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-EXPRESSED NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE OPERABLE BREAST CANCER**

Open Protocol
Protocol ID: BCOG-8065
Projected Accrual: 3,150 patients

**Eligibility**
- Node-positive or high-risk, 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) + T (qw x 40 weeks)

**ARM 3**
- (Docetaxel + C) x 6 + H (qw x 18 weeks) + T (qw x 34 weeks)

**Clinical Trials**
- *Sparano JA.* 2001;344(11):783-792.
- *Cardiac toxicity of trastuzumab (Herceptin): Implications for clinical use of adjuvant trastuzumab* — *Melody Cobleigh, MD* 2002

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

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

**Eligibility**
- Node-positive or high-risk, HER2-overexpressing breast cancer previously treated with at least 3 months or 4 courses of approved neoadjuvant or adjuvant chemotherapy or without radiotherapy

**ARM 1**
- H qw x 1 year

**ARM 2**
- H qw x 2 years

**ARM 3**
- No H

**HER-2+trastuzumab**

**Study Contacts:**
- Martino Silvana, Chair. Tel: 310-998-3961
- North Central Cancer Treatment Group
- Peter A Kaufman, Chair. Tel: 603-650-6700
- Breast Cancer Research Group
- Edward H Romond, Chair. Tel: 859-323-8043
- Breast International Group
- Edward H Romond, Chair. Tel: 859-323-8043

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

Protocol ID: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 3,150 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 or without radiotherapy

**ARM 1**
- H qw x 1 year

**ARM 2**
- H qw x 2 years

**ARM 3**
- No H

**HER-2+trastuzumab**

**Study Contacts:**
- Tannir N, Picart-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, October 2002

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

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

**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)

**HER/Taxol/Herceptin**

**Study Contacts:**
- Kaplan A, Kaufman, Chair. Tel: 603-650-6700
- Cancer and Leukemia Group B
- Eastern Comprehensive Cancer Center
- North Central Cancer Treatment Group
- Breast International Group
- Source: NCI Physician Data Query, October 2002

**PHASE III RANDOMIZED STUDY OF DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) IN WOMEN WITH HER2-OVEREXPRESSING BREAST CANCER THAT OVEREXPresses HER2 (TOH)** — *Open Protocol*

Projected Accrual: 3,150 patients

**Eligibility**
- HER2-positive, node-negative breast cancer

**ARM 1**
- AC x 4 + paclitaxel x 4

**ARM 2**
- AC x 4 + paclitaxel x 4 + H qw x 1 year

**HER/trastuzumab**

**Study Contacts:**
- Hinson JM, Comper, Chair. Tel: 603-650-6700
- Breast International Group
- Emmett E, Kaufman, Chair. Tel: 310-996-3363
- SouthWest Oncology Group
- Source: NCI Physician Data Query, October 2002

**SELECT PUBLICATIONS**
- Sparano JA. *Cardiac toxicity of trastuzumab (Herceptin): Implications for the design of adjuvant trials.* Semin Oncol 2001;28(Suppl)3:20-27.
- Tannir N, Picart-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, October 2002

**INTERGROUP 9931 AND NSABP B-31 TRIALS**

Intergroup trial 9931 (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, and the potential risks or benefits the patients may derive from such treatment.

—*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 U.S. 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’s all 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 Coblidge, MD*