Current Trials of Adjuvant Chemotherapy

Two recent Phase III randomized trials have demonstrated that taxane-containing adjuvant regimens may result in an improvement in overall survival. BCIRG 001 compared TAC (docetaxel, doxorubicin and cyclophosphamide) to FAC, and CALGB-9741 evaluated a dose-dense regimen of AC followed by paclitaxel administered with growth factor support. NSABP-B-38 may help to determine which of these two regimens is better. Other ongoing trials are assessing whether the advantage observed with dose-dense scheduling is related to the AC or the paclitaxel portion of that regimen. AC followed by docetaxel is a commonly used taxane-containing adjuvant regimen, even though cited results with that treatment have primarily been reported from a neoadjuvant trial. A US Oncology adjuvant trial is evaluating whether the addition of capecitabine to AC → docetaxel will improve its efficacy. These trials are now complicated by the recent findings of benefit from the use of trastuzumab/chemotherapy as adjuvant treatment of patients with HER2-positive tumors. CALGB-49907 and CALGB-40101 now allow postchemotherapy trastuzumab, and other trials may elect similar strategies or restrict entry to patients with HER2-negative tumors.

ONGOING PHASE III TRIALS OF ADJUVANT CHEMOTHERAPY

Protocol ID	Target accrual	Eligibility	Randomization*
US Oncology 01062 N017629	2,410	T1-3 N1M0 or T2 N0 M0	AC x 4 → docetaxel x 4 AC x 4 → (docetaxel + capecitabine) x 4
SWOG-S0221	4,500	Node-positive or high risk node-negative	[AC + PEG-G (d2) or G (d3-10)] q2wk x 6 → [paclitaxel + PEG-G (d2)] q2wk x 6 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → [paclitaxel + PEG-G (d2)] q2wk x 6 [AC + PEG-G (d2) or G (d3-10)] q2wk x 6 → paclitaxel qwk x 12 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → paclitaxel qwk x 12
FBCG-01-2003	1,500	High risk	Docetaxel x 3 → CEF x 3 (Docetaxel + capecitabine) x 3 → (CE + capecitabine) x 3
ID01-580	930	Stage I-IIIA	Paclitaxel → FEC Docetaxel/capecitabine → FEC
NSABP-B-36	2,700	Node-negative	AC q3wk x 4 FEC q3wk x 6
FRE-FNCLCC-PACS-05/0106, EU-20239	1,512	Stage I	FEC x 6 FEC x 4
CALGB-49907*	600-1,800	Stage I-IIIC, ≥ 65 yrs	C_{oral} + MF x 6 or A + C_{oral} x 4 Capecitabine x 6
GEICAM 2003-02	1,920	High-risk node-negative	FAC x 6 FAC x 4 → paclitaxel x 8
GEICAM 2003-10	1,382	HER2-negative, node-positive	EC x 4 → docetaxel x 4 ET x 4 → capecitabine x 4
LMU-ADEBAR, EU-20221	446	Node-positive 4+	FE + C_{oral} x 6 EC x 4 → docetaxel x 4
IBCSG-27-02, BIG-1-02, NSABP-B-37	978	Locoregional recurrence	Radiotherapy† Chemotherapy x 3 at physician discretion and radiotherapy†

A = doxorubicin; C = cyclophosphamide; PEG-G = pegfilgrastim; G = filgrastim; C_{oral} = oral cyclophosphamide; E = epirubicin; F = fluorouracil; M = methotrexate GM-CSF = sargamostim; NR = not reported

* Protocol may be amended based on adjuvant trastuzumab data.
† Unless patient had clear margins and received prior adjuvant radiotherapy

SOURCES: NCI Physician Data Query, January 2006; ClinicalTrials.gov, January 2006; www.USOncology.com; US Oncology Trial 01062: March 2004 Update (online newsletter).

PHASE III ADJUVANT TRIAL COMPARING THREE CHEMOTHERAPY REGIMENS: TAC; DOSE-DENSE (DD) AC FOLLOWED BY DD PACLITAXEL; DD AC FOLLOWED BY PACLITAXEL/GEMCITABINE

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

Eligibility	Operable, invasive breast cancer Node-positive
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

Primary prophylaxis with PEG-G or G is required.

All Arms are followed by hormonal therapy in patients with ER/PR-positive tumors.

TAC = docetaxel/doxorubicin/cyclophosphamide; AC = doxorubicin/cyclophosphamide

SOURCE: NCI Physician Data Query, January 2006; www.nsabp.pitt.edu.

RANDOMIZED PHASE III ADJUVANT TRIAL OF AC VERSUS PACLITAXEL

Protocol IDs: CALGB-40101, CTSU
Target Accrual: 4,646 (Open)

Eligibility	High-risk node-negative breast cancer
ARM 1	AC q2wk x 4
ARM 2	AC q2wk x 6
ARM 3	Paclitaxel q2wk x 4
ARM 4	Paclitaxel q2wk x 6

Note: Administration of filgrastim, sargramostim or pegfilgrastim is recommended for all Arms. Trastuzumab is allowed for patients whose tumors overexpress HER2.

SOURCES: NCI Physician Data Query, January 2006; Personal communication with Lawrence Shulman, MD, Protocol Chair, January 2006.

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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 Hudis, MD.* Breast Cancer Update *2004 (5)

NSABP-B-38 TRIAL

Two key adjuvant trials have been BCIRG 001, evaluating TAC versus FAC, and the CALGB dose-dense trial 9741 of AC/paclitaxel. Currently, our view is that TAC appears to be the optimal way to administer an anthracycline/docetaxel regimen, and dose-dense AC/paclitaxel is the optimal way to administer those agents. Which is better? It's impossible to answer that question without performing a clinical trial, which is why we developed trial NSABP-B-38. It's a pragmatic design in which we regard TAC as our control arm. A clear advantage of dose-dense therapy is that it is so well tolerated, and it clearly affords the opportunity to add a fourth drug to the paclitaxel. TAC is a maximally tolerated regimen. You really can't push it much more, so we sought a candidate drug to combine with paclitaxel.

— Charles E Geyer Jr, MD.* Breast Cancer Update *2005 (3)

NSABP-B-38 asks a very practical question. The dose-dense data have shown a one- or two-percent survival benefit, and did not look that striking to me though probably more than half the people in the country are using that regimen. The BCIRG-001 data, looking at TAC versus FAC, showed a very positive result with much longer follow-up. At that time, I felt docetaxel was a more effective taxane. However, the 1199 data were not out yet. So we decided to compare TAC to the dose-dense regimen. Then Kathy Albain presented the gemcitabine/paclitaxel data, showing a small survival benefit when you added gemcitabine so we decided to include another arm to see if we could improve outcomes even further.

— Sandra M Swain, MD.* Breast Cancer Update *2006 (2)

ROLE OF TAXANES AS ADJUVANT THERAPY

The precise roles of the taxanes docetaxel and paclitaxel in the adjuvant treatment of early breast cancer remain uncertain. To date three trials (CALGB 9344, BCIRG 001 and PACS 01) have demonstrated an overall survival advantage with the addition of taxanes to anthracycline adjuvant therapy. For women with higher risk disease these agents are increasingly being regarded as standard in adjuvant treatment. However the choice of taxane, how best to incorporate it and optimal doses and scheduling are unknown… There remain several unanswered questions regarding the worth of adjuvant and neoadjuvant taxanes… These questions will be answered over the next few years by the many ongoing clinical trials in this area and by overview analyses likely to be carried out in the near future.

— Alistair E Ring, MR CP, Paul A Ellis, MD.* Cancer Treat Rev *2005;31(8):618-27.

ADJUVANT CLINICAL TRIALS INCORPORATING CAPECITABINE

Vinorelbine/capecitabine is one of numerous capecitabine combinations being evaluated in European adjuvant trials. I'm not aware of any adjuvant or neoadjuvant studies evaluating capecitabine/paclitaxel; however, a number of neoadjuvant and adjuvant trials are evaluating capecitabine/docetaxel. Even if I had data with capecitabine/paclitaxel, I probably would not have considered evaluating that combination — as opposed to capecitabine/docetaxel — in our adjuvant trial. In metastatic disease, docetaxel 75 mg/m^2 in combination with capecitabine has a clear survival advantage compared to docetaxel 100 mg/m^2. Usually, we try to take that advantage in survival in metastatic disease and immediately move it into the adjuvant setting.

— Joyce O'Shaughnessy, MD.* Breast Cancer Update *2005 (3)