Neoadjuvant Chemotherapy

28TH ANNUAL
San Antonio Breast Cancer Symposium
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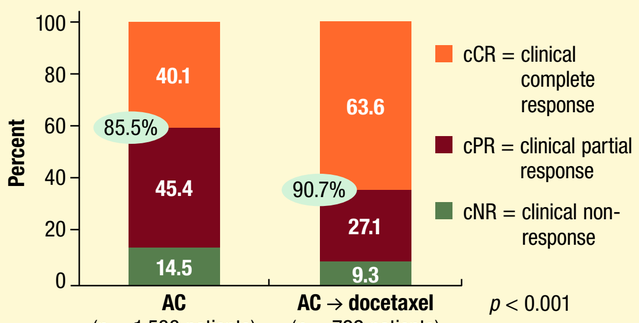
At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27, which evaluated the addition of docetaxel to neoadjuvant AC. Whereas the addition of neoadjuvant docetaxel improved the pathologic complete response rate, no differences were found in overall or disease-free survival. However, relapse-free survival was significantly higher in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant trials is evaluating novel strategies, including dose-dense chemotherapy, *nab* paclitaxel, capecitabine/docetaxel (XT), bevacizumab/docetaxel and other regimens.

PHASE III TRIAL EVALUATING THE ADDITION OF A TAXANE TO PREOPERATIVE AC

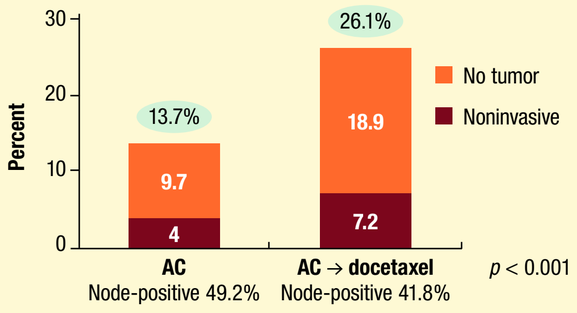
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

Eligibility	Stage IA-IIIA breast cancer
ARM 1	AC x 4 → surgery
ARM 2	AC x 4 → docetaxel x 4 → surgery
ARM 3	AC x 4 → surgery → docetaxel x 4

INITIAL RESULTS: CLINICAL RESPONSE



INITIAL RESULTS: PATHOLOGIC RESPONSE IN THE BREAST



No difference in rate of breast conservation: 61% versus 63%

SOURCE: Bear HD et al. *J Clin Oncol* 2003;21(22):4165-74.

68-MONTH UPDATE OF STUDY ENDPOINTS (HAZARD RATIOS COMPARED TO AC)

Variable	AC → T → surgery (n = 803)	AC → surgery → T (n = 799)
Overall survival	0.94 (p = 0.57)	1.07 (p = 0.53)
Disease-free survival With cPR after AC	0.86 (p = 0.10) 0.68 (p = 0.003)	0.91 (p = 0.27) 0.90 (p = 0.40)
Relapse-free survival	0.81 (p = 0.03)	0.91 (p = 0.32)

No significant difference in overall survival or disease-free survival by treatment but improved relapse-free survival in Arm 2 (preoperative docetaxel HR = 0.81, p = 0.03) versus Arm 1 (AC); T = docetaxel

68-MONTH UPDATE: HAZARD RATIOS OF PCR VERSUS NON-PCR

Variable	Hazard ratio	p-value
Overall survival	0.33	<0.0001
Disease-free survival	0.45	<0.0001

Pathologic complete response in the breast associated with improved overall survival and disease-free survival in all treatment groups

SOURCE: Bear HD. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

AC AND PACLITAXEL WITH OR WITHOUT FILGRASTIM IN WOMEN WITH INFLAMMATORY OR LOCALLY ADVANCED BREAST CANCER

Protocol IDs: SWOG-S0012, CTSU, NCT00016406
Target Accrual: 350 (Open)

Eligibility	Stage IIB, IIIA/B breast cancer
ARM 1	AC x 5 q3wk → paclitaxel qwk x 12
ARM 2	AC_{oral} + G-CSF qwk x 15 → paclitaxel qwk x 12

Objectives:
- Compare microscopic pathologic response rates in women with inflammatory or locally advanced breast cancer treated with standard neoadjuvant AC followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclophosphamide with filgrastim (G-CSF) followed by weekly paclitaxel
- Compare toxic effects of these regimens
- Compare delivered dose intensity of these regimens
- Evaluate association between microscopic pathologic complete response and clinical complete response at the primary tumor site

Trial lead organization: *Southwest Oncology Group*
Georgiana Ellis, MD, Protocol Chair, Ph: 206-288-6711

SOURCE: NCI Physician Data Query, September 2005.

MD ANDERSON PHASE III NEOADJUVANT TRIAL OF WEEKLY PACLITAXEL VERSUS CAPECITABINE/ DOCETAXEL → FEC AND LOCAL THERAPY

Protocol IDs: ID01-580, NCT00050167
Target Accrual: 930 (Open)

Eligibility	Stage IIA-IIIA breast cancer
ARM 1	Paclitaxel qwk x 12 → FEC x 4 → local therapy (surgery or RT)*
ARM 2	(Capecitabine 750 mg/m² BID 14d q3wk + docetaxel) x 4 → FEC x 4 → local therapy (surgery or RT)*

* ER/PR-positive patients will receive endocrine therapy after completion of local therapy.

Study contacts: *Debbie Frye, RN; Cynthia Carter, RN*
MD Anderson Cancer Center, Ph: 713-792-2817

SOURCES: NCI Physician Data Query, September 2005.
Livingston R. *Oncology* 2002;16(10 Suppl 12):29-32.

ONGOING TRIALS OF NEOADJUVANT CHEMO

Protocol	Phase	N	Regimen
NSABP-B-40 (pending activation)	III	1,200	AC x 4 → docetaxel 100 mg/m² x 4 AC x 4 → (docetaxel 75 mg/m² + capecitabine 825 mg/m² BID d1-14) x 4 AC x 4 → (docetaxel 75 mg/m² + gemcitabine) x 4
JHOC-J0266 JHOC-03012301	II	40	Docetaxel + pegfilgrastim q2wk x 4
EORTC-10994	III	1,850	One of three regimens of fluorouracil + epirubicin + cyclophosphamide Docetaxel → epirubicin + docetaxel
NCCTG-N0338	II	25-58	Docetaxel + carboplatin + pegfilgrastim q2wk x 4
NSABP FB-AX-003	II	Not reported	*Nab* paclitaxel qwk x 12 → FEC q3wk x 4

SOURCES: NCI Physician Data Query, October 2005; NSABP Protocol Summary, September 2005.

SELECT PUBLICATIONS

Bear HD et al. **A randomized trial comparing preoperative (preop) doxorubicin/ cyclophosphamide (AC) to preop AC followed by preop docetaxel (T) and to preop AC followed by postoperative (postop) T in patients (pts) with operable carcinoma of the breast: Results of NSABP B-27.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

Bear HD et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74.

Gianni L et al. **Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer.** *J Clin Oncol* 2005;23(29):7265-77.

Hannemann J et al. **Changes in gene expression associated with response to neoadjuvant chemotherapy in breast cancer.** *J Clin Oncol* 2005;23(15):3331-42.

Hutcheon AW et al. **Docetaxel primary chemotherapy in breast cancer: A five year update of the Aberdeen trial.** *Breast Cancer Res Treat* 2003;Abstract 11.

Livingston R. **Current and planned trials with capecitabine in adjuvant/ neoadjuvant therapy of breast cancer.** *Oncology (Willinston Park)* 2002;16(10 Suppl 12):29-32.

Mauri D et al. **Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis.** *J Natl Cancer Inst* 2005;97(3):188-94.

NSABP-B-27: 68-MONTH UPDATED RESULTS

NSABP trial B-27 was based on the results of the preceding neoadjuvant trial, B-18, in which we compared four cycles of preoperative AC to post-operative AC given adjuvantly. In that trial, there was no difference between neoadjuvant and adjuvant treatment, but patients receiving neoadjuvant therapy who had a pathologic complete response had a much better long-term outcome than patients who had less of a response.

The addition of preoperative docetaxel to AC doubled the pathologic complete response rate from 13 percent to 26 percent. No difference occurred between groups in terms of overall survival, but there was a trend toward improved disease-free survival with the addition of docetaxel, particularly when given preoperatively. A significant improvement in relapse-free survival occurred with the addition of preoperative docetaxel compared to AC alone.

— *Harry D Bear, MD, PhD.* Breast Cancer Update *2005 (7)*

NEOADJUVANT CAPECITABINE/DOCETAXEL TRIAL

In one of our ongoing neoadjuvant studies, we're trying to take advantage of genomics and proteomics to improve the individualization of therapy. The trial is based on the capecitabine/docetaxel (XT) regimen that Joyce O'Shaughnessy evaluated in the metastatic setting. For their first cycle of chemotherapy, patients will be randomly assigned to either capecitabine or docetaxel monotherapy. After that initial cycle, all patients will receive four cycles of both drugs in combination.

We're collecting fresh tissue and a serum sample for serum proteomic analyses before the start of chemo-therapy, after the first cycle of monotherapy and after the combination at the time of surgery. We are hopeful that the serum proteomics will be useful in predicting response because for many patients it is difficult to obtain a fresh tumor sample.

— *Kathy D Miller, MD.* Breast Cancer Update *2004 (9)*

MD ANDERSON NEOADJUVANT/ADJUVANT TRIAL

We are currently evaluating the role of capecitabine/ docetaxel in the adjuvant and neoadjuvant settings. All patients entering the trial with intact primary tumors are randomly assigned to receive either paclitaxel followed by FEC or capecitabine/docetaxel followed by FEC in the neoadjuvant setting. Patients who have previously undergone surgery receive the same randomized treatment, but they receive it in the adjuvant setting.

The control arm is similar to the control arm we used in our neoadjuvant trastuzumab study. The only difference is that we are using weekly versus every three-week paclitaxel for 12 weeks. The final endpoint will combine the neoadjuvant and adjuvant subgroup data and evaluate disease-free and overall survival. The neoadjuvant group has an advantage in that we will be able to find the clinical complete remission rate, the pathologic complete remission rate and a number of other endpoints.

— *Aman U Buzdar, MD.* Breast Cancer Update *2004 (8)*

SWOG TRIAL S0012 OF NEOADJUVANT THERAPY IN LOCALLY ADVANCED AND INFLAMMATORY DISEASE

In the Southwest Oncology Group, we have a trial of neoadjuvant therapy for women with locally advanced and inflammatory disease, comparing intermittent AC versus AC plus G-CSF. That trial is accruing reasonably well. All patients receive paclitaxel, but it's a two-arm study, and paclitaxel is administered weekly for 12 weeks. I would like to see an Intergroup trial in which patients who have resectable disease but want to receive neoadjuvant therapy are randomly assigned to a dose-dense versus a less dose-dense schedule — in other words, a trial asking the same basic question that we're asking in SWOG-S0221 — because with an endpoint of pathologic complete response in a two-arm design, we could potentially have an answer in a couple of years while we're still completing the adjuvant study.

— *Robert B Livingston, MD.* Breast Cancer Update *2004 (6)*