair. Tel: 114 226 5213
EORTC Breast Cancer Group

SOURCE: NCI Physician Data Query, January 2003

PHASE III RANDOMIZED STUDY OF DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) IN WOMEN WITH HER2-OVEREXPRESSING NODE-POSITIVE BREAST CANCER — Open Protocol

Protocol IDs: NCCTG-N9831, CLB-49909, E-N9831, SWOG-N9831
Projected Accrual: 3,000 patients (1,000 per treatment arm)

Eligibility	Node-positive, HER2-overexpressing breast cancer
ARM 1	AC x 4 ➜ T qw x 12
ARM 2	AC x 4 ➜ T qw x 12 ➜ H qw x 52
ARM 3	AC x 4 ➜ (T + H) qw x 12 ➜ H qw x 40

T=paclitaxel; H=trastuzumab
All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor x 5 years.
Patients may undergo radiotherapy at the completion of chemotherapy.

Study Contacts:
Peter A Kaufman, Chair. Tel: 603-650-6700
Cancer and Leukemia Group B

Nancy E Davidson, Chair. Tel: 410-955-8489
Eastern Cooperative Oncology Group

Edith A Perez, Chair. Tel: 507-284-2111
North Central Cancer Treatment Group

Silvana Martino, Chair. Tel: 310-998-3961
Southwest Oncology Group

SOURCE: NCI Physician Data Query, January 2003

PHASE III RANDOMIZED STUDY OF DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) IN WOMEN WITH NODE-POSITIVE BREAST CANCER THAT OVEREXPRESSES HER2

Open Protocol

Protocol ID: NSABP-B-31
Projected Accrual: 1,000-2,700 patients

Eligibility	HER2-positive, node-positive breast cancer
ARM 1	AC x 4 ➜ paclitaxel x 4
ARM 2	AC x 4 ➜ paclitaxel x 4 + H qw x 1 year

H=trastuzumab
All ER/PR-positive patients receive tamoxifen x 5 years.
Lumpectomy patients undergo radiotherapy at completion of chemotherapy and concurrent with trastuzumab.

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

SOURCE: NCI Physician Data Query, January 2003

SELECT PUBLICATIONS

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):41-46.

Leyland-Jones B. **Dose scheduling—Herceptin.** *Oncology* 2001;61(Suppl) 2:31-36.

Nabholtz JM, Slamon D. **New adjuvant strategies for breast cancer: Meeting the challenge of integrating chemotherapy and trastuzumab (Herceptin).** *Semin Oncol* 2001;281(Suppl)3:1-12.

Piccart-Gebhart MJ. **Herceptin: The future in adjuvant breast cancer therapy.** *Anticancer Drugs* 2001;12(Suppl)4:S27-33.

Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20(5):1215-1221.

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-792.

Smith I. **Future directions in the adjuvant treatment of breast cancer: The role of trastuzumab.** *Ann Oncol* 2001;12(Suppl)1:S75-79.

Sparano JA. **Cardiac toxicity of trastuzumab (Herceptin): Implications for the design of adjuvant trials.** *Semin Oncol* 2001;281(Suppl)3:20-27.

INTERGROUP 9831 AND NSABP B-31 TRIALS

Intergroup trial 9831 (NCCTG-N9831) is an adjuvant study in patients with node-positive, HER2-positive breast cancer. We are also testing the question of whether trastuzumab should be used sequentially or concurrently with chemotherapy. NSABP B-31 has very similar eligibility criteria. Both adjuvant trastuzumab trials — NCCTG N9831 and NSABP B-31 — are carefully attending to cardiac tolerability. In our adjuvant trial, we have attempted to ameliorate the risk of cardiotoxicity by not using trastuzumab concurrently with anthracyclines and by limiting the dose of doxorubicin to 240 mg/m2.

If someone uses adjuvant trastuzumab outside of a clinical trial setting, they're essentially shooting in the dark. We do not yet understand how long this therapy should be given, what schedule should be used in combination with chemotherapy or the potential risks or benefits the patients may derive from such treatment.

—Edith A Perez, MD

NONANTHRACYCLINE COMBINATIONS IN THE ADJUVANT SETTING

The Breast Cancer International Research Group's (BCIRG's) trastuzumab adjuvant trial 006 is evaluating conventional chemotherapy strategies — four cycles of AC followed by four cycles of docetaxel in combination with trastuzumab. The arm we are most excited about is the docetaxel/carboplatin/trastuzumab arm. This is a nonanthracycline combination of synergistic drugs. There is synergy between docetaxel/trastuzumab, as well as carboplatin/trastuzumab. In addition, we don't have to worry as much about cardiotoxicity with that combination.

—Mark Pegram, MD

ADJUVANT TRASTUZUMAB TRIALS

I feel strongly that trastuzumab should not be combined with anthracycline-based therapy in the adjuvant setting. Yet, two US cooperative groups have trials utilizing trastuzumab with anthracycline-based therapy. In patients with HER2-positive metastatic breast cancer, which is very aggressive and uniformly lethal with the old treatments, taking risks makes sense as long as the patient and physician are aware and patients are monitored. In the adjuvant setting, some patients may be cured by the initial radiation and surgery. Therefore, I think it is ill advised to put those women at risk for cardiac dysfunction, particularly if there are regimens that look superior in terms of their efficacy based on preclinical synergy.

— Dennis J Slamon, MD, PhD

CLINICAL USE OF ADJUVANT TRASTUZUMAB

I do not use adjuvant trastuzumab outside of a clinical trial, and there are adjuvant trials available at most large cancer centers. Trastuzumab is a very promising drug, which has generated tremendous enthusiasm, but there are concerns about long-term side effects. While all of us hope to bring the answers to our patients as soon as possible, we have tried very hard to limit the use of adjuvant trastuzumab to patients on a study.

—Harold J Burstein, MD, PhD

I have not used adjuvant trastuzumab in a nonprotocol setting. Our experience with bone marrow transplant taught us that we could not always trust our preconceived notions about what would work. We need to answer the questions regarding adjuvant trastuzumab quickly, so I have only been entering patients — even those with high risk (10 or more positive nodes or inflammatory disease) — on clinical trials.

—Melody Cobleigh, MD