Neoadjuvant Chemotherapy

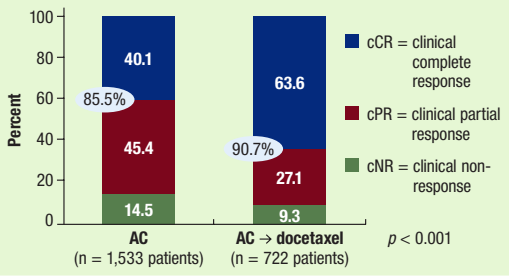
NSABP-B-27, which evaluated the addition of docetaxel to neoadjuvant AC, demonstrated that neoadjuvant docetaxel improved the pathologic complete response rate but not overall or disease-free survival. Relapse-free survival was significantly higher in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. At the 2005 San Antonio Breast Cancer Symposium, data from a Phase III trial showed superior efficacy with preoperative docetaxel/capecitabine versus doxorubicin/cyclophosphamide. A new generation of neoadjuvant trials is evaluating novel strategies, including dose-dense chemotherapy, *nab* paclitaxel, and bevacizumab/docetaxel.

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

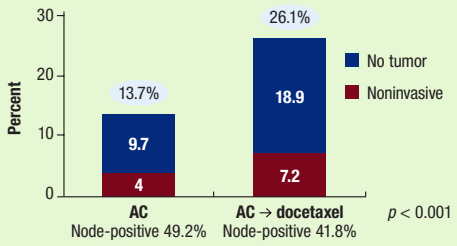
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

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 et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

DOCETAXEL/CAPECITABINE (TX) VERSUS DOXORUBICIN/CYCLOPHOSPHAMIDE (AC)

Accrual: 209 (Closed)

Eligibility	Stage II/III breast cancer Axillary lymph node involvement
ARM 1	TX → surgery → AC
ARM 2	AC → surgery → TX

TX = (docetaxel 75 mg/m^2 day 1 + capecitabine 1,000 mg/m^2 BID days 1-14) q3wk x 4

AC = (doxorubicin 60 mg/m^2 day 1 + cyclophosphamide 600 mg/m^2 day 1) q3wk x 4

Parameter	AC (n = 101)	TX (n = 103)	p-value
Clinical overall response	67%	84%	0.0047
Complete response	4%	5%	NR
Partial response	63%	79%	NR
Pathological complete response Tumor Lymph nodes	 10% 23%	 23%* 33%	 NR NR
Stable disease	23%	14%	NR
Progressive disease	8%	1%	NR
Breast conservation rate Stage II Stage III	 70% 62%	 84% 55%	 NR NR

NR = not reported
* Significantly more primary tumor pathological complete responses were seen in patients with ER/PR-positive breast cancer who received TX (p = 0.006)

SOURCE: Lee KS et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5052.

ONGOING TRIALS OF NEOADJUVANT CHEMO

Protocol	Phase	N	Regimen(s)
NSABP-B-40 (pending activation)	III	1,200	AC x 4 → docetaxel 100 mg/m^2 x 4 AC x 4 → (docetaxel 75 mg/m^2 + capecitabine 825 mg/m^2 BID d1-14) q3wk x 4 AC x 4 → (docetaxel 75 mg/m^2 + gemcitabine) x 4
JHOC-J0266 JHOC-03012301	II	40	Docetaxel + pegfilgrastim q2wk x 4
EORTC-10994	III	1,850	One of three regimens of FEC Docetaxel → epirubicin + docetaxel
NCCTG-N0338	II	25-58	Docetaxel + carboplatin + pegfilgrastim q2wk x 4
NSABP FB-AX-003	II	66	*Nab* paclitaxel qwk x 12 → FEC q3wk x 4
ID01-580	III	930	Paclitaxel qwk x 12 → FEC x 4 (Capecitabine 750 mg/m^2 BID 14d q3wk + docetaxel) x 4 → FEC x 4
UCLA-0502123-01, TORI-B-02	II	90	Bevacizumab 7.5 mg/kg q3wk → TAC + bevacizumab 7.5 mg/kg q3wk x 7 Placebo $^{\text{lower dose}}$ → TAC + placebo q3wk x 7 Bevacizumab 15 mg/kg q3wk → TAC + bevacizumab 15 mg/kg q3wk x 7 Placebo $^{\text{higher dose}}$ → TAC + placebo q3wk x 7

FEC = fluorouracil/epirubicin/cyclophosphamide

SOURCES: Livingston R. *Oncology* 2002;16(10 Suppl 12):29-32; NCI Physician Data Query, January 2006; NSABP Protocol Summary, September 2005.

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)*

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)*

PHASE III TRIAL OF DOCETAXEL/CAPECITABINE (TX) VERSUS DOXORUBICIN/CYCLOPHOSPHAMIDE (AC)

This trial randomly assigned patients with Stage II/III breast cancer to receive either TX or AC as preoperative therapy. What's interesting is that after surgery, the patients crossed over and received the opposite regimen. By the end of the trial, all the patients had received the same drugs.

In this relatively small study, TX significantly increased the pathological response rates (pCR), compared with AC, and it increased downsizing in the lymph nodes. They also noted, across a variety of toxicities, that TX was safer. They concluded, based on the pCR, TX might be a more active and superior regimen. This trial was underpowered to examine disease-free or overall survival. Even if it had been larger, it would be difficult to interpret those outcomes since all the patients received the same four agents.

— *Clifford Hudis, MD.* Breast Cancer Update *2006 (1)*

NEOADJUVANT SYSTEMIC THERAPY

Preoperative systemic treatment (PST) is a valid option not only for advanced breast cancer stages but also for operable breast cancer. We know that disease-free and overall survival after PST are equivalent to those after adjuvant therapy. Furthermore, PST is able to improve surgical treatment by increasing the rate of breast conservation surgery, which minimises psychological distress for patients fearing mastectomy. Response to PST is a predictor of long-term outcome and gives prognostic information after a short-term interval in contrast to adjuvant trials, which do not show their results until after a 5- to 10-year follow-up. … If PST is performed outside clinical trials, anthracycline/taxane-based regimens should be used, especially in sequential prolonged schedules.

— *Manfred Kaufmann, MD et al.* Breast *2005;14(6):576-81.*

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.

Kaufmann M et al. **Preoperative (neoadjuvant) systemic treatment of breast cancer.** *Breast* 2005;14(6):576-81.

Lee KS et al. **Mature results from a randomized phase III trial of docetaxel/capecitabine (TX) vs doxorubicin/cyclophosphamide (AC) as primary chemotherapy for patients with stage II/III breast cancer.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5052.

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.

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