# Ongoing Clinical Trials of Adjuvant Chemotherapy



**The encouraging results of CALGB-9741 have led to a new generation of Phase III randomized trials evaluating dose-dense chemotherapy. NSABP-B-38 is a new trial comparing every two-week dose-dense AC → paclitaxel to the other major taxane-containing regimen evaluated in large Phase III adjuvant trials, TAC (docetaxel, doxorubicin, cyclophosphamide) and a third experimental arm including dose-dense AC → paclitaxel/gemcitabine. The follow-up Intergroup trial to CALGB-9741 is SWOG-S0221, comparing a dose-dense metronomic regimen of AC to every two-week dose-dense AC → paclitaxel. A second randomization compares weekly to every two-week paclitaxel. Another strategy being investigated in current trials is the addition of capecitabine to docetaxel, which is included in ongoing US Oncology and MD Anderson studies.**

### PHASE III TRIAL COMPARING AC FOLLOWED BY EITHER DOCETAXEL (T) OR CAPECITABINE PLUS DOCETAXEL (XT)

Protocol ID: US Oncology 01-062
Accrual: 1,810 (Open)

| Eligibility | Node-positive or high-risk node-negative operable breast cancer |
|---|---|
| ARM 1 | AC x 4 → docetaxel x 4 |
| ARM 2 | AC x 4 → (docetaxel + capecitabine) x 4 |

Note: ER- and/or PR-positive patients receive tamoxifen or anastrozole (postmenopausal only) x 5 years

SOURCE: US Oncology Protocol 01-062, June 2002.

### PHASE III STUDY OF AC FOLLOWED BY DOCETAXEL (T) VERSUS AT VERSUS ATC

Protocol IDs: NSABP-B-30, CTSU
Target Accrual: 5,300 (Closed)

| Eligibility | Stage I, II or IIIA breast cancer with at least one positive axillary lymph node |
|---|---|
| ARM 1 | (Doxorubicin + cyclophosphamide) q3wk x 4 → docetaxel q3wk x 4 |
| ARM 2 | (Doxorubicin + docetaxel) q3wk x 4* |
| ARM 3 | (Doxorubicin + cyclophosphamide + docetaxel) q3wk x 4* |

* Note: Primary prophylaxis with growth factors at investigators' discretion will be given

SOURCE: NCI Physician Data Query, February 2004.

### PHASE III ADJUVANT TRIALS INCORPORATING DOSE-DENSE SCHEDULES

| Protocol ID | Target accrual | Eligibility | Randomization |
|---|---|---|---|
| SWOG-S0221 | 4,500 | Node-positive or high-risk node-negative | [AC + PEG-G (d2)] q2wk x 6 → [P + PEG-G (d2)] q2wk x 6<br>[A + $C_{oral}$ (d1-7) + G (d2-7)] qwk x 15 → [P + PEG-G (d2)] q2wk x 6<br>[AC + PEG-G (d2)] q2wk x 6 → P qwk x 12<br>[A + $C_{oral}$ (d1-7) + G (d2-7)] qwk x 15 → P qwk x 12 |
| NSABP-B-38 | 4,800 | Node-positive | TAC q3wk x 6<br>AC q2wk x 4 → paclitaxel q2wk x 4<br>AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4 |
| CAN-NCIC-MA21 | 1,500 | Node-positive or high-risk node-negative | [E + 5-FU (d1-8) + $C_{oral}$ (d1-14)] q4wk x 6<br>[EC + G (d2-13)*] q2wk x 6 → [P + G (d2-13)*] q3wk x 4<br>AC q3wk x 4 → [P + G (d2-13)*] q3wk x 4 |
| CALGB-40101 | 4,646 | High-risk node-negative | AC q2wk x 4<br>AC q2wk x 6<br>Paclitaxel q2wk x 4<br>Paclitaxel q2wk x 6 |

C = cyclophosphamide; E = epirubicin; G = filgrastim; PEG-G = pegfilgrastim; A = doxorubicin; $C_{oral}$ = oral cyclophosphamide; P = paclitaxel; T = docetaxel;
* Epoetin alpha is administered weekly in patients with a hemoglobin <13 g/dL.

SOURCES: NCI Physician Data Query, September 2004. Protocol Summaries, NSABP Group Meeting, June 2004.

### COMPARISON OF TWO COMBINATION CHEMOTHERAPY REGIMENS WITH OR WITHOUT CELECOXIB IN TREATING WOMEN WITH BREAST CANCER

Protocol ID: NSABP-B-36, CTSU
Accrual: 2,700 (Open)

| Eligibility | T1-3 node-negative breast cancer |
|---|---|
| ARM 1 | AC q3wk x 4 → oral celecoxib BID x 3 years → oral placebo BID x 3 years |
| ARM 2 | FEC q3wk x 6 → oral celecoxib BID x 3 years → oral placebo BID x 3 years |

Note: ER- and/or PR-positive patients receive tamoxifen or anastrozole (postmenopausal only) x 5 years

SOURCE: NCI Physician Data Query, September 2004.

### PHASE III RANDOMIZED STUDY OF THREE DIFFERENT ADJUVANT CHEMOTHERAPY REGIMENS

Protocol ID: NSABP-B-38, CTSU
Target Accrual: 4,800 (Open)

| Eligibility | Node-positive breast cancer, with known ER status and PR status known only if ER-negative |
|---|---|
| ARM 1 | TAC q3wk x 6 |
| ARM 2 | AC q2wk x 4 → paclitaxel q2wk x 4 |
| ARM 3 | AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4 |

T = docetaxel
Note: Beginning 3-12 weeks after the last dose of chemotherapy, patients with ER-positive and/or PR-positive tumors receive tamoxifen or an aromatase inhibitor.

SOURCE: NCI Physician Data Query, October 2004.

## SELECT PUBLICATIONS

Altundag K et al. **Addition of granulocyte-colony stimulating factor (G-CSF) to adjuvant treatment may increase survival in patients with operable breast cancer: Interaction of G-CSF with dormant micrometastatic breast cancer cells.** *Med Hypotheses* 2004;63(1):56-8.

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of nodepositive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9.

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-43.

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.

Hudis CA, Schmitz N. **Dose-dense chemotherapy in breast cancer and lymphoma.** *Semin Oncol* 2004;31(3 Suppl 8):19-26.

Steger GG et al. **6 vs 3 cycles of epirubicin/docetaxel + G-CSF in operable breast cancer: Results of ABCSG-14.** *Proc ASCO* 2004:Abstract 553.

Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients: Results from GONO — MIG1 study.** *Breast Cancer Res Treat* 2003;Abstract 12.



### *NEW STRATEGIES FOR ADJUVANT THERAPY*

I believe the adjuvant trials studying the combination of capecitabine and docetaxel are wonderful trials to evaluate extremely active drugs in the adjuvant setting. We have several outstanding agents with high response rates in the metastatic setting, such as capecitabine, vinorelbine and gemcitabine, which haven't been evaluated in the adjuvant setting. I support the strategy of moving these agents into the adjuvant course of treatment.

*— Hyman B Muss, MD*

### *SWOG-S0221: DOSE-DENSE VERSUS CONTINUOUS CHEMOTHERAPY*

In this study, AC is administered in either a dose-dense manner with pegfilgrastim versus what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment. Data suggests six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of vasculogenesis occurs between cycles and hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

*— G Thomas Budd, MD*

### *NSABP-B-30: AC FOLLOWED BY DOCETAXEL (T) VERSUS AT VERSUS ATC*

Many investigators believed that docetaxel was the most active agent in metastatic disease and that it should be investigated in the adjuvant setting, which is why we included it in all three arms of B-30. We also wanted to compare the various durations of treatment. The AC followed by docetaxel arm is a six-month treatment, while the other arms are shorter in duration. NSABP data showed four cycles of AC was effective, and we felt that four cycles of AT or TAC would be effective. Perhaps with hindsight, based on the TAC data, it would have been better to go with six cycles of TAC, but there's really no data showing six is superior to four cycles. We added growth factors, and it is up to the investigators whether they use the long- or shorter-acting growth factor.

*— Sandra Swain, MD*

### *INTEGRATING DOSE DENSITY INTO CLINICAL TRIALS*

CALGB-40101 incorporates the every two-week schedule comparing paclitaxel to AC in patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-on testament. It's not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it's worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it's worth it.

*— Clifford A Hudis, MD*

### *NSABP TRIAL B-38*

NSABP-B-38 will compare two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It's a good trial design because in addition to determining whether one of the two standard combinations is superior, it examines an agent new to the adjuvant setting — gemcitabine. At the 2004 ASCO meeting, Kathy Albain reported on a metastatic trial that showed an advantage for gemcitabine/paclitaxel versus paclitaxel alone. While the every two-week schedule is a bit of a leap, it was necessary to make it comparable to the dose-dense paclitaxel schedule.

*— G Thomas Budd, MD*