Neoadjuvant Chemotherapy

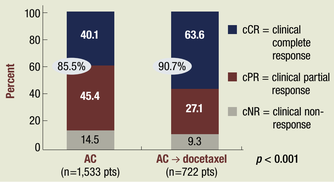
While neoadjuvant chemotherapy may downstage tumors and improve the chance for breast conservation, disease-free and overall survival rates are not altered. At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27 evaluating the addition of docetaxel to neoadjuvant AC. The addition of neoadjuvant docetaxel improved the pathologic complete response rate, but no differences were found in overall or disease-free survival. However, relapse-free survival was significantly improved in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant studies is evaluating a variety of novel neoadjuvant strategies including dose-dense chemotherapy, taxanes, capecitabine/docetaxel (XT) and other combination regimens.

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

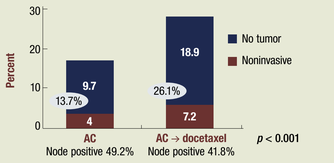
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

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

NSABP-B-27 INITIAL RESULTS: CLINICAL RESPONSE



NSABP-B-27 INITIAL RESULTS: PATHOLOGIC RESPONSE IN BREAST



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

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

NSABP-B-27: 68-MONTH UPDATE OF STUDY ENDPOINTS (HAZARD RATIOS COMPARED TO AC)

Variable	AC → T → surg (n=803)	AC → surg → T (n=799)
Overall survival	0.94 (p = 0.57)	1.07 (p = 0.53)
Disease-free survival With cPR after AC (n=378,350)	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) vs Arm 1 (AC).
T = docetaxel

NSABP-B-27: 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 H. Presentation. SABCS, 2004.

PREOPERATIVE CAPECITABINE OR GEMCITABINE PLUS DOCETAXEL IN SEQUENCE WITH AC

Protocol IDs: NSABP-B-40, CTSU
Accrual: 1,200 (Pending)

Eligibility	Stage II or IIIA operable breast cancer
ARM 1	AC → T 100 mg/m² x 4 → surgery
ARM 2	AC → T 75 mg/m² + capecitabine* x 4 → surgery
ARM 3	AC → T 75 mg/m² + gemcitabine x 4 → surgery
ARM 4	T 100 mg/m² x 4 → AC x 4 → surgery
ARM 5	T 75 mg/m² x 4 + capecitabine* x 4 → AC x 4 → surgery
ARM 6	T 75 mg/m² x 4 + gemcitabine x 4 → AC x 4 → surgery

* Capecitabine dose = 825 mg/m² BID days 1-14 q3wk

SOURCE: NSABP Protocol Summary, November 2004.

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

Protocol IDs: ID01-580, NCT00050167
Projected 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 + 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:
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SOURCES: NCI Physican Data Query, January 2005; Livingston R. *Oncology* 2002;16(10 Suppl 12):29-31.

PATHOLOGIC COMPLETE RESPONSE RATES BY TUMOR ER STATUS: PREOPERATIVE TRIALS FROM MD ANDERSON CANCER CENTER

Chemotherapy	No. of pts	Pathologic complete response	
		ER-negative	ER-positive
FAC x 3	532	14.5%	1.2%
FAC x 4	78	27.6%	6.1%
Paclitaxel x 4	81	7.1%	5.7%
Paclitaxel q3wk → FAC x 4	127	30.9%	5.6%
Paclitaxel q1wk → FAC x 4	128	54.5%	14.3%
(A + docetaxel) x 4	72	15.9%	7.1%
Total	**1018**	**20.6%**	**5.0%**

SOURCE: Buzdar AU et al. *Breast Cancer Res Treat,* 2003.

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 postoperative 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

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 chemotherapy, 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.

Investigators have evaluated the role of serum proteomics in identifying patients at risk of developing a malignancy or segregating patients with cancer from patients with some benign condition. We're trying to take proteomics a step further and determine whether it will predict for response to individual therapies.

— Kathy D Miller, MD

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 → FEC or capecitabine/docetaxel → 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.

We currently have more than 200 patients enrolled in the study. In the first cohort, we gave a somewhat higher dose of capecitabine and saw an increase in morbidity. We reduced the dose of capecitabine and, with the use of this attenuated dose, we are seeing more acceptable toxicity.

Now the big question remains: What is the long-term and short-term efficacy? The data are continuously being monitored, but we won't have definitive information until we have enough patients in the neoadjuvant setting to determine whether the regimens are similar or one is better than the other.

— Aman U Buzdar, MD

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.

Buzdar AU et al. **Pathological complete response to chemotherapy is related to hormone receptor status.** *Breast Cancer Res Treat* 2003;82(Suppl 1):69;Abstract 302.

Chollet P et al. **Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer.** *Br J Cancer* 2002;86(7):1041-6.

Fisher B et al. **Effect of preoperative chemotherapy on the outcome of women with operable breast cancer.** *J Clin Oncol* 1998;16(8):2672-85.

Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC — Final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;Abstract 135.

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. **International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: Review and recommendations.** *J Clin Oncol* 2003;21(13):2600-8.