Neoadjuvant Trastuzumab in HER2-Positive Breast Cancer

28TH ANNUAL San Antonio Breast Cancer Symposium 16

In women with HER2-positive early breast cancer, the addition of one year of adjuvant trastuzumab to chemotherapy has been shown to significantly improve disease-free and overall survival. Several trials investigating the addition of trastuzumab to neoadjuvant chemotherapy have reported pathologic complete response (pCR) rates ranging from seven to 42 percent. At the 2004 ASCO meeting, Dr Aman Buzdar reported the results from a randomized neoadjuvant trial of paclitaxel → FEC with or without trastuzumab in women with HER2-positive breast cancer. This neoadjuvant trastuzumab/chemotherapy regimen yielded a pCR of 65.2 percent compared to 26.3 percent for chemotherapy alone. NSABP-B-41 has been designed to compare two neoadjuvant regimens: FEC → paclitaxel plus trastuzumab and paclitaxel plus trastuzumab → FEC plus trastuzumab. Another important study, conducted by Dr Jenny Chang, demonstrated impressive clinical responses and interesting intracellular changes after three weeks of neoadjuvant trastuzumab monotherapy.

RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

Trial	Neoadjuvant regimen	Number of patients	Pathologic complete response rate
Wenzel 2004	(Trastuzumab + epirubicin + docetaxel) qwk x 6	14	7%
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%
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%
Carey 2002	AC x 4 → (trastuzumab + paclitaxel) qwk x 12	22	22%
Steger 2002	Trastuzumab qwk x 12 + docetaxel qwk + epirubicin qwk	9	22%

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.

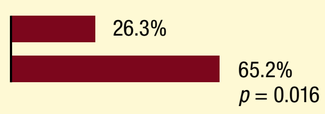
MD ANDERSON PHASE III TRIAL OF NEOADJUVANT TRASTUZUMAB/CHEMOTHERAPY

Accrual: 42 (Early closure by DSMB)

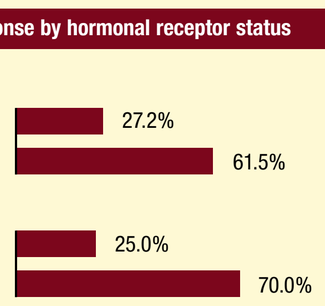
Eligibility	T1-3, N0-1, M0 breast cancer HER2-positive by FISH or IHC 3+
ARM 1	Paclitaxel q3wk x 4 → FEC x 4
ARM 2	Paclitaxel q3wk x 4 + H x 12 → FEC x 4 + H x 12

H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly

Overall pathologic complete response



Pathologic complete response by hormonal receptor status



"These results represent the highest reported pCR rate in this patient population. The most logical explanation for this high pCR rate is the use of two potentially noncross-resistant chemotherapies administered sequentially in combination with trastuzumab. Other possibilities include longer duration of neoadjuvant therapy compared with earlier studies."

P = paclitaxel

SOURCE: Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85.

NEOADJUVANT DOCETAXEL/CARBOPLATIN WITH OR WITHOUT TRASTUZUMAB

Protocol IDs: UCLA-9911084, AVENTIS-GIA-11156, GENENTECH-H2269s
Target Accrual: 75 (Open)

Eligibility	T3 or T4, any N patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy
ARM 1	(Trastuzumab qwk x 12) + ([docetaxel + carboplatin] q3wk x 4)
ARM 2	(Docetaxel + carboplatin) q3wk x 4

* Patients with HER2-negative disease receive neoadjuvant chemotherapy only, as in Arm 2. Within four to six weeks after surgery, patients with responding disease receive four additional courses of docetaxel and carboplatin as during neoadjuvant chemotherapy. Patients with HER2-positive disease also receive trastuzumab qwk x 12 weeks and then q3wk x 40 weeks.

Study contact: *Helena Chang, MD, PhD, Ph: 310-794-5624*

SOURCE: NCI Physician Data Query, September 2005.

RANDOMIZED TRIAL OF NEOADJUVANT CHEMOTHERAPY AND TRASTUZUMAB

Protocol ID: NSABP-B-41/ACOSOG-Z1041 (Proposed)
Target Accrual: Pending

Eligibility	Palpable, operable HER2-positive breast cancer
ARM 1	T qwk x 12 + H x 12 → FEC x 4 + H x 12
ARM 2	FEC x 4 → T qwk x 12 + H x 12

T = paclitaxel; H = trastuzumab
Note: Cardiac monitoring = NSABP-B-31 methodology
Trastuzumab continued postoperatively to complete one year of therapy.

SOURCE: Aman Buzdar, MD, personal communication, September 2005.

SELECT PUBLICATIONS

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 pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85.

Jahanzeb M et al. **Dose-dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support.** *Proc ASCO* 2005;Abstract 591.

Mehta RS et al. **Phase II study of neoadjuvant biweekly doxorubicin and cyclophosphamide (AC) with GM-CSF followed by weekly paclitaxel, carboplatin +/- trastuzumab (TC +/- H) in the treatment of breast cancer (BC).** *Proc ASCO* 2005;Abstract 826.

Montemurro F et al. **A phase II study of three-weekly docetaxel and weekly trastuzumab in HER2-overexpressing advanced breast cancer.** *Oncology* 2004;66(1):38-45.

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

As soon as we had results from 34 patients, we could see that 65 percent of patients in the trastuzumab arm had no tumor, whereas only 25 percent of patients who received chemotherapy alone were tumor free. This was much higher than we had anticipated. 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. Our institutional Data Monitoring Committee 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.* Breast Cancer Update *2004 (8)*

Many of us would have guessed that the pathologic complete response (pCR) rate would be high in the Buzdar study. However, we were all surprised when we saw the magnitude of difference for the neoadjuvant trastuzumab regimen. We had never seen pCR rates so high. Obviously, this needs to be validated in a larger study, and one is planned. A potential explanation for such a high pCR rate is that the patients received longer duration chemotherapy (paclitaxel and FEC) instead of just four cycles. Another reason might be that synergy exists between the anthracyclines and trastuzumab, which has not been previously tested because of the concerns of cardiotoxicity.

— *Debu Tripathy, MD.* Breast Cancer Update *2005 (5)*

PROPOSED NSABP TRIAL B-41: FOLLOW-UP TO THE MD ANDERSON STUDY

In NSABP-B-41, we will compare a B-31-like standard trastuzumab regimen to the Buzdar regimen. Patients in our control arm will receive FEC followed by paclitaxel/trastuzumab. On the investigational side, they'll get the Buzdar regimen of paclitaxel/trastuzumab followed by FEC with trastuzumab. We wanted to ask: Does giving concurrent trastuzumab with the anthracycline make a big difference? If you give paclitaxel/trastuzumab first and stop the trastuzumab, you've obviously got trastuzumab for a good bit of the epirubicin. We have to have that apparent asymmetry in order to try to isolate that question as best we can.

— *Charles E Geyer Jr, MD.* Breast Cancer Update*: Special NSABP Edition 2005*

NEOADJUVANT TRASTUZUMAB INDUCES APOPTOSIS

We evaluated the activity and efficacy of neoadjuvant single-agent trastuzumab in treatment-naïve women with HER2-overexpressing, locally advanced breast cancer. We administered three weeks of single-agent trastuzumab and measured the tumor size before and after treatment. The endpoints assessed in the study were twofold: (1) efficacy and (2) the mechanism of action of trastuzumab. For the second endpoint, we evaluated several pathways — proliferation, growth factor and apoptosis pathways. We enrolled 40 patients, and after only three weeks of trastuzumab, 25 percent of the patients had a partial response (50 percent reduction). It was stunning because these were all enormous, inflammatory breast cancers. Within the first few weeks, the patients would tell you: "The redness is going, and the mass is getting softer." This was independently verified by at least two oncologists, so it's real. The other patients had stabilization of disease, and none progressed. At that point, we used four cycles of docetaxel and continued weekly trastuzumab. All of the patients underwent surgery, and the pCR rate was very high — in the 35 percent range. Not surprisingly, trastuzumab's primary mechanism of action is the induction of apoptosis. This has important implications. First, trastuzumab is unlikely to be antagonistic with chemotherapy because they both affect apoptosis, so they would more likely be synergistic. Second, we might think that in studies of patients with metastatic disease we could consider trastuzumab for a period of time, stopping, evaluating how the patients do, then reintroducing trastuzumab in the future.

— *Jenny C Chang, MD.* Breast Cancer Update *2005 (2)*