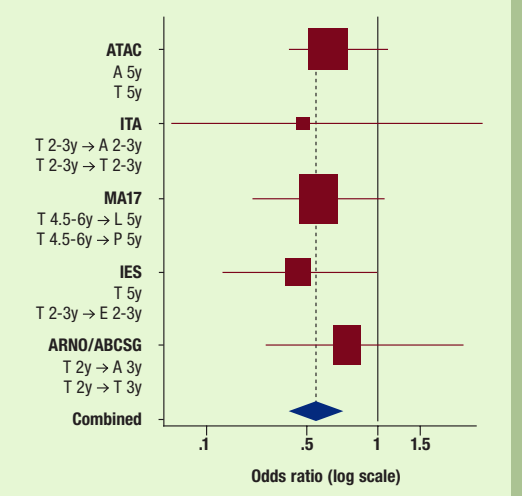
Breast Cancer Prevention

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 the American Society of Clinical Oncology. Cuzick J. Aromatase inhibitors for breast cancer prevention. *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	45	Exemestane
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
CAN-NCIC-MAP.1, NCT00238316	High-risk, postmenopausal, mammographic density occupying ≥25% of the breast	120	Letrozole vs placebo
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, December 2005.

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Chlebowski RT et al; American Society of Clinical Oncology Breast Cancer Technology Assessment Working Group. **American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition.** *J Clin Oncol* 2002;20(15):3328-43.

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.

Cuzick J. **Aromatase inhibitors for breast cancer prevention.** *J Clin Oncol* 2005;23(8):1636-43.

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.

Fisher B et al. **Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.** *J Natl Cancer Inst* 1998;90(18):1371-88.

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.

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.

— 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

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. At the 2005 San Antonio meeting, the recurrence score was also shown to predict locoregional failure. Another valuable resource is the Adjuvant! Online computer program, developed by Dr Peter Ravdin, which calculates 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.

ONCOTYPE DX 21-GENE RECURRENCE SCORE ASSAY

Sixteen cancer and five reference genes from three studies

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

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

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

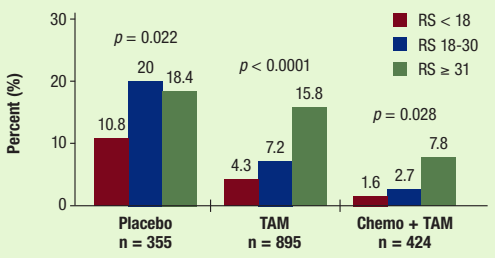
Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

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.

ASSOCIATION BETWEEN RECURRENCE SCORE AND LOCOREGIONAL FAILURE: NSABP-B-14 AND B-20

10-Year LR Failure Rates According to Treatment and RS Category



RS = recurrence score; LR = locoregional

SOURCE: Mamounas E et al. Presentation. San Antonio Breast Cancer Symposium 2005.

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

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

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

	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-2 0 patients.

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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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.

Mamounas E et al. **Association between the 21-gene recurrence score assay (RS) and risk of locoregional failure in node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** Presentation. San Antonio Breast Cancer Symposium 2005.

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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.

ONCOTYPE 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 ONCOTYPE 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?

Evidence from a number of recent studies suggests 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

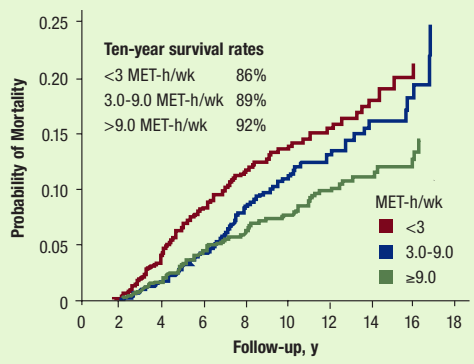
EXAMPLES OF MET SCORES

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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Winters BL et al. **Dietary patterns in women treated for breast cancer who successfully reduce fat intake: The Women's Intervention Nutrition Study (WINS).** *J Am Diet Assoc* 2004;104(4):551-9.

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

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

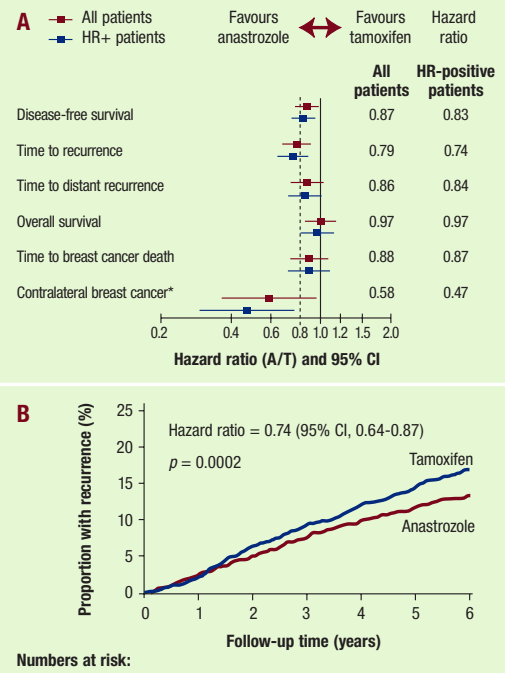
Being in the highest versus the lowest quartile of plasma total carotenoid concentration was associated with an estimated 43% reduction in risk for a new breast cancer event. Plasma carotenoids are a biologic marker of vegetable and fruit intake, so these results support the suggestion from prior studies, 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):6631-8.*

Aromatase Inhibitors as Adjuvant Therapy

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 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. A new central review of ER, PR and HER2 status in this trial was reported at San Antonio in December and demonstrated a similar benefit to the aromatase inhibitor regardless of PR status.

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

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

* 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 for breast cancer, 60-2, 2005, with permission 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 (0.40-1.50)
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. *Proc SABCS* 2003;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, December 2005.

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

	HR (95% CI)	*p*-value
Disease-free survival	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)

SOURCES: BIG 1-98 Collaborative Group. www.ibcsg.org; Thürlimann BJ. Presentation. ASCO 2005.

BIG 1-98 CENTRAL REVIEW PROJECT: DISEASE-FREE SURVIVAL (DFS) IN BIG 1-98 ACCORDING TO HORMONE RECEPTOR AND HER2-RECEPTOR STATUS

DFS	HR	95% CI
All patients (N = 4,399)	0.71	—
According to ER/PR status		
ER+/PR+ (n = 3,330)	0.67	0.51-0.88
ER+/PR- (n = 832)	0.88	0.55-1.41
According to HER2 status		
HER2+ (n = 234)	0.68	0.33-1.41

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

Presenter's conclusions:

- Benefit of letrozole versus tamoxifen is maintained irrespective of PR status in patients with ER+ tumors
- Tamoxifen resistance for ER+/PR- tumors was not observed
- Resistance to endocrine treatments for ER+/HER2+ tumors requires further evaluation

SOURCE: Viale G et al. Presentation. San Antonio Breast Cancer Symposium 2005.

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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.

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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.

Viale G et al. **Central review of ER, PgR and Her-2 in Big 1-98 evaluating letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005.

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)*

CONTROVERSIES IN SELECTION OF INITIAL TREATMENT

I think that when you look at a randomized study like ATAC where, in the first two years, more patients recur on tamoxifen than on the AI, it is pretty hard to suggest that you start tamoxifen and then switch. And, to me, until somebody shows me in a randomized fashion that those patients end up better at the end of five years, I'm approaching virtually all my postmenopausal patients up front about starting with an AI.

— Kathy I Pritchard, MD.
Breast Cancer Update *2006 (2)*

There are two key points made favoring up-front therapy with an aromatase inhibitor. The first is that potentially fatal distant metastases occur in the first 24 months at a slightly higher rate in women on tamoxifen. The second is that tamoxifen-treated women have a higher risk of serious side effects than those receiving an AI. So the argument is made that tamoxifen in those initial two years is inappropriate, and you should give the AI up front.

However, theoretical models have been created — such as Cuzick's and Burstein's — using mathematical gymnastics to determine the optimal strategy over a 10-year period in different patients. Right now, we don't have definitive evidence about which strategy is superior, and that's why the guidelines are split. I don't think that this can be resolved by further debate. It can only be resolved by further data.

— Paul E Goss, MD, PhD.
Breast Cancer Update *2006 (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. 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)*

Optimal Long-Term Endocrine Therapy

The optimal adjuvant hormonal therapy strategy for postmenopausal women is controversial. The ITA, IES, ABCSG-8 and ARNO 95 trials demonstrated significant advantages for women switching to an aromatase inhibitor (AI) after two to three years of tamoxifen, and a meta-analysis of these trials evaluating switching to the AI anastrozole presented in San Antonio demonstrated a survival advantage to the switch. Other presentations at San Antonio highlighted the distinction between switching and sequencing analyses. Ultimately, this question will be answered by the BIG FEMTA trial which randomly assigned patients to letrozole or tamoxifen initially and after two to three years. Additional data from trial MA17, which randomly assigned postmenopausal women who had completed 4.5 to six years of adjuvant tamoxifen to five years of placebo or letrozole, was also presented in San Antonio and demonstrated a significant benefit in the patients who were rerandomized from the placebo arm of MA17 to letrozole after unblinding and a benefit to increasing durations of letrozole following adjuvant tamoxifen up to 48 months.

SWITCHING OR SEQUENCING* 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)

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

EXTENDED ADJUVANT HORMONAL THERAPY 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)

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

META-ANALYSIS OF TRIALS EVALUATING SWITCHING TO ANASTROZOLE: ARNO 95, ABCSG-8 AND ITA (N = 4,006)

	Hazard ratio [95% CI]	p-value
DFS (ITT population)	0.59 [0.48-0.74]	<0.0001
OS (ITT population)	0.71 [0.52-0.98]	0.038

DFS = disease-free survival; ITT = intention to treat; OS = overall survival

Hazard ratios are for anastrozole/tamoxifen.
Hazard ratio <1.0 favors anastrozole.

"As was observed in the individual trials, this meta-analysis demonstrates that patients switched to anastrozole experience significantly fewer recurrences than those patients remaining on tamoxifen. These advantages translate into a benefit in the long-term endpoint of overall survival. Consistency of effect was seen between the three trials. …Switching to anastrozole results in a benefit in overall survival. These data confirm that postmenopausal women currently receiving adjuvant tamoxifen should be switched to anastrozole."

SOURCE: Jonat W et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 18.

MA17 POST-UNBLINDING: PATIENTS SWITCHING FROM PLACEBO TO LETROZOLE (N = 1,655) VERSUS CONTINUING PLACEBO (N = 613)

	Adjusted hazard ratio [95% CI]	p-value
DFS	0.31 [0.18-0.55]	<0.0001
DDFS	0.28 [0.13-0.62]	0.002
OS	0.53 [0.28-1.00]	0.05
CBC	0.23 [0.07-0.77]	0.017

DFS = disease-free survival; DDFS = distant disease-free survival
OS = overall survival; CBC = contralateral breast cancer

Hazard ratios are for those switching to letrozole/placebo. Hazard ratio <1.0 favors switching from placebo to letrozole.

Note: Patients who completed five years of letrozole on MA17 are eligible for rerandomization on NCIC-CAN-MA17R comparing letrozole x five years versus placebo x five years.

SOURCES: Goss PE et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 16; National Cancer Institute of Canada Clinical Trials Group, September 2005.

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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. **Updated analysis of NCIC CTG MA17 post unblinding.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 16.

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.

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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.

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.

Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 trial, ABCSG Trial 8, and the ITA trial.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 18.

SWITCHING TO 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 (AI). We have excellent data for both exemestane and anastrozole. 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.

— 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)

There is a lot of interesting statistical work that has come out of Dana-Farber looking at modeling of outcomes from natural history studies and meta-analyses. The model attempted to see if a sequencing strategy might be better than five years of an aromatase inhibitor. And their publication suggests that it would be, which is a fascinating hypothesis. My feeling is that we should find out, and the BIG 1-98 study is designed to answer that question.

Until 1-98 shows a difference in outcome for patients who receive five years of letrozole versus a sequence of tamoxifen and letrozole, I think that the standard of care for a newly diagnosed patient is to give them five years of an aromatase inhibitor.

— Kevin R Fox, MD (Interview, September 2005)

I have been impressed by the results of MA17. This is an indication that hormone receptor-positive patients are extremely difficult to cure and are at risk of relapse five, 10, 12 years after diagnosis.

On the other hand, we clearly have an increasing number of active endocrine agents. I think the optimal therapy in the future is going to be a smart sequence of agents covering at least 10 years. And I think it's because of this that I don't like the idea of giving an AI up front to everybody.

Maybe you can give an AI for 10 years, but nobody knows that. And there are patients who are going to develop resistance to the drug. So in view of that, I tend to look at the profile of the tumor and if I'm dealing with a highly endocrine-responsive tumor, with low proliferation genes, I think there is a very low risk of relapse for this patient if you put her on tamoxifen for two years.

— Martine J Piccart-Gebhart, MD, PhD.
Breast Cancer Update *2006 (2)*

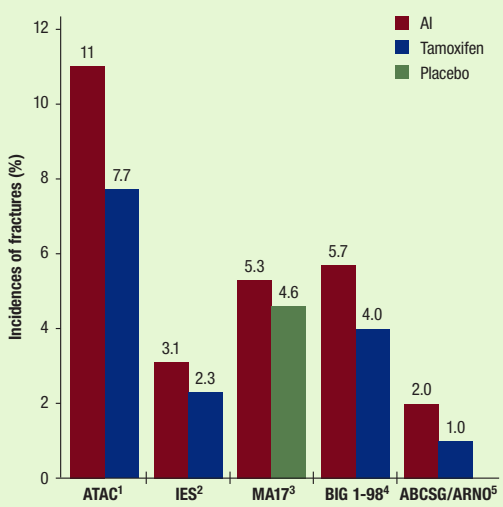
It is important to study the duration of aromatase inhibitor therapy. The NSABP will take patients who complete five years of an aromatase inhibitor or took tamoxifen for two to three years and then switched to an aromatase inhibitor and randomly assign them to either continue an aromatase inhibitor — 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)*

Short- and Long-Term Adverse Events of Endocrine Therapy with Tamoxifen and Aromatase Inhibitors

The long-term toxicities associated with adjuvant tamoxifen have been well delineated, with particular concerns about increased risk of thromboembolic events, endometrial cancer and gynecologic procedures. Several recent trials have demonstrated an efficacy advantage for the third-generation aromatase inhibitors compared to tamoxifen but have revealed a higher incidence of arthralgias and fractures. Preliminary data suggest that there may be distinct differences in the toxicities of anastrozole, letrozole and exemestane, particularly with regard to serum lipids and cardiovascular events. The LEAP trial reported at the 2005 San Antonio Breast Cancer Symposium revealed a differential impact of the three aromatase inhibitors on serum lipids in healthy postmenopausal women. Additional studies and longer-term follow-up will be necessary to further characterize the distinct toxicity profiles of the aromatase inhibitors.

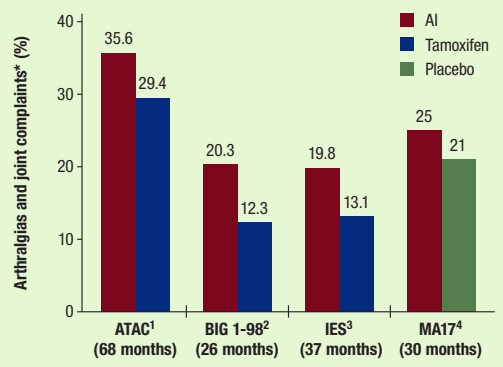
FRACTURES IN ADJUVANT AI TRIALS



AI = aromatase inhibitor; ATAC = Arimidex® (anastrozole), Tamoxifen, Alone or in 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.

JOINT SYMPTOMS AND ARTHRALGIAS IN ADJUVANT 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.

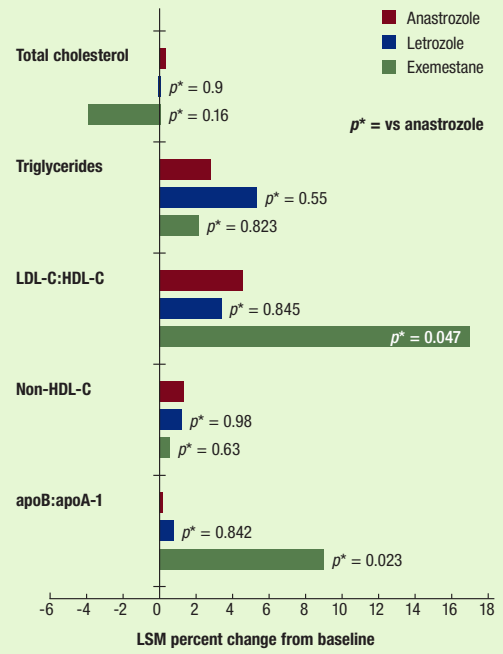
THE INCIDENCE OF GYNECOLOGIC ADVERSE EVENTS AND INTERVENTIONS IN THE ATAC TRIAL

Gynecologic event	Anastrozole (n = 3,092)	Tamoxifen (n = 3,094)	*p*-value
Vaginal bleeding	5.4%	10.2%	<0.0001
Vaginal discharge	3.5%	13.2%	<0.0001
Endometrial cancer*	0.2%	0.8%	0.02
Gynecologic intervention			
Ultrasound	8.1%	8.6%	NR
Polypectomy*	1.3%	3.1%	NR
Hysteroscopy*	1.8%	6.1%	NR
Dilatation and curettage*	1.3%	4.3%	NR
Endometrial biopsy*	1.3%	2.1%	NR
Oophorectomy	1.1%	1.9%	NR
Hysterectomy*	1.4%	5.3%	NR

NR = not reported
* Percentages calculated based on the number of patients with an intact uterus at baseline (anastrozole n = 2,228; tamoxifen n = 2,236)

SOURCE: Duffy SR, on behalf of the ATAC Trialists' Group. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2056.

LEAP STUDY: CHANGE IN LIPIDS FOLLOWING 24 WEEKS OF AROMATASE INHIBITORS IN HEALTHY POSTMENOPAUSAL WOMEN



SOURCE: McCloskey E et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2052.

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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)*

AROMATASE INHIBITORS AND MUSCULOSKELETAL DISORDERS

Arthralgia is a condition with effective available treatment options. Whereas the incidence of arthralgias 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.

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

GYNECOLOGIC INTERVENTIONS DURING ADJUVANT ENDOCRINE THERAPY

The incidence of gynecologic adverse events in the main ATAC trial was significantly lower for anastrozole compared with tamoxifen. An almost four-fold reduction in the incidence of both hysteroscopy and hysterectomy was observed in patients receiving anastrozole… .

The significant difference in the incidence of gynecologic AEs previously reported for anastrozole compared with tamoxifen in the ATAC trial appears to translate to a requirement for fewer gynecologic interventions in patients receiving the AI. Therefore, treatment with anastrozole rather than tamoxifen may avoid the psychologic distress and the associated costs of the investigation/treatment of gynecologic events in many women. These findings offer further support to the use of anastrozole as the preferred primary adjuvant treatment for postmenopausal women with early breast cancer.

— Sean R Duffy, MD et al. Poster 2056. San Antonio Breast Cancer Symposium 2005

DIFFERENTIAL EFFECTS OF THE AVAILABLE AROMATASE INHIBITORS ON SERUM LIPIDS

I wrote a paper several years ago speculating before any of these data were published that these drugs will have a different safety signal because they are structurally different. And now these data are emerging. With exemestane there is small but definite increased risk of cardiac dysfunction. If you look at the letrozole data, at 25 months there is small but definite increased risk of cerebrovascular accident (CVA) and increased risk of myocardial infarct. At 68 months' follow-up in ATAC, none of those things are true. For cardiac deaths, it is 46 versus 49 at 68 months and CVAs are substantially reduced with anastrozole compared to tamoxifen.

Also, the LEAP study took close to 102 healthy postmenopausal volunteers and gave them up to 24 weeks of anastrozole, letrozole or exemestane in a blinded fashion. The study looked at their effects on lipids and demonstrated that these effects are totally different between these drugs, specifically with the steroidal compound. So I think we have to be cognizant of this. I do not think we can say, "An AI is an AI and just pull one out of a hat and use it."

— Aman U Buzdar, MD. Meet The Professors Session San Antonio Breast Cancer Symposium 2005

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 experienced ovarian ablation from chemotherapy, and a subset analysis demonstrated a benefit of goserelin in patients who continued to menstruate after chemotherapy. Ongoing clinical trials — SOFT and TEXT — 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 help 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 (Closed)	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
* The PERCHE trial has closed. Accrual as of December 16, 2005 = 15/1,750.

SOURCES: www.ibcsg.org; NCI Physician Data Query, January 2006.

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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Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen — Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** *Breast Cancer Res Treat* 2004;Abstract 6.

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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 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)*

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)*

Tamoxifen remains the mainstay of treatment for premenopausal patients. Certainly, in Europe there is a very strong feeling that the published data seem to indicate that the addition of ovarian ablation to tamoxifen is superior to either of those modalities alone. In Europe, it's very hard to convince the vast majority of oncologists that the question of treatment approach in these patients has not already been answered.

However, the fact that we have the SOFT, TEXT and PERCHE* trials examining this very issue indicates that, at least in the minds of most North American oncologists, the question remains unanswered as to the best adjuvant therapy for premenopausal patients. The answers are not in and won't be in for many years. In the meantime, oncologists are stuck deciding what to do.

Do you or don't you believe that the addition of ovarian ablation adds to orally administered hormonal therapy? Certainly, you cannot use an aromatase inhibitor in premenopausal patients and expect it to work unless you render them postmenopausal.

* The PERCHE trial has closed. Accrual as of December 16, 2005 = 15/1,750.

— Charles L Vogel, MD.
Breast Cancer Update *2005 (9)*

Research To Practice: Adjuvant Endocrine Therapy

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 emerging research results but also evaluates, through needs assessment, the implementation of research results by physicians in practice. Data from the *Breast Cancer Update* Patterns of Care Study, a survey conducted in September 2005 of breast cancer investigators and 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%	86%	11%	11%	3%	3%
After 2 to 3 years of adjuvant tamoxifen	17%	37%	12%	18%	71%	45%
After 5 years of adjuvant tamoxifen	5%	19%	90%	73%	5%	8%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	63%	72%	78%	80%	92%	83%
Letrozole	5%	—	4%	—	4%	—
Exemestane	—	2%	—	—	—	2%
Tam x 5y	5%	4%	—	4%	—	4%
Tam x 2-3y → AI	25%	16%	16%	8%	4%	9%
Tam x 5y → AI	2%	6%	2%	8%	—	2%

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

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	2%	16%	2%	12%	—	6%
Start letrozole	98%	78%	88%	62%	20%	18%
Start exemestane	—	2%	—	2%	—	2%
Use no further hormonal therapy	—	2%	10%	24%	80%	74%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	5%	24%	2%	4%	5%	8%
Stop tamoxifen	—	—	—	2%	—	—
Stop tamoxifen and switch to exemestane	72%	38%	70%	40%	67%	36%
Stop tamoxifen and switch to anastrozole	14%	26%	19%	40%	21%	44%
Stop tamoxifen and switch to letrozole	9%	12%	9%	14%	7%	12%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

CHOICE OF 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	47%	52%	47%	50%	37%	46%
Tam x 5y → AI	9%	10%	7%	10%	9%	12%
Tam x 2-3y → AI	—	4%	—	4%	—	4%
Tam + LHRH or OA	20%	20%	11%	20%	12%	26%
AI + LHRH or OA	22%	6%	33%	6%	33%	6%
Other	2%	6%	2%	4%	9%	4%
None	—	2%	—	6%	—	2%

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

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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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. 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)*

2004 ASCO TECH ASSESSMENT ON THE USE OF ADJUVANT AROMATASE INHIBITORS

Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, or 5 years.

— Eric P Winer, MD et al.
J Clin Oncol *2005;23:619-29.*

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

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

BCIRG 001: ADJUVANT TAC VERSUS FAC

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

KPS = Karnofsky performance status

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hazard ratios < 1 indicate values in favor of TC

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

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

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

DFS = disease-free survival

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

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

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

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

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

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

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

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

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

BCIRG 001: ADJUVANT TAC VERSUS FAC

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

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

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

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

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

CURRENT STATUS OF DOSE-DENSE CHEMOTHERAPY

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

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

ECOG-E1199 EVALUATING TAXANE TYPE AND SCHEDULE

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

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

ADJUVANT DOCETAXEL/CYCLOPHOSPHAMIDE IS SUPERIOR TO AC

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

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

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

Current Trials of Adjuvant Chemotherapy

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

ONGOING PHASE III TRIALS OF ADJUVANT CHEMOTHERAPY

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

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

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

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

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

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

Eligibility	Operable, invasive breast cancer Node-positive
ARM 1	TAC q3wk x 6
ARM 2	AC q2wk x 4 → paclitaxel q2wk x 4
ARM 3	AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4

Primary prophylaxis with PEG-G or G is required.

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

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

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

RANDOMIZED PHASE III ADJUVANT TRIAL OF AC VERSUS PACLITAXEL

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

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

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

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

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INTEGRATING DOSE DENSITY INTO CLINICAL TRIALS

CALGB-40101 incorporates the every two-week schedule comparing paclitaxel to AC in patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-on testament. It's not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it's worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it's worth it.

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

NSABP-B-38 TRIAL

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

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

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

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

ROLE OF TAXANES AS ADJUVANT THERAPY

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

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

ADJUVANT CLINICAL TRIALS INCORPORATING CAPECITABINE

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

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

Research To Practice: Adjuvant Chemotherapy

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 survey of breast cancer clinical investigators and randomly selected US-based medical oncologists, are presented here. In patients with node-positive tumors, dose-dense AC → paclitaxel is the most common choice. AC is the most common regimen utilized in patients with node-negative tumors. Adjuvant chemotherapy is less frequently utilized in older patients, particularly octogenarians.

CLINICAL USE OF ONCO*TYPE* DX ASSAY

Have you ordered the Onco*type* DX assay?		
Yes	80%	34%
No	20%	66%
If you have ordered this assay, in how many patients? (Mean)	8	5
How helpful was this test in your treatment decisions? (N = 17)		
Very helpful	26%	18%
Somewhat helpful	61%	64%
Not helpful	13%	18%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

CLINICAL USE OF ADJUVANT TAXANES

How many times a month do you start a breast cancer patient on a taxane?		
Mean	6	5
What percent of your patients in each of the following categories receiving adjuvant chemotherapy receive adjuvant taxanes?		
Node-negative (all)	32%	28%
High-risk, node-negative	70%	58%
Node-positive	92%	90%
What percentage of your adjuvant taxane use is with each of the following agents?		
Docetaxel	33%	42%
Paclitaxel	67%	58%
Do you most often prescribe the taxane after or combined with AC when using AC and a taxane?		
After AC	82%	86%
Combined with AC	9%	14%
Other	9%	—

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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%	11%	14%	2%	—
AC x 4 q2wk	—	—	—	—	2%	2%	5%	2%
FAC or FEC x 6	—	—	—	—	2%	6%	—	2%
AC x 4 → paclitaxel x 4 q3wk	—	6%	—	6%	—	6%	—	—
AC x 4 → paclitaxel x 4 q2wk	53%	44%	55%	44%	24%	14%	2%	2%
AC x 4 q3wk → paclitaxel qwk x 12	7%	4%	7%	8%	9%	8%	2%	2%
AC x 4 → docetaxel x 4 q3wk	—	2%	—	4%	—	8%	—	—
AC x 4 → docetaxel x 4 q2wk	9%	18%	9%	18%	7%	6%	2%	2%
CMF	—	—	—	—	7%	18%	—	8%
TAC (docetaxel) x 6	27%	22%	20%	16%	2%	2%	—	2%
Other	4%	—	9%	—	9%	2%	—	2%
No chemotherapy	—	—	—	—	27%	14%	87%	78%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	39%	44%	34%	34%	2%	10%	—	4%
AC x 4 q2wk	11%	12%	7%	10%	—	6%	—	—
FAC or FEC x 6	14%	6%	5%	6%	—	2%	—	—
AC x 4 → paclitaxel x 4 q3wk	—	4%	—	2%	—	—	—	—
AC x 4 → paclitaxel x 4 q2wk	9%	10%	5%	8%	—	2%	—	—
AC x 4 → docetaxel x 4 q2wk	—	10%	—	4%	—	2%	—	—
CMF	7%	8%	5%	8%	—	10%	—	10%
TAC (docetaxel) x 6	2%	2%	2%	—	—	—	—	—
Other	2%	2%	5%	4%	—	—	—	—
No chemotherapy	16%	2%	37%	24%	98%	68%	100%	86%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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ONCOTYPE 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 Onco*type* 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)*

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 use this regimen. We also saw in San Antonio [2004] 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)*

One of the things that's interesting about Dr Berry's presentation at San Antonio in 2004 is that in the three CALGB/Intergroup studies, the particular correlation between a greater degree of benefit in the ER-negative population than the ER-positive population was absolutely consistent. That's not consistent across all trials, however, and in many trials that correlation is not seen. One of the trials in which that's not seen is the TAC versus FAC trial. In fact, there was an equivalent amount of benefit for the TAC regimen over FAC in both the ER-negative population and the ER-positive population.

It's interesting that, if you look at the dose-dense study, there was essentially no additional benefit for making the therapy dose-dense in terms of overall survival in the ER-positive population. Almost all of the benefit was carried by the ER-negative population. Theoretically, if you compared TAC and dose-dense chemotherapy, maybe they would be fairly equal in the ER-negative populations, but in ER-positive populations, TAC might be better. I think that's a very speculative thing to say, but it will be tested.

There's an NSABP trial that has the dose-dense regimen being compared to the TAC regimen. It will be interesting to see which of the regimens is better, specifically to see if there can be identifiers that select one regimen over the other in given subsets of the patients.

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

Adjuvant Trastuzumab Clinical Trial Results

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 and 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 (updated in San Antonio) which demonstrated that adjuvant trastuzumab could improve disease-free survival when started after a variety of chemotherapy regimens. At the San Antonio meeting, data were also presented from BCIRG 006 in which adjuvant trastuzumab was found again to significantly improve disease-free survival with both AC → docetaxel and a nonanthracycline-containing chemotherapy regimen of carboplatin plus docetaxel. These four landmark studies will 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, December 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.

BCIRG 006 INTERIM EFFICACY ANALYSIS (N = 3,222)

	Median follow-up	AC-docetaxel/trastuzumab	Docetaxel/carboplatin/trastuzumab
Hazard ratios for disease-free survival relative to AC-docetaxel	23 months	0.49 [95% CI: 0.37-0.65] $p < 0.0001$	0.61 [95% CI: 0.47-0.79] $p = 0.0002$

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

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]	< 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]	< 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]	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 endpoint (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

SOURCES: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72; Gelber RD et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

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Baselga J et al. **Future options with trastuzumab for primary systemic and adjuvant therapy.** *Semin Oncol* 2004;31(5 Suppl 10):51-7.

Gelber RD on behalf of the HERA Study Team. **Trastuzumab (Herceptin) following adjuvant chemotherapy significantly improves disease-free survival in HER2-positive early breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

Nabholtz JM et al. **HER-2 positive breast cancer: Update on Breast Cancer International Research Group trials.** *Clin Breast Cancer* 2002;3(Suppl 2):75-9.

Perez EA et al. **NCCTG N9831 May 2005 update.** Presentation. 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.

Slamon D et al. **Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2-positive early breast cancer patients: First interim efficacy analysis.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

Spicer J et al. **Adjuvant trastuzumab for HER2-positive breast cancer.** *Lancet* 2005;366(9486):634.

COMBINED ANALYSIS: NSABP-B-31 AND 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.

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 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 Onco*type* 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***

In the HERA trial, node-negative patients were allowed to enter if their tumor size was greater than one centimeter. It was the only criterion. We didn't require other aggressive features such as high proliferation or the absence of hormone receptors. It was purely based on pathological size. I don't see why these women would not derive a substantial benefit with trastuzumab and provided these women are well informed about cardiotoxicity risk, and are not elderly, we are discussing the possibility of adjuvant trastuzumab with them.

— Martine J Piccart-Gebhart, MD, PhD.
(Interview, December 2005)

Unresolved Issues in the Use of Adjuvant Trastuzumab

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. Another important research issue 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 — presented in San Antonio in December — reveal a benefit for both AC → docetaxel/trastuzumab and docetaxel/carboplatin/trastuzumab. Another important research issue is the optimal duration of adjuvant trastuzumab, which is being addressed in the HERA trial comparing one- to two-year treatment.

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
FinHer	Node-positive or high-risk node-negative	Docetaxel → FEC* Vinorelbine → FEC* *HER2-positive further randomized to H qwk x 9 weeks vs no H	Brief duration of H Effect of combination with potentially synergistic chemotherapy

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

SOURCES: Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7; Joensuu H et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2; NCI Physician Data Query, September 2005.

SEQUENTIAL VERSUS 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

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

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

PROTOCOL-DEFINED CARDIAC EVENTS

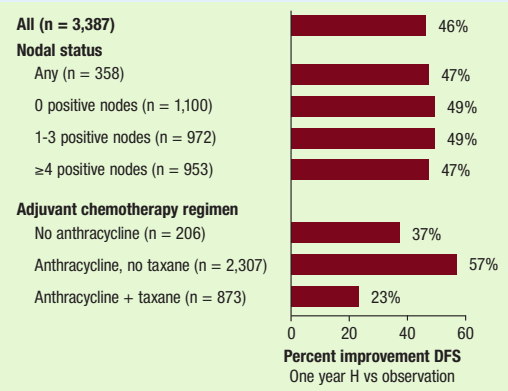
Trial	Arm of study	Protocol-defined cardiac event rate*
BCIRG 006[1]	AC → D AC → DH CDH	1% 2% 1%
NSABP-B-31[2]	AC → TH AC → T	4% 1%
NCCTG-N9831[3]	AC → T AC → T → H AC → TH → H	0% 2% 3%
BIG 1-01, HERA[4]	Observation One year H	2% 8%

AC = doxorubicin/cyclophosphamide; D = docetaxel; H = trastuzumab
C = carboplatin; T = paclitaxel

* Note that the definition of cardiac events varied between protocols

SOURCES: [1] Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1. [2] Romond EH et al. *N Engl J Med* 2005;353:1673-84. [3] Perez EA et al. Presentation. ASCO 2005;Abstract 556. [4] Gelber RD. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

HERA TRIAL: RELATIVE REDUCTION IN RECURRENCE RATE



DFS = disease-free survival; H = trastuzumab

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

SELECT PUBLICATIONS

Gelber RD on behalf of the HERA Study Team. **Trastuzumab (Herceptin) following adjuvant chemotherapy significantly improves disease-free survival in HER2-positive early breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

Joensuu H et al. **Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: The FinHer trial.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2.

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.

Slamon D et al. **Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: First interim efficacy analysis.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

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

What was particularly exciting about Dr Slamon's presentation was that it appears that he has identified a predictive marker for who requires anthracyclines in this population. Mike Press from UCLA looked at the little strip of DNA that's amplified in HER2-driven breast cancer, and noted that some of the amplicons were short and only included the HER2 gene, but some were substantially longer and also included the topoisomerase2 alpha gene (TOPO2A). TOPO2A is the target for anthracyclines. And to everyone's pleasant surprise, in the one third of patients who had coamplification of the HER2 and TOPO2 genes, the anthracycline was very effective.

What they found for the two thirds of patients who did not have the coamplification — where only HER2 was amplified — TCH seemed to be superimposable over the top of the anthracycline-containing arm.

— John Mackey, MD (Interview, December 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, peerwise, 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

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 cross over 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)

OPTIMAL DURATION OF ADJUVANT TRASTUZUMAB

The FinHer trial was a provocative study. It was a small study, but it looked at a short duration of trastuzumab exposure, on the order of nine weeks, and it suggested that women who got even a short exposure of trastuzumab did better than women who did not receive trastuzumab. That underscores the fact that the one-year duration of trastuzumab chosen for the major adjuvant trials was an arbitrary time point.
I think now that we've established a principle of therapy, it is going to be important to nail down the optimal duration and sequencing.

— Harold J Burstein, MD, PhD. Meet The Professors Session San Antonio Breast Cancer Symposium 2005

Research To Practice: Adjuvant Trastuzumab

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 post-ASCO survey of breast cancer investigators and 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 commonly 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 — presented at the San Antonio meeting in December — 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, 3 positive nodes	
Chemotherapy alone	20%	30%	2%	14%	—	6%
Trastuzumab + chemotherapy	78%	70%	98%	86%	100%	94%
AC	9%	12%	6%	14%	—	—
AC → paclitaxel	56%	40%	79%	48%	82%	68%
TAC	2%	—	—	4%	—	10%
FAC/ FEC x 6	—	6%	—	4%	—	—
AC → docetaxel	7%	12%	9%	16%	14%	16%
Other	4%	—	4%	—	4%	—

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	76%	58%	96%	82%	96%	84%
One year after completion of chemotherapy	50%	32%	70%	54%	82%	58%
Two years after completion of chemotherapy	2%	8%	14%	14%	36%	38%
Four years after completion of chemotherapy	—	4%	5%	8%	9%	22%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	7%	22%
In most or all node-positive and high-risk, node-negative patients	91%	58%
In some node-positive patients	—	4%
In some node-positive and high-risk, node-negative patients	2%	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	100%	90%	100%	90%	84%	66%	31%	38%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	4%	20%
Concurrently, with all chemotherapy	—	20%
Sequentially, after the completion of anthracycline portion of chemotherapy but concurrent with taxane	96%	60%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

DEFINING HER2 POSITIVITY

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

FISH+	36%	34%
IHC 3+	—	4%
Both FISH+ and IHC 3+	9%	12%
Either FISH+ or IHC 3+	55%	50%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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)*

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

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

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.

Neoadjuvant Trastuzumab in HER2-Positive Breast Cancer

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. These data were updated at the San Antonio Breast Cancer Symposium in December. 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

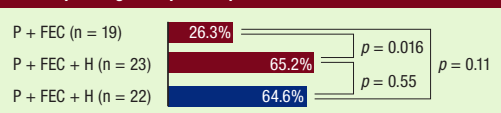
Accrual: 42 (Early closure by DSMB) + 22*

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

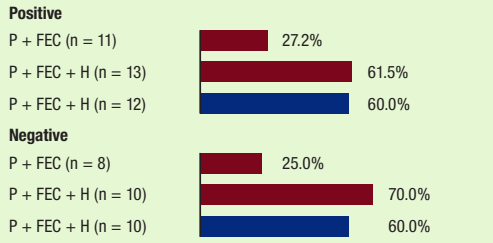
H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly

* An additional 22 patients were treated on protocol with chemotherapy + H after closure of control arm

Overall pathologic complete response



Pathologic complete response by hormonal receptor status



"Additional data support the initial observation that this approach can result in high pCR in patients with HER-2 positive breast cancer. With additional follow-up of initial study population, the efficacy and safety data remain unchanged."

P = paclitaxel

SOURCE: Buzdar AU et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5049.

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
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, January 2006.

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: Buzdar AU. Personal communication, September 2005.

SELECT PUBLICATIONS

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.

Buzdar AU et al. **Prospective data of additional patients treated with neoadjuvant therapy with paclitaxel followed by FEC chemotherapy with trastuzumab in HER2 positive operable breast cancer, and an update of initial study population.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5049.

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.

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

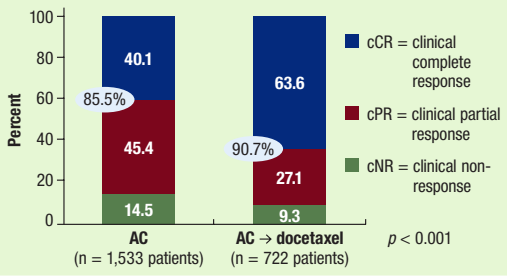
NSABP-B-27, which evaluated the addition of docetaxel to neoadjuvant AC, demonstrated that neoadjuvant docetaxel improved the pathologic complete response rate but not overall or disease-free survival. Relapse-free survival was significantly higher in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. At the 2005 San Antonio Breast Cancer Symposium, data from a Phase III trial showed superior efficacy with preoperative docetaxel/capecitabine versus doxorubicin/cyclophosphamide. A new generation of neoadjuvant trials is evaluating novel strategies, including dose-dense chemotherapy, *nab* paclitaxel, and bevacizumab/docetaxel.

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

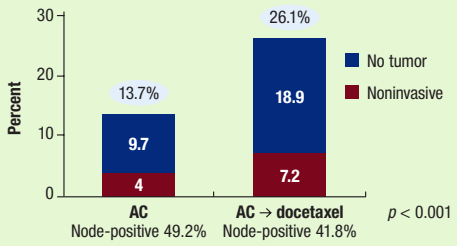
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

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 et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 26.

DOCETAXEL/CAPECITABINE (TX) VERSUS DOXORUBICIN/CYCLOPHOSPHAMIDE (AC)

Accrual: 209 (Closed)

Eligibility	Stage II/III breast cancer Axillary lymph node involvement
ARM 1	TX → surgery → AC
ARM 2	AC → surgery → TX

TX = (docetaxel 75 mg/m^2 day 1 + capecitabine 1,000 mg/m^2 BID days 1-14) q3wk x 4

AC = (doxorubicin 60 mg/m^2 day 1 + cyclophosphamide 600 mg/m^2 day 1) q3wk x 4

Parameter	AC (n = 101)	TX (n = 103)	p-value
Clinical overall response	67%	84%	0.0047
Complete response	4%	5%	NR
Partial response	63%	79%	NR
Pathological complete response Tumor Lymph nodes	 10% 23%	 23%* 33%	 NR NR
Stable disease	23%	14%	NR
Progressive disease	8%	1%	NR
Breast conservation rate Stage II Stage III	 70% 62%	 84% 55%	 NR NR

NR = not reported
* Significantly more primary tumor pathological complete responses were seen in patients with ER/PR-positive breast cancer who received TX (p = 0.006)

SOURCE: Lee KS et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5052.

ONGOING TRIALS OF NEOADJUVANT CHEMO

Protocol	Phase	N	Regimen(s)
NSABP-B-40 (pending activation)	III	1,200	AC x 4 → docetaxel 100 mg/m^2 x 4 AC x 4 → (docetaxel 75 mg/m^2 + capecitabine 825 mg/m^2 BID d1-14) q3wk x 4 AC x 4 → (docetaxel 75 mg/m^2 + gemcitabine) x 4
JHOC-J0266 JHOC-03012301	II	40	Docetaxel + pegfilgrastim q2wk x 4
EORTC-10994	III	1,850	One of three regimens of FEC Docetaxel → epirubicin + docetaxel
NCCTG-N0338	II	25-58	Docetaxel + carboplatin + pegfilgrastim q2wk x 4
NSABP FB-AX-003	II	66	*Nab* paclitaxel qwk x 12 → FEC q3wk x 4
ID01-580	III	930	Paclitaxel qwk x 12 → FEC x 4 (Capecitabine 750 mg/m^2 BID 14d q3wk + docetaxel) x 4 → FEC x 4
UCLA-0502123-01, TORI-B-02	II	90	Bevacizumab 7.5 mg/kg q3wk → TAC + bevacizumab 7.5 mg/kg q3wk x 7 Placebo $^{\text{lower dose}}$ → TAC + placebo q3wk x 7 Bevacizumab 15 mg/kg q3wk → TAC + bevacizumab 15 mg/kg q3wk x 7 Placebo $^{\text{higher dose}}$ → TAC + placebo q3wk x 7

FEC = fluorouracil/epirubicin/cyclophosphamide

SOURCES: Livingston R. *Oncology* 2002;16(10 Suppl 12):29-32; NCI Physician Data Query, January 2006; NSABP Protocol Summary, September 2005.

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)*

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)*

PHASE III TRIAL OF DOCETAXEL/CAPECITABINE (TX) VERSUS DOXORUBICIN/CYCLOPHOSPHAMIDE (AC)

This trial randomly assigned patients with Stage II/III breast cancer to receive either TX or AC as preoperative therapy. What's interesting is that after surgery, the patients crossed over and received the opposite regimen. By the end of the trial, all the patients had received the same drugs.

In this relatively small study, TX significantly increased the pathological response rates (pCR), compared with AC, and it increased downsizing in the lymph nodes. They also noted, across a variety of toxicities, that TX was safer. They concluded, based on the pCR, TX might be a more active and superior regimen. This trial was underpowered to examine disease-free or overall survival. Even if it had been larger, it would be difficult to interpret those outcomes since all the patients received the same four agents.

— *Clifford Hudis, MD.* Breast Cancer Update *2006 (1)*

NEOADJUVANT SYSTEMIC THERAPY

Preoperative systemic treatment (PST) is a valid option not only for advanced breast cancer stages but also for operable breast cancer. We know that disease-free and overall survival after PST are equivalent to those after adjuvant therapy. Furthermore, PST is able to improve surgical treatment by increasing the rate of breast conservation surgery, which minimises psychological distress for patients fearing mastectomy. Response to PST is a predictor of long-term outcome and gives prognostic information after a short-term interval in contrast to adjuvant trials, which do not show their results until after a 5- to 10-year follow-up. … If PST is performed outside clinical trials, anthracycline/taxane-based regimens should be used, especially in sequential prolonged schedules.

— *Manfred Kaufmann, MD et al.* Breast *2005;14(6):576-81.*

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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.

Kaufmann M et al. **Preoperative (neoadjuvant) systemic treatment of breast cancer.** *Breast* 2005;14(6):576-81.

Lee KS et al. **Mature results from a randomized phase III trial of docetaxel/capecitabine (TX) vs doxorubicin/cyclophosphamide (AC) as primary chemotherapy for patients with stage II/III breast cancer.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5052.

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.

Neoadjuvant Endocrine Therapy

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.

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

A = anastrozole; E = exemestane; T = tamoxifen

SOURCES: [1] Semiglazov V. et al. *Proc ASCO* 2005;Abstract 530; [2] Semiglazov V. et al. *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-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: NCI Physician Data Query, January 2006.

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	76.0%	75.6%	81.5%	NR
Mammographic objective response	61.9%	62.1%	71.0%	NR
Pathologic complete response	7.4%	3.3%	6.8%	NR
Breast conservation	23.9%	33.3%	34.0%	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 (cPR)	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, January 2006; www.ClinicalTrials.gov, January 2006.

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Dixon JM et al. **Anastrozole demonstrates clinical and biological effectiveness in estrogen receptor-positive breast cancers, irrespective of the erbB2 status.** *Eur J Cancer* 2004;40(18):2742-7.

Dowsett M et al. **Biomarker changes during neoadjuvant anastrozole, tamoxifen, or the combination: Influence of hormonal status and HER-2 in breast cancer — A study from the IMPACT Trialists.** *J Clin Oncol* 2005;23(11):2477-92.

Dowsett M et al. **Ki67 after 2 weeks endocrine treatment predicts relapse-free survival (RFS) in the IMPACT trial.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 45.

Ellis MJ. **Neoadjuvant endocrine therapy for breast cancer: More questions than answers.** *J Clin Oncol* 2005;23(22):4842-4.

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Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patients with hormone-dependent, locally-advanced breast cancer.** *Anticancer Res* 2004;24(2C):1315-8.

Semiglazov V et al. **Anastrozole (A) vs tamoxifen (T) vs combine (A+T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients.** *Proc ASCO* 2003;Abstract 3538.

Semiglazov V et al. **Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1-2, T3N0-1, T4N0M0).** *Proc ASCO* 2005;Abstract 530.

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 et 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.

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 20 to 30 percent of patients who respond well to neoadjuvant chemotherapy are left with 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.

When we 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.

A short-term biomarker that can predict long-term outcome on a particular therapy for early breast cancer could speed drug development and possibly help select individualised patient treatment. We showed in the IMPACT trial (SABCS 2005) that reduction in Ki67 after 2 weeks was significantly greater in patients treated with anastrozole (A) than with tamoxifen (T) or the combination (C), a result parallel to the greater RFS with A in the ATAC adjuvant trial although Ki67 change was only poorly associated with clinical response. We therefore assessed whether 2-week Ki67 was associated with RFS in this trial… .

On univariate analysis 2-week Ki67 was significantly associated with RFS (hazard ratio 2.13; 95% CI: 1.45 – 3.13, $p<0.001$) for log(2-week Ki67)… . Despite the small number of relapses so far, 2-week Ki67 was a significant predictor of RFS. This provides important further support for Ki67 being a marker of treatment benefit after short-term pre-surgical therapy. Additionally, it suggests that analysis of biomarker profiles may more accurately predict long-term outcome if conducted after short-term in vivo exposure to the treatment of choice.

— Mitchell Dowsett, PhD et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 45.

Trials of Hormonal Therapy in Metastatic Disease

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 whose disease has 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 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
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, December 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, December 2005.

PHASE III STUDY OF FULVESTRANT WITH OR WITHOUT ANASTROZOLE VERSUS EXEMESTANE

Protocol IDs: ICR-CTSU-SoFEA, NCT00253422
Target Accrual: 750 (Open)

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

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, December 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, December 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, December 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.

EFECT TRIAL

EFECT is an American and European study that randomly assigns patients who have had disease progression on 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

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. In addition, these agents have similar times to response, despite differences in their route of administration and pharmacokinetics. 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 of US Oncologists, September 2005. (n = 50)

TIME TO RESPONSE (TTR) WITH FULVESTRANT AND ANASTROZOLE IN PHASE III CLINICAL TRIALS

Data source	Median TTR (months)	Range (months)
Trial 0020		
Fulvestrant (n = 46)	3.15	0.9 - 24.9
Anastrozole (n = 36)	3.10	0.7 - 9.4
Trial 0021		
Fulvestrant (n = 36)	3.02	0.9 - 33.1
Anastrozole (n = 34)	2.96	0.8 - 20.2
Combined data (trials 0020 and 0021)		
Fulvestrant (n = 82)	3.10	0.9 - 33.1
Anastrozole (n = 70)	2.99	0.7 - 20.2

Supporting TTR data were subsequently collected from three other randomized Phase III trials of fulvestrant, anastrozole and tamoxifen in advanced breast cancer.

Conclusions and future directions:

- Median TTR was similar between fulvestrant and oral endocrine agents, such as anastrozole and tamoxifen, despite differences in their route of administration and pharmacokinetics.
- These data suggest that patients without rapidly progressive disease should be kept on endocrine treatment for at least three months to allow a response to be achieved prior to considering changing treatments.

SOURCE: Pippen JE. Poster. San Antonio Breast Cancer Symposium 2005; Abstract 5092.

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%
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

* 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.

‡ $p = 0.088$ 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.

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%	—

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

"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."

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

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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 experience disease 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)

The trials of fulvestrant conducted to date do not provide a clear indication as to where we should be using this drug. 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)

Clinical Development of a Novel Taxane, Nanoparticle Albumin-bound Paclitaxel (ABI-007), in Metastatic Breast Cancer

The taxanes docetaxel and paclitaxel are efficacious agents in the metastatic setting. However, both are associated with toxicities that limit their duration of use and combination with other agents. Nanoparticle albumin-bound paclitaxel (*nab* paclitaxel, ABI-007) is a novel taxane that was developed in an attempt to increase the therapeutic index of paclitaxel while avoiding the toxicities associated with Cremophor® delivery and steroid premedication. Recent Phase II and III studies with *nab* paclitaxel on a weekly or every three-week schedule have demonstrated a retention of efficacy with a more favorable toxicity profile in comparison to standard paclitaxel. A Phase II clinical trial to assess the activity and adverse event profile of the combination regimen of *nab* paclitaxel and gemcitabine has recently opened to patient accrual.

PHASE III TRIAL OF NANOPARTICLE PACLITAXEL (ABI-007) VERSUS PACLITAXEL IN METASTATIC BREAST CANCER

Efficacy data	All treated patients		First-line patients	
Investigator response assessments	ABI-007 (n = 229)	Paclitaxel (n = 225)	ABI-007 (n = 97)	Paclitaxel (n = 89)
Overall response rate (CR + PR)	33% (95% CI: 27-39%)	19% (95% CI: 14-24%)	42% (95% CI: 32-52%)	27% (95% CI: 18-36%)
	$p < 0.001$		$p = 0.029$	

Efficacy data	All treated patients		First-line patients	
Independent radiology review	ABI-007 (n = 215)	Paclitaxel (n = 214)	ABI-007 (n = 97)	Paclitaxel (n = 89)
Overall response rate (CR + PR)	21% (95% CI: 16-27%)	10% (95% CI: 6-14%)	29% (95% CI: 20-38%)	14% (95% CI: 6-21%)
	$p = 0.002$		$p = 0.011$	

Time to tumor progression	ABI-007 21.9 weeks	Paclitaxel 16.1 weeks	*p*-value 0.029

Toxicity data	ABI-007 (n = 229)		Paclitaxel (n = 225)		
Parameter	Grade III	Grade IV	Grade III	Grade IV	*p*-value
Neutropenia	25%	9%	31%	22%	<0.001
Sensory neuropathy	10%	0%	2%	0%	<0.001

CR = complete response; PR = partial response

SOURCE: O'Shaughnessy J et al. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 44.

RESPONSE TO *NAB* PACLITAXEL IN PHASE II STUDIES OF TAXANE- AND ANTHRACYCLINE-REFRACTORY METASTATIC BREAST CANCER

Treatment: *Nab* paclitaxel 300 mg/m^2 q3wk without premedication

Efficacy data	
Overall response rate Complete response Partial response	48% (95% CI: 35.3%-60.0%) 3% 44%
Response by prior metastatic regimens 0 1 >2	 64% (95% CI: 49.1%-79.2%) 20% (95% CI: 4.3%-48.1%) 22% (95% CI: 2.8%-60.0%)
Response by prior anthracycline therapy Anthracycline naïve Anthracycline exposed	 58% (95% CI: 38.7%-76.7%) 41% (95% CI: 24.7%-56.4%)
Response by site of dominant lesion Visceral Nonvisceral	 40% (95% CI: 24.9%-54.2%) 68% (95% CI: 47.5%-89.3%)
Median time to progression All patients Responding patients*	 26.6 weeks 48.1 weeks
Median overall survival	63.6 weeks

* Confirmed complete or partial response.

SOURCE: Ibrahim NK et al. *J Clin Oncol* 2005;23(25):6019-26.

PHASE III TRIAL COMPARING *NAB* PACLITAXEL VERSUS STANDARD PACLITAXEL

Accrual: 460 (closed)

Eligibility	Measurable metastatic breast cancer, no prior paclitaxel or docetaxel for metastatic disease
ARM 1	*Nab* paclitaxel 260 mg/m^2 with no premedications q3wk
ARM 2	Standard paclitaxel 175 mg/m^2 with premedications q3wk

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	*Nab* paclitaxel (n = 229)	Standard paclitaxel (n = 225)	*p*-value
Grade IV neutropenia	9%	22%	<0.001
Grade III sensory neuropathy	10%	2%	<0.001
Hypersensitivity (any grade)	<1%	2%	NR
Growth factors used	3%	6%	NR

NR = not reported

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803.

PHASE II STUDY OF ABI-007 AND GEMCITABINE IN WOMEN WITH METASTATIC BREAST CANCER

Protocol ID: NCCTG-N0531
Target accrual: 43 (open)

Eligibility	Metastatic breast cancer with measurable disease, no brain metastasis, no prior chemotherapy for metastatic disease
Protocol	(*Nab* paclitaxel, 125 mg/m^2 + gemcitabine 1,000 mg/m^2) d1, 8 q3wk

Treatment continues in the absence of disease progression or unacceptable toxicity.

SOURCES: NCI Physician Data Query, January 2006; Moreno-Aspitia A, Perez EA. *Clin Breast Cancer* 2005;6(4):361-4.

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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):7794-803.

Compared with three-weekly polyoxyethylated castor oil-based paclitaxel, ABI-007 would seem to have several advantages. First, efficacy with respect to response and time to progression seems superior. Second, and arguably most importantly, this is a taxane that can be given three-weekly, in 30 minutes, and without premedication. For patients with a contraindication to steroids, this is a major advantage. In addition, the lower incidence of myelosuppression favors ABI-007, and although sensory neuropathy was more common, this was reversible and relatively short lived for the majority of patients.

— Mark Harries, MD et al.* J Clin Oncol *2005;23(31):7768-71.

The ability to deliver drugs more safely offers a real potential benefit. Even if the randomized trial, perhaps, didn't show a higher response rate or a modestly longer time to progression compared to paclitaxel (O'Shaughnessy 2003), simply not having to premedicate and not having to worry about serious allergic reactions, in my mind, would make *nab* paclitaxel the obvious choice.

— Andrew D Seidman, MD.* Breast Cancer Update *2005 (8)

An interesting observation, corroborated in the pivotal trial and in the weekly trial that Joanne Blum reported (Blum 2003), is that the behavior of the neuropathy appears to be slightly different than that seen with standard paclitaxel. Although we don't have sufficient data to be absolutely definitive, there is a suggestion that with *nab* paclitaxel the neuropathy is much shorter lived — on the order of 10 days to three weeks — and it tends to diminish to a point where you can re-treat the patients. That's something that warrants further evaluation.

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

NANOPARTICLE PACLITAXEL VERSUS OTHER TAXANES

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 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)

The availability of *nab* paclitaxel is a welcome advance in drug delivery. Combining paclitaxel tightly with a nanoparticle allows it to dissolve without the use of Cremophor, which is one of the compounds in the original paclitaxel formulation that causes acute allergic reactions and necessitates the use of steroids. Evidence also exists from laboratory models that you may have better tumor penetration with *nab* paclitaxel.

What is happening in humans is hard to know, but in a head-to-head study, the clinical endpoints of response rate and time to progression were actually improved with *nab* paclitaxel compared to the original paclitaxel formulation. It was a difficult comparison because the doses weren't the same. It may be that *nab* paclitaxel was more tolerable and patients were able to receive a higher dose; therefore, they had a better response.

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

Taxanes in the Metastatic Setting

The role of taxanes in patients with metastatic breast cancer is evolving. A recent Phase III trial demonstrated that every three-week regimen of docetaxel has better efficacy than every three-week paclitaxel. A Phase III trial found paclitaxel with greater efficacy when administered weekly rather than every three weeks, and 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. A recently conducted meta-analysis concluded there was no overall survival advantage due to the use of taxanes alone or combined with anthracyclines in the first-line treatment of patients with metastatic breast cancer. 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
Grade III/IV hematologic adverse events	**Docetaxel (n = 222)**	**Paclitaxel (n = 222)**	***p*-value**
Neutropenia	93.3%	54.5%	<0.0001
Febrile neutropenia	14.9%	1.8%	<0.001
Anemia	10.4%	7.3%	0.24
Thrombocytopenia	4.6%	2.8%	0.31

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

PHASE II TRIALS OF WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

Grecea et al[1]

ARM 1	Docetaxel 35 mg/m^2 qwk x 8-12 weeks (median = 10 weeks)
ARM 2	Docetaxel 100 mg/m^2 q3wk x 6 cycles

Tabernero et al[2]

ARM 1	Docetaxel 40 mg/m^2 qwk x 6 weeks, then two weeks off*
ARM 2	Docetaxel 100 mg/m^2 q3wk*

Trial	Grecea et al[1]		Tabernero et al[2]	
Parameter	**Weekly (n = 25)**	**3-weekly (n = 35)**	**Weekly (n = 41)**	**3-weekly (n = 42)**
Intent-to-treat overall response rate	36%	42%	34%	33%
Median time to progression (months)	5.2	5.8	5.7	5.3
Incidence of Grade III/IV adverse events	30	64	44	96
Number of patients experiencing Grade III/IV adverse events	12	23	20	31

* Treatment continued until disease progression or unacceptable toxicity.

SOURCES: [1] Grecea D et al. *Proc ASCO* 2005;Abstract 736.
[2] Tabernero J et al. *Ann Oncol* 2004;15(9):1358-65.

CALGB-9840: PHASE III STUDY COMPARING WEEKLY VERSUS THREE-WEEKLY PACLITAXEL (N = 738)

Efficacy end point	Weekly paclitaxel	3-weekly paclitaxel	HR	*p*-value
Tumor response rate	40%	28%	NR	0.017
Time to progression (months)	9	5	1.45	0.0008
Overall survival (months)	24	16	1.19	0.17
Grade III/IV toxicity	**Weekly paclitaxel**	**3-weekly paclitaxel**	**HR**	***p*-value**
Sensory neuropathy	23%	12%	NR	0.001
Motor neuropathy	8%	4%	NR	0.04
Granulocytopenia	5%	15%	NR	0.013

HR = hazard ratio; NR = not reported

SOURCE: Seidman AD et al. Presentation. ASCO 2004;Abstract 512.

META-ANALYSIS OF TRIALS OF TAXANES (T) ALONE OR COMBINED WITH ANTHRACYCLINES (A) IN FIRST-LINE TREATMENT

Single-agent trials, T vs A	
Overall response with taxanes	33%
Overall response with anthracyclines	38%
	T vs A, $p = 0.08$
PFS, T vs A	HR = 1.19, $p = 0.01$
OS, T vs A	HR = 1.01, $p = 0.90$
Combination trials, T-based vs A-based	
Overall response in T-based	56%
Overall response in A-based	45%
	T-based vs A-based, $p < 0.001$
PFS, T-based combination vs A-based	HR = 0.93, $p = 0.06$
OS, T-based combination vs A-based	HR = 0.95, $p = 0.23$

HR = hazard ratio

SOURCE: Piccart MJ et al. *Proc San Antonio Breast Cancer Symposium* 2005; Abstract 6086.

ERASME 3: PHASE III TRIAL OF DOXORUBICIN/ DOCETAXEL VERSUS DOXORUBICIN/PACLITAXEL IN PATIENTS WITH METASTATIC BREAST CANCER

Efficacy parameter	Doxorubicin + docetaxel (n = 107)	Doxorubicin + paclitaxel (n = 103)	*p*-value
Overall response rate	39.6%	41.8%	NS
Median disease-free survival	8.7 months	8.0 months	0.977
Overall survival	21.4 months	27.3 months	0.099

NS = not significant

SOURCE: Cassier PA et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 6087.

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Seidman AD et al. **Phase III study of weekly paclitaxel via 1-hr infusion vs standard 3-hr infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2 positive MBC and randomized for trastuzumab in HER2 normal MBC.** *Proc ASCO* 2004;Abstract 512.

Tabernero J et al. **A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer.** *Ann Oncol* 2004;15(9):1358-65.

PHASE III TRIAL OF DOCETAXEL VERSUS 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.

DOSE AND SCHEDULE OF TAXANE THERAPY

Optimizing the dose and schedule of taxane therapy to maximize antitumor activity while maintaining a favorable toxicity profile remains an important goal in MBC. Weekly, rather than the standard every-3-weeks, dosing of docetaxel and paclitaxel at lower doses is one way to provide an efficacious method of drug delivery while maintaining a favorable toxicity profile. Various studies support weekly taxane dosing as an active regimen in MBC, even in heavily pretreated, refractory disease and in elderly patients or those with poor performance status. Importantly, this regimen is associated with a low incidence of severe hematologic toxicities and acute nonhematologic toxicities.

— Alexandru Eniu, MD.* The Oncologist *2005;10:665-85.

META-ANALYSIS OF TRIALS OF TAXANES WITH OR WITHOUT ANTHRACYCLINES

Single agent A [anthracyclines, doxorubicin or epirubicin] was significantly better than single agent T [taxanes, paclitaxel or docetaxel] in terms of PFS [progression-free survival], marginally better in terms of response rate but not different in terms of OS [overall survival]. T-based combinations were significantly better than A-based combinations in terms of response rates, marginally better in terms of PFS but not different in terms of OS.

— Martine J Piccart-Gebhart, MD, PhD et al.* Proc San Antonio Breast Cancer Symposium *2005;Abstract 6086.

DOXORUBICIN/DOCETAXEL VERSUS DOXORUBICIN/PACLITAXEL

In this study paclitaxel and docetaxel in combination with doxorubicin were equivalent in terms of overall quality of life scores and efficacy. Significant differences in toxicity profile did not result in significant differences in QOL.

— PA Cassier et al.* Poster. San Antonio Breast Cancer Symposium *2005;Abstract 6087.

WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

The present study was conducted to assess the tolerability and activity of weekly and 3-weekly docetaxel in patients with anthracycline-resistant metastatic breast cancer. Weekly docetaxel 40 mg/m^2 and 3-weekly docetaxel 100 mg/m^2 produced overall response rates of 34% and 33%, respectively. The mean cumulative dose of docetaxel was similar for both treatment groups (620 and 614 mg/m^2 for the weekly and 3-weekly schedules, respectively). Although both schedules were well tolerated, the weekly regimen appears to have a more favourable toxicity profile than 3-weekly docetaxel with respect to grade 3–4 neutropenia, neurotoxicity, febrile neutropenia and stomatitis.

— Josep Tabernero et al.* Ann Oncol *2004;15(9):1358-65.

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.

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

Bevacizumab for the Treatment of Metastatic Breast Cancer

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 improve not only the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, in both the adjuvant and metastatic settings. An update of this important study was presented at the 2005 San Antonio Breast Cancer Symposium.

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

Efficacy Endpoints	Paclitaxel + bevacizumab (n = 341)	Paclitaxel (n = 339)	*p*-value
Response rate			
All patients	29.9%	13.8%	<0.0001
Measurable disease	37.7%	16.0%	<0.0001
Progression-free survival	11.4 months	6.11 months Hazard ratio = 0.51 (CI: 0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months Hazard ratio = 0.84 (CI: 0.64-1.05)	0.12
Safety Results	**Paclitaxel + bevacizumab (n = 350)**	**Paclitaxel (n = 332)**	***p*-value**
Hypertension			
Grade III	15%	2%	
Grade IV	<1%	0%	<0.0001
Thromboembolism			
Grade III	2%	2%	
Grade IV	0%	2%	NS
Bleeding			
Grade III	2%	0%	
Grade IV	<1%	0%	0.02
Proteinuria			
Grade III	1%	0%	
Grade IV	1%	0%	0.002
Neuropathy			
Grade III	22%	17%	
Grade IV	1%	1%	NS

NS = not significant

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 3.

RANDOMIZED PHASE II TRIAL OF METRONOMIC CHEMOTHERAPY ± BEVACIZUMAB

Eligibility	Stage IV disease with no prior chemotherapy for metastatic breast cancer
ARM 1	CM alone*
ARM 2	CM + bevacizumab 10 mg/kg q2wk

C = cyclophosphamide 50 mg PO qd; M = methotrexate 2.5 mg PO BID d1, 2 qwk; * Option to cross over upon disease progression

Best overall response	CM alone (n = 21)		CM + bevacizumab (n = 34)	
	N	Percent	N	Percent
Partial response	2 95% CI: 1-30%	10	10 95% CI: 15-50%	29
Stable disease	8	38	14	41
Progressive disease	9	43	9	26
Not available	2	10	1	3

SOURCE: Burstein HJ et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 4.

USE OF BEVACIZUMAB: A SURVEY OF US ONCOLOGISTS, SEPTEMBER 2005

	BCI (N = 45)	CO (N = 50)
Utilized bevacizumab to treat breast cancer off protocol	73%	4%
Have not utilized bevacizumab but intend to use it	18%	64%
Have not utilized and have no immediate intention to use it	9%	32%

BCI = breast cancer investigators; CO = community oncologists

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

CURRENT OR PROPOSED BREAST CANCER CLINICAL TRIALS EVALUATING BEVACIZUMAB

Protocol ID	Setting	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 d + methotrexate qwk x 6mo → bevacizumab q3wk x 6mo
UCLA-0502123-01	Neoadjuvant	90	Bevacizumab 7.5 mg/kg q3wk → TAC + bevacizumab 7.5 mg/kg q3wk Placebo → TAC + placebo Bevacizumab 15 mg/kg q3wk → TAC + bevacizumab 15 mg/kg q3wk Placebo → TAC + placebo higher dose
UAB-0467	Neoadjuvant	NR	Letrozole + bevacizumab 15 mg/kg q3wk x 18wk
XCaliBr† (ML18527)	Metastatic, first-line	92	Capecitabine + bevacizumab → vinorelbine + bevacizumab Capecitabine + bevacizumab → paclitaxel + bevacizumab
UCLA-0109030-03*	Locoregional relapse/metastatic	3-74	Phase I: Trastuzumab + bevacizumab escalated to maximum tolerated dose (MTD) Phase II: Trastuzumab + bevacizumab at MTD
UCLA-0501049-01	Metastatic	150	Docetaxel q3wk (Docetaxel + bevacizumab 15 mg/kg) q3wk
NCI-05-C-0022	Refractory, Metastatic, Unresectable	3-38	Bevacizumab + sorafenib to MTD → Sorafenib at MTD d1-21 → (Sorafenib d1-21 + bevacizumab d1, 15) q28d → Bevacizumab at MTD d1, 15 → (Sorafenib d1-21 + bevacizumab d1, 15) q28d

NR = not reported; * bevacizumab = 10 mg/kg q2wk; † patients with residual breast cancer following preoperative chemotherapy

SOURCES: NCI Physician Data Query, January 2006; Miller KD. *Breast Cancer Update* Meeting 2005.

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Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 3.

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005.

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9.

Schneider BP, Miller KD. **Angiogenesis of breast cancer.** *J Clin Oncol* 2005;23(8):1782-90.

Traina TA et al. **A phase II trial of letrozole in combination with bevacizumab, an anti-VEGF antibody, in patients with hormone receptor-positive metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2030.

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

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 to 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 for Metastatic Disease

Selection of systemic therapy for patients with metastatic disease is a multifaceted decision that is 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 survey conducted in September 2005 of medical oncologists and breast cancer clinical investigators 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	45%	10%	43%	10%	40%	2%
Docetaxel	23%	24%	25%	26%	2%	24%
Nanoparticle paclitaxel	—	8%	—	8%	2%	10%
Capecitabine	16%	14%	18%	14%	48%	34%
Gemcitabine	—	2%	—	2%	—	8%
Vinorelbine	—	—	—	—	2%	8%
Capecitabine + docetaxel	4%	10%	2%	6%	2%	—
Gemcitabine + paclitaxel	—	8%	—	8%	—	2%
Gemcitabine + docetaxel	4%	4%	4%	6%	—	2%
Carboplatin + docetaxel	2%	12%	2%	12%	2%	4%
Carboplatin + paclitaxel	4%	2%	4%	2%	—	—
Other	2%	6%	2%	6%	2%	2%
No chemotherapy	—	—	—	—	—	4%
Would you recommend bevacizumab for this patient?						
Percent responding "yes"	69%	36%	62%	36%	38%	18%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	42%	14%	40%	14%	41%	12%
Docetaxel	9%	22%	12%	24%	2%	24%
Nanoparticle paclitaxel	—	—	—	—	2%	10%
Capecitabine	14%	12%	16%	14%	38%	26%
Gemcitabine	—	—	—	2%	—	4%
Vinorelbine	—	—	—	—	2%	4%
Capecitabine + docetaxel	5%	6%	2%	4%	—	2%
Gemcitabine + paclitaxel	—	2%	—	—	2%	—
Gemcitabine + docetaxel	2%	4%	2%	4%	—	—
Carboplatin + docetaxel	2%	2%	2%	2%	2%	2%
Carboplatin + paclitaxel	5%	—	5%	—	—	—
AC	7%	22%	9%	18%	2%	8%
AC + docetaxel	7%	8%	5%	12%	—	—
AC + paclitaxel	—	8%	—	6%	2%	2%
Other chemotherapy	7%	—	7%	—	7%	4%
No chemotherapy	—	—	—	—	—	2%
Would you recommend bevacizumab for this patient?						
Percent responding "yes"	64%	32%	56%	34%	36%	20%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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	21%	62%	25%	60%
Exemestane	7%	2%	9%	6%
Letrozole	68%	30%	66%	30%
Tamoxifen	—	—	—	—
Fulvestrant	2%	2%	—	—
No therapy	2%	4%	—	4%
Would you recommend bevacizumab for this patient?				
Percent responding "yes"	2%	14%	—	8%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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. General oncologist data (n = 50)

CLINICAL USE OF FULVESTRANT

Do you generally use a loading dose with fulvestrant? (percent responding "yes")	53%	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)	22%	31%
Have you used fulvestrant in premenopausal patients with ER-positive metastatic disease in a nonprotocol setting? (percent responding "yes alone"/percent responding "yes, but only with ovarian suppression/ablation")	16%/32%	20%/6%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

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)*

Fulvestrant is a very good drug that has minimal toxicity, and we're not seeing the degree of joint discomfort that we see with the aromatase inhibitors. In terms of efficacy, fulvestrant seems to be equivalent to anastrozole. Based on data published this year in *Cancer*, there seems to be no difference in overall survival in the randomized trials of anastrozole versus fulvestrant. Fulvestrant is a good drug and a viable alternative to aromatase inhibitors in patients who have disease progression on tamoxifen. We do have to contend with the randomized trial of fulvestrant versus tamoxifen, where we expected a strongly beneficial effect for fulvestrant over tamoxifen, which was not forthcoming. There were some subsets in which fulvestrant appeared to be better, but the overall results were about the same.

— *Charles L Vogel, MD.* Breast Cancer Update *2005 (9)*

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