Optimizing Adjuvant Chemotherapy: Recent Trial Results

BCIRG 001 demonstrated the superiority of TAC (docetaxel, doxorubicin and cyclophosphamide) compared to FAC, and CALGB-9741 provided proof of principle of dose-dense chemotherapy scheduling. At the San Antonio Breast Cancer Symposium in December 2005, BCIRG trial 005 reported on the safety of TAC compared to AC followed by docetaxel. CALGB-9741 was updated with over six years of follow-up with no changes to the initial conclusions reported in 2003. ECOG-E1199 demonstrated no significant differences between type of taxane used following AC chemotherapy (docetaxel or paclitaxel) or schedule utilized (weekly versus every three-week). Finally, in a US Oncology report, the doublet docetaxel/cyclophosphamide was superior to AC in terms of disease-free survival.

BCIRG 001: ADJUVANT TAC VERSUS FAC

Eligibility	Stage T1-3, N1, M0; age 18 to 70; KPS ≥ 80%
ARM 1	TAC (75/50/500 mg/m^2) q3wk x 6
ARM 2	FAC (500/50/500 mg/m^2) q3wk x 6

KPS = Karnofsky performance status

DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL (MEDIAN FOLLOW-UP = 55 MONTHS)

Efficacy endpoint	Hazard ratio* TAC/FAC (95% CI)
Disease-free survival (N = 1,491)	
ITT, adjusted for nodal status	0.72 (0.59-0.88)
1-3 nodes (n = 926)	0.61 (0.46-0.82)
≥4 nodes (n = 565)	0.83 (0.63-1.08)
Hormone receptor-positive (n = 1,132)	0.72 (0.56-0.92)
Hormone receptor-negative (n = 359)	0.69 (0.49-0.97)
Overall survival	
Adjusted for nodal status	0.70 (0.53-0.91)

ITT = intention to treat
* Hazard ratios less than one indicate values in favor of TAC.

SOURCE: Martin M et al. *N Engl J Med* 2005;352(22):2302-13.

BCIRG 005 SAFETY ANALYSIS OF TAC VERSUS AC → T IN NODE-POSITIVE, HER2-NEGATIVE PATIENTS (MEDIAN FOLLOW-UP = 30 MONTHS)

Toxicity (Grade III/IV)	TAC (n = 1,635)	AC → T (n = 1,634)
Prophylactic G-CSF	16%	3%
Total G-CSF use	44%	28%
Neutropenia	60.1%	58.1%
Febrile neutropenia	17.9%	8.5%
Anemia	3.9%	2.8%
Thrombocytopenia	2.1%	1.1%
Sensory neuropathy	0.6%	2.0%
Motor neuropathy	0.3%	0.5%
Myalgia	1.0%	4.9%
Stomatitis	2.6%	3.0%

SOURCE: Eiermann W et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 1069.

CALGB-9741: DOSE-DENSE VERSUS CONVENTIONALLY SCHEDULED CHEMOTHERAPY FOR NODE-POSITIVE BREAST CANCER (MEDIAN FOLLOW-UP = 6.5 YEARS)

Outcome	q2wk	q3wk	*p*-value
Disease-free survival	76.7%	71.7%	0.01
Sequential	75.6%	71.8%	
Concurrent	77.7%	71.6%	
Overall survival	83.0%	79.5%	0.05
Sequential	83.1%	78.1%	
Concurrent	82.8%	80.8%	

Conclusions:
No change to the initial conclusions for DFS and OS

- AC can be given sequentially or concurrently
- Dose-dense (q2wk) scheduling is superior to q3wk
- Q2wk is tolerable, more quickly delivered and there is no evidence of increased late risks

SOURCE: Hudis C et al. Presentation. San Antonio Breast Cancer Symposium 2005.

US ONCOLOGY ADJUVANT TRIAL EVALUATING TC VERSUS AC IN PATIENTS WITH STAGE I-III EARLY BREAST CANCER (MEDIAN FOLLOW-UP = 66 MONTHS)

Parameter	TC (n = 506)	AC (n = 510)	*p*-value
Disease-free survival	86%	80%	0.01
	HR = 0.67 (95% CI: 0.50-0.94)		
ER-/PR-	HR = 0.64 (95% CI: 0.38-1.04)		
ER+ or PR+	HR = 0.71 (95% CI: 0.47-1.03)		
Node-positive	HR = 0.67 (95% CI: 0.45-0.98)		
Node-negative	HR = 0.73 (95% CI: 0.42-1.27)		
Overall survival	90%	87%	0.13
	HR = 0.76		

"TC is the first adjuvant regimen given for 4 courses to prove superior to standard AC. TC can now be considered a standard nonanthracycline adjuvant regimen for appropriate patients with early breast cancer. TC was associated with more low-grade myalgia, arthralgia, edema and febrile neutropenia than AC. AC was associated with more severe nausea and vomiting than TC."

Hazard ratios < 1 indicate values in favor of TC

SOURCE: Jones S et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 40.

ECOG-E1199: AC FOLLOWED BY DOCETAXEL (D) OR PACLITAXEL (P) EVERY THREE WEEKS (3) OR WEEKLY (1) IN NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE BREAST CANCER (MEDIAN FOLLOW-UP 46.5 MONTHS)

DFS, Primary Comparisons	HR	95% CI	*p*-value
Paclitaxel vs docetaxel	0.985	0.84-1.15	0.83
Q3wk vs weekly	1.043	0.89-1.22	0.54
DFS, Secondary Comparisons	**HR**	**95% CI**	***p*-value**
P3 vs P1	1.20	0.99-1.46	0.06
P3 vs D3	1.13	0.94-1.36	0.20
P3 vs D1	1.03	0.85-1.23	0.78

DFS = disease-free survival

SOURCE: Sparano JA et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 48.

ECOG-E1199: MOST COMMON GRADE III-IV TOXICITY (>5%)

	P3	P1	D3	D1
Neutropenia	4%	2%	46%	3%
Febrile neutropenia	<0.5%	1%	16%	1%
Infection	3%	4%	13%	5%
Stomatitis	<0.5%	0%	5%	2.5%
Fatigue	2%	3%	9%	11%
Neuropathy	5%	8%	4%	6%

"Previous studies in patients where cancer had spread to other parts of the body have shown that docetaxel is more effective than paclitaxel when given every 3 weeks, and that paclitaxel is more effective if given weekly rather than every 3 weeks," said Joseph Sparano, MD, professor of medicine at the Albert Einstein College of Medicine in New York City, and director of the Breast Evaluation Center at the Montefiore-Einstein Cancer Center, and clinical trial leader. "This study addressed a question that many medical oncologists have had for some time about whether this would translate into improved success rates for patients with stage II and III disease. At this time, this does not appear to be the case, but further follow-up will be required to confirm our initial findings."

SOURCE: Sparano JA et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 48.

SELECT PUBLICATIONS

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

Eiermann W et al. **Phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (ACT) in Her-2/neu negative early breast cancer patients with positive axillary lymph nodes: Interim analysis of the BCIRG 005 study.** San Antonio Breast Cancer Symposium 2005;Abstract 1069.

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;Abstract 41.

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** San Antonio Breast Cancer Symposium 2005;Abstract 40.

Martin M et al. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13.

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** San Antonio Breast Cancer Symposium 2005;Abstract 48.

BCIRG 001: ADJUVANT TAC VERSUS FAC

This randomized, phase 3 trial of adjuvant chemotherapy in women with operable node-positive breast cancer showed that, at a median follow-up of 55 months, the estimated rate of disease-free survival at 5 years was 75 percent in the TAC group and 68 percent in the FAC group ($P = 0.001$). The relative risk of death was 30 percent lower among women in the TAC group than among those in the FAC group.

Moreover, treatment with TAC, as compared with FAC, was associated with a 28 percent relative reduction in the risk of relapse. The reduction in the risk of relapse did not seem to be driven by nodal status or by hormone-receptor or HER2/neu status.

— Miguel Martin, MD et al.* N Engl J Med *2005; 352(22):2302-13.

On the basis of the available data, one can consider TAC to be a standard of care, as is the dose-dense regimen of doxorubicin and cyclophosphamide followed by paclitaxel, for patients with resected node-positive breast cancer. However, the exclusion of patients older than 70 years and the toxic effects associated with TAC in the BCIRG trial cannot be minimized. With this regimen, prophylactic growth-factor support is necessary to ameliorate myelosuppression and febrile neutropenia. A recommendation for the selection of one regimen over the other must await completion of the prospective National Surgical Adjuvant Breast and Bowel Project trial B-38, for which the accrual of data is expected to be complete in the next few years.

— Edith A Perez, MD.* N Engl J Med *2005;352(22):2346-8.

CURRENT STATUS OF DOSE-DENSE CHEMOTHERAPY

Dose-dense trials have demonstrated that filgrastim facilitated bi-weekly chemotherapy is feasible. Based on the landmark results of CALGB 9741, many groups have adopted this strategy as a new standard of care. However, appropriate caution should be applied in extrapolating these data to any/all regimens outside a clinical trial setting, since unanticipated toxicities may emerge. At Memorial Sloan-Kettering Cancer Center (MSKCC) and elsewhere, feasibility trials are either planned or under way exploring dose-dense regimens containing other agents (e.g., docetaxel). It is intuitive that patients may be willing to endure the minor inconvenience of filgrastim administration to shorten duration of treatment and to gain therapeutically.

— Andrew D Seidman, MD.* Cancer Chemother Pharmacol *2005;56(Suppl 7):s78-83. (Citations Omitted)

ECOG-E1199 EVALUATING TAXANE TYPE AND SCHEDULE

ECOG-E1199, where the different schedules and different types of taxanes were compared, really showed that the weekly versus every three-week schedule didn't make any difference, and the drug, docetaxel or paclitaxel, didn't make any difference. So, in clinical practice, the best plan is to use whatever you're comfortable with. For example, if you like AC followed by weekly paclitaxel, that is effective, or AC followed by docetaxel. I personally would use every three-week instead of weekly docetaxel. Basically, what ECOG-E1199 says is that we have a lot of different options.

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

ADJUVANT DOCETAXEL/CYCLOPHOSPHAMIDE IS SUPERIOR TO AC

Between June 1997 and December 1999, 1,016 patients were randomized to 4 cycles of either standard-dose AC (60/600 mg/m^2) [n = 510], or TC (75/600 mg/m^2) [n = 506], administered intravenously every 3 weeks as adjuvant treatment…

At 5 years, the DFS is significantly better for TC compared to AC. Overall survival (OS) between treatments is not yet statistically significant, but there is a trend in favor of TC. Toxicity has been previously reported (*Proc ASCO* 2001, Abstract 128), and in general, TC was a more tolerable adjuvant regimen for lower-risk early breast cancer.

— Stephen E Jones, MD et al. San Antonio Breast Cancer Symposium 2005