Key Second-Generation Trials of Adjuvant Taxanes

The 2000 NIH Consensus Conference and the 2001 St. Gallen Consensus Conference concluded that there was insufficient evidence to consider taxanes "standard of care" in the adjuvant setting. However, there is currently widespread nonprotocol use of adjuvant taxanes, particularly in node-positive patients. Several second-generation adjuvant trials are ongoing or proposed. These studies will evaluate patient selection, choice of paclitaxel versus docetaxel and optimal dosing and scheduling. Recent phase III randomized trial data demonstrating a survival benefit to capecitabine/docetaxel in metastatic disease has also led to new trials looking at this rationally derived synergistic combination in the adjuvant setting. The most recent data set addressing this question was presented by Nabholtz at the 2002 ASCO meeting. This BCIRG trial demonstrated an advantage for TAC compared to FAC (see below).

ADJUVANT TAC VERSUS FAC

DISEASE-FREE SURVIVAL (DFS) AND OVERALL SURVIVAL FOR 1,491 PATIENTS AFTER A MEDIAN FOLLOW-UP OF 33 MONTHS (TAC: N=745; FAC: N=746)

ARM 1	TAC (docetaxel, doxorubicin, cyclophosphamide 75/50/500 mg/m^2) q3w x 6
ARM 2	FAC (5-fluorouracil, doxorubicin, cyclophosphamide 500/50/500 mg/m^2) q3w x 6

	RR TAC/FAC	Absolute Reduction	p-value
DFS	0.68	8%	0.0011
by nodal status			
1-3	0.50	11%	0.0002
4+	0.86	2%	0.33
by receptor status			
ER-	0.62	—	0.005
ER+	0.68	—	0.02
Overall Survival	0.76	5%	0.11
by nodal status			
1-3	0.46	7%	0.006
4+	1.08	2%	0.75

Nabholtz JM et al. *Proc ASCO* 2002; Abstract 141.

A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE III TRIAL COMPARING AC FOLLOWED BY EITHER DOCETAXEL (T) OR DOCETAXEL PLUS CAPECITABINE (TX) AS ADJUVANT THERAPY FOR FEMALE PATIENTS WITH HIGH-RISK BREAST CANCER — Open Protocol

Protocol ID: US Oncology 01-062

Projected Accrual: 1,810 patients

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

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

"It is expected that treatment with AC followed by TX provides an improvement in the five-year disease-free survival rate from 65% with AC➔T to 71.5% with AC➔TX in patients at substantial risk for systemic recurrence. This corresponds to a 22% reduction in the risk of disease recurrence (i.e. the hazard ratio of AC➔TX versus AC➔T is 0.78) in patients at substantial risk for systemic recurrence."

SOURCE: Protocol 01-062 synopsis.

RECENT AND ONGOING PHASE III ADJUVANT TAXANE TRIALS

STUDY	TRIAL SCHEMA	NODAL STATUS
NSABP B-30	AC x 4 ➔ T x 4 AT x 4 ATC x 4	N+
E-1199	AC x 4 ➔ paclitaxel q3w x 4 AC x 4 ➔ paclitaxel qw x 12 AC x 4 ➔ T q3w x 4 AC x 4 ➔ T qw x 12	N+, high-risk N-
NCI Canada MA.21	FEC x 6 (EC + G-CSF + Epo) x 6 ➔ (paclitaxel + G-CSF + Epo) x 4 AC x 4 ➔ paclitaxel x 4	N+, high-risk N-
CALGB 40101	AC x 4 AC x 6 Paclitaxel qw x 12 Paclitaxel qw x 18	High-risk N-
BCIRG-05	TAC x 6 AC x 4 ➔ T x 4	HER2-, N+
BCIRG-06	AC x 4 ➔ T x 4 AC x 4 ➔ T x 4 + H x 1 year TP x 6 + H x 1 year	HER2+, N+, high-risk N-
EU-20040	Epirubicin x 6 Epirubicin x 3 ➔ T q3w x 3 Patients randomized to receive tamoxifen x 5 years concurrent or sequential to chemotherapy	N+
EU-20109	FEC q3w x 8 OR E x 4 ➔ CMF x 4 FEC x 4 ➔ T x 4	Any N
US Oncology 01-062	AC ➔ T AC ➔ XT	N+, high-risk N-

T=docetaxel; H=trastuzumab; P=cisplatin or carboplatin; X=capecitabine

SOURCE: NCI Physician Data Query, January 2003; BCIRG website.

SELECT PUBLICATIONS

National Institutes of Health. Consensus Development Conference Statement: Adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst Monogr* 2001;30:5-15.

Hortobagyi GN. **Integration of docetaxel into adjuvant breast cancer treatment regimens.** *Oncology (Huntingt)* 2002;16(6 Suppl 6):27-33.

Mamounas EP, Sledge GW Jr. **Combined anthracycline-taxane regimens in the adjuvant setting.** *Semin Oncol* 2001;28(4 Suppl 12):24-31.

Nabholtz JM et al. **Docetaxel in the treatment of breast cancer: An update on recent studies.** *Semin Oncol* 2002;29(3 Suppl 12):28-34.

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG-001 study.** *Proc ASCO* 2002;Abstract 141.

Nabholtz JM, Riva A. **Taxane/anthracycline combinations: Setting a new standard in breast cancer?** *Oncologist* 2001;6 Suppl 3:5-12.

Norton L. **Theoretical concepts and the emerging role of taxanes in adjuvant therapy.** *Oncologist* 2001;6 Suppl 3:30-35.

Piccart MJ et al. **Taxanes in the adjuvant treatment of breast cancer: Why not yet?** *J Natl Cancer Inst Monogr* 2001;(30):88-95.

THE FUTURE OF ADJUVANT TAXANE-BASED THERAPY

"With more than 20,000 women enrolled in trials exploring the potential benefit of taxane incorporation into adjuvant chemotherapy programs, one can be confident that their potential contribution to improved survival, even if modest, will be identified by a well-conducted overview. This overview should explore differential treatment effects in different patient subsets, defined by treatment, patient, or even tumor molecular marker characteristics whenever available."

—Piccart MJ et al. J Natl Cancer Inst Monogr 2001;30:88-95.

US ONCOLOGY ADJUVANT XT TRIAL

US Oncology is conducting a clinical trial in node-positive or high-risk node-negative patients, comparing adjuvant AC followed by either capecitabine/docetaxel or docetaxel alone. There will be a 25% dose reduction for capecitabine compared to the XT trial. This is appropriate because there have been extensive analyses of the effect of capecitabine dose reductions. In our phase III metastatic XT trial, the median delivered dose intensity of capecitabine in the combination arm was 75% of the intended dose, and most patients were dose-reduced by the second cycle of therapy. That dose was maintained for the rest of the study, and a survival advantage still occurred in the capecitabine/docetaxel arm.

— Joyce O'Shaughnessy, MD

SEQUENTIAL VERSUS COMBINATION CHEMOTHERAPY IN THE ADJUVANT SETTING

NSABP B-30 is an important trial since it will address whether sequential chemotherapy is better than combination chemotherapy in the adjuvant setting. The rationale for selecting docetaxel is related to the issue of cardiac toxicity. Initial phase II trials from Europe reported over a 90% response rate for paclitaxel when given in combination with doxorubicin. However, there was an increase in cardiac toxicity when paclitaxel was given in combination with doxorubicin and cyclophosphamide. Although cardiac toxicity may be attenuated by either changing the length of the infusion or separating paclitaxel from doxorubicin by several hours to a day, these maneuvers may also decrease efficacy. In phase II trials, docetaxel, when given in combination with doxorubicin, did not increase cardiac toxicity. This difference in cardiac toxicity may be related to the different vehicles used to dissolve paclitaxel and docetaxel. Paclitaxel is dissolved in cremophor, which is known to increase doxorubicin's area under the concentration curve (AUC). Docetaxel, on the other hand, is dissolved in polysorbate, which does not increase doxorubicin's AUC.

— Eleftherios Mamounas, MD

EFFECT OF ADJUVANT CHEMOTHERAPY IN ER-POSITIVE TUMORS

In the past year, I have been trying to understand why ER-positive patients did not benefit from the addition of paclitaxel to AC x 4 in the Intergroup adjuvant trial 0148 (CALGB 9344). My initial reaction was that because these patients received tamoxifen, there was little additional effect to be gained from chemotherapy. I evaluated this hypothesis by examining all the trials in the Overview that gave one, two and five years of tamoxifen plus or minus chemotherapy. If my hypothesis was correct, then adjuvant chemotherapy would have demonstrated greater benefit in those receiving a shorter compared to a longer duration of tamoxifen. That did not prove to be the case. Currently, my hypothesis is that in both pre- and postmenopausal, ER-positive patients, the effect of adjuvant chemotherapy is mediated through the ovary.

— I Craig Henderson, MD