Current Trials of Adjuvant Chemotherapy

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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 01-062 N017629	2,410	Node-positive or high risk node-negative	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
NSABP-B-38	4,800	Node-positive	TAC q3wk x 6‡ AC q2wk x 4† → paclitaxel q2wk x 4‡ AC q2wk x 4† → paclitaxel/gemcitabine q2wk x 4‡
CALGB-40101*	4,646	High risk node-negative	AC q2wk x 4 AC q2wk x 6 Paclitaxel q2wk x 4 Paclitaxel q2wk x 6
FBCG-01-2003	Not reported	High risk	Docetaxel x 3 → CEF (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

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

* Proposed amendment to allow trastuzumab for patients with HER2-positive disease; G, PEG-G or GM-CSF is strongly recommended for all cycles of therapy
† Protocols may be amended based on adjuvant trastuzumab data. ‡ Primary prophylaxis with PEG-G or G is required.

SOURCES: NCI Physician Data Query, September 2005; Protocol Summaries, NSABP Group Meeting, June 2004; www.USOncology.com.

PHASE II STUDIES EVALUATING NOVEL APPROACHES TO (NEO)ADJUVANT THERAPY

Protocol ID(s)	N	Eligibility	Regimen
05-055	60 40	Stage II/III Completed neoadjuvant chemotherapy	Arm A: Bev q3wk x 12mo Arm B: Bev q3wk + daily C + metho BID twice/wk x 6mo → bev q3wk x 6mo
CWRU-1100, CASE-1100, CWRU-050023, NCI-G00-1877	26	Stage II/IIIA >10 N+	(Paclitaxel + C d1-3 + filgrastim d5-14 or until blood counts recover) q3wk x 3 → (A + filgrastim d2-11) q3wk x 4
ECOG-E2104	42-202	Node-positive	Arm A: AC + bev + (filgrastim d2-11 or pegfilgrastim d2) q2wk x 4 → paclitaxel + bev + (filgrastim d2-11 or pegfilgrastim d2) q2wk x 4 → bev q2wk x 18 Arm B: AC + (filgrastim d2-11 or pegfilgrastim d2) q2wk x 4 → paclitaxel + bev + (filgrastim d2-11 or pegfilgrastim d2) q2wk x 4 → bev q2wk x 22
CWRU-3100, CASE-3100, NCI-2722	60	Stage IIIA/B Stage IV if only locally advanced	Arm A: Docetaxel qwk x 6 + bev q2wk x 4 → surgery/XRT → AC q3wk x 4 Arm B: Docetaxel qwk x 6 → surgery/XRT → AC q3wk x 4
DUMC-4522-04-1-R1	500	High risk N-, N+ Locally advanced or enrolled on CALGB-40101	Treatment on CALGB-40101 **OR** Regimen A: AC q3wk x 4 Regimen B: AC q3wk x 4 → paclitaxel qwk x 12

A = doxorubicin; bev = bevacizumab; C = cyclophosphamide; N = nodes; metho = methotrexate; XRT = radiation therapy

SOURCE: NCI Physician Data Query, September 2005.

SELECT PUBLICATIONS

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Fumoleau P, Cameron D. **Future options with capecitabine (Xeloda) in (neo)adjuvant treatment of breast cancer.** *Semin Oncol* 2004;31(5 Suppl 10):45-50.

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Partridge AH, Winer EP. **Long-term complications of adjuvant chemotherapy for early stage breast cancer.** *Breast Dis* 2004;21:55-64.

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SWOG-S0221: DOSE-DENSE VERSUS CONTINUOUS CHEMOTHERAPY

In this study, AC is administered in either a dose-dense manner with pegfilgrastim or 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 suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other anti-angiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule, a burst of vasculogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

— G Thomas Budd, MD. **Breast Cancer Update** ***2004 (8)***

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)***

ADJUVANT CLINICAL TRIALS INCORPORATING CAPECITABINE

The vinorelbine/capecitabine combination 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)***

It is hoped that through its substantial activity, favorable safety profile (with minimal myelosuppression and alopecia) and convenience, capecitabine will significantly impact the management of early breast cancer. Results to date suggest that every woman with breast cancer should be considered for treatment with capecitabine early in the disease course. The results of the large (neo)adjuvant trials of single-agent capecitabine are eagerly awaited.

— Pierre Fumoleau, MD, David Cameron, MD.
Semin Oncol ***2004;31(5 Suppl 10):45-50.***