Breast Cancer Prevention

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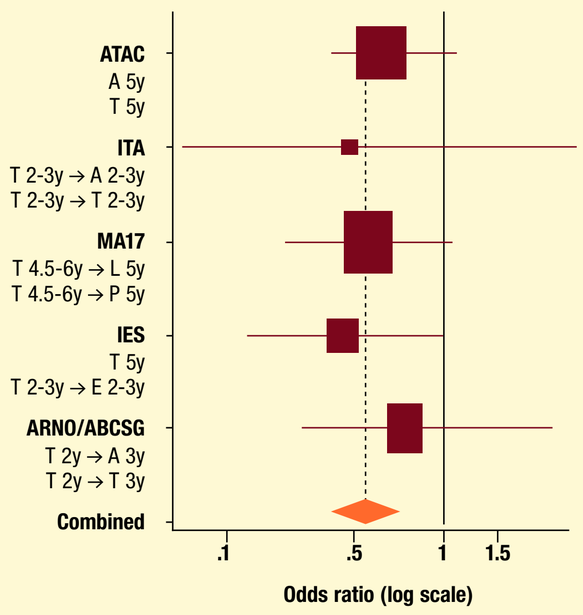
In the NSABP-P-1 and IBIS-1 trials, chemoprevention with tamoxifen was found to reduce the incidence of breast cancer in women at higher risk. The ATAC adjuvant trial demonstrated a further reduction in the incidence of contralateral breast cancer with anastrozole compared to tamoxifen. The aromatase inhibitors are being evaluated in ongoing chemoprevention trials in postmenopausal women. In addition to the reduced rate of second cancers, the more favorable safety and tolerability of these agents is the basis for evaluation in the high-risk setting. NSABP-P-2 (the STAR trial) compares tamoxifen to raloxifene, and it is likely that the agent with the better risk-benefit ratio will be compared in a new trial to an aromatase inhibitor.

CONTRALATERAL BREAST CANCER IN TRIALS OF ADJUVANT AROMATASE INHIBITORS



A = anastrozole; T = tamoxifen; L = letrozole; P = placebo; E = exemestane

BIG 1-98	Letrozole x 5y	Tamoxifen x 5y	*p*-value
Contralateral breast cancer (invasive)	0.4%	0.7%	0.125

SOURCES: Adapted with permission from Cuzick J. *J Clin Oncol* 2005;23(8):1636-43. Thürlimann B, for the BIG 1-98 Collaborative. Presentation. St Gallens 2005.

KEY ADVERSE EVENTS IN ADJUVANT TRIALS OF AROMATASE INHIBITORS VERSUS TAMOXIFEN

	ATAC[1]		BIG 1-98[2]	
	A	T	L	T
Hot flashes	35.7%	40.9%	33.5%	38.0%
Endometrial cancer	0.2%	0.8%	0.2%	0.5%
Hysterectomy	1.3%	5.1%	—	—
Ischemic cerebrovascular events	2.0%	2.8%	1.0%	1.0%
Venous thromboembolic events	2.8%	4.5%	1.5%	3.5%
Joint symptoms/arthralgias	35.6%	29.4%	20.3%	12.3%
Fractures	11.0%	7.7%	5.7%	4.0%

A = anastrozole; T = tamoxifen; L = letrozole

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Thürlimann B et al. Presentation. ASCO 2005.

NSABP-P-1 AND IBIS-1 STUDIES: BREAST CANCER EVENTS

Trial	No. of patients		Total invasive and noninvasive cancers		
	P	T	P	T	OR (95% CI)
NSABP-P-1	6,707	6,681	244	124	0.51 (0.39-0.66)
IBIS-1	3,574	3,578	101	69	0.68 (0.50-0.92)

P = placebo; T = tamoxifen; OR = odds ratio; CI = confidence interval

SOURCES: Chlebowski RT et al. *J Clin Oncol* 2002;20(15):3328-43. IBIS Investigators. *Lancet* 2002;360(9336):817-24.

ONGOING OR RECENTLY CLOSED CHEMOPREVENTION AND DCIS TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAPO-0028-150	High risk, postmenopausal, age 35 and over	4,560	Exemestane vs placebo
NCI-04-C-0044	High risk, postmenopausal	72	Exemestane + celecoxib vs exemestane
SWOG-S0300	High risk, premenopausal, age 18 and over	100	Celecoxib vs placebo
DFCI-00024, UCLA-0210012-02	High risk based on estradiol level >9 pg/mL, postmenopausal, age 35 and over	110	Letrozole vs placebo
UTSMC-0799-302	High risk, pre- or postmenopausal, age 35 and over	130	Tamoxifen vs placebo
KUMC-HSC-8919-02	High risk for ER-negative, premenopausal, age 18 to 55	110	Celecoxib
CHNMC-IRB-02164	High risk, premenopausal, age 21 to 48	10	Deslorelin + estradiol + testosterone
NU-NCI-00B2	Initiating tamoxifen for risk reduction or sole systemic therapy for breast cancer, premenopausal, age 20 to 45	100	Tamoxifen
CRUK-IBIS-IIB, EU-20227	High risk, ER/PR-positive (>5% positive cells) in patients with prior DCIS, postmenopausal, age 40 to 70	6,000	Anastrozole vs placebo
CAN-NCIC-MAP2, PFIZER-971-ONC-0028-088	Radiologic density occupying ≥25% of the breast, postmenopausal	120	Exemestane vs placebo
NCRI-IBIS-RAZOR, EU-20053, UKCCCR-IBIS-RAZOR	High genetic risk, premenopausal, age 30 to 45	150	Goserelin + raloxifene vs surveillance
BCM-H-9315	Known carrier or at risk for BRCA1 or BRCA2 mutation, pre- or postmenopausal, age 18 and over	100	Bexarotene vs placebo
NSABP-P-2 (STAR)	High risk, postmenopausal, age 35 and over	19,000	Tamoxifen vs raloxifene
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, age 40 to 70, ER/PR-positive (>5% positive cells), DCIS	4,000	Anastrozole vs tamoxifen
NSABP-B-35, CTSU	Postmenopausal, ER/PR-positive or borderline, DCIS	3,000	Anastrozole vs tamoxifen

SOURCE: NCI Physician Data Query, September 2005.

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Cuzick J et al; IBIS investigators. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial.** *Lancet* 2002;360(9336):817-24.

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Thürlimann B, for the BIG 1-98 Collaborative. **Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. First results of IBCSG 18-98/BIG 1-98.** Presentation. Primary Therapy of Early Breast Cancer 9th International Conference 2005.

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ATAC TRIAL DATA ON SECOND BREAST CANCERS

The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen. … Since tamoxifen shows a 50% reduction in the occurrence of these tumours in hormone-receptor-positive patients compared with placebo, the findings from the ATAC study suggest that anastrozole treatment might prevent 70 to 80% of hormone-receptor-positive tumours in women at high risk of breast cancer.

— ATAC Trialists' Group.* Lancet *2005;365(9453):60-2.

Some might argue that the reduction of contralateral breast cancer in ATAC looks less promising with the updated data than with the original data — it has gone from about a 60 to about a 50 percent relative reduction in contralateral breast cancer in the receptor-positive group. We had the same experience early on with tamoxifen. This suggests that these agents don't prevent cancer but rather delay the appearance of cancer. Perhaps anastrozole delays the appearance of breast cancer longer than tamoxifen. I am very confident that anastrozole will reduce the risk of new receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm-to-benefit ratio.

— Michael Baum, MD, ChM.* Breast Cancer Update *2003 (2)

RATIONALE FOR CLINICAL TRIALS OF AROMATASE INHIBITORS IN THE PREVENTATIVE SETTING

Data from the adjuvant trials provide a compelling rationale for exploring the use of AIs in the prevention setting. Their efficiency is greater than that of tamoxifen, especially for new contralateral tumors, suggesting that 70% to 80% of ER-positive breast cancers can be prevented with these drugs…

The AIs also are better tolerated than tamoxifen, without the gynecologic and thrombotic complications, but do lead to bone mineral loss and increased fracture rates in the absence of additional bone-sparing therapy. An important question will be the effectiveness of bisphosphonates in arresting and/or reversing bone loss associated with the almost complete depletion of estrogen associated with AIs.

— Jack Cuzick, PhD.* J Clin Oncol *2005;23(8):1636-43.

ONGOING TRIALS EVALUATING AROMATASE INHIBITORS FOR BREAST CANCER PREVENTION

…A number of AI prevention trials are being designed for implementation in high-risk women. Most developed is the IBIS-II trial, which draws on the contralateral benefit demonstrated in ATAC. Consisting of two arms designed around different high-risk populations, this dual study will test anastrozole for its ability to reduce breast cancer risk. In one arm, 4,000 women with ductal carcinoma-in-situ will be randomly assigned to anastrozole versus tamoxifen for 5 years. The other, prevention, arm will randomly assign 6,000 high-risk women to anastrozole versus placebo for 5 years. The IBIS-II prevention arm will focus on invasive and noninvasive breast cancer as a primary end point and osteoporosis and fractures as key secondary end points. The National Cancer Institute of Canada is incorporating exemestane into its Mammary Prevention 3 trial. This trial will randomly assign 5,100 high-risk postmenopausal women in equal numbers to placebo versus exemestane versus exemestane plus celecoxib.

— Barbara K Dunn, MD et al.* J Clin Oncol *2005;23:357-67.

SIDE-EFFECT PROFILE OF AROMATASE INHIBITORS COMPARED TO TAMOXIFEN

The safety profile in the ATAC update still favors anastrozole. The incidence of endometrial cancer is 0.2 percent with anastrozole and 0.8 percent with tamoxifen. The new data revealed a 5.1 percent rate of hysterectomy with tamoxifen and only slightly over one percent with anastrozole. Also, with anastrozole we seldom see gynecological side effects, such as bleeding or discharge, and we see no increased risk of strokes or pulmonary embolism.

— Raimund V Jakesz, MD.* Breast Cancer Update *2005 (3)

Predicting Prognosis in Women with Early Breast Cancer

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In women with early breast cancer, tools that predict both a prognosis and benefit from adjuvant chemotherapy are invaluable to both clinicians and patients. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. Additional data on this assay will be presented at this meeting. Another valuable resource is the Adjuvant! Online computer program, developed by Dr Peter Ravdin, which allows for the calculation of outcomes in women with early breast cancer. In a presentation at the 2004 ASCO meeting, the predictions from Adjuvant! were found to be comparable to actual outcomes observed in patients from British Columbia. These and future tools that predict outcomes should aid in making decisions about adjuvant therapies.

ONCO*TYPE* DX 21-GENE RECURRENCE SCORE ASSAY

Sixteen cancer and five reference genes from three studies

Proliferation
Ki-67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

HER2
GRB7
HER2

Estrogen
ER
PGR
BCL2
SCUBE2

GSTM1

CD68

Reference
ACTB (ß-actin)
GAPDH
RPLPO
GUS
TFRC

Invasion
MMP11 (stromolysin 3)
CTSL2 (cathepsin L2)

BAG1

Recurrence score =

+0.47	x	GRB7 group score
-0.34	x	ER group score
+1.04	x	Proliferation group score
+0.10	x	Invasion group score
+0.05	x	CD68
-0.08	x	GSTM1
-0.07	x	BAG1

Category	Recurrence score (0 - 100)
Low risk of recurrence	<18
Intermediate risk of recurrence	≥18 and <31
High risk of recurrence	≥31

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 16; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

NSABP-B-14 TAM BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Placebo
ARM 2	Tamoxifen

Objective: Determine whether the 21-gene recurrence score assay captures prognosis, response to tamoxifen or both

KAPLAN-MEIER ESTIMATES OF THE 10-YEAR DISTANT RECURRENCE RATE ACCORDING TO A 21-GENE RECURRENCE SCORE (N = 668)

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

RS = recurrence score
$p < 0.001$ for comparison between high- and low-risk groups

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

COMPARISON OF OUTCOMES PREDICTED BY ADJUVANT! AND ACTUAL OUTCOMES OBSERVED BY THE BREAST CANCER OUTCOMES UNIT (BCOU) IN BRITISH COLUMBIA (N = 4,083)

Parameter	Adjuvant! predicted	BCOU observed	Difference between predicted and observed*
10-year OS	71.7%	72.0%	-0.3%
10-year BCSS			
Overall	83.2%	82.5%	+0.7%
No therapy	89.1%	90.1%	-1.0%
T	81.2%	79.4%	+1.8%
C	74.6%	73.7%	+0.9%
T + C	75.2%	70.6%	+4.6%
10-year EFS	71.0%	70.1%	+0.9%

OS = overall survival; BCSS = breast cancer-specific survival
T = tamoxifen; C = chemotherapy; EFS = event-free survival
* All *p*-values are nonsignificant.

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25.

NSABP-B-20 CHEMOTHERAPY BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Tamoxifen + MF
ARM 2	Tamoxifen + CMF
ARM 3	Tamoxifen

Objective: Determine the magnitude of the chemotherapy benefit as a function of the 21-gene recurrence score assay

B-20 EVALUATION PATIENTS (N = 651) SIMILAR TO ALL PATIENTS (N = 2,299)

	Number of eligible patients			
	Tamoxifen	Tamoxifen+MF	Tamoxifen+CMF	Total
All B-20	770	763	766	2,299
GHI-B-20 (% of all B-20)	227 (29.5%)	203 (26.6%)	221 (28.9%)	651 (28.3%)

GHI-B-20 study subjects were similar to all B-20 patients.

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract24; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

TEN-YEAR DISTANT RECURRENCE-FREE SURVIVAL ACCORDING TO A 21-GENE BREAST CANCER RECURRENCE SCORE

Risk group	Percent of patients	Tamoxifen (n = 227)	Tamoxifen + chemotherapy (n = 424)	*p*-value
Low (RS < 18)	51%	96%	95%	0.76
Intermediate (RS = 18-30)	22%	90%	89%	0.71
High (RS ≥ 31)	27%	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 24; Paik S. Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 16; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

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Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91.

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*ONCO*TYPE *DX™ ASSAY TO PREDICT RESPONSE TO CHEMOTHERAPY*

We evaluated the NSABP-B-20 chemotherapy arms to address whether the assay predicted chemotherapy responsiveness. We went into that study with an a priori hypothesis, based on the data presented at the 2004 ASCO meeting by Dr Luca Gianni's group in Milan evaluating samples from a neoadjuvant trial they performed with paclitaxel and doxorubicin. They demonstrated a correlation between the Genomic Health recurrence score and pCR rate. The higher recurrence score correlated strongly with the higher pCR rate.

In NSABP-B-20, the results are quite striking and unlike anything I've ever seen. The absolute benefit from chemotherapy is negative in the low-risk group and zero in the intermediate-risk group. In the high-risk group, the absolute improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent.

The data in the low-risk group are, in a sense, not relevant because the baseline risk after tamoxifen is so low — 6.8 percent — so it's a moot point of whether they need chemotherapy or not. In the intermediate-risk group the confidence interval overlaps with one, so whether patients with intermediate-risk disease gain any benefit or not remains a question.

— Soonmyung Paik, MD.* Breast Cancer Update *2005 (3)

We wanted to determine whether the assay could predict the benefit of chemotherapy, so we examined the data from NSABP-B-20, which randomly assigned patients with receptor-positive, node-negative disease to tamoxifen versus tamoxifen plus CMF chemotherapy versus tamoxifen plus MF chemotherapy. We found that patients at high risk derived benefit from chemotherapy, but patients at low risk, who comprised 50 percent of the cohort, did not appear to derive substantial benefit from the addition of chemotherapy to tamoxifen.

The intermediate group comprised only 20 to 25 percent of the cohort, and we didn't have the power to determine if they benefit from the addition of chemotherapy. We were surprised to find that the relative risk reduction was not uniform — different risk groups did not have the same relative risk reduction. The greatest relative risk reduction was seen in patients at highest risk.

— Norman Wolmark, MD.
Breast Cancer Update *for Surgeons 2005 (1)*

*UTILIZATION OF COMPUTERIZED MODELS AND THE ONCO*TYPE *DX ASSAY*

John Bryant presented data at the last St Gallen meeting evaluating the recurrence score and Adjuvant! Online, and they seem to perform independently to a certain extent. Adjuvant! Online will add to the recurrence score, and the recurrence will add to Adjuvant! Online. Peter Ravdin is working with us to modify Adjuvant! Online to introduce recurrence score. They provide complementary information, which is important for the patient. However, Adjuvant! Online doesn't provide any prediction on benefit from therapy, whereas the recurrence score adds prognostic and predictive value.

— Eleftherios P Mamounas, MD, MPH.
Breast Cancer Update *for Surgeons 2005 (3)*

BENEFITS OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH ER-POSITIVE TUMORS

As with several other recent retrospective studies, Don Berry's presentation at the last San Antonio meeting on sequential trials of adjuvant chemotherapy in CALGB trials, demonstrated that the effects of chemotherapy were substantially greater in patients with ER-negative than ER-positive tumors. A key question is: Do these results apply only to that lineage of chemotherapy or can they be generalized to chemotherapy overall, and how does this relate to the clinical use of adjuvant chemotherapy in patients with ER-positive tumors? This will be a matter of debate for some time to come.

— G Thomas Budd, MD.* Breast Cancer Update *2005 (8)

Can Alterations in Diet and Exercise Reduce the Risk of Relapse and Death from Early Breast Cancer?

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Evidence from a number of recent studies suggest that lifestyle factors, such as diet and physical activity, may reduce the risk of recurrence in patients with early breast cancer. At the 2005 ASCO meeting, Rowan Chlebowski reported the initial results of the Women's Intervention Nutrition Study (WINS), a randomized trial conducted at 37 centers in the United States, which demonstrated a reduction in relapse rate as a result of a modest decrease in dietary fat intake. Surprisingly, this benefit was confined to patients with estrogen receptor-negative breast cancer. Another recent report by Holmes and colleagues demonstrated a reduction in recurrence rate and mortality in breast cancer patients who engaged in regular physical activity, particularly in patients with estrogen receptor-positive tumors. The clinical and research implications of these and other related clinical research findings on complementary oncologic interventions are uncertain but are likely to be of great interest to patients with breast cancer.

RECENT STUDIES EVALUATING THE ASSOCIATION BETWEEN DIETARY FACTORS AND BREAST CANCER RECURRENCE

Study	N	Status	Intervention
Life Without Cancer Epidemiology (LACE)	2,400	Ongoing	Detailed data on dietary intake, physical activity, weight change and recurrence collected at regular intervals
Women's Healthy Eating and Living (WHEL)	3,088	Ongoing	Comprehensive dietary intervention to increase vegetable intake versus control with biological samples collected at baseline and regular intervals to establish the biological link between dietary intake, nutritional factors and the progression of breast cancer
Women's Intervention Nutrition Study (WINS)	2,437	Reported, ASCO 2005	Dietary intervention to reduce fat intake as an adjuvant to standard breast cancer therapy versus control with disease recurrence and survival as trial endpoints

SOURCES: Rock CL. *J Mammary Gland Biol Neoplasia* 2003;8(1):119-32; Chlebowski RT et al. Presentation. ASCO 2005;Abstract 10.

WINS TRIAL DESIGN — RECRUITMENT 1994-2001, MEDIAN FOLLOW-UP: 60 MONTHS

Eligibility	**Women 48-79 years; early breast cancer; primary surgery +/- XRT; systemic therapy*; dietary fat intake ≥20% of calories**
ARM 1	**Dietary intervention (n = 975) to reduce fat intake while maintaining nutritional adequacy**
ARM 2	**Control (n = 1,462)**

* Tamoxifen required, chemo Rx optional for ER+; chemo Rx required for ER-; strata = nodal status; systemic Rx; sentinel node

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005;Abstract 10.

WINS RELAPSE-FREE SURVIVAL BY TREATMENT GROUP

Groups	Diet (events/n)	Control (events/n)	HR (95% CI)	*p*-value*
All patients	96/975	181/1,462	0.76 (0.60-0.98)	0.034
ER-positive	68/770	122/1,189	0.85 (0.63-1.14)	0.277
ER-negative	28/205	59/273	0.58 (0.37-0.91)	0.018

* All *p*-values from adjusted Cox proportional hazards model. The disease-free survival outcome (adding other cancers and all deaths including 389 events) was similar (adjusted Cox HR 0.81, 95% CI 0.65-0.99, $p = 0.042$), favoring dietary intervention.

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005;Abstract 10.

PHYSICAL ACTIVITY AND SURVIVAL AFTER BREAST CANCER DIAGNOSIS

Objective: Determine effect of exercise on breast cancer recurrence and survival

Design, setting and participants: Prospective observational study of 2,987 women from the Nurses' Health Study who were diagnosed with Stage I-III breast cancer between 1984-1998 and followed until death or 2002

Assessment of physical activity: Assessment of eight activities, including duration and intensity, two years after breast cancer diagnosis

Outcome: Breast cancer mortality according to metabolic equivalent task hours per week (MET-h/wk) of physical activities

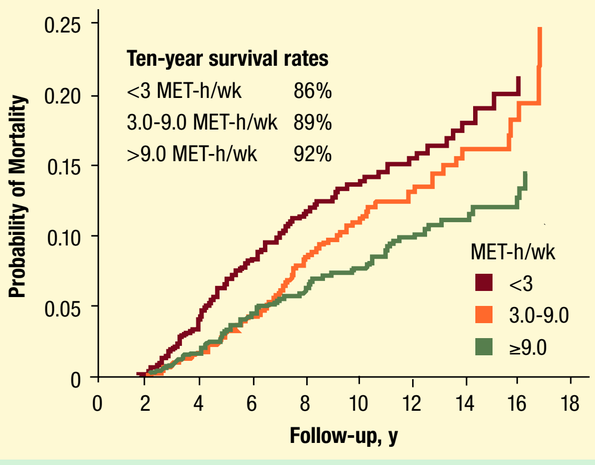
EXAMPLES OF MET SCORES

Activity	MET score
Sitting quietly	1.0
Walking at average pace	3.0
Jogging	7.0
Running	12.0

MET = metabolic equivalent task

SOURCE: Holmes MD et al. *JAMA* 2005;293(20):2479-86.

PROBABILITY OF BREAST CANCER MORTALITY BASED UPON MET-HOURS PER WEEK OF PHYSICAL ACTIVITY



MET = metabolic equivalent task

SOURCE: Reproduced with permission. Holmes MD et al. *JAMA* 2005;293(20):2479-86. Copyright © 2005, American Medical Association. All Rights reserved.

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WOMEN'S INTERVENTION NUTRITION STUDY (WINS): DIETARY FAT INTAKE AND RISK OF RECURRENCE

The issue of dietary fat intake has been around in breast cancer for about 25 years. To address this issue, we conducted a randomized clinical trial and entered 2,437 women about 220 days after initial surgery. Patients at 37 centers in the United States were entered after they completed their primary therapy. The diet group was given a dietary fat gram goal by centrally trained registered dieticians, implementing a predefined, low-fat eating plan. Patients received eight biweekly individual counseling sessions, then one session every three months. Monthly group sessions were held, and patients self-monitored their fat intake. The control group saw the dieticians every three months and talked about nutritional adequacy. Fat gram intake for the intervention group went from about 56 to 33 fat grams per day — about a 40 percent reduction in daily fat gram intake, which was sustained by most of the individuals.

Our primary study endpoint was relapse-free survival, which included all breast cancer recurrence sites, including contralateral breast cancers. We found that the dietary group had a longer relapse-free survival than the control population. In the control group, 12.4 percent had a relapse compared to 9.8 in the diet group, which was a 2.6 percent absolute difference at five years, or a 24 percent reduction in risk of recurrence. We did subgroup analysis by receptor status. The hazard ratio was 0.85 for relapse-free survival in patients with estrogen receptor-positive tumors and not significant. In the 478 patients with ER-negative disease, the hazard ratio was 0.58, with a 42 percent reduction in risk and eight percent absolute difference at five years. This is hypothesis generating but rather intriguing to us.

— Rowan T Chlebowski, MD, PhD.
Breast Cancer Update *2005 (7)*

PHYSICAL ACTIVITY AND SURVIVAL AFTER BREAST CANCER

An expert panel of the International Agency for Research on Cancer of the World Health Organization estimated a 20% to 40% decrease in the risk of developing breast cancer among the most physically active women, regardless of menopausal status, type, or intensity of activity…

Women who engaged in an amount of physical activity equivalent to walking one or more hours per week had better survival compared with those who exercised less than that or not at all. After adjusting for factors predictive of survival after breast cancer, the RRs of adverse outcomes including death, breast cancer death, and breast cancer recurrence were 26% to 40% lower comparing women with the highest to the lowest category of activity. The association was particularly apparent among women with hormone-responsive tumors. Our results suggest a possible hormonal mechanism for improved survival among women who are physically active.

— Michelle D Holmes, MD, DrPH et al.* JAMA *2005;293(20):2479-86.

FRUIT AND VEGETABLE INTAKE, PLASMA CAROTENOIDS AND RISK OF RECURRENCE

Being in the highest versus the lowest quartile of plasma total carotenoid concentration was associated with an estimated 43% reduction in risk for a new breast cancer event. Plasma carotenoids are a biologic marker of vegetable and fruit intake, so these results support the suggestion from prior studies, based on self-reported dietary intakes, that increased consumption of those foods may reduce the risk of recurrence or increase the likelihood of survival after the initial diagnosis and treatment of breast cancer.

— Cheryl L Rock et al.* J Clin Oncol *2005;23(27):6631-38.

Aromatase Inhibitors as Adjuvant Therapy

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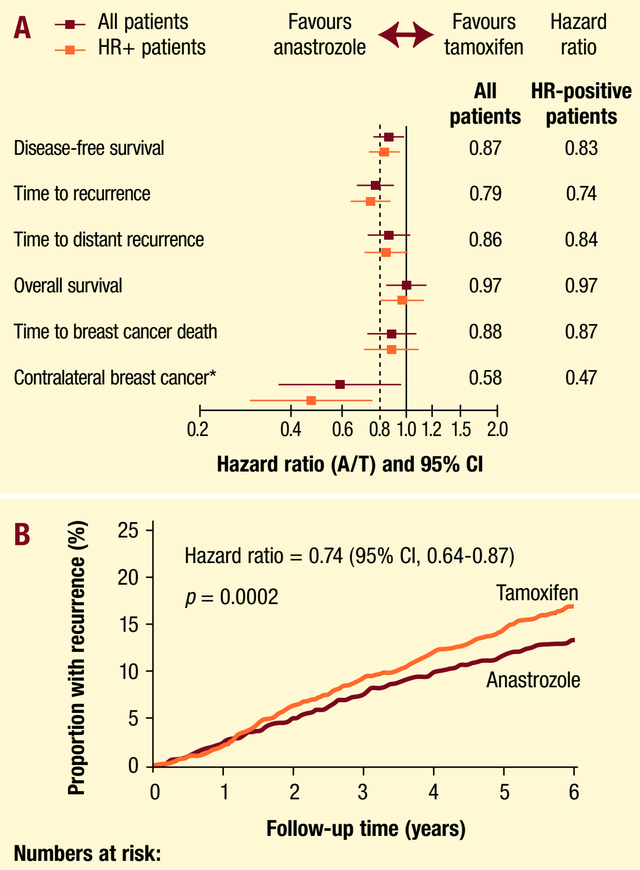
In the 68-month follow-up of the ATAC trial, adjuvant anastrozole continued to significantly prolong disease-free survival and time to recurrence and reduce distant metastases and contralateral breast cancers compared to tamoxifen. Data presented at the 2003 and 2004 San Antonio Breast Cancer Symposia demonstrated a greater advantage associated with adjuvant anastrozole in women with ER-positive, PR-negative tumors as compared to ER/PR-positive tumors. BIG FEMTA, a second trial comparing an aromatase inhibitor to tamoxifen, has now also demonstrated with less than three years of follow-up a significant improvement in disease-free survival, time to recurrence and time to distant metastases with adjuvant letrozole. An ongoing clinical trial will now compare the efficacy of two aromatase inhibitors — anastrozole and exemestane — as adjuvant therapy in women with hormone receptor-positive breast cancer.

ATAC TRIAL 68-MONTH ANALYSIS: EFFICACY ENDPOINTS AND TIMES TO RECURRENCE



Numbers at risk:

Anastrozole	2,618	2,540	2,448	2,355	2,268	2,014	830
Tamoxifen	2,598	2,516	2,398	2,304	2,189	1,932	774
Absolute difference	—	—	—	1.7%	2.4%	2.8%	3.7%

Figure: (A) Efficacy endpoints for all patients and HR-positive patients and (B) time to recurrence in HR-positive patients

A = anastrozole; T = tamoxifen; HR = hormone receptor

* Odds ratio calculated instead of hazard ratio

SOURCE: Reprinted from The Lancet, Vol 365, ATAC Trialists' Group, Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment breast cancer, 60-2, 2005, with permissions from Elsevier.

RECURRENCE RATES IN THE ATAC TRIAL ACCORDING TO ESTROGEN AND PROGESTERONE RECEPTOR STATUS

Receptor status	N	Anastrozole (%)	Tamoxifen (%)	Hazard ratio for anastrozole versus tamoxifen (95% CI)*
ER+/PR+	5,704	7	8	0.82 (0.65-1.03)
ER+/PR-	1,370	9	17	0.48 (0.33-0.71)
ER-/PR+	220	22	26	0.79 (0.40-1.5)
ER-/PR-	699	27	27	1.04 (0.73-1.47)

* Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. *Breast Cancer Res Treat* 2003;82(Suppl 1):7;Abstract 4.

BIG FEMTA/BIG 1-98: LETROZOLE VERSUS TAMOXIFEN AS ADJUVANT ENDOCRINE THERAPY

Protocol IDs: IBSCG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, NCT00004205, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98
Accrual: 8,028 (Closed)

Eligibility	Postmenopausal women; receptor-positive breast cancer
ARM 1	Tamoxifen x 5 years
ARM 2	Letrozole x 5 years
ARM 3	Tamoxifen x 2 years → letrozole x 3 years
ARM 4	Letrozole x 2 years → tamoxifen x 3 years

SOURCE: NCI Physician Data Query, October 2005.

BIG 1-98: 25.8-MONTH EFFICACY ENDPOINTS OF LETROZOLE VERSUS TAMOXIFEN

	HR (95% CI)	*p*-value
Disease-free survival (DFS)	0.81 (0.70-0.93)	0.003
ER+/PR+	0.84	—
ER+/PR-	0.83	—
Overall survival	0.86 (0.70-1.06)	0.16
ER+/PR+	1.00	—
ER+/PR-	0.79	—
Time to recurrence	0.72 (0.61-0.86)	0.0002
Time to distant metastases	0.73 (0.60-0.88)	0.0012

HR = hazard ratio for letrozole versus tamoxifen (<1.0 favors letrozole)

SOURCE: BIG 1-98 Collaborative Group. www.ibcsg.org.

ADJUVANT EXEMESTANE VERSUS ANASTROZOLE IN POSTMENOPAUSAL WOMEN

Protocol IDs: CAN-NCIC-MA27, NCT00066573, CALGB-CAN-NCIC-MA27, ECOG-CAN-NCIC-MA27, NCCTG-N0434, SWOG-CAN-NCIC-MA27
Target Accrual: 5,800 (Open)

Eligibility	Postmenopausal women with Stage I-III invasive ER- and/or PR-positive breast cancer
ARM 1	Anastrozole x 5 years
ARM 2	Exemestane x 5 years

Trial lead organizations:

NCIC-Clinical Trials Group: *Paul E Goss, MD, PhD, Protocol Chair Ph: 617-724-3118*

North Central Cancer Treatment Group: *James N Ingle, MD, Protocol Chair, Ph: 507-284-8432, Email: ingle.james@mayo.edu*

Cancer and Leukemia Group B: *Matthew J Ellis, MB, PhD, Protocol Chair Ph: 314-362-8903; 800-600-3606*

Eastern Cooperative Oncology Group: *George W Sledge Jr, MD, Protocol Chair, Ph: 317-274-0920; 888-600-4822, Email: gsledge@iupui.edu*

Southwest Oncology Group: *G Thomas Budd, MD, Protocol Chair Ph: 216-444-6480*

SOURCE: NCI Physician Data Query, September 2005.

SELECT PUBLICATIONS

Burstein HJ et al. **Optimizing endocrine therapy in postmenopausal women with early stage breast cancer: A decision analysis for biological subsets of tumors.** *Proc ASCO* 2005;Abstract 529.

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 658.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Proc SABCS* 2003;Abstract 4.

Howell A, on behalf of the ATAC Trialists' Group. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 1.

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

Punglia RS et al. **Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: A decision analysis.** *J Clin Oncol* 2005;23(22):5178-87.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

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CONTROVERSIES IN SELECTION OF INITIAL TREATMENT

The present data suggest that it is not appropriate to wait five years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1-3) and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen lend support to the approach of offering the most effective and well-tolerated therapy at the earliest opportunity. Five years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localized breast cancer.

— ATAC Trialists' Group. **Lancet** ***2005;365(9453):60-2.***

Several groups have looked at statistical modeling of the optimal long-term sequencing of an AI after tamoxifen vs immediate use of an AI — Jack Cuzick's group in London, the Dana-Farber group with Hal Burstein, and our own group in Houston with our statistician Sue Hilsenbeck. All of these models suggested similar findings, and they could not rule out a moderate benefit from sequencing compared to immediate use if one looks at the long-term results after 10 years in the large subgroup of ER/PR-positive tumors. Although there is a peak in recurrence at 2-3 years, ultimately more patients recur after year 5 than in the first 5 years, and the sequence of tamoxifen followed by an AI could turn out to be a better strategy. While it is true that we can't necessarily go by the results of mathematical models, they do provide some evidence of what the possibilities of these different strategies might be over the long term.

— C Kent Osborne, MD. **Breast Cancer Update** ***2005, Special CME Meeting Edition***

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The simplest interpretation of the ATAC data is that anastrozole prevents one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival.

In the hazard rate analysis plot from the ATAC trial, we're seeing two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial, not only to help make therapeutic decisions but also to give a fascinating biological insight. The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile, you've lost those patients who will relapse and ultimately die in those first two years.

— Michael Baum, MD, ChM. **Breast Cancer Update** ***2005 (1)***

BIG FEMTA/IBCSG-1-98/BIG 1-98: LETROZOLE VERSUS TAMOXIFEN UP FRONT OR SEQUENTIALLY

The efficacy results in BIG FEMTA were essentially the same as those in the ATAC trial at the 30-month point. The hazard reduction was similar, and the side-effect profile was by and large the same, although it was reported differently. A few differences were seen. They found a benefit for letrozole only in patients with node-positive disease, which is difficult to understand. It's probably a chance finding, but we need to follow that. At this stage, they've found no difference in efficacy between the patients with PR-positive and PR-negative disease. We have to acknowledge that the data are different from what's been observed in other trials. The third and most worrying finding is the substantial excess in cardiovascular deaths for letrozole compared to tamoxifen, which hasn't been observed in the trials with anastrozole. Whether this is due to chance or differences in cardiovascular mortality is important to know. Letrozole is a slightly more potent aromatase inhibitor, and it is not clear whether that has an impact.

— Jack Cuzick, PhD. **Breast Cancer Update** ***2005 (6)***

Sequencing Tamoxifen and Aromatase Inhibitors in Postmenopausal Patients

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The optimal adjuvant hormonal therapy strategy for postmenopausal women is controversial. A number of trials have evaluated the role of aromatase inhibitors following tamoxifen. MA17 randomly assigned postmenopausal women who had completed 4.5 to six years of adjuvant tamoxifen to five years of placebo or letrozole. In ITA, IES, ABCSG-8 and ARNO 95, postmenopausal women who had completed two to three years of adjuvant tamoxifen were randomly assigned to continue tamoxifen or switch to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy have demonstrated significant advantages for women switching to an aromatase inhibitor. In an extension of MA17 and in a proposed trial through the NSABP, women who complete five years of hormonal therapy will be randomly reassigned to another five years of letrozole or placebo.

EVALUATING THE STRATEGY OF SWITCHING FROM ADJUVANT TAMOXIFEN TO AN AROMATASE INHIBITOR

Study	N	Randomization	Study endpoints	Hazard ratio
ABCSG-8/ ARNO 95	3,224	TAM (T) x 2y → anastrozole (A) x 3y TAM x 2y → TAM x 3y	EFS DRFS OS	A/T = 0.60 (p = 0.0009) A/T = 0.61 (p = 0.0067) A/T = 0.76 (p = 0.16)
IBCSG-18-98/ EU-99022/ IBCSG-1-98	8,010	TAM x 5y Letrozole (L) x 5y TAM x 2y → letrozole x 3y Letrozole x 2y → TAM x 3y	DFS* OS*	L/T = 0.81 (p = 0.003) L/T = 0.86 (p = 0.16) NR NR
IES/ICCG-960 EXE031-C1396- BIG9702	4,742	TAM x 5y TAM x 2-3y → exemestane (E) x 2-3y	DFS BCFS OS Time to contralateral breast cancer	E/T = 0.68 (p < 0.001) E/T = 0.63 (p < 0.001) E/T = 0.88 (p = 0.37) E/T = 0.44 (p = 0.04)
Italian (ITA)	426	TAM x 2-3y → anastrozole x 2-3y TAM x 2-3y → TAM x 2-3y	Relapse Death	A/T = 0.36 (p = 0.006) A/T = 0.18 (p = 0.07)
GROCTA 4B	380	TAM x 3y → aminoglutethimide (AG) x 2y TAM x 3y → TAM x 2y	EFS	AG/T = 1 (p = 0.6)

TAM = tamoxifen; EFS = event-free survival; DRFS = distant relapse-free survival; OS = overall survival; DFS = disease-free survival; NR = not yet reported
BCFS = breast cancer-free survival

* Endpoint for monotherapy; analysis of sequential endocrine treatment not yet completed; HR <1.0 favors aromatase inhibitors

EXTENDED ADJUVANT HORMONAL THERAPY WITH AROMATASE INHIBITORS AFTER FIVE YEARS OF TAMOXIFEN

Study	N	Randomization	Study endpoints	Hazard ratio
CAN-NCIC-MA17/SWOG-NCIC-MA17/ IBCSG-BIG97-01/CALGB-49805	5,187	TAM x 4.5-6y → letrozole x 5y TAM x 4.5-6y → placebo x 5y	Relapse Death	L/P = 0.57 (p = 0.00008) L/P = 0.76 (p = 0.25)
ABCSG-6a	856	GROCTA 4B → anastrozole x 3y GROCTA 4B → no treatment x 3y	EFS	Anastrozole/ no treatment = 0.64 (p = 0.047)

TAM = tamoxifen; EFS = event-free survival

SOURCES: Boccardo F et al. *Proc SABCS* 2003;Abstract 3; Boccardo F et al. *J Clin Oncol* 2001;19(22):4209-15; Boccardo F et al. *J Clin Oncol* 2005;23(22):5138-47; Jakesz R et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 2; Thürlimann BJ et al. BIG 1-98. Presentation. ASCO 2005;Abstract 511; Jakesz R et al. *Proc ASCO* 2005;Abstract 527; NCI Physician Data Query, September 2005; Goss PE et al. *N Engl J Med* 2003;349(19):1793-802; Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. NSABP website, www.nsabp.pitt.edu; www.ibcsg.org.

PHASE III RANDOMIZED STUDY OF ADJUVANT EXEMESTANE VERSUS ADJUVANT TAMOXIFEN FOLLOWED BY EXEMESTANE

Protocol IDs: CRC-TU-TEAM, EU-20149, NCT00032136
Target Accrual: 5,700 (Open)

Eligibility	**Stage I-IIIA breast cancer; postmenopausal; age 50 or over with natural amenorrhea for at least one year, chemotherapy-induced amenorrhea for at least two years, radiation-induced amenorrhea; under age 50 with FSH assay confirming postmenopausal status; ER- and/or PR-positive; any age with bilateral oophorectomy or amenorrhea for at least five years**
ARM 1	**Exemestane x 5y**
ARM 2	**Tamoxifen x 2-3y → exemestane x 2-3y***

* In a proposed amendment based on the IES results, Arm 2 will be changed from tamoxifen x five years.

Trial lead organization:

Cancer Research UK Clinical Trials Unit — Birmingham
Daniel Rea, MD, Protocol Chair, Ph: 44-121-507-5241

SOURCES: NCI Physician Data Query, September 2005; Henderson IC. *Am J Oncol* 2005;4(5 Suppl 9):40-3.

PROPOSED NSABP TRIAL OF DURATION OF AROMATASE INHIBITORS

Protocol ID: NSABP (Pending)
Projected Accrual: 3,840 (Planned to open early 2006)

Eligibility	**Stage I-IIIA breast cancer; postmenopausal, ER- and/or PR-positive, five years of hormonal therapy consisting of either five years of an aromatase inhibitor or up to three years of tamoxifen followed by an aromatase inhibitor (for a total of five years)**
ARM 1	**Placebo x 5y**
ARM 2	**Letrozole x 5y**

RERANDOMIZATION OF NCIC-CAN-MA17

Protocol ID: NCIC-CAN-MA17R
Target Accrual: 1,800 (Open)

Women completing approximately five years of letrozole on MA17 who are free of recurrence and completed letrozole no more than six months previously will be eligible for rerandomization on NCIC-CAN-MA17R comparing letrozole x five years versus placebo x five years.

SOURCES: NSABP Protocol Summary, September 2005; National Cancer Institute of Canada Clinical Trials Group, September 2005; Henderson IC. *Am J Oncol* 2005;4(5 Suppl 9):40-3.

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Boccardo F et al. **Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study.** *J Clin Oncol* 2001;19(22):4209-15.

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47.

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802.

Jakesz R, on behalf of the ABCSG. **Benefits of switching postmenopausal women with hormone sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 2.

Jakesz R, on behalf of the ABCSG. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;Abstract 527.

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SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN

I am now absolutely confident that women who have been on tamoxifen for two or three years should switch to an aromatase inhibitor. We have excellent data for both exemestane and anastrozole from three trials. Boccardo's small ITA trial with anastrozole was the first to report, followed by the large IES study with exemestane and the joint Austrian-German study of anastrozole presented in San Antonio. Overwhelming evidence indicates that a switch to an aromatase inhibitor is beneficial. I recommend the switch regardless of whether the patient has been on tamoxifen for one year or four years. You can wait forever for refinements, but no one is ever going to do a trial of a switch at one year or a switch at four years. We just have to stretch the available evidence and be sensible about it, and I think it would be reasonable to switch. The MA17 trial is a well-conducted trial in women who have already received five years of tamoxifen. It shows proof of the principle that you can influence the natural history of breast cancer after five years of tamoxifen.

— *Michael Baum, MD, ChM.* Breast Cancer Update *2005 (2)*

The aromatase inhibitors add benefit immediately after surgery, after two to three years of tamoxifen or as extended adjuvant therapy. In breast cancer, the highest risk of recurrence is typically within the first two to three years after surgery. In women who participated in the ATAC trial, you can see a difference in the disease-free survival curves well before the two and a half year mark. Not only do you lose patients to an early breast cancer recurrence in the first two to three years, but you also lose some women to adverse events on the tamoxifen arm. The IES study and MA17 do not really take those facts into consideration because those patients have already dropped out prior to randomization. I typically offer anastrozole to the majority of postmenopausal patients with receptor-positive tumors after surgery and chemotherapy. When patients come in after two to three years of tamoxifen, I discuss switching them to an aromatase inhibitor. At the end of five years of tamoxifen, I discuss letrozole.

— *Maura N Dickler, MD.* Breast Cancer Update *2005 (2)*

I use exemestane after two to three years of tamoxifen based on the IES data. However, if you compare the IES exemestane data to the data from the combined ARNO 95/ABCSG-8 trials, in which the patients were switched to anastrozole, the agents appear to be similar in terms of efficacy. The hazard ratio for disease-free survival was 0.73 in the IES study and 0.60 in the ARNO study, so I believe these two agents are equivalent in this situation. We now have data to support the use of either anastrozole or exemestane after two or three years of tamoxifen. After five years of tamoxifen, we only have the MA17 trial data, so I use letrozole in this setting.

— *Anthony Howell, MD.* Breast Cancer Update *2005 (4)*

In the combined trials of ABCSG-8 and ARNO 95, more than 3,200 postmenopausal patients, all with receptor-positive disease, were exposed to two years of adjuvant tamoxifen after surgery. We then randomly assigned them to tamoxifen or anastrozole for three years. It was clean, informative data. In the IES trial, exemestane resulted in a risk reduction of approximately 35 percent, whereas in the combined trials, the risk of an event was reduced by 40 percent with anastrozole. Most of the difference in the event rate with anastrozole was due to a huge reduction in distant metastases.

— *Raimund V Jakesz, MD.* Breast Cancer Update *2005 (3)*

It is important to study the duration of aromatase inhibitor therapy. The NSABP will take patients that complete five years of an aromatase inhibitor or took tamoxifen for two to three years and then switched to an aromatase inhibitor and randomly assign them to either continue an aromatase inhibitor — letrozole — versus placebo for five years. We will essentially do what we did in the NSABP-B-14 extension trial but with aromatase inhibitors.

— *Eleftherios P Mamounas, MD, MPH.* Breast Cancer Update *2005 (9)*

Management of Short- and Long-Term Toxicities of Aromatase Inhibitors

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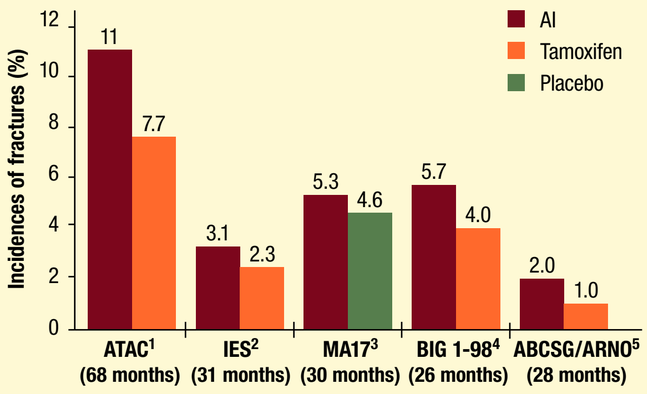
Musculoskeletal symptoms and bone loss are the two major adverse events of long-term adjuvant therapy with aromatase inhibitors (AIs), and both of these potential complications may be ameliorated. An Austrian study demonstrated that zoledronic acid can prevent bone loss in women treated with ovarian suppression and anastrozole. Bone density monitoring and bisphosphonates are now routinely used in patients receiving AIs. Arthralgias are common in breast cancer patients receiving tamoxifen, but the incidence increases with all AIs. A variety of oral and topical medications and nonpharmacologic approaches may improve arthralgias, which also tend to decrease with time on treatment. The spectrum of adverse AI events, including arthralgias, is similar regardless of whether patients received prior chemotherapy.

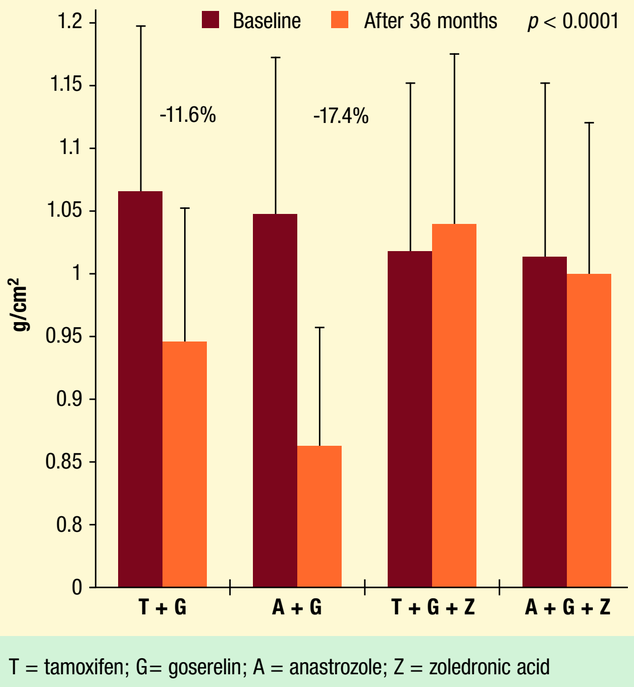
FRACTURES IN ADVJUVANT AI TRIALS



AI = Aromatase inhibitor; ATAC = Arimidex® (anastrozole), tamoxifen, alone or combination; IES = Intergroup exemestane study; MA17 = extended adjuvant treatment with letrozole trial; BIG 1-98 = IBCSG trial of letrozole versus tamoxifen; ABCSG/ARNO = combined Austrian-German trial

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92; [3] Goss PE et al. *J Natl Cancer Inst* 2005;97(17)1262-71; [4] Thürlimann B et al. Presentation. ASCO 2005; [5] Jakesz R et al. *Lancet* 2005;366(9484):455-62.

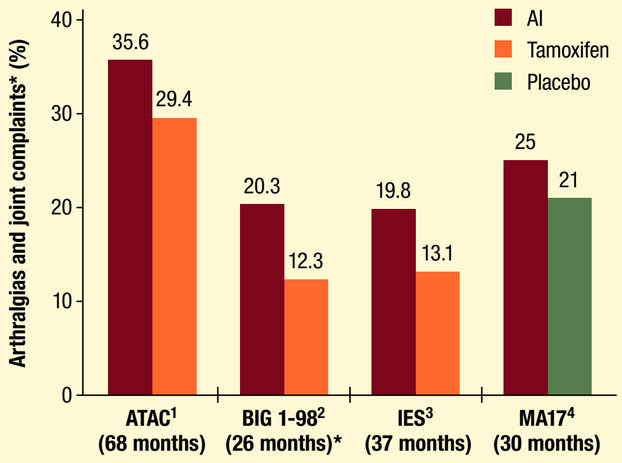
CHANGES IN BONE MINERAL DENSITY OF THE LUMBAR SPINE IN ABCSG-12



T = tamoxifen; G= goserelin; A = anastrozole; Z = zoledronic acid

SOURCE: Gnant M. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 6.

JOINT SYMPTOMS AND ARTHRALGIAS IN ADVJUVANT AI TRIALS



SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Thürlimann B et al. Presentation. ASCO 2005; [3] Plourde P et al. Poster. Lynn Sage Breast Cancer Symposium 2005; [4] Goss PE et al. *J Natl Cancer Inst* 2005;97(17)1262-71.

ATAC TRIAL: ADVERSE EVENTS IN PRIOR CHEMOTHERAPY AND NO CHEMOTHERAPY SUBGROUPS

	N	Relative risk ratio [anastrozole: tamoxifen] (95% CI)		
		Overall population	No prior chemotherapy	Prior chemotherapy
Endometrial cancer	18	0.20 (0.06, 0.69)	0.25 (0.07, 0.90)	0.00*
Fractures	356	1.60 (1.30, 1.97)	1.67 (1.32, 2.12)	1.36 (0.87, 2.11)
Hot flashes	2,328	0.87 (0.81, 0.93)	0.87 (0.81, 0.94)	0.86 (0.76, 0.98)
Ischaemic cerebro-vascular events	104	0.49 (0.32, 0.73)	0.50 (0.33, 0.77)	0.41 (0.13, 1.34)
Musculoskeletal disorders	1,668	1.28 (1.18, 1.40)	1.24 (1.13, 1.37)	1.38 (1.17, 1.62)
Vaginal bleeding	417	0.54 (0.45, 0.66)	0.55 (0.44, 0.68)	0.53 (0.35, 0.79)
Vaginal discharge	472	0.25 (0.20, 0.31)	0.24 (0.18, 0.31)	0.28 (0.18, 0.43)
Venous thrombo-embolic events	184	0.59 (0.44, 0.79)	0.63 (0.46, 0.86)	0.42 (019, 0.92)

N = total number of events

* There were no events for anastrozole in the prior chemotherapy subgroup.

SOURCE: Coleman R. Poster. European Society for Medical Oncology Congress 2004.

POTENTIAL INTERVENTIONS FOR ARTHRALGIAS

Pharmacologic approaches	Nonpharmacologic approaches
Oral treatments • Acetaminophen (≤4 g/day) • NSAID • COX-2 inhibitor • Tramadol • Opioids • Glucosamine • Chondroitin sulfate **Topical treatments** • Capsaicin • Methylsalicylate	• Self-management programs • Social support programs • Weight loss • Aerobic and muscle-strengthening exercises • Physical/occupational therapy • Heat • Patellar taping • Appropriate footwear and lateral wedged insoles • Joint protection

SOURCE: Plourde P et al. Poster. Lynn Sage Breast Cancer Symposium 2005.

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AROMATASE INHIBITORS AND FRACTURES

The five-year overall toxicity data are very favorable for anastrozole compared to tamoxifen because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — are all significantly less with anastrozole. Many oncologists have concern regarding bones, but I believe it's going to be not only a preventable, treatable situation but also something that is likely to go away completely in the near future. There is no difference in hip fractures after 68 months with anastrozole and tamoxifen. This is for a group of patients who had no prescreening when they entered the study and no ongoing protocol-defined follow-up for bone. If you're going to actually do any screening or treating, you're going to have lower numbers than that.

— Rowan T Chlebowski, MD, PhD. **Breast Cancer Update *2005 (7)***

The fracture rate incidence in ATAC is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines begin to come together. As patients stop taking anastrozole, the fracture rate returns to that of the patients randomly assigned to tamoxifen. Furthermore, so far no difference has occurred in fractures of the neck or femur, which are of particular concern. I think the issue of bone is easy to manage. We should be alert to it, monitor bone mineral density, perhaps exclude patients who have established osteoporosis and then be ready to intervene with a bisphosphonate when the patient becomes osteopenic.

— Michael Baum, MD, ChM. **Breast Cancer Update *2005 (1)***

Great strides have been made in terms of the new bisphosphonates. The oral weekly preparations are well tolerated. I am optimistic that bone loss with aromatase inhibitors is completely manageable, and it may lead to a greater public health benefit by paving the way for having osteoporosis dealt with routinely in all postmenopausal women. That could be one of the more beneficial effects of this issue. With the new bisphosphonates and the potential availability of DEXA scans, osteoporosis may be a disease of the past in another decade.

— Jack Cuzick, PhD. **Breast Cancer Update *2005 (6)***

AROMATASE INHIBITORS AND MUSCULOSKELETAL DISORDERS

Arthralgia is a condition with effective available treatment options. Whereas the incidence of arthralgia reported in clinical trials is higher with anastrozole, the absolute difference compared with tamoxifen treatment is relatively small; this finding is similar for the other aromatase inhibitors, letrozole and exemestane… The variability in which this type of adverse event data is collected confounds the ability to make cross-trial comparisons and identify any potential differences in the occurrence of arthralgia among aromatase inhibitors… Better guidance is needed in the differential diagnosis of arthralgia, including consideration of other possible causes.

— Paul Plourde, MD et al. Poster. Lynn Sage Breast Cancer Symposium 2005.

Matt Ellis' group presented an interesting abstract at San Antonio indicating that women on aromatase inhibitors with these joint symptoms may have lowered vitamin D levels and that giving them vitamin D improved some of the joint symptoms. The data are very early, and they are conducting more studies, but if we could solve this joint problem with vitamin D, it would be extraordinary. We know from the ATAC trial that more serious adverse events are associated with tamoxifen than with anastrozole and that despite the joint symptoms, patients tend to stay on anastrozole more than they stay on tamoxifen, which is an important efficacy issue.

— Anthony Howell, MD. **Breast Cancer Update *2005 (4)***

Adjuvant Endocrine Therapy in Premenopausal Patients

Adjuvant tamoxifen has an established role in premenopausal women with ER-positive breast cancer. With a median follow-up of 9.6 years, INT 0101 demonstrated that the addition of tamoxifen to CAF plus goserelin improved the time to recurrence and disease-free survival. However, no benefits were associated with CAF plus goserelin compared to CAF alone, although the analysis was confounded by the fact that most of the premenopausal women in the study achieved ovarian ablation from chemotherapy, and a subset analysis demonstrated a benefit in patients who continued to menstruate after chemotherapy. Ongoing clinical trials — SOFT, TEXT and PERCHE — are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. An Austrian study — ABCSG-AU12 — reported by Dr Michael Gnant at the 2004 San Antonio Breast Cancer Symposium demonstrated that zoledronate counteracted the bone loss associated with both goserelin/tamoxifen and goserelin/anastrozole. Results from ongoing trials will hopefully establish the optimal adjuvant hormonal therapy for premenopausal women.

TRIALS OF ADJUVANT ENDOCRINE THERAPY WITH OVARIAN SUPPRESSION

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Tamoxifen x 5y OFS + tamoxifen x 5y OFS + exemestane x 5y
IBCSG-25-02 (TEXT trial)	1,845 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + tamoxifen x 5y Triptorelin ± chemotherapy + exemestane x 5y
IBCSG-26-02 (PERCHE trial)	1,750 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	OFS + tamoxifen or exemestane x 5y OFS + any chemotherapy + tamoxifen or exemestane x 5y

OFS = ovarian function suppression with triptorelin or surgical oophorectomy or ovarian irradiation

SOURCES: www.ibcsg.org; NCI Physician Data Query, September 2005.

PHASE III STUDY COMPARING AN LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONATE

Protocol ID: ABCSG-AU12
Target Accrual: 1,800 (Open)

Eligibility	Premenopausal women with hormone-responsive breast cancer, Stages I/II
ARM 1	Tamoxifen + goserelin
ARM 2	Anastrozole + goserelin
ARM 3	Tamoxifen + goserelin + zoledronate
ARM 4	Anastrozole + goserelin + zoledronate

SOURCE: Gnant M et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 6.

RANDOMIZED TRIAL OF CHEMOHORMONAL THERAPY IN PREMENOPAUSAL, NODE-POSITIVE, RECEPTOR-POSITIVE BREAST CANCER (INT 0101)

Protocol ID: INT 0101, E5188
Accrual: 1,503 (Closed)

Eligibility	Premenopausal patients with node-positive, hormone receptor-positive breast cancer
ARM 1	CAF x 6
ARM 2	CAF x 6 → Z x 5y
ARM 3	CAF x 6 → ZT x 5y

CAF = cyclophosphamide, doxorubicin and fluorouracil; Z = goserelin
T = tamoxifen

SOURCE: Davidson N et al. *J Clin Oncol* 2005;23(25):5973-82.

INT 0101 TRIAL RESULTS: 9.6 YEARS' FOLLOW-UP

	CAF (n = 494)	CAF-Z (n = 502)	CAF-ZT (n = 507)	Hazard ratio (HR)* (CAF-Z/CAF)	Hazard ratio (HR)* (CAF-ZT/CAF-Z)
Nine-year disease-free survival	57%	60%	68%	0.90 ($p = 0.15$)	0.74 ($p < 0.01$)
Nine-year overall survival	70%	73%	76%	0.86 ($p = 0.10$)	0.91 ($p = 0.23$)
Nine-year time to recurrence	58%	61%	68%	0.91 ($p = 0.17$)	0.73 ($p < 0.01$)

CAF = cyclophosphamide, doxorubicin and fluorouracil; Z = goserelin; T = tamoxifen
* HR adjusted for age, nodal and ER/PR status; p is one sided (compared with $\propto = 0.025$).

SOURCE: Davidson N et al. *J Clin Oncol* 2005;23(25):5973-82.

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INT 0101 (E5188) TRIAL

A major strength is that trial eligibility was defined by a physiological definition for the premenopausal state, rather than age, as truly premenopausal women are most likely to benefit from such an approach. Further, participation was restricted to patients with an ER- and/or PR-positive tumor — the subset of women most likely to benefit from endocrine therapy. …

E5188 provides the most extensive information to date about the utility of chemoendocrine therapy in premenopausal women with node-positive, receptor-positive breast cancer. The findings from this study clearly support the use of tamoxifen after chemotherapy for premenopausal, node-positive, receptor-positive breast cancer. …

— Nancy E Davidson, MD et al.* J Clin Oncol *2005;23(25):5973-82.

AROMATASE INHIBITOR USE IN PREMENOPAUSAL WOMEN

The data today are quite convincing that the aromatase inhibitors should play a role as adjuvant hormonal therapy for postmenopausal women with ER-positive breast cancer. Precisely how to sequence or to incorporate those data into the premenopausal subset is much less clear. We do know that the aromatase inhibitors do not suppress circulating estrogen levels adequately in women with functioning ovaries, whether or not they have menstrual function. Therefore, if you're going to use an AI for a young woman, you have to be certain that she is postmenopausal, or I think she should be enrolled in one of the prospective trials evaluating the use of ovarian suppression and an aromatase inhibitor in premenopausal women.

We do know that a number of women stop having menstrual function or periods subsequent to cytotoxic chemotherapy, yet their ovaries continue to cycle. A substantial proportion of women also stop having ovarian function with cytotoxic chemotherapy, at least over the short term, but on further follow-up, their ovarian function returns.

— Robert W Carlson, MD.* Meet The Professors *2005 (3)

Cessation of menses does not necessarily mean absence of ovarian function, as premenopausal estradiol levels may be found in women experiencing chemotherapy-related amenorrhea. There is widespread agreement that aromatase inhibitors should not be employed as monotherapy in premenopausal women. This view stems from the lack of evidence for adequate estrogen suppression and potential for stimulation of the ovaries via increased gonadotropin release.

— 2004 ASCO Technology Report on Use of Aromatase Inhibitors as Adjuvant Therapy

We were particularly interested in younger patients because they are physiologically used to higher levels of estrogen from their functioning ovaries. We undertook ABCSG-12 to first establish the severity of that treatment-induced bone loss and, second, whether it can be prevented or treated. We found out that a significant loss occurs — on average close to 15 percent — in these premenopausal women treated with endocrine therapy. We also discovered that it could be prevented with zoledronic acid given twice a year.

— Michael Gnant, MD.* Breast Cancer Update *2005 (4)

Three important randomized trials are enrolling premenopausal women with hormone-receptive disease — SOFT, TEXT and PERCHE. The ABCSG-AU12 trial randomly assigned approximately 2,000 patients to goserelin plus tamoxifen versus goserelin plus anastrozole, with a second randomization to zoledronic acid or not. That study will report in one or two years and should tell us whether tamoxifen or an aromatase inhibitor is superior when combined with goserelin in premenopausal women. We expect that goserelin with anastrozole will be better, which is why so many patients are already being treated off protocol.

— Anthony Howell, MD.* Breast Cancer Update *2005 (4)

Research To Practice: Adjuvant Endocrine Therapy

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Extensive resources are allocated for the evaluation of breast cancer treatments. In contrast, minimal investments are made to determine how these therapeutic strategies are implemented in clinical practice. Continuing medical education not only informs clinicians about ongoing clinical trials and emerging research results, but it can also evaluate the implementation of research results by physicians in clinical practice. Data from the *Breast Cancer Update* Patterns of Care Study, a telephone survey conducted in September 2005 of randomly selected medical oncologists in the United States, are presented here. One of the key facets of this initiative was the use of adjuvant hormonal therapy. In postmenopausal women, the adjuvant trials evaluating the aromatase inhibitors as initial therapy and following two to three or five years of adjuvant tamoxifen have had a dramatic impact on the clinical use of adjuvant endocrine therapy. In premenopausal women, controversy continues with regard to the use of ovarian ablation/suppression.

CHOICE OF AROMATASE INHIBITORS AS ADJUVANT THERAPY

When you use an aromatase inhibitor in each of the following settings, what percentage of this use is with each of the following agents?

	Anastrozole	Letrozole	Exemestane
Initial adjuvant therapy	86%	11%	3%
After 2 to 3 years of adjuvant tamoxifen	37%	18%	45%
After 5 years of adjuvant tamoxifen	19%	73%	8%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CHOICE OF ADJUVANT ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN

Which endocrine therapy would you be most likely to recommend to a 55-year-old postmenopausal woman with each of the following tumors?

	1.2-cm, ER+/PR+, HER2-, N-	1.2-cm, ER+/PR+, HER2-, 3N+	1.2-cm, ER+/PR-, HER2-, 3N+
Anastrozole	72%	80%	83%
Letrozole	—	—	—
Exemestane	2%	—	2%
Tam x 5y	4%	4%	4%
Tam x 2-3y → AI	16%	8%	9%
Tam x 5y → AI	6%	8%	2%

Tam = tamoxifen; AI = aromatase inhibitor; N = node

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SEQUENCING ADJUVANT THERAPY AFTER FIVE YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER/PR-positive, HER2-negative, Grade II tumor and three positive lymph nodes who has completed five years of tamoxifen therapy. How would you manage this patient's endocrine therapy?

	Has just completed 5 years of tamoxifen	Completed 5 years of tamoxifen 1 year ago	Completed 5 years of tamoxifen 3 years ago
Continue tamoxifen	2%	—	—
Start anastrozole	16%	12%	6%
Start letrozole	78%	62%	18%
Start exemestane	2%	2%	2%
Use no further hormonal therapy	2%	24%	74%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SWITCHING ADJUVANT THERAPY AFTER TWO TO THREE YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER/PR-positive, HER2-negative, Grade II tumor and three positive lymph nodes on tamoxifen for two years. How would you manage this patient's endocrine therapy?

	Tolerability of tamoxifen		
	No side effects with tamoxifen	Complains of 20-pound weight gain	Complains of moderate hot flashes
Continue tamoxifen	24%	4%	8%
Stop tamoxifen	—	2%	—
Stop tamoxifen and switch to exemestane	38%	40%	36%
Stop tamoxifen and switch to anastrozole	26%	40%	44%
Stop tamoxifen and switch to letrozole	12%	14%	12%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Which endocrine therapy would you be most likely to recommend to a 35-year-old premenopausal woman with each of the following tumors?

	1.2-cm, ER+/PR+, HER2-, 3N+	1.2-cm, ER+/PR-, HER2-, 3N+	1.2-cm, ER+/PR+, HER2+, 3N+
Tam x 5y	52%	50%	46%
Tam x 5y → AI	10%	10%	12%
Tam x 2-3y → AI	4%	4%	4%
Tam + LHRH or OA	20%	20%	26%
AI + LHRH or OA	6%	6%	6%
Other	6%	4%	4%
None	2%	6%	2%

Tam = tamoxifen; AI = aromatase inhibitor; LHRH = LHRH agonist
OA = ovarian ablation; N = node

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

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THE ROLE OF ADJUVANT AROMATASE INHIBITORS IN POSTMENOPAUSAL WOMEN

Based on data from various adjuvant endocrine therapy trials, I believe it is unreasonable to withhold aromatase inhibitors from postmenopausal women with hormone receptor-positive disease. ATAC is still the definitive adjuvant trial in terms of comparing tamoxifen to an aromatase inhibitor, and the data are very compelling. An aromatase inhibitor is now my drug of choice, and that changed in just the past years.

As for switching patients from tamoxifen to an aromatase inhibitor, I discuss this with every postmenopausal patient on tamoxifen. My tendency, which is based on my intuition rather than data, is to advise patients on tamoxifen to complete two or three years and then switch. We don't know the optimal time to switch, and we don't know the optimal duration of various endocrine therapies. While we know that five years of tamoxifen is as good as or better than 10 years, the optimal duration of aromatase inhibitors is unknown at this time.

— I Craig Henderson, MD.* Breast Cancer Update *2005 (2)

If you start with tamoxifen, after two and a half, three or five years, more patients will have relapsed than on an aromatase inhibitor. A substantial number of those patients will be irretrievable — they have incurable disease — and so you're banking on the fact that you'll be able to capture more patients later, but we don't have any data for that. That's just speculation. While I believe sequencing therapy may be better, ultimately, I still don't see any reason not to start with the most effective therapy. An aromatase inhibitor followed by tamoxifen or a nonsteroidal aromatase inhibitor makes more sense to me. We have to wait to see the data from the BIG FEMTA trial, which includes an arm with letrozole as initial treatment followed by tamoxifen.

— Rowan T Chlebowski, MD, PhD.* Breast Cancer Update *2005 (7)

I believe a clear, consistent story is emerging without a lot of conflicts and conundrums: Adjuvant aromatase inhibitors are better than tamoxifen. Whether the aromatase inhibitors are used at the time of initial diagnosis, after two to three years or five years of tamoxifen, there is a favorable impact on local, distant and even contralateral breast cancer recurrences.

The unresolved questions are: Should you use a little tamoxifen, maybe two years and then cross over? Should you only use an aromatase inhibitor right off the bat and maybe even think of continuing beyond five years? The trial that will provide the most information in this regard is the BIG FEMTA/BIG 1-98 trial.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)

I sit on the NCCN guidelines committee. If you evaluate the next rendition of the guidelines, you'll find we have not dismissed the use of tamoxifen but rather moved the use of aromatase inhibitors up front. Within the NCCN guidelines, we're trying to select the aromatase inhibitor to be used based on the design of the study. For first-line therapy, we would use anastrozole. If a patient has been on tamoxifen for a period of time, exemestane is now a legitimate choice, and after five years of tamoxifen, letrozole is an option. We view all of these agents as active and well tolerated.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)

ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

I have combined an LHRH agonist with an aromatase inhibitor in premenopausal women, but it's rare because for women who are at high enough risk for that therapy — multiple positive nodes or even node-positive, HER2-positive breast cancer — I generally recommend oophorectomy, and then I'm comfortable with an aromatase inhibitor.

— Joyce O'Shaughnessy, MD.* Patterns of Care *2004 (2)

Optimizing Adjuvant Chemotherapy: Recent Trial Results

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Phase III randomized trials have demonstrated that taxane-containing adjuvant regimens enhance relapse-free and overall survival. BCIRG 001 compared TAC (docetaxel, doxorubicin and cyclophosphamide) to FAC, and CALGB-9741 evaluated a dose-dense regimen of AC and paclitaxel administered with growth factor support. GEICAM 9805 demonstrated that the incidence of febrile neutropenia associated with TAC could be reduced with the use of filgrastim. In a Phase III randomized trial, pegfilgrastim was also found to reduce the incidence of febrile neutropenia associated with docetaxel. Additional trials have evaluated growth factor support with pegfilgrastim in patients receiving dose-dense chemotherapy.

PHASE III TRIAL OF ADJUVANT TAC VERSUS FAC

Protocol ID: BCIRG 001
Accrual: 1,491 (Closed)

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)

Disease-free survival N = 1,491	Hazard ratio* TAC/FAC (95% CI)
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.

DISEASE-FREE SURVIVAL IN THREE TRIALS EVALUATING DOSE-DENSE CHEMOTHERAPY: CALGB-N9741 AND THE SEATTLE TRIALS

	CALGB dose-dense trial	Seattle pilot trials	
	N9741[1] (N = 2,005)	(F)AC + G[2] (N = 52)	AC + G/T[3] (N = 54)
Median positive nodes	3	4	5
ER- and/or PR-positive	65%	65%	80%
HER2-positive	—	42%	22%
3y disease-free survival	81-85%	86%	90%

G = filgrastim; T = paclitaxel

SOURCES: [1] Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9; [2] Ellis GK et al. *J Clin Oncol* 2002;20(17):3637-43; [3] Ellis GK et al. *Proc ASCO* 2005;Abstract 628.

EFFECTS OF IMPROVEMENTS IN ADJUVANT CHEMOTHERAPY IN NODE-POSITIVE BREAST CANCER: 20-YEAR EXPERIENCE OF CALGB AND UNITED STATES BREAST INTERGROUP

		Average hazard reduction (confidence interval)			
Trial comparison		CALGB-8541 dose of CAF low → high	CALGB-9344 paclitaxel without → with	CALGB-9741 Rx interval 21d → 14d	Overall low → 14d
DFS	ER-neg	36% (15-52%)	25% (11-36%)	23% (0-42%)	63% (43-76%)
	ER-pos	14% (-18-37%)	12% (-4-25%)	10% (-19-33%)	32% (-7-56%)
OS	ER-neg	29% (3-48%)	25% (11-37%)	22% (-5-43%)	59% (34-74%)
	ER-pos	8% (-27-36%)	10% (-10-26%)	1% (-44-32%)	18% (-41-52%)

Adjusted for positive nodes, tumor size, menopausal status
DFS = disease-free survival; OS = overall survival

SOURCE: Berry DA et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 29.

PHASE III TRIAL OF ADJUVANT TAC VERSUS FAC

Protocol ID: GEICAM 9805
Accrual: 448 (Closed)

Eligibility	Operable, high-risk breast cancer; node-negative; 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

After enrollment of 224 patients, a protocol amendment mandated the use of prophylactic G-CSF for all subsequent patients receiving TAC. An interim safety analysis assessed the impact of G-CSF on the incidence of febrile neutropenia (fever ≥ Grade II with Grade IV neutropenia) and other Grade III/IV toxicities.

INTERIM SAFETY ANALYSIS

	TAC		FAC	
	Without mandatory G-CSF*	With G-CSF*	Before protocol amendment*	After protocol amendment*
Febrile neutropenia	23.8%	3.5%	0.9%	1.7%
Other Grade III/IV toxicities	50.4%	20%	27%	26.5%

* Protocol amendment mandated the use of prophylactic G-CSF for patients receiving TAC.

SOURCE: Martin M et al. *Proc ASCO* 2004;Abstract 620.

PHASE III STUDY OF PEGFILGRASTIM VERSUS PLACEBO IN PATIENTS RECEIVING DOCETAXEL

Accrual: 928 (Closed)

Eligibility	Breast cancer, ECOG performance of 0-2 ≥18 years of age
ARM 1	Docetaxel 100 mg/m^2 + pegfilgrastim*
ARM 2	Docetaxel 100 mg/m^2 + placebo*

* Patients on either arm experiencing febrile neutropenia entered an open-label phase in which they received docetaxel with pegfilgrastim.

EFFICACY DATA

Parameter	Placebo† (n = 465)	Pegfilgrastim† (n = 463)	*p*-value
Febrile neutropenia (FN)	17%	1%	<0.001
FN-related hospitalizations	14%	1%	<0.001
FN-related IV anti-infective use	10%	2%	<0.001
Chemotherapy planned dose on time (cycles 2-4)‡	78%	80%	Not reported

† 62 percent of patients had metastatic disease.
‡ Placebo arm included patients receiving open-label pegfilgrastim.

Conclusions:

- Pegfilgrastim was well tolerated.
- Early intervention with pegfilgrastim prevents FN by 94 percent and further prevents hospitalizations and use of IV anti-infectives by 80 percent.
- 67 percent of FN occurred during the first cycle in the placebo group.

SOURCE: Vogel CL et al. *J Clin Oncol* 2005;23(6):1178-84.

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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.

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

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

Martin M et al. **Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study.** *Proc ASCO* 2004;Abstract 620.

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BCIRG 001: ADJUVANT TAC VERSUS FAC

In our first study, BCIRG 001, 1,500 women from 21 countries were randomly assigned to six cycles of adjuvant TAC or FAC. The women enrolled in the trial had node-positive disease. We now have mature results with five years of follow-up. The trial demonstrated that adjuvant TAC significantly improved disease-free survival by 28 percent in relative terms ($p = 0.001$). Overall survival was also strikingly improved; the trial demonstrated a 30 percent relative reduction in mortality with adjuvant TAC, which was an absolute six percent improvement in overall survival. This would be a perfect story if an increase in side effects did not occur. In fact, TAC was associated with a high rate of febrile neutropenia. Approximately 25 percent of the women receiving TAC experienced an episode of febrile neutropenia, which was not unexpected because primary prophylaxis with G-CSF was not allowed. We now know that if we were to do the study again and administer TAC with G-CSF, we would see a febrile neutropenia rate, on a per-patient basis, of about three to six percent.

— *John Mackey, MD.* Breast Cancer Update *2005 (1)*

DEVELOPMENTS IN ADJUVANT CHEMOTHERAPY

The development of the dose-dense approach has marked a recent step in the progressive improvement of prospects for women with node-positive primary breast cancer, especially HR-negative cases. Other stages on the way have been the benefits achieved by increasing the doses of cyclophosphamide, doxorubicin, and 5-fluorouracil used in CAF and the advent of the taxanes. Further improvements may stem from current research aimed at: (A) reducing the interval between cycles from 14 days to 10 or 11 days; (B) extending the period for which anthracyclines and taxanes can be given; (C) adding noncytotoxic agents such as the humanized anti-HER2 antibody trastuzumab to chemotherapy in HER2-positive cases; and (D) adding antiangiogenesis agents, eg bevacizumab.

— *Larry Norton, MD.* Oncologist *2005;10(6):370-81.*

TRIAL OF PEGFILGRASTIM VERSUS PLACEBO

The objective of this study was to determine if pegfilgrastim significantly reduces febrile neutropenia in patients receiving a chemotherapy regimen associated with an expected rate of approximately 20 percent. Patients were eligible for the trial whether they were receiving docetaxel in the adjuvant or the metastatic setting. In this double-blind, randomized trial, patients received docetaxel with pegfilgrastim versus a placebo. If patients developed febrile neutropenia, they were able to subsequently receive pegfilgrastim. Febrile neutropenia, related hospitalizations and intravenous anti-infective use were all significantly reduced by pegfilgrastim. While the difference in the rates of patients receiving their planned chemotherapy dose on time doesn't look impressive, all the placebo patients who developed febrile neutropenia received pegfilgrastim. Consequently, both groups experienced delivery of the planned dose on time.

— *Charles L Vogel, MD.* Breast Cancer Update *Think Tank, August 2004*

This study provides compelling evidence that administering pegfilgrastim in the first and subsequent cycles of moderately myelosuppressive chemotherapy can significantly reduce the risk of potentially life-threatening infections that can result in hospitalizations and require intravenous antibiotics. Approximately 600,000 chemotherapy patients are at risk of developing neutropenia, which has traditionally been treated reactively. Doctors usually reserve proactive use of pegfilgrastim for only those patients considered at very high risk of developing chemotherapy-induced neutropenia. This study may give physicians the evidence they need to help protect cancer patients from chemotherapy-induced neutropenic complications beginning in the first cycle of chemotherapy treatment.

— *Lee Schwartzberg, MD. Interview, Multinational Association of Supportive Care in Cancer 2004 Annual Meeting*

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.

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Tack DK et al. **Anthracycline vs nonanthracycline adjuvant therapy for breast cancer.** *Oncology (Williston Park)* 2004;18(11):1367-76.

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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.***

Chemotherapy in Elderly Women

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Limited data exist about the risks and benefits of adjuvant chemotherapy in elderly women. An important adjuvant trial led by Dr Hyman Muss, CALGB-49907, randomly assigns elderly women to either capecitabine versus AC or CMF. A small clinical trial in the metastatic setting has suggested that in older women with advanced breast cancer, capecitabine 1,000 mg/m^2 twice a day for 14 of 21 days may be better tolerated and result in equal or greater efficacy than the package-insert dose. Retrospective studies of women treated with adjuvant chemotherapy have found that (1) it is not offered as often to elderly women with high-risk breast cancer and (2) age does not significantly predict for any toxicity risk other than dose reductions.

ACTIVE CHEMOTHERAPY TRIALS IN ELDERLY WOMEN WITH BREAST CANCER

Protocol ID	Phase	Eligibility	Target accrual	Schema
CALGB-49907	III	Age: ≥65, Stage I-IIIC, operable breast cancer	600-1,800	CMF or AC vs capecitabine 1,000 mg/m^2 BID d1-14 q3wk*
DO03-21-022	II/III	Age: ≥60, metastatic breast cancer	NR	Pegylated liposomal doxorubicin versus capecitabine
SWS-SAKK-25/99	I/II	Age: ≥65, metastatic breast cancer	98-110	Phase I: Escalating doses of capecitabine and vinorelbine Phase II: Capecitabine and vinorelbine at dose preceding MTD
FRE-FNCLCC-GERICO-04/0406	II	Age: ≥70, metastatic breast cancer	53	Docetaxel
IBCSG 32-05/ BIG 1-05	III	Age: ≥66, endocrine-nonresponsive early breast cancer, ineligible for standard chemotherapy	1,296	R1†: Pegylated liposomal doxorubicin versus no adjuvant therapy R2†: Pegylated liposomal doxorubicin versus metronomic cyclophosphamide and methotrexate

* Patients with insufficient LVEF must receive CMF, not AC. Protocol under amendment to allow the addition of trastuzumab in patients with tumors positive for HER2 by IHC 3+ or FISH; † randomization option at physician's/patient's preference; NR = not reported; MTD = maximum tolerated dose

SOURCES: NCI Physician Data Query, October 2005; www.ibcsg.org; personal communication with CALGB, October 2005.

ADJUVANT CHEMOTHERAPY OFFERED TO BREAST CANCER PATIENTS[1]

Patients	≥70 years (n = 97)	<70 years (n = 168)	*p*-value
High-risk group*	51.6%	92.9%	<0.0001
HR-negative (HR-)	77.3%	100%	0.0002
Node-positive (N+)	60.2%	95.7%	<0.0001
Grade III tumor	57.8%	91.2%	<0.0001
pT2-pT3	50%	88.3%	<0.0001
N+, HR+	52.6%	93.4%	<0.0001
N+, HR-	94.1%	100%	0.2290

* Presenting with one or more risk factors (pT2-3, Grade III, node-positive, HR-negative); HR+ = hormone receptor-positive

RATES OF CLINICAL TRIAL PARTICIPATION IN WOMEN WITH BREAST CANCER (N = 154)[2]

Mean age (years)	Offered protocol	Consented when offered
48	51%	56%
74	35%	50%

SOURCES: [1] Brunello A et al. *Ann Oncol* 2005;16:1276-82; [2] Kemeny MM et al. *J Clin Oncol* 2003;21(12):2268-75.

CAPECITABINE DOSING IN OLDER WOMEN WITH ADVANCED BREAST CANCER

Efficacy	Capecitabine 1,250 mg/m^2 BID (n = 30)	Capecitabine 1,000 mg/m^2 BID (n = 43)
Median survival	10 months	16 months
Overall response	36.7%	34.9%
Median duration of response	4.3 months	4.3 months
Stable disease	33%	46%
Median time to progression	3.9 months	4.1 months
Grade III/IV toxicities	**Capecitabine 1,250 mg/m^2 BID (n = 30)**	**Capecitabine 1,000 mg/m^2 BID (n = 43)**
Fatigue	7%	12%
Diarrhea	13%	2%
Dyspnea	10%	5%
Nausea	7%	5%
Dose reductions required	30%	5%
Lethal toxicities	7%	2%

SOURCE: Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61.

ROLE OF AGE, CHEMOTHERAPY REGIMEN AND COMORBIDITY IN RISK OF TOXICITY FROM ADJUVANT CHEMOTHERAPY IN WOMEN OVER AGE 65 WITH BREAST CANCER

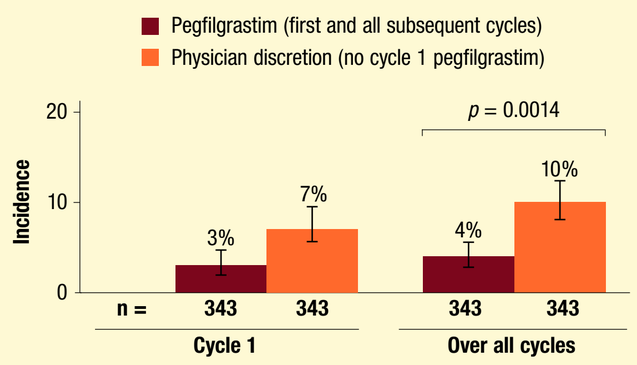
Variable	Age[1]	Chemotherapy regimen[2]	Comorbidity[3]
Toxicity outcome	***p*-value**	***p*-value**	***p*-value**
Hospitalization	0.51	**<0.01**	0.62
Fever and neutropenia	0.07	**<0.01**	0.27
Dose reduction	**0.02**	0.13	0.34
Any Grade III/IV toxicity	0.89	**0.02**	0.99
Grade III/IV nonhematologic toxicity	0.37	**0.02**	0.66
Treatment delay for low ANC	0.31	**<0.01**	0.36

"The type of chemotherapy regimen (anthracycline compared to CMF) was a better predictor for toxicity than increased age or comorbidity score."

[1] Age continuous variable; [2] anthracycline vs CMF; [3] comorbidity score: 0 vs ≥1 (patients with score ≥1 = 17%); ANC = absolute neutrophil count

SOURCE: Hurria A et al. *Breast Cancer Res Treat* 2005;92:151-6.

INCIDENCE OF FEBRILE NEUTROPENIA*



The proportion of patients experiencing febrile neutropenia was statistically significantly lower for patients receiving pegfilgrastim in all cycles compared to patients in the physician discretion arm.

Error bars represent 95% confidence intervals.

* Febrile neutropenia is defined as ANC <1 x 10^9/L and temperature ≥38° C.

SOURCE: Balducci L et al. Presentation. ASCO 2005.

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INCLUSION OF OLDER PATIENTS IN TRIALS OF ADJUVANT CHEMOTHERAPY

Our study adds to the increasing number of trials that suggest that older patients in fair to good health tolerate standard chemotherapy regimens, and even more intensive regimens, almost as well as younger patients. Moreover, and more importantly, this study suggests that the added value gained from more intensive chemotherapy regimens commonly used in the adjuvant setting might be shared by older patients and not limited to younger age groups.

— Hyman B Muss, MD et al. JAMA *2005;293(9):1073-81.*

ENROLLMENT OF ELDERLY IN CLINICAL TRIALS

…The number of patients at low risk who can be spared adjuvant chemotherapy appears to be markedly increased when the prognostic genetic signature is used. These findings are of great interest, especially in elderly patients, who more frequently have comorbidities and/or impaired organ functions than younger people, and the real benefit from tolerance of adjuvant chemotherapy is still a major issue. Clinical trials specifically designed for elderly patient subpopulations with breast cancer are critically needed and must incorporate gene expression profiling as a potential way of identifying those patients who can be spared adjuvant systemic treatment despite having traditionally defined high-risk disease (ie, node-positive, high grade). The prognostic genetic signature could have this potential, but it has been investigated only in younger women and therefore needs to be prospectively validated in elderly patients as well.

— Laura Biganzoli, MD et al. Clin Breast Cancer *2004;5(3):188-95.*

CALGB-49907

Hyman Muss has made some changes to try to make the eligibility more streamlined and easier for physicians and patients to participate in the study.

We strongly believe that this trial will address a very good question: How does an oral agent compare to traditional intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

— Jeffrey Abrams, MD. Breast Cancer Update *2004 (5)*

CAPECITABINE DOSE IN ELDERLY WOMEN WITH ADVANCED BREAST CANCER

This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens. In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m^2 twice daily merits consideration as 'standard' for women aged 70 years and older who are candidates to cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function.

— Emilio Bajetta, MD et al. J Clin Oncol *2005;23(10):2155-61.*

PEGFILGRASTIM FOR FEBRILE NEUTROPENIA IN THE ELDERLY

This large, prospective, community-based trial in older patients was both feasible to conduct and demonstrated that myleosuppressive chemotherapy can be given to older patients with cancer.

Pegfilgrastim from the first cycle of chemotherapy resulted in reduced incidence of febrile neutropenia, hospitalizations, IV anti-infective use and chemotherapy dose reductions and delays compared with current community practice, which may include pegfilgrastim in later cycles.

Pegfilgrastim use from the first cycle was associated with fewer serious adverse events compared with pegfilgrastim given at physician discretion in later cycles.

— Lodovico Balducci, MD. Presentation. ASCO 2005.

Research To Practice: Adjuvant Chemotherapy

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Clinical decisions regarding adjuvant chemotherapy are complex and multifactorial. Tumor-related factors such as nodal status, tumor size and predictors like the Onco*type* DX™ assay must be balanced against issues such as patient age and comorbidities. Computer models, such as Peter Ravdin's Adjuvant! Online program, are frequently utilized by oncologists to assist in estimating the absolute impact of adjuvant therapy, and these must be balanced against the risk of side effects and toxicities with treatment. An important facet of Adjuvant! is that it factors in nonbreast cancer sources of competing mortality based on the patient's age and general health status. Data from the 2005 *Breast Cancer Update* Patterns of Care Study, a telephone survey of randomly selected US-based medical oncologists, are presented here. In patients with node-positive tumors, dose-dense AC → paclitaxel is a common choice, but many other regimens are also utilized. AC is the most common regimen utilized in patients with node-negative tumors. Adjuvant chemotherapy is less frequently utilized in older patients, particularly octogenarians.

USE OF COMPUTER MODELS IN CLINICAL PRACTICE

In which of the following situations do you tend to use computer models* to estimate breast cancer patients' risk of relapse and/or mortality? (percent of physicians who use a computer model)	
To review risk estimates with patients	100%
To decide whether to use chemotherapy in node-negative cases	81%
To decide whether to use endocrine therapy in node-negative cases	25%
To select type of chemotherapy to use	34%
To select type of endocrine therapy to use	9%
Other situations	0%

* 44% percent of oncologists surveyed use the Adjuvant! model, 2% use the Mayo clinic model, 18% use both models, and 36% of physicians do not use either model.

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CLINICAL USE OF ONCO*TYPE* DX ASSAY

Have you ordered the Onco*type* DX assay?	
Yes	34%
No	66%
If you have ordered this assay, in how many patients?	Median = 2
How helpful was this test in your treatment decisions? (N = 17)	
Very helpful	18%
Somewhat helpful	64%
Not helpful	18%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

ADJUVANT CHEMOTHERAPY FOR NODE-NEGATIVE DISEASE

The patient is a woman in average health with a 1.2-cm, ER/PR-positive, HER2-negative (as confirmed by FISH), Grade II tumor and negative lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35	Age 55	Age 75	Age 85
AC x 4 q3wk	44%	34%	10%	4%
AC x 4 q2wk	12%	10%	6%	—
FAC or FEC x 6	6%	6%	2%	—
AC x 4 → paclitaxel x 4 q3wk	4%	2%	—	—
AC x 4 → paclitaxel x 4 q2wk	10%	8%	2%	—
AC x 4 → docetaxel x 4 q2wk	10%	4%	2%	—
CMF	8%	8%	10%	10%
TAC (docetaxel) x 6	2%	—	—	—
Other	2%	4%	—	—
No chemotherapy	2%	24%	68%	86%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE DISEASE

The patient is a woman in average health with a 1.2-cm, ER/PR-positive, HER2-negative (as confirmed by FISH), Grade II tumor and three positive lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35	Age 55	Age 75	Age 85
AC x 4 q3wk	4%	4%	14%	—
AC x 4 q2wk	—	—	2%	2%
FAC or FEC x 6	—	—	6%	2%
AC x 4 → paclitaxel x 4 q3wk	6%	6%	6%	—
AC x 4 → paclitaxel x 4 q2wk	44%	44%	14%	2%
AC x 4 q3wk → paclitaxel qwk x 12	4%	8%	8%	2%
AC x 4 → docetaxel x 4 q3wk	2%	4%	8%	—
AC x 4 → docetaxel x 4 q2wk	18%	18%	6%	2%
CMF	—	—	18%	8%
TAC (docetaxel) x 6	22%	16%	2%	2%
Other	—	—	2%	2%
No chemotherapy	—	—	14%	78%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

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*ONCO*TYPE *DX AND COMPUTERIZED RISK MODELS*

Peter Ravdin notes that in the Adjuvant! program, the relative benefit of chemotherapy is presumed to be equal for patients at higher and lower risk, but it's likely that the estimation of chemotherapy benefit in the group with low-risk disease is an overestimation. Conversely, the benefit in the group with higher-risk disease may be underestimated. I believe our studies with Onco*type* DX demonstrate this, and Ravdin's model may need to be modified slightly. My prediction is that when people see these data from NSABP-B-20, they will want the assay performed because nobody wants to receive chemotherapy when it will not work.

— Soonmyung Paik, MD.* Breast Cancer Update *2005 (3)

CHEMOTHERAPY AND RECEPTOR STATUS

The estrogen and progesterone receptor status may be important in determining the potential benefit from adjuvant chemotherapy. SWOG-8814 demonstrated that patients with highly ER- and PR-positive tumors received no benefit from FAC chemotherapy. Similarly, data from the Ludwig group showed that highly endocrine-responsive patients received little or possibly no benefit from chemotherapy. Finally, Don Berry's analysis of a series of CALGB/Intergroup studies suggested little or no additional benefit for taxanes added to AC or for dose-dense chemotherapy in the ER-positive group of patients.

— C Kent Osborne, MD.* Breast Cancer Update *2005, Special CME Meeting Edition

SELECTION OF ADJUVANT CHEMOTHERAPY

For patients with ER-positive disease and multiple positive nodes, I usually use AC with or without a taxane, often dose dense. As we learn more about the biology of these diseases and separate out the cancers by more than just ER-positive and ER-negative, I hope that we can give fewer people chemotherapy.

— Ann H Partridge, MD, MPH.* Patterns of Care *2005 (1)

For adjuvant chemotherapy in the lower-risk, node-negative setting, I generally use four cycles of AC. The controversial issue is whether to use the traditional every three-week schedule or dose-dense therapy with growth factor support. Dose-dense schedules are somewhat better tolerated because of the growth factors, and the patient finishes therapy faster. They come with a great deal of additional cost. Most importantly, however, we probably could benefit from additional validation that AC given every two weeks has an advantage over an every three-week administration. Clearly, dose-dense AC → paclitaxel showed an advantage in CALGB-9741 that most oncologists have accepted. However, whether we can convert that benefit to a lower-risk, node-negative setting with AC times four alone is controversial. In my practice, I discuss with patients the benefits of quicker therapy, the downside in terms of additional injections and cost, and the uncertainty regarding the additional benefit of dose-dense AC. I'm comfortable, however, if a patient chooses to go that route, that we're not doing her any harm.

— Gary H Lyman, MD, MPH.* Patterns of Care *2005 (1)

AC → docetaxel, the control arm in our current US Oncology study, is a very reasonable treatment that doesn't require growth factors. TAC would also be an option. TAC requires growth factors but has about the same treatment duration as dose-dense therapy, and I would use this regimen. We also saw in San Antonio that FEC/docetaxel was significantly better than the standard six cycles of FEC. This is also a legitimate treatment option. In the patient at higher risk, I would pick one of these regimens, and I tend to use AC → docetaxel.

— Stephen E Jones, MD.* Patterns of Care *2005 (1)

Adjuvant Trastuzumab Clinical Trial Results

28TH ANNUAL
San Antonio Breast Cancer Symposium 13

At the 2005 ASCO meeting, practice-changing results from several adjuvant trastuzumab trials — NCCTG-N9831, NSABP-B-31 and HERA — were presented. The combined analysis of NCCTG-N9831/NSABP-B-31 demonstrated that the addition of trastuzumab to AC → paclitaxel significantly improved disease-free and overall survival in women with HER2-positive breast cancer. Data were also presented from the HERA trial, which demonstrated that adjuvant trastuzumab could improve disease-free survival when started after a variety of chemotherapy regimens. At this San Antonio meeting, data will be presented from BCIRG 006, in which adjuvant trastuzumab was found again to significantly improve disease-free survival, both with AC → docetaxel and a nonanthracycline-containing chemotherapy regimen of carboplatin plus docetaxel. These four landmark studies will now be followed by a new generation of adjuvant trials, and one issue of great interest — as in HER2-negative disease — will be the potential role of bevacizumab.

PHASE III CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Target accrual	Eligibility	Randomization	Primary endpoint
BCIRG 006	3,150	Node-positive or high risk node-negative HER2+ (FISH+)	AC x 4 → docetaxel 100 mg/m^2 q3wk x 4 AC x 4 → docetaxel 100 mg/m^2 q3wk x 4 + H qwk x 12 → H q3wk remainder of 1y Carboplatin + docetaxel 75 mg/m^2 q3wk x 6 + H qwk x 12 → H q3wk remainder of 1y Note: H 4 mg/kg LD → 2 mg/kg during chemo (after chemo, 6 mg/kg q3wk)	Disease-free survival
NSABP-B-31	2,700	Node-positive HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel q3wk* x 4 AC x 4 → paclitaxel q3wk* x 4 + H qwk x 52 Note: H 4 mg/kg LD → 2 mg/kg qwk x 51	CHF rate Overall survival
NCCTG-N9831	3,300	Node-positive or high risk node-negative HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 52 AC x 4 → paclitaxel qwk x 12 + H qwk x 52 Note: H 4 mg/kg LD → 2 mg/kg qwk x 51	Cardiac tolerability Disease-free survival
BIG-01-01, HERA	4,482	Node-positive or node-negative HER2+ (IHC 3+ or FISH+) Any chemo + XRT	H q3wk x 12 months H q3wk x 24 months Observation Note: H 8 mg/kg LD → 6 mg/kg q3wk x 1y	Disease-free survival

H = trastuzumab; chemo = chemotherapy; LD = loading dose; CHF = congestive heart failure; * protocol amended to allow weekly or every three-week paclitaxel

SOURCES: NCI Physician Data Query, October 2005; Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7; Nabholtz JM et al. *Clin Breast Cancer* 2002;3(Suppl 2):75-9.

ADJUVANT CHEMOTHERAPY WITH OR WITHOUT TRASTUZUMAB: COMBINED ANALYSIS OF NSABP-B-31/NCCTG-N9831 EFFICACY DATA

Parameters	AC → paclitaxel (n = 1,679)	AC → paclitaxel with trastuzumab (n = 1,672)	Hazard ratio [95% CI]	*p*-value*
Disease-free survival			0.48 [0.39-0.59]	$p < 0.0001$
Three-year disease-free survival	75.4%	87.1%		
Four-year disease-free survival	67.1%	85.3%		
Time to first distant recurrence			0.47 [0.37-0.61]	$p < 0.0001$
Three years from randomization	81.5%	90.4%		
Four years from randomization	73.7%	89.7%		
Overall survival			0.67 [0.48-0.93]	$p = 0.015$
Three years from randomization	91.7%	94.3%		
Four years from randomization	86.6%	91.4%		

* All *p*-values were two sided.

SOURCE: Romond EH et al. *N Engl J Med* 2005;353:1673-84.

FIRST RESULTS OF HERA: TRASTUZUMAB FOR ONE VERSUS TWO YEARS VERSUS PLACEBO AFTER CHEMOTHERAPY FOR HER2-POSITIVE BREAST CANCER

Efficacy (One-year median follow-up)	Placebo (n = 1,693)	Trastuzumab for one year (n = 1,694)	Hazard ratio [95% CI]	*p*-value
Two-year disease-free survival	77.4%	85.8%	0.54 [0.43-0.67]	<0.0001
Distant recurrence-free survival	82.8%	90.6%	0.49 [0.38-0.63]	<0.0001
Overall survival	95.1%	96.0%	0.76 [0.47-1.23]	0.26

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

BCIRG 006 INTERIM EFFICACY ANALYSIS: RISK OF RELAPSE RELATIVE TO AC → T (N = 3,222)

	Median follow-up	AC-docetaxel/trastuzumab	Docetaxel/carboplatin/trastuzumab
Relative reduction in risk of relapse	23 months	51% (95% CI: 35-63%)	39% (95% CI: 21-53%)

SOURCE: www.bcirg.org/Internet/Press+Releases, September 2005.

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COMBINED ANALYSIS: NSABP-B-31/NCCTG-N9831

Our conclusions for high-risk HER2-positive breast cancer: Trastuzumab, when given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at three years by 52 percent. This benefit should change the standard of care. The benefit was present and of similar magnitude in virtually all subsets of patients analyzed. There is not, however, statistical power to establish efficacy in the node-negative subset. The addition of trastuzumab reduced the probability of developing distant recurrence by 53 percent at three years, and the hazard of developing distant metastases appears, thus far, to decrease over time. Early results at a median follow-up of two years show a statistically significant survival advantage with a relative risk reduction of 33 percent.

— Edward H Romond, MD et al. Presentation. ASCO 2005.

HERA: TRASTUZUMAB FOR ONE YEAR OR PLACEBO

In conclusion, at one-year median follow-up, trastuzumab given every three weeks for one year following adjuvant chemotherapy significantly prolongs disease-free survival and relapse-free survival and significantly reduces the risk of distant metastasis. Trastuzumab's clinical benefits are independent of patients' baseline characteristics and type of adjuvant chemotherapy received. Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure, but clearly, longer follow-up is needed to better quantify this risk. All patients continue to be followed for long-term safety. Results regarding optimal trastuzumab duration, two years versus one year, should be available in 2008.

— Martine J Piccart-Gebhart, MD, PhD et al. Presentation. ASCO 2005.

INITIAL RESULTS OF BCIRG 006

In a three-arm trial with 300 events, we recognize that we're walking a fine line here, but still, both arms crossed their efficacy boundaries. The relevant question will be: How does the TCH arm, the nonanthracycline arm, look relative to the anthracycline-containing arm? The risk reduction in the TCH arm is 0.39, and the risk reduction in the ACTH arm is 0.51, almost identical to what was seen in the trials reported at ASCO for that type of combination. That's based on very few event differences between the two arms. We need to wait until the data mature, and it won't take a long period of time. Physicians should basically do what they feel most comfortable with at this point. If they feel more comfortable with the ACTH data, they should go with that arm, recognizing that those patients will have to be watched very closely for cardiotoxicity.

— Dennis J Slamon, MD, PhD.
Breast Cancer Update: ***Special NSABP Edition 2005***

REDUCTION IN DISTANT DISEASE RECURRENCE

In the joint analysis of NCCTG-N9831 and NSABP-B-31, the hazard rates for distant disease recurrence in patients who received trastuzumab appeared to improve with time. It's still too early to analyze these data because few patients in either trial are four years out; however, the distant disease-free survival curve appears to plateau in the trastuzumab arm. If that's the case, it's astonishing. We've never seen a true plateau in any adjuvant trial. When we examine disease-free survival curves like this, we need to ignore a fair amount of the right side of the curve because there are so few numbers, but if that is maintained it will be exciting.

— George W Sledge Jr, MD. **Breast Cancer Update** ***2005 (6)***

ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE DISEASE

I still have trepidation about using adjuvant trastuzumab in patients with node-negative disease and tumors under one centimeter. If the patient's tumor is ER-negative, the threshold to treat with trastuzumab is lower. On the other hand, for those with ER-positive disease, I would probably want to do an Oncotype DX™ assay because I believe that is a reliable method to determine risk and would really be helpful. If it's a high-risk tumor, I would add trastuzumab to that regimen.

— Norman Wolmark, MD.
Breast Cancer Update: ***Special NSABP Edition 2005***

Unresolved Issues in the Use of Adjuvant Trastuzumab

28TH ANNUAL San Antonio Breast Cancer Symposium 14

Recent results of large randomized adjuvant trials of trastuzumab — NSABP-B-31, NCCTG-N9831, HERA and BCIRG 006 — have changed the management of HER2-positive early breast cancer, but a number of unresolved issues remain. Should adjuvant trastuzumab and chemotherapy be administered concurrently or sequentially? N9831 suggests that adjuvant trastuzumab concurrent with the taxane portion of chemotherapy improves disease-free survival more than sequential trastuzumab, but the HERA trial demonstrates benefit with adjuvant trastuzumab used after the completion of a variety of chemotherapy regimens. What is the optimal chemotherapy regimen in this setting? BCIRG 006 reported a low incidence of cardiac events for adjuvant trastuzumab in combination with a nonanthracycline-containing regimen, and initial efficacy results — announced in a press release and to be presented at this meeting — reveal a benefit for both AC → docetaxel/trastuzumab and docetaxel/carboplatin/trastuzumab, although the relative magnitude of benefit of these two arms is not clearly defined.

BCIRG 006 AND RANDOMIZED TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Eligibility	Randomization	Key issues evaluated
BCIRG 006	Node-positive or high risk node-negative HER2+ (FISH+)	AC → docetaxel AC → docetaxel + H → H (total one year H) Carboplatin + docetaxel + H → H (total one year H)	Nonanthracycline/H combination H concurrent with chemotherapy
NSABP-B-31	Node-positive HER2+ (IHC 3+ or FISH+)	AC → paclitaxel AC → paclitaxel + H (total one year H)	Combined analysis with N9831 Weekly or every three-week taxane with concurrent H
NCCTG-N9831	Node-positive or high risk node-negative HER2+ (IHC 3+ or FISH+)	AC → paclitaxel AC → paclitaxel → H (total one year H) AC → paclitaxel + H (total one year H)	Combined analysis with NSABP-B-31 Weekly taxane with concurrent or sequential H Effect of three-month delay between doxorubicin and H on cardiotoxicity
BIG 1-01, HERA	Node-positive or node-negative HER2+ (IHC 3+ or FISH+) Any chemotherapy ± XRT	Any chemotherapy → H (one year) Any chemotherapy → H (two years) Any chemotherapy	Duration of H Value of H versus no H following adjuvant chemotherapy

H = trastuzumab; AC = doxorubicin/cyclophosphamide; XRT = radiation therapy

SOURCES: NCI Physician Data Query, September 2005; Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7.

COMPARISON OF SEQUENTIAL AND CONCURRENT TRASTUZUMAB WITH CONTROL AC → T: NSABP-B-31/NCCTG-N9831

Parameter	Number of patients	Number of events	Percent improvement	*p*-value*
AC → T vs AC → T + H → H*				
Disease-free survival	2,379	395	52	3×10^{-12}
Overall survival	NR	154	33	0.015
AC → T vs AC → T → H†				
Disease-free survival	1,964	220	13	0.2936
Overall survival	NR	79	15	0.4752

* Joint analysis of NSABP-B-31/NCCTG-N9831; † NCCTG-N9831
AC = doxorubicin/cyclophosphamide; T = paclitaxel; H = trastuzumab; NR = not reported

SOURCE: Perez EA et al. Presentation. ASCO 2005;Abstract 556.

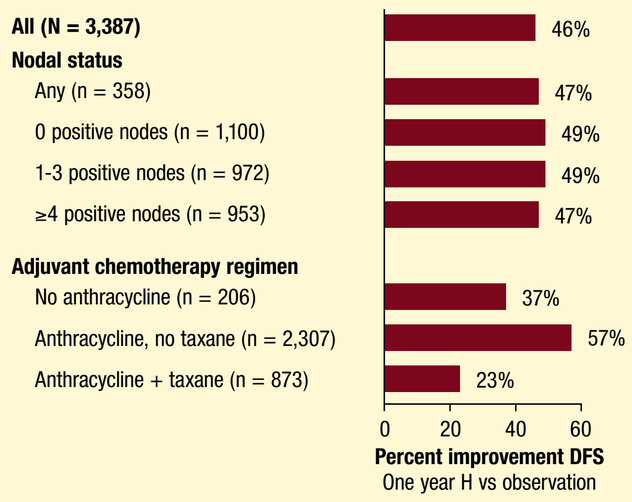
PROTOCOL-DEFINED CARDIAC EVENTS IN ADJUVANT TRASTUZUMAB TRIALS

Trial	Arm of study	Protocol-defined cardiac event rate*
BCIRG 006[1]	AC → D AC → DH CDH	1.2% 2.3% 1.2%
NSABP-B-31[2]	AC → TH AC → T	4.1% 0.8%
NCCTG-N9831[3]	AC → T AC → T → H AC → TH → H	0% 2.2% 3.3%
BIG 1-01, HERA[4]	Observation One year H	2.33% 8.81%

* Note that the definition of cardiac events varied between protocols.
AC = doxorubicin/cyclophosphamide; D = docetaxel; C = carboplatin
T = paclitaxel; H = trastuzumab

SOURCES: [1] Slamon DJ. NSABP Annual Meeting Satellite Symposium 2005. [2] Romond EH et al. *N Engl J Med* 2005;353:1673-84. [3] Perez EA et al. NCCTG N9831 May 2005 Update. Presentation. ASCO 2005;Abstract 556; [4] Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

HERA TRIAL: RELATIVE REDUCTION IN RECURRENCE RATE



H = trastuzumab; DFS = disease-free survival

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

SELECT PUBLICATIONS

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Perez EA et al. **NCCTG N9831 May 2005 Update.** Presentation. ASCO 2005;Abstract 556.

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Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353:1673-84.

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SELECTION OF CHEMOTHERAPY TO COMBINE WITH TRASTUZUMAB

In terms of nonprotocol chemotherapy/trastuzumab combinations, at this point, we try, whenever possible, to avoid anthracycline-containing regimens because of the known interaction in terms of cardiac safety of trastuzumab with anthracyclines, and we're not restricted to TCH when using a nonanthracycline regimen. There are a number of different drugs that interact very well with trastuzumab. However, we usually do use TCH in the adjuvant setting and will continue to do so until we see that it is inferior and the safety profile doesn't make up for that inferiority.

— Dennis J Slamon, MD, PhD.* Breast Cancer Update: *Special NSABP Edition 2005

CONCURRENT VERSUS SEQUENTIAL CHEMOTHERAPY/TRASTUZUMAB

The only test of concomitant versus sequential treatment was from N9831, and when you look at the curves presented and the comparisons, one can't remain neutral. The concomitant arm (with paclitaxel) has a hazard rate that falls in line with what we're seeing in the other trials, whereas the sequential arm is, peer wise, not statistically significant. It is not inappropriate for a medical oncologist to look at that data and be more impressed with concomitant therapy.

— Norman Wolmark, MD.* Breast Cancer Update: *Special NSABP Edition 2005

...Trials of adjuvant treatment have not determined whether the potentiation of the effect of chemotherapy by trastuzumab warrants concurrent chemotherapy and trastuzumab administration, or whether sequential treatments would be adequate. Similarly, the optimal duration of therapy may depend on how, precisely, trastuzumab works. As yet, there is no defined threshold of HER 2 gene amplification that predicts which HER2-positive tumors will respond to treatment. It seems probable that the greater the degree of gene amplification, the greater the potential benefit, but this possibility has not been tested clinically.

— Harold J Burstein MD, PhD.* N Engl J Med *2005;353(16):1652-4.

DURATION OF ADJUVANT TRASTUZUMAB: DELAYED IMPLEMENTATION OF ADJUVANT TRASTUZUMAB

The HERA trial is evaluating the duration question. In their trial, one arm has no trastuzumab, the second arm has one year and the third arm has two years of trastuzumab after chemotherapy. Because the data at this point address one year of trastuzumab, I believe that's the appropriate length of time.

As for the delayed implementation of trastuzumab in the Intergroup trial, they're supplying trastuzumab to the control group of patients who want to crossover out to one year of follow-up. There are theoretical arguments that a year is somewhat of an arbitrary length. The peak in relapses occurs at about two to three years, so I could see a rationale for treating beyond a year, particularly for patients at high risk with multiple nodes. However, that rationale is going beyond the data we have and is somewhat speculative.

— Peter M Ravdin, MD, PhD.* Breast Cancer Update *2005 (8)

TRASTUZUMAB SAFETY AND EFFICACY

We acknowledge that we have only an incomplete picture of the risks associated with trastuzumab. The risk of cardiotoxicity is currently low in our trial, but this could change with longer follow-up.

Another concern is that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. Brain metastases developed in approximately one third of the women receiving trastuzumab as treatment for advanced breast cancer, despite control of systemic disease. It is not clear whether such central nervous system metastases reflect aggressive disease or poor penetration of trastuzumab into the brain.

— Martine J Piccart-Gebhart, MD, PhD et al.* N Engl J Med *2005;353(16):1659-72.

Research To Practice: Adjuvant Trastuzumab

28TH ANNUAL San Antonio Breast Cancer Symposium 15

How have the recent dramatic findings of the adjuvant trastuzumab trials — NSABP-B-31, NCCTG-N9831, HERA and BCIRG 006 — altered the clinical practice of medical oncologists in the United States? In a recent post-ASCO survey of medical oncologists, the overwhelming majority would now recommend adjuvant trastuzumab plus chemotherapy for patients with HER2-positive, node-positive and higher-risk, node-negative breast cancers. When asked about the sequential versus concurrent use of trastuzumab and chemotherapy, most oncologists stated they would utilize adjuvant trastuzumab following the completion of the anthracycline portion of the chemotherapy and concurrent with the taxane. Additionally, oncologists are offering patients delayed adjuvant trastuzumab, particularly in patients with node-positive tumors, within a year of completing adjuvant chemotherapy. MUGA scans are the most common approach to monitoring cardiac effects of therapy, and trastuzumab is much less frequently recommended for patients in their seventies and eighties, perhaps because of cardiac concerns. This survey was done prior to the press release of BCIRG data on trial 006, and it will be interesting to evaluate how this data set — which will be presented at this San Antonio meeting — will impact selection of chemotherapy regimens, including the choice of paclitaxel versus docetaxel, and the use of TCH (docetaxel/carboplatin/trastuzumab).

CLINICAL USE OF ADJUVANT TRASTUZUMAB

What adjuvant therapy would you recommend for a 55-year-old woman in average health with an ER/PR-negative, HER2-positive (confirmed by FISH), Grade II tumor (tumor size and nodal status as indicated)?

	1.2-cm, negative nodes	2.4-cm, negative nodes	1.2-cm, 1 positive node	1.2-cm, 3 positive nodes	1.2-cm, 10 positive nodes
Chemotherapy alone	**30%**	**14%**	**6%**	**6%**	**6%**
Trastuzumab + chemotherapy	**70%**	**86%**	**94%**	**94%**	**94%**
AC	12%	14%	2%	—	—
AC → paclitaxel	40%	48%	66%	68%	64%
TAC	—	4%	8%	10%	12%
FAC/ FEC x 6	6%	4%	2%	—	—
AC → docetaxel	12%	16%	16%	16%	18%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

DELAYED ADJUVANT TRASTUZUMAB

The patient is a 55-year-old woman who receives adjuvant AC → paclitaxel for a 2.4-cm, ER/PR-negative, HER2-positive, Grade II tumor (node status specified below). Would you recommend adjuvant trastuzumab at each of the following time points?

	Node-negative	3 positive nodes	10 positive nodes
Six months after completion of chemotherapy	58%	82%	84%
One year after completion of chemotherapy	32%	54%	58%
Two years after completion of chemotherapy	8%	14%	38%
Four years after completion of chemotherapy	4%	8%	22%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CLINICAL USE OF ADJUVANT TRASTUZUMAB

In which type of patients with HER2-positive disease have you utilized or do you plan to utilize adjuvant trastuzumab?

In most or all node-positive patients	22%
In most or all node-positive and high-risk, node-negative patients	58%
In some node-positive patients	4%
In some node-positive and high-risk, node-negative patients	16%

Would you recommend adjuvant trastuzumab for a patient who is in average health with a 1.2-cm, ER/PR-positive, HER2-positive, Grade II tumor with three positive nodes?

	Age 35	Age 55	Age 75	Age 85
Yes	90%	90%	66%	38%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SEQUENCING OF ADJUVANT TRASTUZUMAB

In general, which of the following best describes how you utilize adjuvant trastuzumab?

Sequentially, after the completion of all adjuvant chemotherapy	20%
Concurrently, with all chemotherapy	20%
Sequentially, after the completion of anthracycline portion of chemotherapy but concurrent with taxane	60%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

DEFINING HER2 POSITIVITY

What documentation of HER2 positivity do you require to use adjuvant trastuzumab?

FISH+	34%
IHC 3+	4%
Both FISH+ and IHC 3+	12%
Either FISH+ or IHC 3+	50%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SELECT PUBLICATIONS

Geyer CE Jr et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** San Antonio Breast Cancer Symposium 2003;Abstract 23.

Perez EA et al. **HER2 testing by local, central, and reference laboratories in the NCCTG N9831 Intergroup Adjuvant Trial.** *Proc ASCO* 2004;Abstract 567.

Perez EA et al. **NCCTG N9831 May 2005 Update.** Presentation. ASCO 2005.

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;Abstract 556.

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353:1659-72.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353:1673-84.

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OVERVIEW OF NSABP-B-31, NCCTG-N9831 AND HERA

As a result of the data presented at ASCO in 2005, trastuzumab has now become a standard of care in the adjuvant setting for HER2-positive breast cancer. We saw a stunning validation of the biology of HER2 and the concept that we could diminish the likelihood of recurrence and improve overall survival through the use of targeted therapy. We saw that by two years after randomization, one quarter of the patients in the control arm had relapsed.

In the joint analysis of NCCTG-N9831 and NSABP-B-31, around 25 percent had relapsed by approximately three years. This is a bad disease, and partly because of that, we see a high event rate early in these trials.

A striking benefit was seen with trastuzumab, including a survival benefit with a median follow-up of just two years. That is unprecedented in any adjuvant trial. In the HERA trial, all the patients received trastuzumab after rather than concurrent with chemotherapy, and those data were positive with an impressive 45 percent reduction in hazard rate.

— *George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)*

NCCTG-N9831: CARDIAC SAFETY OF ADJUVANT TRASTUZUMAB

Although our trial demonstrated that clinical cardiac events are observed in patients receiving adjuvant trastuzumab, the difference is less than four percent compared to the control arm. The numbers are actually a bit lower than the numbers in NSABP-B-31 but statistically quite similar. At this point, we have not seen any difference in cardiac events between the two trastuzumab-containing arms. Not every patient has a reversal of their cardiac events, but most patients definitely improve not only in terms of the clinical symptomatology but also measurable left ventricular ejection fraction.

— *Edith A Perez, MD.* Breast Cancer Update *2005 (4)*

ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE TUMORS

The HERA study included patients with node-negative disease as long as their tumors were greater than one centimeter. The NSABP trial had no patients with node-negative disease, and in the NCCTG study, patients with node-negative disease accounted for 14 percent of the total population but only six percent of the events. It's unlikely that the relative benefits of trastuzumab will differ in patients with node-negative versus node-positive disease. On the other hand, the absolute benefit will differ, because patients with node-negative disease, particularly with small tumors, have a lower risk of recurrence. In my mind, it's reasonable to consider trastuzumab for patients who were eligible for the studies. The group of women that I'm a little more cautious about are those with relatively small, ER-positive, node-negative breast cancer.

— *Eric P Winer, MD.* Breast Cancer Update *2005 (7)*

ROLE OF DELAYED ADJUVANT TRASTUZUMAB

The HERA trial suggests that administering trastuzumab after chemotherapy may be beneficial, so the question becomes, how long after chemotherapy will it be beneficial? In the case of estrogen receptors, we have two European randomized trials that evaluated the late use of tamoxifen in patients with estrogen receptor-positive breast cancer, and both were positive. Will we see a similar benefit with delayed adjuvant trastuzumab? It's a reasonable and important question, particularly for those patients in the control arms of N9831 and B-31 who are more than 18 months out from treatment. I'm not going to be dogmatic about this, but I do believe it's reasonable to discuss the option of trastuzumab with such patients.

— *George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)*

Neoadjuvant Trastuzumab in HER2-Positive Breast Cancer

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In women with HER2-positive early breast cancer, the addition of one year of adjuvant trastuzumab to chemotherapy has been shown to significantly improve disease-free and overall survival. Several trials investigating the addition of trastuzumab to neoadjuvant chemotherapy have reported pathologic complete response (pCR) rates ranging from seven to 42 percent. At the 2004 ASCO meeting, Dr Aman Buzdar reported the results from a randomized neoadjuvant trial of paclitaxel → FEC with or without trastuzumab in women with HER2-positive breast cancer. This neoadjuvant trastuzumab/chemotherapy regimen yielded a pCR of 65.2 percent compared to 26.3 percent for chemotherapy alone. NSABP-B-41 has been designed to compare two neoadjuvant regimens: FEC → paclitaxel plus trastuzumab and paclitaxel plus trastuzumab → FEC plus trastuzumab. Another important study, conducted by Dr Jenny Chang, demonstrated impressive clinical responses and interesting intracellular changes after three weeks of neoadjuvant trastuzumab monotherapy.

RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

Trial	Neoadjuvant regimen	Number of patients	Pathologic complete response rate
Wenzel 2004	(Trastuzumab + epirubicin + docetaxel) qwk x 6	14	7%
Bines 2003	Trastuzumab qwk x 14 + (docetaxel qwk x 6 → 2 wk off) x 2	33	12%
Burstein 2003	Trastuzumab qwk x 12 + paclitaxel q3wk x 4	40	IHC 3+: 19% IHC 2+: 13%
Harris 2003	Trastuzumab qwk x 12 + vinorelbine qwk	39	21%
Hurley 2003	Trastuzumab qwk x 12 + (cisplatin + docetaxel q3wk x 4 + G-CSF + EPO)	44	20%
Limentani 2003	Trastuzumab qwk x 12 + ([docetaxel + vinorelbine] q2wk + G-CSF) x 6	12	42%
Moluçon 2003	Trastuzumab qwk x 18 + docetaxel q3wk x 6	18	28%
Schiffhauer 2003	Trastuzumab qwk x 12 + docetaxel q3wk	16	25%
Carey 2002	AC x 4 → (trastuzumab + paclitaxel) qwk x 12	22	22%
Steger 2002	Trastuzumab qwk x 12 + docetaxel qwk + epirubicin qwk	9	22%

G-CSF = granulocyte colony-stimulating factor; EPO = erythropoietin

SOURCES: Bines J et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):56;Abstract 243; Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53; Carey LA et al. *Breast Cancer Res Treat* 2002;76(Suppl 1):109;Abstract 424; Harris LN et al. *Proc ASCO* 2003;Abstract 86; Hurley J et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):54;Abstract 238; Limentani SA et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):55;Abstract 240; Moluçon C et al. *Breast Cancer Res Treat* 2003;82(Suppl 1):59;Abstract 253; Schiffhauer LM et al. *Proc ASCO* 2003;Abstract 969; Steger GG et al. *Proc ASCO* 2002;Abstract 1966; Wenzel C et al. *J Cancer Res Clin Oncol* 2004;130(7):400-4.

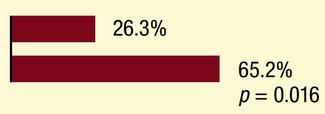
MD ANDERSON PHASE III TRIAL OF NEOADJUVANT TRASTUZUMAB/CHEMOTHERAPY

Accrual: 42 (Early closure by DSMB)

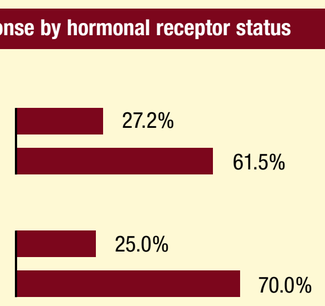
Eligibility	T1-3, N0-1, M0 breast cancer HER2-positive by FISH or IHC 3+
ARM 1	Paclitaxel q3wk x 4 → FEC x 4
ARM 2	Paclitaxel q3wk x 4 + H x 12 → FEC x 4 + H x 12

H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly

Overall pathologic complete response



Pathologic complete response by hormonal receptor status



"These results represent the highest reported pCR rate in this patient population. The most logical explanation for this high pCR rate is the use of two potentially noncross-resistant chemotherapies administered sequentially in combination with trastuzumab. Other possibilities include longer duration of neoadjuvant therapy compared with earlier studies."

P = paclitaxel

SOURCE: Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85.

NEOADJUVANT DOCETAXEL/CARBOPLATIN WITH OR WITHOUT TRASTUZUMAB

Protocol IDs: UCLA-9911084, AVENTIS-GIA-11156, GENENTECH-H2269s
Target Accrual: 75 (Open)

Eligibility	T3 or T4, any N patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy
ARM 1	(Trastuzumab qwk x 12) + ([docetaxel + carboplatin] q3wk x 4)
ARM 2	(Docetaxel + carboplatin) q3wk x 4

* Patients with HER2-negative disease receive neoadjuvant chemotherapy only, as in Arm 2. Within four to six weeks after surgery, patients with responding disease receive four additional courses of docetaxel and carboplatin as during neoadjuvant chemotherapy. Patients with HER2-positive disease also receive trastuzumab qwk x 12 weeks and then q3wk x 40 weeks.

Study contact: *Helena Chang, MD, PhD, Ph: 310-794-5624*

SOURCE: NCI Physician Data Query, September 2005.

RANDOMIZED TRIAL OF NEOADJUVANT CHEMOTHERAPY AND TRASTUZUMAB

Protocol ID: NSABP-B-41/ACOSOG-Z1041 (Proposed)
Target Accrual: Pending

Eligibility	Palpable, operable HER2-positive breast cancer
ARM 1	T qwk x 12 + H x 12 → FEC x 4 + H x 12
ARM 2	FEC x 4 → T qwk x 12 + H x 12

T = paclitaxel; H = trastuzumab
Note: Cardiac monitoring = NSABP-B-31 methodology
Trastuzumab continued postoperatively to complete one year of therapy.

SOURCE: Aman Buzdar, MD, personal communication, September 2005.

SELECT PUBLICATIONS

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53.

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85.

Jahanzeb M et al. **Dose-dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support.** *Proc ASCO* 2005;Abstract 591.

Mehta RS et al. **Phase II study of neoadjuvant biweekly doxorubicin and cyclophosphamide (AC) with GM-CSF followed by weekly paclitaxel, carboplatin +/- trastuzumab (TC +/- H) in the treatment of breast cancer (BC).** *Proc ASCO* 2005;Abstract 826.

Montemurro F et al. **A phase II study of three-weekly docetaxel and weekly trastuzumab in HER2-overexpressing advanced breast cancer.** *Oncology* 2004;66(1):38-45.

Wenzel C et al. **Preoperative therapy with epidoxorubicin and docetaxel plus trastuzumab in patients with primary breast cancer: A pilot study.** *J Cancer Res Clin Oncol* 2004;130(7):400-4.

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MD ANDERSON PREOPERATIVE TRIAL OF TRASTUZUMAB AND CHEMOTHERAPY

As soon as we had results from 34 patients, we could see that 65 percent of patients in the trastuzumab arm had no tumor, whereas only 25 percent of patients who received chemotherapy alone were tumor free. This was much higher than we had anticipated. The clinical response rate was even more striking, as 87 percent of the patients had clinical complete remission in the trastuzumab arm compared to about 50 percent in the chemotherapy-alone arm. Our institutional Data Monitoring Committee came to the conclusion that the findings were so striking that even if we continued the trial to reach accrual, the results would be similar. Thus the trial was stopped early.

— *Aman U Buzdar, MD.* Breast Cancer Update *2004 (8)*

Many of us would have guessed that the pathologic complete response (pCR) rate would be high in the Buzdar study. However, we were all surprised when we saw the magnitude of difference for the neoadjuvant trastuzumab regimen. We had never seen pCR rates so high. Obviously, this needs to be validated in a larger study, and one is planned. A potential explanation for such a high pCR rate is that the patients received longer duration chemotherapy (paclitaxel and FEC) instead of just four cycles. Another reason might be that synergy exists between the anthracyclines and trastuzumab, which has not been previously tested because of the concerns of cardiotoxicity.

— *Debu Tripathy, MD.* Breast Cancer Update *2005 (5)*

PROPOSED NSABP TRIAL B-41: FOLLOW-UP TO THE MD ANDERSON STUDY

In NSABP-B-41, we will compare a B-31-like standard trastuzumab regimen to the Buzdar regimen. Patients in our control arm will receive FEC followed by paclitaxel/trastuzumab. On the investigational side, they'll get the Buzdar regimen of paclitaxel/trastuzumab followed by FEC with trastuzumab. We wanted to ask: Does giving concurrent trastuzumab with the anthracycline make a big difference? If you give paclitaxel/trastuzumab first and stop the trastuzumab, you've obviously got trastuzumab for a good bit of the epirubicin. We have to have that apparent asymmetry in order to try to isolate that question as best we can.

— *Charles E Geyer Jr, MD.* Breast Cancer Update*: Special NSABP Edition 2005*

NEOADJUVANT TRASTUZUMAB INDUCES APOPTOSIS

We evaluated the activity and efficacy of neoadjuvant single-agent trastuzumab in treatment-naïve women with HER2-overexpressing, locally advanced breast cancer. We administered three weeks of single-agent trastuzumab and measured the tumor size before and after treatment. The endpoints assessed in the study were twofold: (1) efficacy and (2) the mechanism of action of trastuzumab. For the second endpoint, we evaluated several pathways — proliferation, growth factor and apoptosis pathways. We enrolled 40 patients, and after only three weeks of trastuzumab, 25 percent of the patients had a partial response (50 percent reduction). It was stunning because these were all enormous, inflammatory breast cancers. Within the first few weeks, the patients would tell you: "The redness is going, and the mass is getting softer." This was independently verified by at least two oncologists, so it's real. The other patients had stabilization of disease, and none progressed. At that point, we used four cycles of docetaxel and continued weekly trastuzumab. All of the patients underwent surgery, and the pCR rate was very high — in the 35 percent range. Not surprisingly, trastuzumab's primary mechanism of action is the induction of apoptosis. This has important implications. First, trastuzumab is unlikely to be antagonistic with chemotherapy because they both affect apoptosis, so they would more likely be synergistic. Second, we might think that in studies of patients with metastatic disease we could consider trastuzumab for a period of time, stopping, evaluating how the patients do, then reintroducing trastuzumab in the future.

— *Jenny C Chang, MD.* Breast Cancer Update *2005 (2)*

Neoadjuvant Chemotherapy

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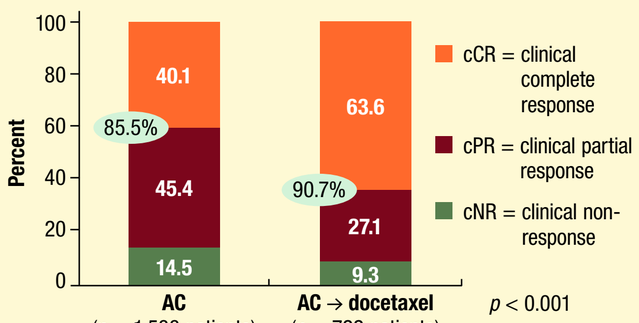
At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27, which evaluated the addition of docetaxel to neoadjuvant AC. Whereas the addition of neoadjuvant docetaxel improved the pathologic complete response rate, no differences were found in overall or disease-free survival. However, relapse-free survival was significantly higher in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant trials is evaluating novel strategies, including dose-dense chemotherapy, *nab* paclitaxel, capecitabine/docetaxel (XT), bevacizumab/docetaxel and other regimens.

PHASE III TRIAL EVALUATING THE ADDITION OF A TAXANE TO PREOPERATIVE AC

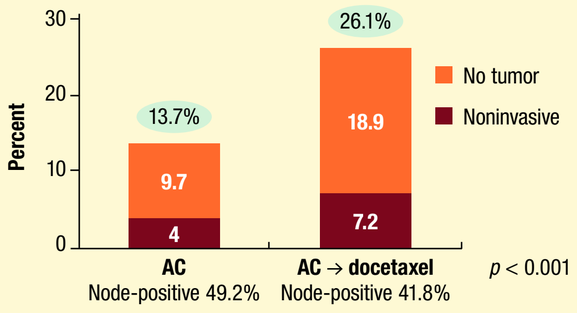
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

Eligibility	Stage IA-IIIA breast cancer
ARM 1	AC x 4 → surgery
ARM 2	AC x 4 → docetaxel x 4 → surgery
ARM 3	AC x 4 → surgery → docetaxel x 4

INITIAL RESULTS: CLINICAL RESPONSE



INITIAL RESULTS: PATHOLOGIC RESPONSE IN THE BREAST



No difference in rate of breast conservation: 61% versus 63%

SOURCE: Bear HD et al. *J Clin Oncol* 2003;21(22):4165-74.

68-MONTH UPDATE OF STUDY ENDPOINTS (HAZARD RATIOS COMPARED TO AC)

Variable	AC → T → surgery (n = 803)	AC → surgery → T (n = 799)
Overall survival	0.94 (p = 0.57)	1.07 (p = 0.53)
Disease-free survival With cPR after AC	0.86 (p = 0.10) 0.68 (p = 0.003)	0.91 (p = 0.27) 0.90 (p = 0.40)
Relapse-free survival	0.81 (p = 0.03)	0.91 (p = 0.32)

No significant difference in overall survival or disease-free survival by treatment but improved relapse-free survival in Arm 2 (preoperative docetaxel HR = 0.81, p = 0.03) versus Arm 1 (AC); T = docetaxel

68-MONTH UPDATE: HAZARD RATIOS OF PCR VERSUS NON-PCR

Variable	Hazard ratio	p-value
Overall survival	0.33	<0.0001
Disease-free survival	0.45	<0.0001

Pathologic complete response in the breast associated with improved overall survival and disease-free survival in all treatment groups

SOURCE: Bear HD. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

AC AND PACLITAXEL WITH OR WITHOUT FILGRASTIM IN WOMEN WITH INFLAMMATORY OR LOCALLY ADVANCED BREAST CANCER

Protocol IDs: SWOG-S0012, CTSU, NCT00016406
Target Accrual: 350 (Open)

Eligibility	Stage IIB, IIIA/B breast cancer
ARM 1	AC x 5 q3wk → paclitaxel qwk x 12
ARM 2	AC_{oral} + G-CSF qwk x 15 → paclitaxel qwk x 12

Objectives:
- Compare microscopic pathologic response rates in women with inflammatory or locally advanced breast cancer treated with standard neoadjuvant AC followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclophosphamide with filgrastim (G-CSF) followed by weekly paclitaxel
- Compare toxic effects of these regimens
- Compare delivered dose intensity of these regimens
- Evaluate association between microscopic pathologic complete response and clinical complete response at the primary tumor site

Trial lead organization: *Southwest Oncology Group*
Georgiana Ellis, MD, Protocol Chair, Ph: 206-288-6711

SOURCE: NCI Physician Data Query, September 2005.

MD ANDERSON PHASE III NEOADJUVANT TRIAL OF WEEKLY PACLITAXEL VERSUS CAPECITABINE/ DOCETAXEL → FEC AND LOCAL THERAPY

Protocol IDs: ID01-580, NCT00050167
Target Accrual: 930 (Open)

Eligibility	Stage IIA-IIIA breast cancer
ARM 1	Paclitaxel qwk x 12 → FEC x 4 → local therapy (surgery or RT)*
ARM 2	(Capecitabine 750 mg/m² BID 14d q3wk + docetaxel) x 4 → FEC x 4 → local therapy (surgery or RT)*

* ER/PR-positive patients will receive endocrine therapy after completion of local therapy.

Study contacts: *Debbie Frye, RN; Cynthia Carter, RN*
MD Anderson Cancer Center, Ph: 713-792-2817

SOURCES: NCI Physician Data Query, September 2005.
Livingston R. *Oncology* 2002;16(10 Suppl 12):29-32.

ONGOING TRIALS OF NEOADJUVANT CHEMO

Protocol	Phase	N	Regimen
NSABP-B-40 (pending activation)	III	1,200	AC x 4 → docetaxel 100 mg/m² x 4 AC x 4 → (docetaxel 75 mg/m² + capecitabine 825 mg/m² BID d1-14) x 4 AC x 4 → (docetaxel 75 mg/m² + gemcitabine) x 4
JHOC-J0266 JHOC-03012301	II	40	Docetaxel + pegfilgrastim q2wk x 4
EORTC-10994	III	1,850	One of three regimens of fluorouracil + epirubicin + cyclophosphamide Docetaxel → epirubicin + docetaxel
NCCTG-N0338	II	25-58	Docetaxel + carboplatin + pegfilgrastim q2wk x 4
NSABP FB-AX-003	II	Not reported	*Nab* paclitaxel qwk x 12 → FEC q3wk x 4

SOURCES: NCI Physician Data Query, October 2005; NSABP Protocol Summary, September 2005.

SELECT PUBLICATIONS

Bear HD et al. **A randomized trial comparing preoperative (preop) doxorubicin/ cyclophosphamide (AC) to preop AC followed by preop docetaxel (T) and to preop AC followed by postoperative (postop) T in patients (pts) with operable carcinoma of the breast: Results of NSABP B-27.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

Bear HD et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74.

Gianni L et al. **Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer.** *J Clin Oncol* 2005;23(29):7265-77.

Hannemann J et al. **Changes in gene expression associated with response to neoadjuvant chemotherapy in breast cancer.** *J Clin Oncol* 2005;23(15):3331-42.

Hutcheon AW et al. **Docetaxel primary chemotherapy in breast cancer: A five year update of the Aberdeen trial.** *Breast Cancer Res Treat* 2003;Abstract 11.

Livingston R. **Current and planned trials with capecitabine in adjuvant/ neoadjuvant therapy of breast cancer.** *Oncology (Willinston Park)* 2002;16(10 Suppl 12):29-32.

Mauri D et al. **Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis.** *J Natl Cancer Inst* 2005;97(3):188-94.

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NSABP-B-27: 68-MONTH UPDATED RESULTS

NSABP trial B-27 was based on the results of the preceding neoadjuvant trial, B-18, in which we compared four cycles of preoperative AC to post-operative AC given adjuvantly. In that trial, there was no difference between neoadjuvant and adjuvant treatment, but patients receiving neoadjuvant therapy who had a pathologic complete response had a much better long-term outcome than patients who had less of a response.

The addition of preoperative docetaxel to AC doubled the pathologic complete response rate from 13 percent to 26 percent. No difference occurred between groups in terms of overall survival, but there was a trend toward improved disease-free survival with the addition of docetaxel, particularly when given preoperatively. A significant improvement in relapse-free survival occurred with the addition of preoperative docetaxel compared to AC alone.

— *Harry D Bear, MD, PhD.* Breast Cancer Update *2005 (7)*

NEOADJUVANT CAPECITABINE/DOCETAXEL TRIAL

In one of our ongoing neoadjuvant studies, we're trying to take advantage of genomics and proteomics to improve the individualization of therapy. The trial is based on the capecitabine/docetaxel (XT) regimen that Joyce O'Shaughnessy evaluated in the metastatic setting. For their first cycle of chemotherapy, patients will be randomly assigned to either capecitabine or docetaxel monotherapy. After that initial cycle, all patients will receive four cycles of both drugs in combination.

We're collecting fresh tissue and a serum sample for serum proteomic analyses before the start of chemo-therapy, after the first cycle of monotherapy and after the combination at the time of surgery. We are hopeful that the serum proteomics will be useful in predicting response because for many patients it is difficult to obtain a fresh tumor sample.

— *Kathy D Miller, MD.* Breast Cancer Update *2004 (9)*

MD ANDERSON NEOADJUVANT/ADJUVANT TRIAL

We are currently evaluating the role of capecitabine/ docetaxel in the adjuvant and neoadjuvant settings. All patients entering the trial with intact primary tumors are randomly assigned to receive either paclitaxel followed by FEC or capecitabine/docetaxel followed by FEC in the neoadjuvant setting. Patients who have previously undergone surgery receive the same randomized treatment, but they receive it in the adjuvant setting.

The control arm is similar to the control arm we used in our neoadjuvant trastuzumab study. The only difference is that we are using weekly versus every three-week paclitaxel for 12 weeks. The final endpoint will combine the neoadjuvant and adjuvant subgroup data and evaluate disease-free and overall survival. The neoadjuvant group has an advantage in that we will be able to find the clinical complete remission rate, the pathologic complete remission rate and a number of other endpoints.

— *Aman U Buzdar, MD.* Breast Cancer Update *2004 (8)*

SWOG TRIAL S0012 OF NEOADJUVANT THERAPY IN LOCALLY ADVANCED AND INFLAMMATORY DISEASE

In the Southwest Oncology Group, we have a trial of neoadjuvant therapy for women with locally advanced and inflammatory disease, comparing intermittent AC versus AC plus G-CSF. That trial is accruing reasonably well. All patients receive paclitaxel, but it's a two-arm study, and paclitaxel is administered weekly for 12 weeks. I would like to see an Intergroup trial in which patients who have resectable disease but want to receive neoadjuvant therapy are randomly assigned to a dose-dense versus a less dose-dense schedule — in other words, a trial asking the same basic question that we're asking in SWOG-S0221 — because with an endpoint of pathologic complete response in a two-arm design, we could potentially have an answer in a couple of years while we're still completing the adjuvant study.

— *Robert B Livingston, MD.* Breast Cancer Update *2004 (6)*

Neoadjuvant Endocrine Therapy

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The most commonly utilized neoadjuvant therapy in the United States is chemotherapy. However, in Europe, preoperative endocrine therapy is used extensively in women with ER-positive breast cancer. A small, randomized, neoadjuvant trial demonstrated that the efficacy of the aromatase inhibitors was comparable to chemotherapy in terms of objective and pathologic response rates, local recurrence and breast conservation rates. The IMPACT trial — comparing neoadjuvant anastrozole, tamoxifen or the combination — found that more women receiving anastrozole became eligible for breast-conserving surgery. An upcoming ACOSOG trial will compare the three aromatase inhibitors as neoadjuvant therapy, and an ongoing trial will compare two different doses of fulvestrant.

IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION

Eligibility: Postmenopausal, ER-positive breast cancer			
Efficacy data (N = 330)	**A**	**T**	**C**
Objective clinical response (caliper)	37%	36%	39%
Patients who became eligible for breast-conserving surgery* after three months of treatment	46%	22%	26%
Geometric mean reductions in Ki-67 after two weeks of treatment†	76%	60%	64%

A = anastrozole; T = tamoxifen; C = combination of A + T

* Of the 220 patients with surgeon's preferred surgery recorded at baseline, 56% were deemed to need a mastectomy.

† The geometric mean suppression of Ki-67 was significantly greater at both two and 12 weeks with anastrozole than with tamoxifen.

IMPACT TRIAL: INFLUENCE OF HER2 OVEREXPRESSION ON CLINICAL RESPONSE

HER2-positive (n = 34)	Anastrozole	Tamoxifen	Anastrozole + tamoxifen	*p*-value
Clinical response	58%	22%	31%	0.18

SOURCES: Smith IE et al. *J Clin Oncol* 2005;23(22):5108-16. Dowsett M et al. *J Clin Oncol* 2005;23(11):2477-92.

RESPONSE TO NEOADJUVANT ENDOCRINE THERAPY WITH AROMATASE INHIBITORS VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN

Response rate	E[1]	T[1]	A[2]	T[2]
Clinical objective response (%)	76	40	70	44
Mammographic response (%)	64	37	56	36
Ultrasound response (%)	61	37	44	30
Breast-conserving surgery (%)	37	20	42	28

E = exemestane; T = tamoxifen; A = anastrozole

SOURCES: [1] Semiglazov V. *Proc ASCO* 2005;Abstract 530; [2] Semiglazov V. *Proc ASCO* 2003;Abstract 3538.

RANDOMIZED PHASE III STUDY COMPARING NEOADJUVANT EXEMESTANE, LETROZOLE AND ANASTROZOLE IN ER/PR-POSITIVE BREAST CANCER

Protocol ID: ACOSOG Z1031
Target Accrual: 375 (Pending)

Eligibility	Postmenopausal, Stage II/III operable breast cancer ≥2 cm, ER- or PR-positive
ARM 1	Exemestane 25 mg qd x 16wk → surgery
ARM 2	Letrozole 2.5 mg qd x 16wk → surgery
ARM 3	Anastrozole 1 mg qd x 16wk → surgery

SOURCE: Personal communication, ACOSOG, September 2005.

NEOADJUVANT TRIAL OF ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER: EFFICACY DATA

Efficacy parameter	Chemo*	A	E	*p*-value
Clinical objective response	76%	75.6%	81.5%	NR
Mammographic objective response	61.9%	62.1%	71%	NR
Pathologic complete response	7.4%	3.3%	6.8%	NR
Breast conservation	23.9%	33.3%	34%	0.054
Local recurrence rate	3.2%	3.3%	3.4%	>0.5

A = anastrozole; E = exemestane; NR = not reported
* Chemotherapy = doxorubicin + paclitaxel

SOURCE: Semiglazov V et al. Presentation. ASCO 2004;Abstract 519.

RESPONSE RATES FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Clinical response (n = 74)	Response rate
Complete clinical response (cCR)	57%
Partial clinical response (cPR)	26%
Objective response (cCR + cPR)	83%
Pathologic response (n = 61)*	**Response rate**
Complete pathologic response (pCR)	23%
Partial pathologic response (pPR)	77%

* Pathologic response data limited to patients showing an objective response who then underwent a mastectomy

SOURCE: Milla-Santos A et al. *Anticancer Res* 2004;24(2C):1315-8.

RANDOMIZED PHASE II NEOADJUVANT STUDY OF FULVESTRANT 500 MG VERSUS 250 MG IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER

Protocol IDs: 9238IL/0065, NCT00093002
Target Accrual: 160 (Open)

Eligibility	Postmenopausal; T2-4b, N0-3, M0, ER-positive invasive breast cancer
ARM 1	Fulvestrant 500 mg
ARM 2	Fulvestrant 250 mg

Study contact:
AstraZeneca Cancer Support Network
Ph: 866-992-9276

SOURCES: NCI Physician Data Query, October 2005; www.ClinicalTrials.gov, October 2005.

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Semiglazov V et al. **The relative efficacy of neoadjuvant endocrine therapy vs chemotherapy in postmenopausal women with ER-positive breast cancer.** Presentation. ASCO 2004;Abstract 519.

Semiglazov VF et al. **Neoadjuvant endocrine therapy vs chemotherapy for postmenopausal ER-positive breast cancer patients.** *Proc SABCS* 2004;Abstract 2090.

Smith IE at al. **Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial.** *J Clin Oncol* 2005;23(22):5108-16.

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ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN THE NEOADJUVANT SETTING

We're significantly more likely to be successful performing breast-conserving surgery after neoadjuvant endocrine therapy than chemotherapy. One reason for this is that approximately 20 to 30 percent of patients who respond well to neoadjuvant chemotherapy are left with multiple islands of tumor scattered throughout an area of the breast that corresponds to the size of the original tumor, whereas the pattern following neoadjuvant endocrine therapy is that the tumor shrinks and implodes.

The number of patients receiving neoadjuvant endocrine therapy has increased significantly, and many oncologists who have tried this approach and found that it worked have adopted this strategy. I believe more physicians should be utilizing this because it's effective at downstaging some large tumors, making inoperable tumors operable.

When we're selective and treat only patients with ER-rich tumors, meaning Allred scores 6, 7 and 8, the number of patients who progress or actually fail to respond is very small. We have also learned that we can treat patients longer than three or four months with neoadjuvant therapy and see continued response. We've treated patients for up to a year and found that the number of patients with a complete response continues to rise the longer we treat them. If the tumor is shrinking but still not small enough for breast-conserving surgery at three or four months, continuing therapy will give added benefit, and eventually, most of these tumors will become small enough for breast conservation.

— J Michael Dixon, MD.* Breast Cancer Update *2005 (5)

I believe it was a mistake to evaluate chemotherapy rather than endocrine therapy in some of the earlier animal studies. The perioperative phase is critical and while no evidence indicates that preoperative chemotherapy improves survival, that's nonspecific treatment, and it doesn't mean that neoadjuvant endocrine therapies will fail. I view neoadjuvant endocrine treatment as a biological response modifier, and I believe using the aromatase inhibitors up front might have a greater impact on long-term outcome.

— Michael Baum, MD, ChM.* Breast Cancer Update *2005 (1)

SURROGATE OUTCOMES OF NEOADJUVANT ENDOCRINE THERAPY

A decision regarding neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy would be made easier if there were predictive tests that could select a subpopulation of tumors whose response to the neoadjuvant aromatase inhibitor is in a range of 80 to 90 percent. If such a test also identified a tumor subtype for which chemotherapy did not improve outcomes, then we would have made real progress toward making neoadjuvant endocrine therapy a new standard of care.

— Matthew J Ellis, MB, PhD.* J Clin Oncol *2005;23(22):4842-4.

Neoadjuvant treatment provides a useful clinical model and the opportunity to obtain primary tumour material by which to explore molecular mechanisms associated with de novo resistance and early acquired resistance. The model has already demonstrated that the absence of tumour ER confers endocrine resistance. … There are also suggestions that high expression of c-erbB2 is associated with high cellular proliferation even after effective oestrogen deprivation. Whether this translates eventually into endocrine resistance and a poor outcome remains to be determined. The present studies are not definitive and require larger groups of patients. It should also be noted that whereas the particular protocol involving neoadjuvant therapy for three months can provide evidence of de novo resistance and early forms of acquired resistance, it is unlikely to be useful in identifying processes that occur in the longer term.

— William R Miller, PhD, DSc et al.* Endocr Relat Cancer *2005;12:S119-S123.

Trials of Hormonal Therapy in Metastatic Disease

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The number of hormonal therapy options for postmenopausal women with estrogen receptor-positive metastatic breast cancer expanded with the introduction of the aromatase inhibitors and fulvestrant. Ongoing clinical trials — SoFEA and EFECT — are evaluating endocrine strategies in women who have progressed on the usual first-line therapies (nonsteroidal aromatase inhibitors). Based on the theoretical advantage of utilizing fulvestrant in a lower-estrogen environment, the SoFEA trial and SWOG-S0226 are both investigating the combination of fulvestrant with an aromatase inhibitor. Biologic agents, including trastuzumab, and the tyrosine kinase inhibitors are also being assessed in combination with various endocrine interventions.

ONGOING CLINICAL TRIALS OF NOVEL COMBINATIONS OF HORMONAL THERAPIES AND BIOLOGIC AGENTS

Protocol ID	Phase	Trial design
ROCHE-B016216	II/III	**Anastrozole with or without trastuzumab** in postmenopausal women with HER2-overexpressing metastatic breast cancer
GSK-EGF30008	III	**Letrozole with or without lapatinib** in postmenopausal women with Stage IIIB, IIIC or IV breast cancer
3066A1-303	III	**Letrozole with or without temsirolimus** in postmenopausal women with locally advanced or metastatic breast cancer
Biomed 777-CLP-30	III	**Atamestane + toremifene versus letrozole** in postmenopausal women with advanced breast cancer
WSU-C-2876	II	**Lapatinib + tamoxifen** in women with tamoxifen-resistant, locally advanced or metastatic breast cancer
UCLA-0502057-01	II	**Fulvestrant + trastuzumab versus fulvestrant versus trastuzumab** as first-line treatment in postmenopausal women with HER2-overexpressing, Stage IV breast cancer
UCLA-0403073-01	II	**Anastrozole with or without lonafarnib** in postmenopausal women with Stage IIIB, IIIC or IV breast cancer
ZD1839US/0713	II	**Anastrozole with or without gefitinib** in postmenopausal women with metastatic breast cancer
DMS-0236	II	**Gefitinib with or without tamoxifen** in women with tamoxifen-resistant, metastatic breast cancer
NYWCCC-NCI-6205	II	**Fulvestrant + tipifarnib** as second-line therapy in postmenopausal women with inoperable, locally advanced or metastatic breast cancer with progressive disease after prior first-line endocrine therapy
ZD1839IL/0225	II	**Tamoxifen with or without gefitinib** in women with metastatic breast cancer
ECOG-4101	II	**Anastrozole + gefitinib versus fulvestrant + gefitinib** in postmenopausal women with recurrent or metastatic breast cancer
EORTC-10021	II	**Anastrozole with or without gefitinib** in postmenopausal women with locally recurrent or metastatic breast cancer

SOURCE: NCI Physician Data Query, September 2005.

PHASE III STUDY OF SINGLE-AGENT FULVESTRANT

Protocol IDs: D6997C00002, NCT00099437
Target Accrual: 720 (Open)

Eligibility	Postmenopausal Estrogen receptor-positive advanced breast cancer Failure on a previous endocrine treatment
ARM 1	Fulvestrant 500 mg
ARM 2	Fulvestrant 250 mg

Study contact:
AstraZeneca Pharmaceuticals LP, AstraZeneca Cancer Support Network
Ph: 866-992-9276

SOURCE: NCI Physician Data Query, September 2005.

PHASE III STUDY OF FULVESTRANT WITH OR WITHOUT ANASTROZOLE VERSUS EXEMESTANE

Protocol ID: SoFEA
Target Accrual: 750 (Open)

Eligibility	Postmenopausal Estrogen and/or progesterone receptor-positive Progression on a nonsteroidal aromatase inhibitor
ARM 1	Fulvestrant (LD)
ARM 2	Exemestane
ARM 3	Fulvestrant (LD) + anastrozole

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study chair:
Dr Stephen Johnston, Royal Marsden Hospital,
NHS Trust and Institute of Cancer Research, Ph: 44 (0) 20 7808 2745

SOURCES: Institute of Cancer Research, www.icr.ac.uk/ctsu, September 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

PHASE III STUDY OF ANASTROZOLE WITH OR WITHOUT FULVESTRANT AS FIRST-LINE THERAPY

Protocol IDs: SWOG-S0226, NCT00075764, CAN-NCIC-SWOG-S0226
Target Accrual: 690 (Open)

Eligibility	Postmenopausal Estrogen and/or progesterone receptor-positive
ARM 1	Anastrozole
ARM 2	Anastrozole + fulvestrant (LD)

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study contacts:
Rita Mehta, MD, Southwest Oncology Group, Ph: 714-456-5153
Theodore Vandenberg, MD, NCIC-Clinical Trials Group, Ph: 519-685-8640

SOURCES: NCI Physician Data Query, September 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

PHASE III STUDY COMPARING FULVESTRANT AND EXEMESTANE

Protocol IDs: 9238IL/0048, NCT00065325, EFECT
Target Accrual: 660 (Open)

Eligibility	Postmenopausal women Hormone receptor-positive Progression on a nonsteroidal aromatase inhibitor
ARM 1	Fulvestrant (LD)
ARM 2	Exemestane

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study contact:
AstraZeneca Pharmaceuticals LP, AstraZeneca Cancer Support Network
Ph: 866-992-9276

SOURCES: NCI Physician Data Query, September 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

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Perey L et al. **Fulvestrant (Faslodex) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and aromatase inhibitors: Update of a phase II SAKK trial.** San Antonio Breast Cancer Symposium 2004;Abstract 6048.

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EFECT TRIAL

EFECT is an American and European study that randomly assigns patients who have failed therapy with a nonsteroidal aromatase inhibitor to fulvestrant or exemestane. Our own study, SoFEA, is slightly different from EFECT because it is based on the observation that the addition of small amounts of estrogen to cells that have been estrogen deprived for a long time reduces the effectiveness of fulvestrant. That scenario equates to the withdrawal of a nonsteroidal aromatase inhibitor and the addition of fulvestrant. Hence, the third arm of our trial includes a nonsteroidal aromatase inhibitor and fulvestrant. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone.

— Mitchell Dowsett, PhD.* Breast Cancer Update *2004 (6)

OPTIMAL SEQUENCING OF AGENTS IN POSTMENOPAUSAL PATIENTS

If you evaluate most of the available data with endocrine agents in the metastatic setting — tamoxifen, steroidal or nonsteroidal aromatase inhibitors or fulvestrant — the question that comes up is whether one sequence enhances patient outcome more than another. This becomes important because if you can demonstrate that one sequence enhances the time to disease progression, it may be built on over time so that overall outcome is improved.

In theory, simply having an improvement in recurrence or progression of metastatic disease impacts quality of life. Patients now typically receive a nonsteroidal aromatase inhibitor — anastrozole or letrozole — as the first treatment. The question then becomes, if patients progress on one of those agents, what would be the next best therapy? Should it be the steroidal aromatase inhibitor exemestane, or should it be fulvestrant? Indirect data evaluating the sequence of a nonsteroidal aromatase inhibitor to fulvestrant suggest that 25 to 30 percent of patients may benefit with that approach.

An important issue is whether fulvestrant 250 mg is optimal. Some of the data suggest that the dose is really on the low end of the curve where you might expect the optimal response rate. Some strategies have evaluated quickly increasing serum levels of fulvestrant, including administering loading doses of 500 mg and within two weeks administering another 250 mg and then proceeding to the monthly schedule. Those strategies are based on mathematical modeling that has shown an ability to achieve steady-state levels much more quickly and consequently achieve a biologically relevant dose of drug circulating much faster.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)

Assuming an aromatase inhibitor and fulvestrant are equivalent in efficacy, the choice of which agent to use may come down to patient preference. Some of my patients are perfectly happy with a monthly injection, while others prefer an oral agent. For many patients, fulvestrant is financially favorable because of our arcane reimbursement system. We know that responses can be seen with either sequence — an aromatase inhibitor followed by fulvestrant or the opposite — but I believe it's important that we determine which is superior.

I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too low because by the time steady state was reached, many patients were off study, presumably because of progression. In my group, we administer loading doses of 500 mg of fulvestrant followed by 500 mg two weeks later and then 250 mg monthly.

The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population might not have revealed the true efficacy of fulvestrant. It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior. We may need to repeat some of these studies with a more appropriate dosing schedule.

— Gabriel N Hortobagyi, MD.* Breast Cancer Update *2004 (9)

Sequencing of Hormonal Therapies in Metastatic Disease

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The preferred sequence for hormonal therapies in postmenopausal women with metastatic disease has become a topic of considerable interest. As more postmenopausal women are being treated with aromatase inhibitors instead of tamoxifen in the adjuvant setting, the optimal therapy to use at initial relapse is not well defined. As first-line therapy, aromatase inhibitors are superior to tamoxifen, but the efficacy of fulvestrant — an estrogen receptor downregulator — is comparable to tamoxifen. As second-line therapy, fulvestrant and anastrozole have similar efficacy. A retrospective analysis of the proportion of patients with a prolonged duration of response suggests a benefit for fulvestrant over anastrozole. Future clinical trials are required to determine the optimal sequencing of the current hormonal therapy options.

SEQUENCING HORMONAL THERAPIES

How do you normally sequence endocrine therapy in postmenopausal patients with metastases and *no prior endocrine therapy*?

	1st-line	2nd-line	3rd-line
Tamoxifen	12%	18%	12%
Anastrozole	56%	12%	—
Letrozole	30%	14%	2%
Exemestane	2%	18%	26%
Fulvestrant	—	38%	34%
Megestrol acetate	—	—	10%
High-dose estrogen	—	—	4%
No endocrine therapy	—	—	12%

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen *one year previously*?

	1st-line	2nd-line	3rd-line
Tamoxifen	4%	4%	10%
Anastrozole	54%	8%	2%
Letrozole	38%	14%	—
Exemestane	4%	18%	34%
Fulvestrant	—	54%	26%
Megestrol acetate	—	—	12%
High-dose estrogen	—	—	4%
No endocrine therapy	—	2%	12%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

RETROSPECTIVE ANALYSIS OF PATIENTS RESPONDING IN TWO PHASE III STUDIES OF FULVESTRANT VERSUS ANASTROZOLE

Response	Fulvestrant 250 mg (n = 428)	Anastrozole 1 mg (n = 423)	*p*-value
Total patients with OR	19.2%	16.5%	0.3070
Patients with OR ≥1y	10.0%	7.1%	0.1627
Patients with OR ≥1.5y	4.0%	3.1%	—
Patients with OR ≥2y	0.9%	0.5%	—
Total patients with CB	43.5%	40.9%	0.5059
Patients with CB ≥1y	19.2%	13.9%	0.0692
Patients with CB ≥1.5y	7.5%	5.7%	—
Patients with CB ≥2y	1.4%	0.9%	—

"This analysis suggests that fulvestrant has benefits over anastrozole in terms of the number of patients with prolonged duration of response. These data support the initial DOR findings in these trials. Fulvestrant is an important new endocrine agent in breast cancer."

OR = objective response; CB = clinical benefit (complete response + partial response + stable disease ≥24 weeks); DOR = duration of response

SOURCE: Jones SE et al. *Proc SABCS* 2004;Abstract 6047.

PHASE III RANDOMIZED TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

	All patients		Patients with ER/PR-positive tumors	
	Fulvestrant (n = 313)	Tamoxifen (n = 274)	Fulvestrant (n = 247)	Tamoxifen (n = 212)
Complete response rate	9.6%	6.9%	8.9%	5.7%
Partial response rate	22.0%	27.0%	24.3%	25.5%
Stable disease ≥24 weeks	22.7%	28.1%	23.9%	31.6%
Objective response rate*	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate†	54.3%	62.0%	57.1%	62.7%

* Objective response indicates a complete or partial response; $p = 0.45$ for all patients; $p = 0.64$ for patients with ER/PR-positive tumors.

† Clinical benefit indicates a complete or partial response or stable disease ≥24 weeks; $p = 0.026$ for all patients; $p = 0.22$ for patients with ER/PR-positive tumors.

Median time to progression‡	6.8 months	8.3 months	8.2 months	8.3 months
Estimated median survival§	36.9 months	38.7 months	39.3 months	40.7 months

‡ $p = 0.088$ for all patients (upper limit of 95% confidence interval did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen); $p = 0.39$ for patients with ER/PR-positive tumors.

§ $p = 0.04$ for all patients; $p = 0.30$ for patients with ER/PR-positive tumors (upper limit of 95% confidence interval did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen).

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13.

RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY* IN PATIENTS ENROLLED IN TWO PHASE III TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY: RETROSPECTIVE ANALYSIS

	Patients who derived clinical benefit from fulvestrant (n = 54)	Patients who did not derive clinical benefit from fulvestrant (n = 51)
Partial response	4 (7%)	1 (2%)
Stable disease ≥24 weeks	21 (39%)	17 (33%)
Disease progression	29 (54%)	33 (65%)

* More than 80 percent received an aromatase inhibitor as subsequent endocrine therapy.

SOURCE: Vergote I et al. *Breast Cancer Res Treat* 2003;79(2):207-11.

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SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

Most clinicians consider fulvestrant a third-line therapy for patients who have failed tamoxifen and an aromatase inhibitor; however, clinical trials have shown that fulvestrant is equivalent to anastrozole after tamoxifen failure and, in a recently published European study comparing front-line fulvestrant to tamoxifen, I did not view fulvestrant as inferior to tamoxifen. I use third-line fulvestrant, but I also use it first line, particularly with women who can't afford an aromatase inhibitor. In addition, I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day.

— *Adam M Brufsky, MD, PhD.* Breast Cancer Update *2004 (7)*

The overall results of Trials 20 and 21 showed no significant difference between anastrozole and fulvestrant, but differences occurred in subset analyses. The duration of response seemed to be longer in patients who responded to fulvestrant, and patients who had visceral disease seemed to respond better than those who did not. I think the takeaway message is that they're equally efficacious; however, there may be subsets of patients in whom you might prefer to use fulvestrant, particularly those for whom compliance may be an issue or those with visceral disease.

The other important point is that anecdotal studies argue that you can use one and switch to the other. Third-line aromatase inhibitors are efficacious after fulvestrant and vice versa.

— *Gershon Locker, MD.* Meet The Professors *2004 (2)*

Generally, patients are either going to relapse on tamoxifen or after adjuvant tamoxifen. In that setting and in the fulvestrant versus anastrozole clinical trials, evidence exists that a proportion of women have a longer response to fulvestrant than to anastrozole when given right after tamoxifen. I've had patients with long responses to fulvestrant.

I prefer fulvestrant to an aromatase inhibitor after tamoxifen because approximately 20 percent of patients have long responses with it in this setting. However, 99 percent of oncologists will choose an aromatase inhibitor after tamoxifen. Fulvestrant is generally being used as third-line therapy. Despite Trials 20 and 21, most physicians start with anastrozole rather than fulvestrant because of the way the data have been presented.

We are just beginning to see patients who have been treated with two or three years of adjuvant anastrozole and then relapsed. Currently, there are few data on treatment options in this setting. It's somewhat of a "dealer's choice" because there are no hard and fast rules. There are multiple options including fulvestrant, exemestane and even tamoxifen — if the patient hasn't seen it — because it's obviously still a useful drug. So the sequence is going to be all over the map for most folks.

— *Stephen E Jones, MD.* Patterns of Care *2005 (1)*

In the up-front study, tamoxifen and fulvestrant were essentially equivalent. As second-line therapy, fulvestrant seemed to perform equally as well as anastrozole. At this point in time, the sequencing and timing for fulvestrant are unclear. I think it's reasonable to use the drug — maybe not up front, but as second- or third-line therapy. This is when you might consider the patient's preferences in terms of an intramuscular or an oral drug. A recent study of 261 women with metastatic breast cancer demonstrated that about one third preferred a monthly intramuscular injection. I've always assumed that oral drugs were preferable, if they were equally effective. Therefore, I was surprised to see that many patients preferred an intramuscular injection. I need to query my patients more when I start evaluating these options.

— *Debu Tripathy, MD.* Breast Cancer Update *2005 (5)*

Combination Chemotherapy Regimens for Metastatic Disease

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In E1193, the Phase III trial comparing sequential single-agent and combination chemotherapy, patients treated with doxorubicin/paclitaxel did not have an improvement in overall survival. In contrast, two Phase III trials comparing nonsequential single-agent and combination chemotherapy reported an improvement in overall survival in patients receiving capecitabine/docetaxel or gemcitabine/paclitaxel, although neither trial included crossover for the single-agent arm. Capecitabine/paclitaxel, a regimen with encouraging results, has been evaluated in two Phase II trials. Breast cancer clinical investigators generally support the use of sequential single-agent chemotherapy in most patients with metastatic disease. Ongoing clinical trials will define the role for combination regimens, which may also include biologics.

PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY

	XT Trial[1]: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193[2]: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	**Docetaxel**	**Capecitabine/docetaxel**	**Doxorubicin**	**Paclitaxel**	**Doxorubicin/paclitaxel**
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months*	18.9 months	22.2 months	22.0 months

* $p = 0.0126$

SOURCES: [1] O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23; [2] Sledge GW et al. *J Clin Oncol* 2003;21(4):588-92.

PHASE III TRIAL OF GEMCITABINE/PACLITAXEL VERSUS PACLITAXEL AS FIRST-LINE TREATMENT IN PATIENTS WITH ANTHRACYCLINE-PRETREATED METASTATIC BREAST CANCER: INTERIM SURVIVAL REPORT

Accrual: 529 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer Prior adjuvant anthracycline treatment No prior therapy for advanced disease**
ARM 1	**Gemcitabine + paclitaxel q3wk**
ARM 2	**Paclitaxel q3wk**

Endpoint	GT (n = 267)	T (n = 262)	*p*-value
Response rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.2, 27.2)	<0.0001
Median TTP (95% CI)	5.2 mo (4.2, 8.6)	2.9 mo (2.6, 3.7)	<0.0001
Median overall survival (95% CI)	18.5 mo (16.5, 21.2)	15.8 mo (14.4, 17.4)	0.018

G = gemcitabine; T = paclitaxel; TTP = time to progression

SOURCE: Albain KS. Presentation. ASCO 2004;Abstract 510.

MULTICENTER PHASE II STUDY OF CAPECITABINE PLUS PACLITAXEL AS FIRST-LINE THERAPY (N = 47)

Efficacy endpoints	No. of responders	Response rate
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 mo	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)

Grade III/IV adverse events	No. of patients	Percent
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m^2 twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m^2 every three weeks

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2004;22(12):2321-7.

PHASE II TRIAL OF CAPECITABINE AND WEEKLY PACLITAXEL IN TAXANE-NAÏVE PATIENTS

Response (N = 54 evaluable patients)	Percent	Grade III/IV adverse events (>5%)	No. of patients Grade III/IV	Percent Grade III/IV
Complete response	0	Hand-foot syndrome	10/0	18.2
Partial response	50	Neutropenia	3/4	12.7
Stable disease	30	Nausea	3/0	5.5
Clinical benefit (CR + PR + SD ≥6 months)	65	Leukopenia	1/2	5.5
		Diarrhea	3/0	5.5

SOURCE: Blum JL. Poster 5053. San Antonio Breast Cancer Symposium 2004.

ACTIVE PHASE III TRIALS OF NOVEL COMBINATIONS OF CHEMOTHERAPY AND BIOLOGIC AGENTS

Protocol ID	Target accrual	Eligibility	Randomization
CA163-048	Not reported	Prior anthracycline and taxane; no more than two prior chemotherapy regimens	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF100151	372	Progression in metastatic disease or relapse within six months after adjuvant taxane and anthracycline	Lapatinib (GW572016) + capecitabine Capecitabine
CA163-046	Not reported	Two or three prior chemotherapy regimens, one in the metastatic setting; taxane resistant and prior anthracycline	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF30001	570	No prior chemotherapy for Stage IV HER2-negative or unknown	Paclitaxel + lapatinib (GW572016) Paclitaxel + placebo

SOURCE: NCI Physician Data Query, September 2005.

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Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92.

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FIRST-LINE THERAPY FOR PATIENTS WITH PRIOR ADJUVANT AC AND A TAXANE

I usually consider these patients as being anthracycline and taxane refractory, but if a long period has passed (ie, two or more years) since the adjuvant therapy, one could certainly retry a taxane. Nanoparticle paclitaxel or a weekly regimen of the original paclitaxel formulation would be attractive choices. However, I'm generally treating these patients as anthracycline and taxane refractory, and I'm using capecitabine. Not only is capecitabine FDA approved for that indication, it seems to have among the higher response rates in the anthracycline- and taxane-refractory group of patients.

Alternatives to capecitabine would include vinorelbine and gemcitabine. I believe combinations of these drugs are also something to consider. We're so geared toward thinking of single agents, but combinations do have a role, particularly for more symptomatic patients. It's hard to know which combination wins out. Data exist on combinations of vinorelbine/capecitabine, gemcitabine/vinorelbine and gemcitabine/capecitabine.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)

CAPECITABINE/PACLITAXEL IN PATIENTS WITH TAXANE-NAÏVE METASTATIC BREAST CANCER

In our trial evaluating capecitabine plus weekly paclitaxel, patients could have undergone one prior chemotherapy regimen for metastatic breast cancer, which is in contrast to the front-line trial conducted by Bill Gradishar that evaluated a similar regimen but used paclitaxel 175 mg/m^2 every three weeks. Our response rate was very exciting, with 50 percent of patients achieving a partial response and an additional 30 percent of patients with stable disease for greater than six months, which is comparable to the 70 percent clinical benefit seen in Dr Gradishar's trial. The median progression-free survival is 12.1 months, and overall median survival has not yet been reached. The combination was remarkably well tolerated, and the hand-foot syndrome that occurred in 18 percent of patients was easily managed with dose modification.

— Joanne L Blum, MD, PhD. Meet The Professors Session at the 2004 San Antonio Breast Cancer Symposium

PHASE II TRIAL OF CAPECITABINE/PACLITAXEL AS FIRST-LINE THERAPY

The rationale behind our study was to determine whether we could see a similar benefit to that observed in Joyce O'Shaughnessy's docetaxel/capecitabine randomized trial. There were differences in the two trials. Our study was largely in the first line, whereas O'Shaughnessy's trial had a mix of patients receiving first-, second- and third-line therapy. The other distinction was the dose of the capecitabine. We started at 825 mg/m^2 twice a day for 14 days out of 21 days, as opposed to the FDA-approved dose (1,250 mg/m^2 BID) utilized in the other trial. We found the lower dose was better tolerated, which reflects the experience of most physicians using capecitabine as a single agent or in combination.

Dose reduction is usually necessary when starting at the FDA-approved dose. In practice, most physicians utilize 1 g/m^2/BID. So when combining with paclitaxel, the decision was made that we would use a lower starting dose. There was a very good response rate of approximately 50 percent, which is similar to O'Shaughnessy's results in patients treated first line.

If one is making the decision to combine capecitabine with a taxane, one could choose either docetaxel or paclitaxel and expect a robust response rate. It's a reasonable combination if one is wedded to the idea of using a combination in a particular patient. Joanne Blum evaluated another regimen of capecitabine with paclitaxel and demonstrated results similar to ours. Multiple studies have evaluated capecitabine plus a taxane. All of the studies are imperfect because none of them address the fundamental issue of whether one might accomplish the same objective with sequential, rather than combination, therapy. Studies are ongoing to address that issue.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)

Taxanes in the Metastatic Setting

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In patients with metastatic breast cancer, the roles of the taxanes — docetaxel, paclitaxel and *nab* paclitaxel — are evolving. Recent Phase III trials have demonstrated that every three-week regimens of docetaxel or *nab* paclitaxel have better efficacy than every three-week paclitaxel. *Nab* paclitaxel presents the advantage of not requiring premedication, which avoids side effects, particularly of steroid premedication. Another advantage of *nab* paclitaxel is that it can be administered over 30 minutes. *Nab* paclitaxel has also been evaluated in two Phase II trials on a weekly schedule, which seems to retain efficacy with less toxicity. A Phase II trial found weekly docetaxel comparable to every three-week docetaxel in terms of efficacy, but weekly docetaxel appeared to have a more favorable toxicity profile. Clinical trials will continue to delineate the role of the taxanes in the metastatic setting.

PHASE III TRIAL COMPARING DOCETAXEL VERSUS PACLITAXEL IN PATIENTS WHO HAD PROGRESSED AFTER AN ANTHRACYCLINE-CONTAINING REGIMEN

Response to treatment (intention-to-treat population)	Docetaxel q3wk (n = 225)	Paclitaxel q3wk (n = 224)	*p*-value
Overall response rate	32.0% (95% CI 25.9-38.1)	25.0% (95% CI 19.3-30.7)	0.10
Time to tumor progression	5.7 months	3.6 months	<0.0001
Duration of response	7.5 months (95% CI 5.8-9.1)	4.6 months (95% CI 3.9-6.0)	0.01
Overall survival	15.4 months	12.7 months	0.03
Hematologic adverse events	**Docetaxel (n = 222)**	**Paclitaxel (n = 222)**	***p*-value**
Grade III/IV neutropenia	93.3%	54.5%	<0.0001
Febrile neutropenia	14.9%	1.8%	<0.001
Grade III/IV anemia	10.4%	7.3%	0.24
Grade III/IV thrombocytopenia	4.6%	2.8%	0.31

SOURCE: Jones SE et al. *J Clin Oncol* 2005;23(24):5542-51.

PHASE III TRIAL COMPARING *NAB* PACLITAXEL VERSUS STANDARD PACLITAXEL

Efficacy data	*Nab* paclitaxel* (n = 229)	Standard paclitaxel† (n = 225)	*p*-value
Response rates			
All patients	33% (95% CI 27.09-39.29)	19% (95% CI 13.58-23.76)	0.001
First-line therapy	42% (95% CI 32.44-52.10)	27% (95% CI 17.75-36.19)	0.029
Second line or greater	27% (95% CI 18.98-34.05)	13% (95% CI 7.54-18.93)	0.006
Prior anthracycline therapy	34% (95% CI 27.09-41.09)	18% (95% CI 12.56-24.01)	0.002
Time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
All patients	65.0 weeks	55.7 weeks	0.374
Second line or greater	56.4 weeks	46.7 weeks	0.024
Safety data			
Grade IV neutropenia	9%	22%	<0.001
Grade III sensory neuropathy	10%	2%	<0.001
Growth factors used	3%	6%	NR

* *Nab* paclitaxel = 260 mg/m^2 IV every three weeks without premedication.
† Standard paclitaxel = 175 mg/m^2 IV every three weeks with premedication.
NR = not reported

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31);[Epub ahead of print].

PHASE II STUDY OF WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

Accrual: 60 (Closed)

Eligibility	Metastatic breast cancer
ARM 1	Docetaxel 35 mg/m^2 qwk x 8 – 12 cycles
ARM 2	Docetaxel 100 mg/m^2 q3wk x 6 cycles

Proportion of patients receiving docetaxel as: first-line treatment, 83.3%; second-line treatment, 16.6%

EFFICACY DATA

Parameter	Weekly docetaxel (n = 25)	3-weekly docetaxel (n = 35)
Intent to treat overall response rate	36%	42%
Median time to progression	5.2 months	5.8 months
Toxicity data		
Incidence of Grade III/IV adverse events	30	64
Number of patients experiencing Grade III/IV adverse events	12	23

Conclusions: "Weekly docetaxel is an active regimen in metastatic breast cancer with comparable efficacy to 3-weekly docetaxel. Both schedules were well tolerated, weekly docetaxel appears to have a more favourable toxicity profile, providing an attractive strategy for palliative treatment of metastatic breast cancer."

SOURCE: Grecea D et al. *Proc ASCO* 2005;Abstract 736.

ANTHRACYCLINES WITH OR WITHOUT TAXANES AS FIRST-LINE CHEMOTHERAPY: POOLED META-ANALYSIS OF 2,805 PATIENTS

Parameter	Risk ratio*	95% CI	*p*-value
Time to progression	1.10	1.00-1.21	0.05
Overall response rate	1.21	1.10-1.32	<0.001
Complete response rate	2.04	1.41-2.94	<0.001
Overall survival	1.05	0.90-1.23	0.58
Neutropenia	1.19	1.11-1.29	<0.001
Febrile neutropenia	2.82	1.39-5.69	<0.001

"All Phase III peer-reviewed published or presented trials were considered eligible. A pooled analysis (Method A) and a literature-based meta-analysis (Method B) were accomplished, and event-based relative risk ratios (RR_{A-B}) with 95% confidence intervals were derived. Both analyses were performed to examine for significant differences in time to disease progression (TTP), overall response rate (ORR), overall survival (OS), complete response rate (CR), neutropenia, and febrile neutropenia (FN).

"The adjunction of taxanes to anthracyclines in first-line chemotherapy for metastatic breast carcinoma yielded a significant benefit in activity (ORR, CR), a slight advantage in TTP, and a trend in OS, although with a significant cost in hematologic toxicity."

* Risk ratio of anthracycline + taxane vs anthracycline + nontaxane

SOURCE: Bria E et al. *Cancer* 2005;103(4):672-9.

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PHASE III TRIAL OF DOCETAXEL VS PACLITAXEL

This is the first clinical trial to compare directly the taxanes docetaxel and paclitaxel as monotherapy for patients with advanced breast cancer. Using US Food and Drug Administration-approved doses and schedules for each agent, this phase III study has demonstrated that docetaxel is superior to paclitaxel in TTP (5.7 *v* 3.6 months; $p < .0001$), response duration (7.5 *v* 4.6 months; $p = .01$), and OS (15.4 *v* 12.7 months; $p = .03$). The overall response rate was also greater with docetaxel (32% *v* 25%; $p = .10$). The survival advantage for docetaxel was observed despite the increased incidence of toxicities leading to dose reductions and treatment withdrawal, and the slightly greater use of salvage treatment in patients randomly assigned to paclitaxel. The results of this study are consistent with those reported for previous phase III studies of single-agent docetaxel and paclitaxel...

— Stephen E Jones, MD et al.* J Clin Oncol *2005;23(24):5542-51.

NANOPARTICLE VERSUS STANDARD PACLITAXEL

The superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 [nanoparticle paclitaxel] make this novel albumin-bound paclitaxel an important advance in the treatment of patients with MBC [metastatic breast cancer]. ABI-007 warrants further investigation, using additional dosing regimens (eg, weekly) and in combination with other treatment modalities, as front-line treatment of breast cancer and other solid tumors.

— William J Gradishar, MD et al.* J Clin Oncol *2005;23(31):[Epub ahead of print].

NANOPARTICLE PACLITAXEL COMPARED TO OTHER TAXANES

I believe nanoparticle paclitaxel is more active than paclitaxel based on the randomized trials. In cross-study comparisons of nanoparticle paclitaxel versus docetaxel, each given every three weeks, the response rates were similar in the 30 percent range. However, docetaxel in the metastatic setting, whether given weekly or every three weeks, is toxic because of side effects like asthenia, fluid retention and neutropenia, and it's difficult to administer for long periods of time.

One can give docetaxel in the adjuvant setting where treatment is short term, but I believe nanoparticle paclitaxel is better tolerated. I don't use single-agent docetaxel in the metastatic setting, and I would use nanoparticle paclitaxel in lieu of weekly paclitaxel.

I would like to see more data on combinations with nanoparticle paclitaxel to learn more about the toxicity profiles before using it in a combination off protocol.

— Joanne L Blum, MD, PhD.* Breast Cancer Update *2005 (1)

CHOICE OF TAXANES IN THE METASTATIC SETTING

A weekly regimen of the original paclitaxel formulation would have been my choice in the past. Now that we have data with *nab* paclitaxel, I think that's a reasonable option also. From the data, *nab* paclitaxel may be preferable. It outperformed the original paclitaxel formulation when administered every three weeks. A weekly regimen also seems to outperform an every three-week regimen of the original paclitaxel formulation, and I'm left wondering which is the best drug to use. For patients who prefer an every three-week schedule, I believe *nab* paclitaxel is the way to go. Otherwise, it's a toss-up between every three-week *nab* paclitaxel and a weekly regimen of the original paclitaxel formulation. I don't believe there's a way to compare the two. CALGB is planning to conduct a head-to-head trial comparing weekly regimens of *nab* paclitaxel and the original paclitaxel formulation.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)

ECOG Trial E2100: Paclitaxel Alone or with Bevacizumab

The importance of angiogenesis in cancer biology has been recognized for decades. One of the first angiogenesis-stimulating factors identified was the vascular endothelial growth factor (VEGF). Bevacizumab, a monoclonal antibody, inhibits the activity of VEGF. At the 2005 ASCO meeting, Dr Kathy Miller reported the results from ECOG-E2100, a Phase III randomized trial evaluating the addition of bevacizumab to paclitaxel as first-line therapy in women with metastatic breast cancer. The addition of bevacizumab was found to not only improve the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, both in the adjuvant and metastatic settings. An update of this important study will be presented at this meeting.

ECOG-E2100: PHASE III RANDOMIZED TRIAL OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB AS FIRST-LINE THERAPY IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER

Protocol IDs: ECOG-E2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 715 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer HER2-positive only if prior treatment with or contraindication to trastuzumab, no prior chemotherapy for metastatic disease, adjuvant taxane allowed if disease-free interval >12 months, PS 0 or 1, no CNS metastases**
ARM 1	**Paclitaxel 90 mg/m^2 (days 1, 8 and 15) + bevacizumab 10 mg/kg (days 1 and 15)**
ARM 2	**Paclitaxel 90 mg/m^2 (days 1, 8 and 15)**

SOURCE: Miller KD et al. Presentation. ASCO 2005.

ECOG-E2100 SAFETY RESULTS

	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy‡		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

* $p < 0.0001$; † $p = 0.0004$; ‡ $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005.

ECOG-E2100: FIRST PLANNED INTERIM ANALYSIS OF PRIMARY AND SECONDARY EFFICACY ENDPOINTS

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate			
All patients	28.2%	14.2%	<0.0001
Measurable disease	34.3%	16.4%	<0.0001
Progression-free survival	10.97 months	6.11 months	
	Hazard ratio = 0.498 (CI: 0.401-0.618)		<0.001
Overall survival	Hazard ratio = 0.674 (CI: 0.495-0.917)		0.01

SOURCE: Miller KD et al. Presentation. ASCO 2005.

INCORPORATION OF BEVACIZUMAB INTO TREATMENT OF BREAST CANCER: A SURVEY OF US ONCOLOGISTS, SEPTEMBER 2005 (N = 50)

Utilized bevacizumab to treat breast cancer off protocol	4%
Have not utilized bevacizumab but intend to use it	64%
Have not utilized and have no immediate intention to use it	32%
If utilized, for what duration?	
Until disease progression	74%
Beyond disease progression	20%
Other	6%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CURRENT OR PROPOSED BREAST CANCER CLINICAL TRIALS EVALUATING BEVACIZUMAB

Protocol	Setting	Target Accrual	Protocol
ECOG-E2104*	Adjuvant	42-202	Dose-dense AC q2wk x 4 + bevacizumab → bevacizumab + paclitaxel q2wk x 4 → bevacizumab q2wk x 18 Dose-dense AC q2wk x 4 → bevacizumab + paclitaxel q2wk x 4 → bevacizumab q2wk x 22
Dana-Farber/ Beth Israel, 05-055*‡	Adjuvant	100	Bevacizumab q3wk x 12mo Bevacizumab q3wk + cyclophosphamide daily + methotrexate qwk x 6mo → bevacizumab q3wk x 6mo
UCLA-0502123-01	Neoadjuvant	90	Bevacizumab → TAC + bevacizumab Placebo → TAC + placebo Bevacizumab $^{\text{higher dose}}$ → TAC + bevacizumab $^{\text{higher dose}}$ Placebo $^{\text{higher dose}}$ → TAC + placebo $^{\text{higher dose}}$
CWRU-3100*	Locally advanced	60	Docetaxel + bevacizumab Docetaxel
XCaliBr† (ML18527)	Metastatic, first line	92	Capecitabine + bevacizumab → vinorelbine + bevacizumab Capecitabine + bevacizumab → paclitaxel + bevacizumab
DFCI-03083*	Metastatic	36-66	Metronomic cyclophosphamide/methotrexate + bevacizumab Metronomic cyclophosphamide/methotrexate
NCCTG-N0432†	Metastatic, first line	47	Docetaxel + capecitabine + bevacizumab
UCLA-0109030-03*	Locoregional relapse/ metastatic	3-74	Phase I: Trastuzumab + bevacizumab escalated to maximum tolerated dose (MTD; [closed 11/04]) Phase II: Trastuzumab + bevacizumab at MTD

Metronomic cyclophosphamide = low dose, oral daily days 1-28; metronomic methotrexate = low dose, oral BID days 1, 2, 8, 9, 15, 16, 22, 23
* Bevacizumab = 10 mg/kg q2wk; † bevacizumab = 15 mg/kg q3wk; ‡ patients with residual breast cancer following preoperative chemotherapy

SOURCES: NCI Physician Data Query, September 2005; Miller KD. *Breast Cancer Update* Meeting 2005.

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ECOG-E2100: PACLITAXEL WITH OR WITHOUT BEVACIZUMAB AS FIRST-LINE THERAPY

...In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. Future studies in this area should begin to explore the role of bevacizumab in the adjuvant setting and continue to investigate methods to identify those patients who are most likely to benefit from VEGF-targeted therapies.

The next step in this process will activate soon in a trial known as E2104. This adjuvant pilot trial will investigate the safety and feasibility of incorporating bevacizumab into standard adjuvant chemotherapy, using the dose-dense anthracycline followed by paclitaxel regimen, as used in the previous CALGB-9741 trial.

— Kathy D Miller, MD et al. Presentation. ASCO 2005.

ECOG-E2100: SAFETY

As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for discontinuing E2100 if we saw an excess number of patients developing Grade IV hypertension or bleeding. When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer. Fortunately, early analyses demonstrated that was not an issue in breast cancer. The side effects were relatively minimal. Predominantly, we saw mild to moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we'll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a low incidence of serious bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy.

— George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)

IMPLICATIONS OF E2100

I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would use it in a first-line setting, optimally in combination with paclitaxel as administered in the study. I doubt that the interaction is specific between paclitaxel and bevacizumab, although I'm well aware that when given with capecitabine in more advanced disease, bevacizumab seemed to be less active. However, I believe that's probably related to the setting rather than the drug.

— Eric P Winer, MD.* Breast Cancer Update *2005 (7)

NEW CLINICAL TRIALS OF BEVACIZUMAB

An ECOG pilot trial of adjuvant bevacizumab, which will be primarily evaluating safety issues, will involve over 200 patients and will open within the next few months. Our belief is that given adequate safety data in the adjuvant setting — which we hope to have within 12 to 18 months — we'll be able to go directly to a large Phase III trial comparing chemotherapy to chemotherapy plus bevacizumab. Of course, many questions can be asked in the adjuvant setting with bevacizumab — which combination chemotherapy or what duration of therapy — and these may require more than one trial to answer. We will also need more than one trial because we'll have to evaluate both HER2-negative and HER2-positive disease.

— George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)

The XCaliBr trial will start very soon. This trial will evaluate newly diagnosed patients — essentially the same group as in the E2100 trial — who need chemotherapy but use capecitabine in combination with bevacizumab. This trial allows but does not require patients to continue bevacizumab after initial progression either with vinorelbine or paclitaxel, at the patients' and investigators' choice. This is a fairly small Phase II trial with only 92 patients, so it will not be definitive. Randomization to continuing bevacizumab or not is not included. That is an open question we need to address quickly.

— Kathy D Miller, MD.* Breast Cancer Update *2005 (7)

Research To Practice: Systemic Therapy of Metastatic Disease

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Selection of systemic therapy in patients with metastatic disease is a multi-faceted decision which is frequently influenced by the patient's age, prior adjuvant systemic therapy and a variety of other biopsychosocial considerations. Data from the *Breast Cancer Update* Patterns of Care Study, a telephone survey conducted in September 2005 of randomly selected medical oncologists in the United States, are presented here. For patients with minimally symptomatic metastatic disease, single-agent docetaxel is a common choice, and in older patients, capecitabine is commonly utilized. In addition, bevacizumab is a common consideration, particularly in patients receiving paclitaxel as first-line treatment. As more postmenopausal women receive adjuvant aromatase inhibitors, the selection of first-line endocrine therapy for metastatic disease is changing. In postmenopausal women, fulvestrant is a popular choice after progression on adjuvant anastrozole, while the aromatase inhibitors are commonly utilized after progression on adjuvant tamoxifen.

CHEMOTHERAPY FOR METASTATIC DISEASE AFTER PRIOR ADJUVANT AC → PACLITAXEL

The patient was treated two years ago with adjuvant AC → paclitaxel for an ER/PR-negative, HER2-negative tumor and now has bone and lung metastases with minimal symptoms. What first-line treatment are you likely to recommend for this patient?

	Age 40	Age 57	Age 75
Paclitaxel	10%	10%	2%
Docetaxel	24%	26%	24%
Nanoparticle paclitaxel	8%	8%	10%
Capecitabine	14%	14%	34%
Gemcitabine	2%	2%	8%
Vinorelbine	—	—	8%
Capecitabine + docetaxel	10%	6%	—
Gemcitabine + paclitaxel	8%	8%	2%
Gemcitabine + docetaxel	4%	6%	2%
Carboplatin + docetaxel	12%	12%	4%
Carboplatin + paclitaxel	2%	2%	—
AC	2%	2%	—
AC + paclitaxel	2%	2%	2%
AC + docetaxel	2%	2%	—
No chemotherapy	—	—	4%
Would you recommend bevacizumab for this patient?			
Percent responding "yes"	36%	36%	18%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CHEMOTHERAPY FOR METASTATIC DISEASE (NO PRIOR CHEMOTHERAPY)

The patient has received no prior systemic therapy for an ER/PR-negative, HER2-negative tumor and bone and lung metastases with minimal symptoms. What first-line treatment are you likely to recommend for this patient?

	Age 40	Age 57	Age 75
Paclitaxel	14%	14%	12%
Docetaxel	22%	24%	24%
Nanoparticle paclitaxel	—	—	10%
Capecitabine	12%	14%	26%
Gemcitabine	—	2%	4%
Vinorelbine	—	—	4%
Capecitabine + docetaxel	6%	4%	2%
Gemcitabine + paclitaxel	2%	—	—
Gemcitabine + docetaxel	4%	4%	—
AC	22%	18%	8%
AC + docetaxel	8%	12%	—
AC + paclitaxel	8%	6%	2%
Other chemotherapy	2%	2%	6%
No chemotherapy	—	—	2%
Would you recommend bevacizumab for this patient?			
Percent responding "yes"	32%	34%	20%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

HORMONE THERAPY FOR METASTATIC DISEASE AFTER ADJUVANT TAMOXIFEN

The patient has been on adjuvant tamoxifen for four years for an ER/PR-positive, HER2-negative tumor and now has bone and lung metastases with minimal symptoms. What first-line endocrine treatment are you likely to recommend for this patient?

	Age 57	Age 75
Anastrozole	62%	60%
Exemestane	2%	6%
Letrozole	30%	30%
Tamoxifen	—	—
Fulvestrant	2%	—
No therapy	4%	4%
Would you recommend bevacizumab for this patient?		
Percent responding "yes"	14%	8%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

HORMONE THERAPY FOR METASTATIC DISEASE AFTER ADJUVANT ANASTROZOLE

The patient has been on adjuvant anastrozole for four years for an ER/PR-positive, HER2-negative tumor and now has bone and lung metastases with minimal symptoms. What first-line treatment are you likely to recommend for this patient?

	Age 57	Age 75
Exemestane	10%	12%
Letrozole	2%	8%
Tamoxifen	26%	24%
Fulvestrant	50%	46%
No therapy	12%	10%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CLINICAL USE OF FULVESTRANT

Do you generally use a loading dose with fulvestrant? (percent responding "yes")	16%
What percentage of patients with metastatic breast cancer do you believe would prefer a monthly injection rather than a daily oral endocrine agent? (mean)	31%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

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CHEMOTHERAPY FOR METASTATIC DISEASE

I decide whether a patient should receive combination chemotherapy or sequential single agents based on the burden and pace of the disease. For example, women with quite a bit of visceral involvement — particularly liver involvement — may need combination therapy. For the patient with much more indolent disease, particularly the patient with a long disease-free interval who may have had sequential hormonal therapy and is now hormone therapy refractory, I use sequential single agents. Many of my patients receive capecitabine as the first chemotherapy in this situation because it's orally administered, does not cause alopecia and is extremely well tolerated. It is similar to taking a hormone pill.

— *Joanne L Blum, MD, PhD.* Breast Cancer Update *2005 (1)*

Many times in metastatic disease, we use all of the available therapies, so what we're really deciding on is the order — what to start with. Many patients make that decision based on their personal values. I find many of my older patients are attracted to capecitabine because it is an oral agent. Some of my younger patients think of intravenous therapy as more aggressive, and they prefer that strategy. However, this perception is based on gut reaction rather than reality. I am a big fan of capecitabine. Maybe it comes from being a "hormonal therapy person" who prefers pills to begin with because I use capecitabine a lot for salvage chemotherapy in women who have already had an anthracycline and a taxane for metastatic disease. In oncology, we tend to remember our successes, but I have seen several impressive responses with capecitabine in dire circumstances. I have had women on capecitabine for a considerable period of time with relatively good quality of life.

— *Nancy E Davidson, MD.* Breast Cancer Update *2005 (5)*

ENDOCRINE THERAPY FOR POSTMENOPAUSAL WOMEN WITH METASTATIC DISEASE

Previously, patients received tamoxifen in the adjuvant setting, so we would use an aromatase inhibitor as front-line therapy in the metastatic setting. Fulvestrant was used second line, or we could use megestrol acetate, but for many women fulvestrant has a more convenient side-effect profile. Now that more women receive aromatase inhibitors in the adjuvant setting, we're using tamoxifen or fulvestrant as first-line treatment in the metastatic setting.

— *Harold J Burstein MD, PhD.* Patterns of Care *2005 (1)*

In my experience, patients tolerate the fulvestrant injections just fine. We have randomized data comparing fulvestrant versus anastrozole in patients who have already received tamoxifen, but the optimal sequence for using fulvestrant is still undetermined. In choosing between an aromatase inhibitor and fulvestrant, I ask my patients whether they prefer an injection or a pill. If they have transportation problems, then I use an oral agent. However, for the Medicare population, these drugs are very expensive. If the patient does not have adequate insurance coverage and can't afford them, a monthly injection may be better. Compliance is also an issue to be considered when choosing between a daily oral agent and a monthly injection.

— *Joanne L Blum, MD, PhD.* Patterns of Care *2005 (1)*

I use fulvestrant as third-line therapy in patients whose disease has progressed on tamoxifen and an aromatase inhibitor. That's the current indication, but it wouldn't surprise me to see it moved up because data from the randomized trials clearly suggest it is as effective as aromatase inhibitors in patients who progressed after tamoxifen. The clinical question is whether the patient prefers a pill versus a parenteral injection. For some patients, the injection is easier, but most patients prefer taking a pill. In my experience, the tolerability of fulvestrant is similar to that of the aromatase inhibitors.

— *Daniel F Hayes, MD.* Breast Cancer Update *2004 (6)*