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.

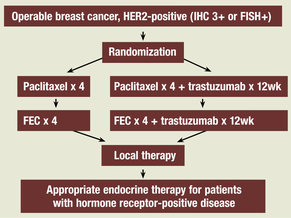
RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

Trial	Neoadjuvant regimen	Number of patients	Pathologic complete response rate
Bines 2003	Trastuzumab qwk x 14 + (docetaxel qwk x 6 → 2 wk off) x 2	33	12%
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%
Harris 2003	Trastuzumab qwk x 12 + vinorelbine qwk	39	21%
Hurley 2003	Trastuzumab qwk x 12 + (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%
Moluçon 2003	Trastuzumab qwk x 18 + docetaxel q3wk x 6	18	28%
Schiffhauer 2003	Trastuzumab qwk x 12 + docetaxel q3wk	16	25%
Steger 2002	Trastuzumab qwk x 12 + docetaxel qwk + epirubicin qwk	9	22%
Wenzel 2004	(Trastuzumab + epirubicin + docetaxel) qwk x 6	14	7%

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; Harris LN et al. *Proc ASCO* 2003;Abstract 86; 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; Schiffhauer LM et al. *Proc ASCO* 2003;Abstract 969; Steger GG et al. *Proc ASCO* 2002;Abstract 1966; Wenzel C et al. *J Cancer Res Clin Oncol* 2004;130(7):400-4.

MD ANDERSON 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; FEC = 5-fluorouracil, epirubicin and cyclophosphamide

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

PHASE III RANDOMIZED TRIAL 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: 75 (Open)

Eligibility	**T3 or T4, any N patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy**
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. 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).

Study Contact:
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SOURCE: NCI Physician Data Query, January 2005.

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.** *Proc ASCO* 2004;22(Suppl 4);Abstract 520.

Carey LA et al. **Responag 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(7):400-4.

MD ANDERSON PREOPERATIVE TRIAL OF TRASTUZUMAB AND CHEMOTHERAPY

All of the patients enrolled in the trial received four courses of every three-week paclitaxel followed by 12 weeks of FEC. We used epirubicin instead of doxorubicin because it has a better cardiac safety profile. One half of these patients also received weekly trastuzumab for 24 weeks. Every patient had a baseline cardiac scan and then repeat scans at 12 and 24 weeks.

In our previous experience with this chemotherapeutic regimen, about 21 percent of unselected patients had pathologic complete remissions. Pathologic complete remission is defined as having no tumor left in the breast or in the lymph nodes after therapy. We were hoping the addition of trastuzumab to chemotherapy would elevate the pathologic complete response rate from 21 percent to 41 percent — a 20 percent improvement.

The trial was interesting because we knew what the pathologic outcome was as soon as the patient completed surgery. As soon as we had results from 34 patients, we were able to see that 65 percent of the patients in the trastuzumab arm had no tumor, whereas only 25 percent of the patients who received chemotherapy alone were tumor-free.

This was much higher than we had anticipated or hoped. The clinical response rate was even more striking, as 87 percent of the patients had clinical complete remission in the trastuzumab arm compared to about 50 percent in the chemotherapy-alone arm.

We observed a slightly increased incidence of reduced ejection fractions in patients enrolled in the trastuzumab arm compared to the patients in the chemotherapy-alone arm. All of these changes were observed on cardiac scan. What was also surprising was that in almost all of the patients who had drops in their cardiac ejection fractions, the LVEFs returned to normal after therapy was completed.

We discussed these data with our institutional Data Monitoring Committee, which looked at them independently and came to the conclusion that the findings were so striking that even if we continued the trial to reach accrual, the results would be similar. Thus the trial was stopped early.

— Aman U Buzdar, MD

Despite the early closure of this randomized trial, its findings are provocative. If we think about the number of papers reporting on various regimens of preoperative chemotherapy, never stratified by HER2, they've always shown pathologic complete response rates of 15 to 20 percent, especially in hormone receptor-negative tumors. This literature just became irrelevant because we now know that we can triple the pathologic complete response rate in HER2-positive tumors by adding trastuzumab.

However, this trial has some caveats. Let's assume the adjuvant trastuzumab trials are positive and that, in general, they share a common design feature of an anthracycline followed by trastuzumab plus a taxane. In the metastatic setting, trastuzumab is less active if the tumor is resistant to chemotherapy, so perhaps we should have administered trastuzumab first before chemotherapy. This would have allowed a safety analysis for concurrent use of up-front chemotherapy.

Additionally, if 200 women were treated, the trial may have shown an improvement in the rate of breast-conserving surgery, which is the only rationale for preoperative treatment outside a clinical trial. Furthermore, because few oncologists have experience with the regimen utilized, I'm not sold on this regimen as a widespread nonprotocol option.

— Harold J Burstein, MD, PhD