Neoadjuvant Trials of Trastuzumab in HER2-Positive Breast Cancer

In women with breast cancer, neoadjuvant chemotherapy may have potential advantages over adjuvant chemotherapy, including an increased rate of breast conservation and a decreased rate of distant metastases. It has been postulated that the pathologic response of the primary tumor to neoadjuvant chemotherapy may correlate with long-term survival. In women with HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy has been shown to improve the response rate, progression-free survival and overall survival. Several trials have investigated the addition of trastuzumab to neoadjuvant chemotherapy regimens in women with HER2-positive disease. The neoadjuvant chemotherapy regimens have included taxanes, vinorelbine, cisplatin and epirubicin; the pathologic complete response rates have ranged from seven percent to 42 percent. Dr Aman Buzdar recently reported (ASCO 2004) results from a trial that randomly assigned women with HER2-positive breast cancer to paclitaxel → FEC with or without trastuzumab as neoadjuvant therapy. The addition of neoadjuvant trastuzumab yielded a pathologic complete response rate of 65.2% in those patients compared to 26.3% with chemotherapy alone. As these data mature and further results are obtained from other neoadjuvant trials, the role of neoadjuvant trastuzumab will continue to evolve.

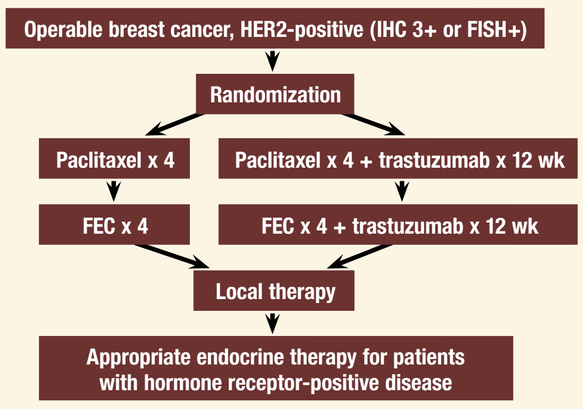
RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

	Neoadjuvant regimen	Number of patients	Pathologic complete response rate
Burstein 2003	Trastuzumab qwk x 12 + paclitaxel q3wk x 4	40	IHC 3+: 19% IHC 2+: 13%
Carey 2002	AC x 4 → (trastuzumab + paclitaxel) qwk x 12	22	22%
Bines 2003	Trastuzumab week 1 → qwk x 14 + (docetaxel qwk x 6 → 2 wk off) x 2	33	12%
Moluçon 2003	Trastuzumab qwk x 17 + docetaxel q3wk x 6	18	28%
Wenzel 2004	(Trastuzumab + epirubicin + docetaxel) qwk x 6	14	7%
Hurley 2003	Trastuzumab qwk x 11 + (cisplatin + docetaxel) q3wk x 4 + G-CSF + EPO	44	20%
Limentani 2003	Trastuzumab qwk x 12 + ([docetaxel + vinorelbine] q2wk + G-CSF) x 6	12	42%

G-CSF = granulocyte colony stimulating factor; EPO = erythropoietin

SOURCES: Bines J et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):56;Abstract 243. Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53. Carey LA et al. *Breast Cancer Res Treat* 2002;76(Suppl 1):109;Abstract 424. Hurley J et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):54;Abstract 238. Limentani SA et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):55;Abstract 240. Moluçon C et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):59;Abstract 253. Wenzel C et al. *J Cancer Res Clin Oncol* 2004;130:400-4.

RANDOMIZED TRIAL OF NEOADJUVANT TRASTUZUMAB AND CHEMOTHERAPY



PATHOLOGIC COMPLETE RESPONSE RATES FOR NEOADJUVANT THERAPY

	Trastuzumab + P + FEC	P + FEC	*p*-value
Overall (n=23,19)	65.2%	26.3%	0.016
Hormone receptor-positive (n=13,11)	61.5%	27.2%	—
Hormone receptor-negative (n=10,8)	70.0%	25.0%	—

P = paclitaxel; F = 5-fluorouracil; E = epirubicin; C = cyclophosphamide

SOURCE: Buzdar AU et al. Presentation. ASCO, 2004.

PHASE III RANDOMIZED STUDY OF NEOADJUVANT DOCETAXEL AND CARBOPLATIN WITH VERSUS WITHOUT TRASTUZUMAB IN WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Protocol IDs: UCLA-9911084, AVENTIS-GIA-11156, GENENTECH-H2269s
Projected Accrual: 400 (Open)

Eligibility	**T3 or T4, any N Patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy as follows:**
ARM 1	**[Trastuzumab days 1, 8 and 15 q21d x 4] + [(docetaxel + carboplatin) q3wk x 4]**
ARM 2	**(Docetaxel + carboplatin) q3wk x 4**

* Patients who do not have HER2-positive disease receive neoadjuvant chemotherapy only, as in arm 2.

Note: Within 4-6 weeks after surgery, patients with responding disease receive 4 additional courses of docetaxel and carboplatin as during neoadjuvant chemotherapy. All patients with HER2-positive disease also receive trastuzumab IV once weekly for 12 weeks and then every 3 weeks for 40 weeks (total of 52 weeks of trastuzumab therapy).

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Tel: 310-794-5624

SOURCE: NCI Physician Data Query, October 2004.

SELECT PUBLICATIONS

Bines J et al. **Weekly docetaxel (Taxotere) and trastuzumab (Herceptin) as primary therapy in stage III, HER-2 overexpressing breast cancer – a Brazilian multicenter study.** *Breast Cancer Res Treat* 2003;82(Suppl 1):56;Abstract 243.

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53.

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease.** *J Clin Oncol* 2004;22(Supp1 4);Abstract 520.

Carey LA et al. **Response to trastuzumab (Herceptin) given with paclitaxel (Taxol, T) immediately following 4AC as initial therapy for primary breast cancer (BrCa).** *Breast Cancer Res Treat* 2002;76(Suppl 1):109;Abstract 424.

Hurley J et al. **Platinum salts and docetaxel as primary therapy of locally advanced and inflammatory breast cancer: The final report of three sequential studies.** *Breast Cancer Res Treat* 2003;82(Suppl 1):54;Abstract 238.

Limentani SA et al. **Dose dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support.** *Breast Cancer Res Treat* 2003;82(Suppl 1):55;Abstract 240.

Moluçon C et al. **Pathological complete response with neoadjuvant (NA) chemotherapy (trastuzumab (T) and docetaxel (D)) in HER2 positive (3+) locally advanced (LA) breast cancer (BC) patients.** *Breast Cancer Res Treat* 2003;82(Suppl 1):59;Abstract 253.

Wenzel C et al. **Preoperative therapy with epidoxorubicin and docetaxel plus trastuzumab in patients with primary breast cancer: A pilot study.** *J Cancer Res Clin Oncol* 2004;130:400-4.

NEOADJUVANT TRASTUZUMAB/PACLITAXEL TRIAL

This study is novel for several reasons. It is the first trial evaluating neoadjuvant trastuzumab, and much interest exists in defining the response rate. Also, we performed cardiac analyses during the neoadjuvant trastuzumab/paclitaxel therapy and again during the adjuvant AC. Our results are very similar to George Sledge's — a significant number of women had a 10 to 20 percent decline in their ejection fractions. Fortunately, none of the patients developed any symptoms of congestive heart failure, and the changes in ejection fraction appear to reverse with time. The decline in ejection fraction occurred either during or at the end of adjuvant AC in three of the four women, and did not change much during the trastuzumab/paclitaxel therapy. Most of us believe these kinds of changes in ejection fraction are consistent with what occurs with AC alone, but because this is not a randomized trial, we do not know if the addition of trastuzumab influences the ejection fraction.

— Harold J Burstein, MD, PhD

NEOADJUVANT TRASTUZUMAB

The neoadjuvant data for trastuzumab exemplify a totally different set of circumstances. With chemotherapy alone, clinical response rates are in the 70 to 90 percent range. It is not surprising then that trastuzumab combinations show those same response rates. Because the pathologic complete response rate is a surrogate for survival, we are interested in that. The CALGB neoadjuvant trastuzumab trial was designed to determine the efficacy of dexrazoxane, trastuzumab in combination with paclitaxel, and trastuzumab following surgery. First, the patients are randomly assigned to receive doxorubicin/cyclophosphamide with or without dexrazoxane. This part of the trial will determine whether the introduction of a cardioprotectant can have a long-term effect on controlling cardiotoxicity. In the second phase of the study, the patients will receive paclitaxel with or without trastuzumab. Then, the patients will undergo surgery and continue on trastuzumab or observation alone.

— Debu Tripathy, MD

NONPROTOCOL USE OF NEOADJUVANT AND ADJUVANT TRASTUZUMAB

Before our neoadjuvant trastuzumab data were available, we did not offer neoadjuvant trastuzumab to any patient outside the context of a clinical trial. However, now that the data are in the public domain, I think it is our responsibility to share the information and discuss the issue with our patients. As long as the patient and the physician understand that uncertainties exist regarding the data, the cardiac safety and the long-term outcome, I believe it is a reasonable approach.

At our institution, based on the recommendation of the Data Monitoring Committee, we stopped the control arm of the study. Currently, all patients are being offered chemotherapy with trastuzumab in the neoadjuvant setting. We want to expand our experience, determine whether these data are reproducible and acquire long-term safety data.

On the other hand, if a woman with high-risk node-positive disease comes to MD Anderson seeking adjuvant trastuzumab — which we debate within our group once a month — we are divided on the issue. Some physicians within our group believe that a woman at high risk should be offered this therapy in the nonprotocol neoadjuvant or adjuvant setting whereas others want to be conservative and not offer it.

My experience is that patients who have four or more positive nodes tend to not do well, especially if they have HER2-positive disease. I think we have to discuss these options and let the patients know about these treatments because "the genie is out of the bottle." After appropriate discussion, if the patient agrees and accepts the uncertainties and the limitations of the available data, I am inclined to offer this therapy.

— Aman Buzdar, MD