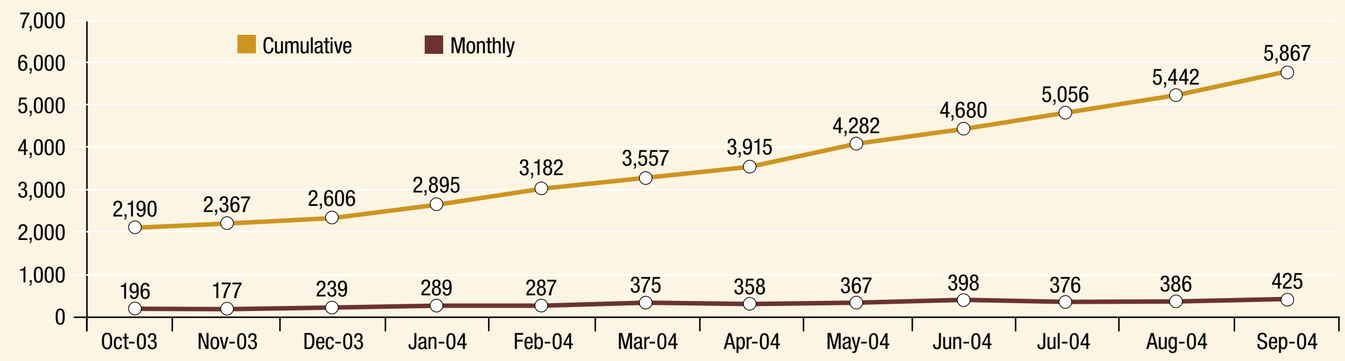
Cancer Trials Support Unit and Central Institutional Review Board

The primary goal of this system is to rapidly accelerate the pace of clinical cancer research by enabling oncologists in the United States to offer patients NCI-sponsored clinical trials and by simplifying and standardizing procedures related to participation. The Cancer Trials Support Unit (CTSU) promotes cross-group accrual among Cooperative Group members. Features include standardization of data collection and online data reporting, simplified informed consent and a Central Institutional Review Board (CIRB) process. The CIRB model shares responsibility for protection of research participants between the local IRB and the CIRB, which conducts full board review, the results of which are distributed to participating local IRBs via a confidential website.

CTSU ACCRUAL SUMMARY AS OF 09/30/04



SOURCE: CTSU correspondence, October 2004.

PHASE III BREAST CANCER TRIALS OPEN THROUGH THE CTSU

Study number	Study name	Accrual to date/goal as of date
ACOSOG-Z0011	Axillary node dissection in women with clinical T1 or T2, N0, M0 breast cancer who have a positive sentinel node	849/1900 (09/29/04)
CALGB-40101	Adjuvant CA (4 vs 6 cycles q2wk) versus paclitaxel (4 vs 6 cycles q2wk) for women with node-negative breast cancer	1221/4646 (09/27/04)
CALGB-49907	Adjuvant chemotherapy with standard regimens, CMF or AC, versus capecitabine in women 65 years and older with node-positive or high-risk node-negative breast cancer	239/720 (09/27/04)
IBCSG-24-02 (SOFT)	Adjuvant tamoxifen versus Ovarian Function Suppression (OFS) + tamoxifen versus OFS + exemestane in premenopausal women with endocrine-responsive breast cancer	75/3000 (09/30/04)
IBCSG-25-02 (TEXT)	Adjuvant triptorelin + exemestane versus triptorelin + tamoxifen in premenopausal women with endocrine-responsive breast cancer	147/1845 (09/30/04)
IBCSG-26-02 (PERCHE)	OFS + tamoxifen or exemestane ± adjuvant chemotherapy in premenopausal women with endocrine-responsive breast cancer	3/1750 (09/30/04)
NCIC-MA.20	Regional radiation therapy in early breast cancer	1051/1822 (10/04/04)
NCIC-MA.21	Adjuvant sequenced EC + filgrastim + epoetin alfa followed by paclitaxel versus sequenced AC followed by paclitaxel versus CEF for premenopausal women and early postmenopausal women with node-positive or high-risk node-negative breast cancer	1789/2100 (10/04/04)
NCIC-MA.27	Exemestane versus anastrozole ± celecoxib in postmenopausal women with receptor-positive primary breast cancer	1176/6830 (10/04/04)
NSABP-B-35	Anastrozole versus tamoxifen in postmenopausal patients with DCIS undergoing lumpectomy with radiation therapy	1157/3000 (10/04/04)
NSABP-B-36	Adjuvant FEC x six cycles versus AC x four cycles, ± celecoxib in women with node-negative breast cancer	175/2700 (10/04/04)
NSABP-B-38	Adjuvant TAC versus dose-dense (DD) AC followed by DD paclitaxel versus DD AC followed by DD paclitaxel + gemcitabine	0/4800 (10/07/04)
RTOG-98-04	Whole-breast radiotherapy versus observation ± tamoxifen in women with DCIS	468/1790 (10/04/04)
SWOG-S0012	Neoadjuvant standard AC followed by weekly paclitaxel versus weekly doxorubicin + daily oral cyclophosphamide + G-CSF followed by weekly paclitaxel for women with inflammatory and locally advanced breast cancer	247/350 (10/01/04)
SWOG-S0221	Adjuvant continuous-schedule AC + filgrastim versus every two-week AC + pegfilgrastim, followed by paclitaxel given every two weeks versus weekly for 12 weeks in women with node-positive or high-risk node-negative breast cancer	340/4500 (10/01/04)
SWOG-S0226	Anastrozole versus anastrozole + fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer	11/690 (10/01/04)

SOURCES: CTSU website (CTSU Active Protocol List & Accrual Report), October 2004; NCI Physician Data Query, October 2004.

USE OF FACILITATED REVIEW BY GROUP

Cooperative group	Number of studies on CIRB menu	Number of facilitated reviews accepted for group's studies
ECOG	15	285
CALGB	12	242
SWOG	13	185
NSABP	7	160
NCIC	2	73
RTOG	7	84
GOG	4	61
NCCTG	1	48

SOURCE: CTSU correspondence, October 2004.

CIRB PROTOCOL REVIEW OUTCOMES

78 protocols reviewed (01/22/01 – 10/01/04)	
Approved	65 (100%)
Disapproved	0 (0%)
Results of first review	
Approved	1 (1%)
Approved pending modification	65 (84%)
Disapproved	0 (0%)
Tabled*	12 (15%)

* Tabled means the project cannot be approved without significant modification or there is insufficient information available to fairly judge the protocol.

SOURCE: CTSU correspondence, October 2004.

SELECT PUBLICATIONS

Comis RL et al. **Public attitudes toward participation in cancer clinical trials.** *J Clin Oncol* 2003;21(5):830-5.

Kornblith AB et al. **Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials.** *Cancer* 2002;95(5):989-96.

Paskett ED et al. **Clinical trial enrollment of rural patients with cancer.** *Cancer Pract* 2002;10(1):28-35.

Sateren WB et al. **How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials.** *J Clin Oncol* 2002;20(8):2109-17.

Simon MS et al. **Factors associated with breast cancer clinical trials participation and enrollment at a large academic medical center.** *J Clin Oncol* 2004;22(11):2046-52.

CENTRAL INSTITUTIONAL REVIEW BOARD

"The Central Institutional Review Board (CIRB) initiative is a pilot project sponsored by the National Cancer Institute (NCI), in consultation with the DHHS Office of Human Research Protections. Created to develop an innovative approach to human subjects' protection, the unique feature of the CIRB is its 'facilitated review' process that can streamline local IRB review for national multi-center cancer treatment trials. Local IRBs enrolled in the pilot can download CIRB reviews from a confidential webpage and decide whether or not to utilize the CIRB's review for a particular protocol. This 'facilitated review' can take place rapidly. …

"A major benefit for local IRBs participating in the pilot will be the reduction in review workload while still retaining its authority to accept or reject a 'facilitated review' on a protocol-by-protocol basis."

— CIRB Website www.ncicirb.org

RECRUITMENT OF PARTICIPANTS IN CLINICAL TRIALS

"An effective national cancer program can never be implemented without patient-oriented research. This requires that individuals be willing, able, and available to participate in clinical trials. Participation in clinical trials is an opportunity not only for discovery, but also to experience the most promising and valuable new preventions, diagnoses, screening procedures, and therapies. Despite the potential therapeutic advantage of participating in clinical trials, the current number of eligible cancer patients entering clinical research studies is less than three percent. This is related primarily to the impediments to enrollment into cancer clinical trials as well as the limited funding of cooperative groups, which is the critical rate-limiting barrier to increased accrual. And even in studies where accrual is good, compliance and retention are not optimal. As a result, slow accrual and retention rates give way to delayed completion of clinical trials, resulting in cost inefficiencies, slowed translation of bench science, and potentially inequitable distribution of the risks and benefits of research."

— NCI Armitage Report http://deainfo.nci.nih.gov/advisory/BSA/bsa_program/bsactprgmin.htm

BENEFITS OF THE CTSU

The CTSU has developed a single regulatory support system. Instead of oncologists having to register and file different applications every year with each cooperative group they belong to, they register once and each group utilizes that information. The centralization of that data and the centralization of all the IRB data on a per-study basis has been very helpful. This system should ease the burden of clinical trial participation on investigators in the community and academic institutions and increase the speed in which we complete important trials, as witnessed by the recent MA17 trial evaluating letrozole after adjuvant tamoxifen. More than 5,000 patients enrolled in that study, and although the NCI of Canada led that trial, 3,500 of the patients enrolled were from the United States cooperative groups. We completed accrual to that trial in less than four years and had results about one and a half years later. The system does work, and it can rapidly provide answers to important questions.

— Jeffrey Abrams, MD

The concept behind the CTSU is that a fairly large number of physicians don't want to belong to a cooperative group, but would love to enroll their patients in clinical trials. The cooperative groups themselves were heavily involved in the development of the process. All of the major adjuvant breast cancer trials are going on the CTSU menu. Advertising the trials and educating physicians about participation is going to be important. This is a real experiment that is still being de-bugged, but I hope it works because we need more patients enrolled in these clinical trials. I suspect there is a large reservoir of oncologists who have never filled out the CTSU form — not because it's difficult, but just because no one suggested that they do it.

— George W Sledge Jr, MD

Controversies in HER2 and Estrogen Receptor Testing

27TH ANNUAL
San Antonio Breast Cancer Symposium 2

Systemic treatment of breast cancer has become an oncologic model for the use of tissue predictors of tumor response. Specifically, clinicians routinely utilize estrogen and progesterone receptor assays in considering endocrine treatment and HER2 testing when trastuzumab is an option. Estrogen receptor results may also predict response to chemotherapy, and HER2 testing may correlate with response to specific cytotoxic agents. The clinical importance of these two tissue analyses in both clinical research and practice is complicated by inconsistencies in performance and interpretation of these assays. Recent quality control reports on HER2 testing from the NSABP and Intergroup trials have led to concerns about community-based testing. Dr Craig Allred's work on inconsistent quality control of ER testing in the community has also raised concerns that selection of patients for endocrine therapy may be suboptimal.

NSABP-B-24 DATA: CLINICAL COMPARISON OF ER-NEGATIVE RESULTS FROM OUTSIDE AND CENTRAL LABS

		Events/patients (%)			
Lab	n	Placebo	Tamoxifen	Relative risk	*p*-value
Outside lab ER-negative results	64	10/39 (26%)	3/25 (12%)	0.43 (↓57%)	0.20
Central lab ER-negative results	89	11/48 (23%)	11/41 (27%)	0.99 (↓1%)	0.98

SOURCE: Allred DC. **ER status and response to tamoxifen in ductal carcinoma in situ (DCIS).** Presentation. San Antonio Breast Cancer Symposium, 2002.

ALLRED SCORE FOR ER STATUS (0-8)*

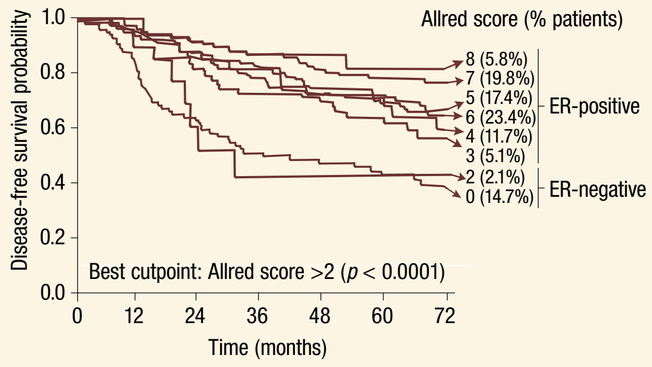
% staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	none	0	none
1	<1/100	1	weak
2	1/100 to 1/10	2	intermediate
3	1/10 to 1/3	3	strong
4	1/3 to 2/3		
5	>2/3		

* Allred Score = percent staining score + intensity score

DERIVED FROM: Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81.

ALLRED SCORING OF ER STATUS BY IHC PREDICTS RESPONSE TO ADJUVANT ENDOCRINE THERAPY

Patients receiving any endocrine therapy (n=777)



DERIVED WITH PERMISSION FROM: Harvey JM et al. *J Clin Oncol* 1999;17(5):1474-81.

DETERMINATION OF ESTROGEN RECEPTOR STATUS BY MEDICAL ONCOLOGISTS

How do you define ER positivity?	
Any staining	24%
Staining above lab cutoff	70%
Staining above individual cutoff value you determine	6%
Do you request ER status for ductal carcinoma *in situ*?	
Yes	58%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

COMPARISON OF LOCAL AND CENTRAL HER2 TESTING IN NCCTG-N9831 AND NSABP-B-31

Study	Local testing IHC 3+ confirmed by central HercepTest®	Local testing IHC 3+ HER2 gene amplification exhibited in central testing
NCCTG-N9831 (n=119)[1]	74%	66%
NSABP-B-31 (n=104)[2]	79%	79%

SOURCES: [1] Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.
[2] Paik S et al. *J Natl Cancer Inst* 2002;94(11):852-4.

HER2 STATUS FOLLOWING PREOPERATIVE TRASTUZUMAB AND PACLITAXEL

	Baseline HER2 status			
	3+ (n=32)		2+ (n=8)	
HER2 status after preoperative therapy	No. of patients	%	No. of patients	%
3+	17	53	1	13
2+	2	6	0	0
1+ or 0	4	13	3	37
Not assessable	3	9	3	37
Pathologic complete response	6	19	1	13

SOURCE: Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53.

FALSE-POSITIVE RATES FOR HER2 TESTS PERFORMED BY NSABP-APPROVED LABORATORIES

Original assay used by NSABP-approved laboratory	Central PathVysion® FISH assay not amplified
FISH (n=133)	4.5%
IHC (n=107)	2%
Total (n=240)	3%

SOURCE: Paik S. Presentation, San Antonio Breast Cancer Symposium, 2002. **Successful Quality Assurance Program for HER2 Testing in the NSABP Trial for Herceptin®.** *Breast Cancer Res Treat* 2002;76(Suppl 1);Abstract 9.

SELECT PUBLICATIONS

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;76(Suppl 1);Abstract 30.

Allred DC et al. **Prognostic and predictive factors in breast cancer by immunohistochemical analysis.** *Mod Pathol* 1998;11(2):155-68.

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

Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81.

Paik S et al. **Real world performance of HER2 testing – National Surgical Adjuvant Breast and Bowel Project Experience.** *J Natl Cancer Inst* 2002;94(11):852-4.

Press MF et al. **Comparison of HER-2/neu status determined by fluorescence in situ hybridization (FISH) in the BCIRG central laboratories with HER-2/neu status determined by immunohisto-chemistry or FISH in outside laboratories.** Poster. SABCS, 2002;Abstract 238.

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the Breast Intergroup Trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7.

Taucher S et al. **Do we need HER-2/neu testing for all patients with primary breast carcinoma?** *Cancer* 2003;98(12):2547-53.

DEFINING ER POSITIVITY

Assessment of ER status remains problematic. While the IHC method can be performed in any pathology laboratory, in some the quality control is poor. The real problem with false-negative results occurs for tumors with low levels of ER — between one and 20 percent of positively staining cells — which comprises 10 percent of patients. These patients will be labeled ER-negative and will not receive the benefit of endocrine therapy.

— Anthony Howell, MD

DEFINING ER STATUS

We are in an era in which every pathology laboratory should report the percentage of tumor cells staining positive for estrogen receptors, rather than just reporting "positive" or "negative." Negative should be defined as tumors with virtually no cells staining positively — truly "stone cold zero." Data show that women whose tumors with just a few percent of cells expressing estrogen receptors derive benefit from endocrine therapy. A common standard in the United States is for laboratories to report a specimen with less than 10 percent of tumor cells staining as being negative. When invasive breast cancer is reported to be ER-negative, you should call your pathologist and verify the numbers. It's not just academic any more; it's very important in treating patients.

— Hyman B Muss, MD

ASSESSMENT OF ER STATUS IN PATIENTS WITH DCIS

In the original NSABP-B-24 study, which randomly assigned women with DCIS to adjuvant tamoxifen or placebo, ER status was not measured. Craig Allred and the NSABP subsequently retrieved 600 to 800 blocks from that trial and found that ER status strongly influenced the benefit from tamoxifen, whereas in patients with ER-negative disease, the recurrence rates were almost identical and the small, nonsignificant benefit seen was probably related to quality control of the ER assay. Quality control in determining estrogen receptor status is an important issue. Grade I DCIS is almost always positive; if it's reported as ER-negative, one should question the accuracy of the assay.

— Seema A Khan, MD

LOCAL VERSUS CENTRAL HER2 TESTING

We were surprised when we found poor concordance between community and central laboratory HER2 testing, in terms of both HER2 protein expression and gene amplification. The data from the first 119 cases were so important that we actually changed the eligibility criteria for this trial (NCCTG-N9831). Physicians can still conduct local HER2 testing, but we test the tumor specimens again by the HercepTest® and the PathVysion® FISH assay. If neither demonstrates HER2 positivity, we send the specimen to another central laboratory and if that laboratory also finds that the tumor is HER2-negative by both assays, then we notify the physician that the patient should not participate in the trial.

— Edith A Perez, MD

INFLUENCE OF TRASTUZUMAB ON HER2 STATUS

We don't know what happens to a patient's HER2 status after they have been treated with trastuzumab. In the metastatic setting, some case series of pre- and post-treatment biopsies have reported conflicting results. Because most of the trastuzumab trials have been conducted in patients with metastatic disease, in whom it is difficult to obtain biopsies, no good database of pre- and post-treatment tumor tissues exists.

HER2 gene amplification appears to be very stable. Several studies have shown good concordance between the HER2 status in the primary tumor and the metastases. Given that level of concordance and the presumed genetic stability for HER2 amplification, I would be very surprised if trastuzumab could change HER2 gene amplification. I suspect that if one rebiopsied residual tumor after trastuzumab therapy, one would find the HER2 gene still amplified. It's just mind-boggling that we haven't done that yet. We need to do a better job of obtaining tissue for laboratory analysis.

— Mark D Pegram, MD

Chemoprevention and Management of DCIS

Tamoxifen reduced the incidence of breast cancer in women at high risk in the NSABP-P-1 and IBIS-I trials. NSABP-P-2 (the STAR trial) compares another SERM (raloxifene) to tamoxifen in that setting. Data from the ATAC trial — demonstrating an advantage to anastrozole over tamoxifen in reduction of contralateral cancers — hint toward the future use of aromatase inhibitors in a chemoprevention setting, such as the recently launched IBIS-II trial comparing anastrozole to a placebo. The widespread utilization of screening mammography has led to a dramatic increase in the number of women diagnosed with DCIS. NSABP trials B-17 and B-24 demonstrated a stepwise improvement in local and contralateral tumor control with the use of breast radiotherapy and tamoxifen in women who underwent a lumpectomy. NSABP-B-35 and IBIS-II will compare anastrozole to tamoxifen in postmenopausal patients with DCIS.

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

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

Tam = tamoxifen; OR = odds ratio; CI = confidence interval

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

CONTRALATERAL BREAST CANCER IN THE ATAC TRIAL

	Anastrozole (n=3,125)	Tamoxifen (n=3,116)
CL (invasive)	20	35
CL (DCIS)	5	5

CL = contralateral breast cancer

"Reductions in contralateral breast cancer rates remained in favor of anastrozole (OR=0.62 [0.38–1.02], p=0.062), with statistical significance achieved in the hormone-receptor positive sub-group (OR=0.56 [0.32–0.98], p=0.042)."

SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10.

ACTIVE CLINICAL TRIALS COMPARING TAMOXIFEN TO ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH DCIS

Protocol ID	Eligibility	Randomization	Target accrual
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, ages 40-70 ER/PR-positive, (>5% positive cells)	Anastrozole versus tamoxifen	4,000
NSABP-B-35, CTSU, ACOSOG-NSABP-B-35, NCCTG-NSABP-B-35, SWOG-NSABP-B-35	Postmenopausal, ER/PR-positive or borderline	Anastrozole versus tamoxifen	3,000

SOURCE: NCI Physician Data Query, September 2004.

INCIDENCE OF INVASIVE BREAST CANCER FOLLOWING RALOXIFENE THERAPY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS: MORE AND CORE TRIAL DATA

Trial	Incidence of invasive breast cancer		
	Raloxifene	Placebo	Hazard ratio
Four years of raloxifene therapy versus placebo*	1.3 per 1,000 women-years	4.7 per 1,000 women-years	0.28 (95% CI = 0.17-0.46) n=61 $p < 0.001$
Eight years of raloxifene therapy versus placebo†	1.4 per 1,000 women-years	4.2 per 1,000 women-years	0.34 (95% CI = 0.22-0.50) n=7705 $p < 0.001$

*MORE trial: Patients were randomly assigned to raloxifene 60 mg/day vs raloxifene 120 mg/day vs placebo x 4 years. Breast cancer incidence was a secondary outcome of the MORE trial.

†MORE trial followed by CORE trial in which patients were randomly assigned to raloxifene 60 mg/day vs placebo x 4 years. Breast cancer incidence was a primary endpoint of the CORE trial.

SOURCE: Martino S. Presentation. ASCO, 2004;Abstract 1000.

ONGOING OR RECENTLY CLOSED CHEMOPREVENTION TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAPO-0028-150	High-risk, postmenopausal, age 35 and over	5,100	Exemestane vs exemestane + celecoxib vs placebo
NCI-04-C-0044	High-risk, postmenopausal	72	Exemestane + celecoxib vs exemestane
SWOG-S0300	High-risk, premenopausal, age 18 and over	100	Celecoxib vs placebo
DFCI-00024, UCLA-0210012-02	High-risk based on estradiol level >9 pg/mL, postmenopausal, age 35 and over	110	Letrozole vs placebo
KUMC-HSC-8919-02	High-risk for ER-negative, premenopausal, age 18 to 55	110	Celecoxib
CHNMC-IRB-02164	High-risk, premenopausal, age 21 to 48	10	Deslorelin + estradiol + testosterone
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, PHARMACIA-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

SOURCE: NCI Physician Data Query, September 2004.

SELECT PUBLICATIONS

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.

Cuzick J. **Aromatase inhibitors in prevention—data from the ATAC (arimidex, tamoxifen alone or in combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study).** *Recent Results Cancer Res* 2003;163:96-103.

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

Fisher B et al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** *The Lancet* 1999;353(9169):1993-2000.

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.

Martino S et al. **Incidence of invasive breast cancer following 8 years of raloxifene therapy in postmenopausal women with osteoporosis: Results from the Continuing Outcomes Relevant to Evista (CORE) trial.** *Proc ASCO* 2004;Abstract 1000.

ATAC TRIAL DATA ON SECOND BREAST CANCERS

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 percent 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 for 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, ChM

CLINICAL TRIALS OF AROMATASE INHIBITORS IN DCIS

NSABP-B-35 and IBIS-II are important trials, both comparing anastrozole and tamoxifen in postmenopausal patients with DCIS. In our experience with large numbers of patients, aromatase inhibitors are better tolerated than tamoxifen. Despite the results of the randomized trials, patients complain of weight gain on tamoxifen. Other problems include hot flashes, menopausal symptoms and possibly a low level of clinical depression. Patients also worry about endometrial cancer and blood clots. With aromatase inhibitors, some arthralgias are reported, but these agents are very well tolerated.

Aromatase inhibitors have already proven to have a significant effect in invasive cancer, and it's highly likely they will impact DCIS as well. We know that the majority of DCIS lesions are likely to be ER-positive. Craig Allred has shown that age-per-age, tumor-for-tumor, DCIS is even more likely to be ER-positive than invasive cancer. If that's true, then we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

— Patrick I Borgen, MD

The NSABP study comparing tamoxifen and anastrozole for patients with DCIS is essentially a trial aimed at preventing invasive breast cancer. Aromatase inhibitors have emerged as good agents for the treatment of metastatic breast cancer, both second- and first-line, and the pivotal results from the ATAC trial demonstrated adjuvant anastrozole was more effective than tamoxifen in reducing recurrence rates and contralateral breast cancers. If patients with DCIS fail, it's usually in the ipsilateral or contralateral breast rather than in the regional nodes or distant sites. Aromatase inhibitors are well tolerated in general. In the ATAC trial, the safety profile of anastrozole was impressive. Patients had fewer thromboembolic events, endometrial cancers and menopausal symptoms than with tamoxifen, but with aromatase inhibitors we need to monitor bone density and fractures.

— Eleftherios P Mamounas, MD, MPH

ESTROGEN RECEPTOR STATUS AND TAMOXIFEN EFFICACY

NSABP-B-24 compared adjuvant tamoxifen to placebo in patients with DCIS. After four or five years of follow-up, the tamoxifen arm showed a 30 percent benefit, but we didn't understand the relationship of this response rate to the tumor's hormone receptor status. When the trial was initiated, assessing hormone receptors wasn't required, but tumors were banked to conduct biological studies. In a central lab, we later measured the estrogen and progesterone receptors by immunohistochemistry on approximately 600 paraffin blocks distributed between the two arms of the study. The data convincingly demonstrated that the benefit from tamoxifen was entirely restricted to the ER-positive cohort; the ER-negative cohort showed no evidence of benefit. Approximately 25% of DCIS cases are truly ER-negative and we can conclude from our data that tamoxifen does not reduce the recurrence rate in patients with ER-negative DCIS.

— D Craig Allred, MD

Neoadjuvant Chemotherapy

Randomized clinical trials have demonstrated that while neoadjuvant chemotherapy often downstages tumors and improves the chance for breast conservation, disease-free and overall survival are similar to that of patients who undergo postoperative therapy. A new generation of neoadjuvant studies is evaluating a variety of strategies, including dose-dense chemotherapy, taxanes, the synergistic XT combination of capecitabine and docetaxel, and other combination regimens. The neoadjuvant setting is also being utilized to evaluate new systemic agents and predictors of tumor response, including DNA microarray analysis. At this meeting, Bear and colleagues will present updated results of NSABP-B-27 evaluating sequential neoadjuvant therapy with AC → docetaxel.

NSABP-B-27 TRIAL: PHASE III RANDOMIZED STUDY OF PREOPERATIVE DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) VERSUS PREOPERATIVE AC FOLLOWED BY DOCETAXEL VERSUS PREOPERATIVE AC AND POSTOPERATIVE DOCETAXEL IN WOMEN WITH OPERABLE CARCINOMA OF THE BREAST — Closed Protocol

Eligibility	Clinically palpable, node-negative and node-positive breast cancer
ARM 1	AC x 4 → surgery
ARM 2	AC x 4 → T x 4 → surgery
ARM 3	AC x 4 → surgery → T x 4

AC = doxorubicin/cyclophosphamide; T = docetaxel
Patients undergoing breast-conserving surgery received radiation therapy.

SOURCE: NSABP website, September 2004.

NSABP-B-27: TYPE OF SURGERY AND PATHOLOGIC FINDINGS AFTER PREOPERATIVE CHEMOTHERAPY

	AC	AC → T	*p*-value
Lumpectomy	61.6%	63.7%	0.33
Pathologic CR	13.7%	26.1%	0.001
Node-negative	50.8%	58.2%	0.001
Deaths	0.1%	0.4%	—
Grade 4 toxicity	10.3%	23.4%	—

SOURCES: NSABP presentation. San Antonio Breast Cancer Symposium, 2001. Bear H et al. *J Clin Oncol* 2003;21(22):4165-74.

PHASE III RANDOMIZED STUDY OF NEOADJUVANT DOXORUBICIN, CYCLOPHOSPHAMIDE AND PACLITAXEL WITH OR WITHOUT FILGRASTIM IN WOMEN WITH INFLAMMATORY OR LOCALLY ADVANCED BREAST CANCER

Protocol ID: SWOG-S0012, CTSU
Projected Accrual: 350 patients (175 per arm) (Open)

Eligibility	Inflammatory or locally advanced breast cancer Stage IIB or IIIA/B
ARM 1	AC q3wk x 5 → T qwk x 12 → surgery
ARM 2	[A qwk + Co qd + G-CSF] x 15 → T qwk x 12 → surgery

A = doxorubicin; C = IV cyclophosphamide; Co = oral cyclophosphamide; G-CSF = filgrastim; T = paclitaxel

Within 3-6 weeks after completion of chemotherapy, patients with stable or responsive disease undergo surgical resection of tumor and affected nodes.

Study Contact:
Georgiana Ellis, MD, Chair
Southwest Oncology Group
Tel: 206-288-6711

SOURCE: NCI Physician Data Query, October 2004.

PROPOSED NSABP-B-27R PREOPERATIVE CHEMOTHERAPY REPLACEMENT TRIAL

AC q3wk ↔ docetaxel q3wk → surgery
AC q3wk ↔ docetaxel/capecitabine q3wk → surgery
AC q3wk ↔ docetaxel/gemcitabine q3wk → surgery

In this proposed 3 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

SOURCE: NSABP website, June 2004.

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

Protocol ID: ID01-580, NCT00050167
Projected Accrual: 930 (Open)

Eligibility	Stage IIA-IIIA breast cancer
ARM 1	Paclitaxel qwk x 12 → FEC x 4 → local therapy (surgery or RT)
ARM 2	(Capecitabine + docetaxel) x 4 → FEC x 4 → local therapy (surgery or RT)

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

Study Contacts:
Debbie Frye, RN; Cynthia Carter, RN
MD Anderson Cancer Center
Tel: 713-792-2817

SOURCE: NCI Physicans Data Query, October 2004.

PATHOLOGIC COMPLETE RESPONSE IN RECENTLY COMPLETED COMPARATIVE CLINICAL TRIALS OF NEOADJUVANT CHEMOTHERAPY

Study	No. of evaluable patients (OR)	Therapy	pCR	OR
NSABP-B-27[1]	752[4] 1,534[4]	AC x 4 → docetaxel x 4 AC x 4	26% 14%	91% 86%
Aberdeen Trial[2]	 52 52	CVAP x 4 Responders randomized → CVAP x 4 → docetaxel x 4	 15% 31%	66% 64% 85%
MD Anderson[3]	 50 68 51 67	Paclitaxel qwk → FAC Node-positive Node-negative Paclitaxel q3wk → FAC Node-positive Node-negative	 28% 29% 14% 13%	 NA NA NA NA

pCR = pathological complete response;
OR = objective response (complete + partial clinical response)

SOURCES: [1] Bear H et al. *J Clin Oncol* 2003;21(22):4165-74.

[2] At a median follow-up of 65 months, the survival rates were 93% in the docetaxel group versus 78% in the CVAP group ($p = 0.04$).
Hutcheon AW et al. Presentation. San Antonio Breast Cancer Symposium, 2003. *Breast Cancer Res Treat* 2003;Abstract 6.

[3] Green MC et al. *Proc ASCO* 2002;Abstract 135.

[4] These numbers reflect pCR; number of evaluable patients for OR is 722 for AC → T and 1,534 for AC.

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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**.**

Chollet P et al. **Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer.** *Br J Cancer* 2002;86(7):1041-6.

Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;Abstract 135.

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Kaufmann M et al. **International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: Review and recommendations.** *J Clin Oncol* 2003;21:2600-8.

Pusztai L et al. **Emerging science: Prospective validation of gene expression profiling based prediction of complete pathologic response to neoadjuvant paclitaxel/FAC chemotherapy in breast cancer.** *Proc ASCO* 2003;Abstract 1.

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Thomas E et al. **The use of alternate, non-cross-resistant adjuvant chemotherapy on the basis of pathologic response to a neoadjuvant doxorubicin-based regimen in women with operable breast cancer: Long-term results from a prospective randomized trial.** *J Clin Oncol* 2004;22(12):2294-302.

PREDICTING PATHOLOGIC RESPONSE TO NEOADJUVANT CHEMOTHERAPY BASED ON GENETIC PROFILING

In NSABP-B-27, all patients received AC and were randomly assigned to one of three arms: surgery, surgery followed by docetaxel, or docetaxel followed by surgery. The question is whether we can identify patients whose response to AC alone is sufficient and their risk is too low to warrant further adjuvant chemotherapy. Perhaps we can identify patients resistant to all therapies, in which case further chemotherapy is not indicated.

Lajos Pusztai and his colleagues reported a preliminary study suggesting they could identify patients most likely to have a complete pathologic response to combination chemotherapy based on gene expression profiling. Similarly, two or three other studies, including work conducted at Georgetown, suggest that not only can general resistance to all chemotherapies be predicted, but resistance to single agents in neoadjuvant therapy — such as a taxane versus doxorubicin — can also be predicted.

This research is very much in its infancy, and Dr Pusztai will chair a SWOG neoadjuvant trial with fine-needle aspiration before treatment to confirm his preliminary findings. While Dr Pusztai's study evaluated combination chemotherapy, we know that cyclophosphamide, doxorubicin and 5-FU work in very different ways. Logic tells us we'll probably find that some genes are associated with resistance to all chemotherapy and other genes are specific for individual drugs. For a long time we have fantasized about being able to individualize therapy based on a patient's genes, and I believe we're beginning to develop the tools and the technology to do just that.

— Daniel F Hayes, MD

SWOG-S0012: NEOADJUVANT THERAPY IN LOCALLY ADVANCED AND INFLAMMATORY DISEASE

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

— Robert B Livingston, MD

NEW STRATEGIES FOR NEOADJUVANT CHEMOTHERAPY

The neoadjuvant setting is an arena in which I believe we need more research. It is not uncommon for us to see patients after preoperative therapy and surgery who have seven positive nodes and scattered tumor throughout the breast. We don't know what to do in these cases. Obviously we put patients with ER- or PR-positive tumors on endocrine therapy, but I don't think any of us believe this is going to be a great strategy.

I believe exploring agents such as capecitabine in those patients is a great idea. I also think that some types of breast cancer have very few cells in cycle kinetically — like low-grade lymphoma. We will never cure these patients with aggressive agents, but perhaps metronomic, low-dose therapy — whether it's weekly taxanes, weekly anthracyclines or capecitabine for a prolonged period of time — would treat that component of cells that aren't cycling. All of these are great options for future studies.

— Hyman B Muss, MD

Neoadjuvant Endocrine Therapy

Chemotherapy is the most frequent form of neoadjuvant systemic therapy utilized in the United States; in Europe, preoperative endocrine therapy has been used extensively in women with ER-positive cancers. Phase II and III clinical trials have suggested that the antitumor effect of endocrine therapy in these patients is comparable to what has been observed with chemotherapy, although the time to achieve a response may be somewhat longer. Tamoxifen and ovarian ablation/suppression were initially utilized in neoadjuvant studies, and more recently, third-generation aromatase inhibitors and the estrogen receptor downregulator fulvestrant have demonstrated significant antitumor activity in this setting. At last year's San Antonio Breast Cancer Symposium, data were presented from the IMPACT trial comparing anastrozole, tamoxifen and the combination. As was observed in a previous trial comparing letrozole to tamoxifen, breast-conserving surgery was much more common in women treated with anastrozole than in women treated with tamoxifen.

IMPACT TRIAL: A RANDOMIZED DOUBLE-BLIND TRIAL OF PREOPERATIVE TAMOXIFEN, ANASTROZOLE OR THE COMBINATION IN POSTMENOPAUSAL BREAST CANCER PATIENTS

Eligibility	Postmenopausal, ER/PR-positive T2 (≥2 cm), T3, T4b N0-2, M0 breast cancer patients
ARM 1	Tamoxifen x 3 months → surgery
ARM 2	Anastrozole x 3 months → surgery
ARM 3	Anastrozole + tamoxifen x 3 months → surgery

SOURCE: Smith I, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;Abstract 1.

ANASTROZOLE (A) VERSUS TAMOXIFEN (T) VERSUS THE COMBINATION (C) AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL PATIENTS WITH ESTROGEN RECEPTOR-POSITIVE BREAST CANCER: THE IMPACT TRIAL (N=330)

	A	T	C
Objective clinical tumor response[1]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after 3 months of treatment[1]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment[2]**	76%	59%	64%

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

** Reductions in Ki67 were virtually maximal at 2 weeks with only marginal changes between 2 and 12 weeks.

SOURCES: [1] Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003:Abstract 1.

[2] Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;Abstract 2.

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%
Pathological response (n=61)*	**Response rate**
Complete pathologic response (pCR)	23%
Partial pathologic response (pPR)	77%

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

SOURCE: Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patient with hormone-dependent, locally-advanced breast cancer.** *Anticancer Research* 2004;24:1315-8.

ANASTROZOLE (A) VERSUS TAMOXIFEN (T) VERSUS COMBINED (A+T) AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL BREAST CANCER PATIENTS (N=87)

	A	T	A+T	*p*-value
Overall objective response (clinical)	70%	44.4%	49%	0.048
Mammographic response	56%	36%	40%	0.058
Ultrasound response	44%	30%	32%	0.072
Breast-conserving surgery	42%	28%	30%	0.056

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

RESPONSE DATA COMPARING NEOADJUVANT LETROZOLE TO TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER

Therapy	n	Overall response	Underwent successful breast-conserving surgery*	*p*-value
Letrozole	124	60%	48%	0.004
Tamoxifen	126	41%	36%	0.036

* At baseline, all tumors were considered not amenable to breast-conserving surgery.

SOURCE: Ellis MJ. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a Phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16.

EFFICACY OF FOUR TO EIGHT MONTHS OF DAILY PREOPERATIVE LETROZOLE IN POSTMENOPAUSAL WOMEN WITH ER/PGR-POSITIVE BREAST CANCER (N=33)

Complete or partial response based on length of therapy	
Up to 4 months	57%
Longer than 4 months	90%

SOURCE: Paepke S et al. **A multi-center study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PGR positive breast cancer.** *Proc ASCO* 2003;Abstract 321.

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Dixon JM. **Role of endocrine therapy in the neoadjuvant surgical setting.** *Ann Surg Oncol* 2004;11(1 Suppl):18-23.

Dowsett M, on behalf of the IMPACT Trialists, Royal Marsiden Hospital, London, United Kingdom. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;Abstract 2.

Dowsett M et al. **Molecular effects of anastrozole (A) and tamoxifen (T) alone and combined (C) in the IMPACT trial of neoadjuvant treatment of primary breast cancer.** *Proc ASCO* 2004;Abstract 537.

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16.

Ellis MJ. **Neoadjuvant endocrine therapy as a drug development strategy.** *Clin Cancer Res* 2004;10(1 Pt 2):391S-5S.

Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patient with hormone-dependent, locally-advanced breast cancer.** *Anticancer Research* 2004;24:1315-8.

Paepke S et al. **A multi-center study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PGR positive breast cancer.** *Proc ASCO* 2003;Abstract 321.

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

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

Smith I, on behalf of the IMPACT Trialists, Royal Marsden Hospital, London, United Kingdom. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;Abstract 1.

Wong ZW, Ellis MJ. **Neoadjuvant endocrine therapy for breast cancer: an overlooked option?** *Oncology (Huntingt)* 2004;18(4):411-20.

IMPACT NEOADJUVANT TRIAL

The IMPACT trial compared anastrozole, tamoxifen and a combination of the two as neoadjuvant therapy in postmenopausal women with ER-positive tumors more than two centimeters. In the intent-to-treat analysis for clinical response, no difference was found between anastrozole, tamoxifen and the combination. However, in women requiring mastectomy at baseline, anastrozole demonstrated a significant advantage over tamoxifen in terms of rendering the women eligible for breast-conserving surgery — between 40 and 50 percent of the women in the anastrozole arm and just over 20 percent in the tamoxifen arm.

In a previous neoadjuvant trial comparing an aromatase inhibitor to tamoxifen, letrozole was used. In that particular study, all of the patients required mastectomy at baseline. For some biological reason, patients requiring mastectomy seem to do better with an aromatase inhibitor than with tamoxifen. It would be interesting to find out why the aromatase inhibitors have greater antitumor effect in these larger tumors.

— Mitchell Dowsett, PhD

PREDICTING RESPONSE TO NEOADJUVANT ENDOCRINE THERAPY

Neoadjuvant chemotherapy and neoadjuvant hormonal therapy offer great potential advantages. If we can find surrogate markers to predict outcomes, we can speed up, by many years, the ability to determine which treatments work in the adjuvant setting. The investigators from the IMPACT trial were trying to make that point. In terms of reducing Ki67, anastrozole was better than tamoxifen, which parallels the ultimate outcome of the ATAC trial. I don't believe in using a single marker as the only surrogate. However, if we can use a surrogate marker to predict the ultimate outcome and correlate it with survival, then these trials may not need to enroll 3,000 to 5,000 patients. Instead, they can enroll 300 to 400 patients and provide an answer within a year. Now we need to prove that surrogates correlate with survival, and the IMPACT trial was an interesting first step in that direction.

The IMPACT trial seemed to confirm that the aromatase inhibitors might be better than tamoxifen in patients with HER2-positive disease. It could be that the benefit associated with anastrozole in the ATAC trial was largely due to the population with HER2-positive disease, and tamoxifen and anastrozole may be equally effective in patients who don't overexpress HER2. It's also possible that anastrozole is better even in the patients with HER2-negative disease. I would like to see that analysis of the ATAC trial data.

— Jeffrey Abrams, MD

NEOADJUVANT CLINICAL TRIALS OF AROMATASE INHIBITORS

We conducted a neoadjuvant trial comparing letrozole to tamoxifen in postmenopausal women with ER-positive breast cancer. Like the IMPACT trial, our study showed aromatase inhibitors to be more beneficial in favorably impacting the rates of breast-conserving surgery. The IMPACT trial had three arms whereas our trial had only two, so theirs wasn't as well powered to show a difference between just tamoxifen and an aromatase inhibitor.

In addition, the IMPACT trial allowed smaller tumors and, clinically, it's difficult to be certain you're measuring response with these smaller tumors. This might explain why their trial did not show much difference in clinical response between the arms.

We're moving ahead with an ACOSOG neoadjuvant study comparing exemestane with or without celecoxib in postmenopausal women with ER-positive, Stage II/III breast cancer who are ineligible for breast-conserving surgery or whose tumors are inoperable. In the United Kingdom, Mike Dixon is the principal investigator for a trial comparing neoadjuvant letrozole and anastrozole. I believe it's important to compare the various aromatase inhibitors because ultimately these agents will be off patent and inexpensive. Knowing which is the most efficacious will be important.

— Matthew J Ellis, MD, PhD

Neoadjuvant Trials of Trastuzumab in HER2-Positive Breast Cancer

In women with breast cancer, neoadjuvant chemotherapy may have potential advantages over adjuvant chemotherapy, including an increased rate of breast conservation and a decreased rate of distant metastases. It has been postulated that the pathologic response of the primary tumor to neoadjuvant chemotherapy may correlate with long-term survival. In women with HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy has been shown to improve the response rate, progression-free survival and overall survival. Several trials have investigated the addition of trastuzumab to neoadjuvant chemotherapy regimens in women with HER2-positive disease. The neoadjuvant chemotherapy regimens have included taxanes, vinorelbine, cisplatin and epirubicin; the pathologic complete response rates have ranged from seven percent to 42 percent. Dr Aman Buzdar recently reported (ASCO 2004) results from a trial that randomly assigned women with HER2-positive breast cancer to paclitaxel → FEC with or without trastuzumab as neoadjuvant therapy. The addition of neoadjuvant trastuzumab yielded a pathologic complete response rate of 65.2% in those patients compared to 26.3% with chemotherapy alone. As these data mature and further results are obtained from other neoadjuvant trials, the role of neoadjuvant trastuzumab will continue to evolve.

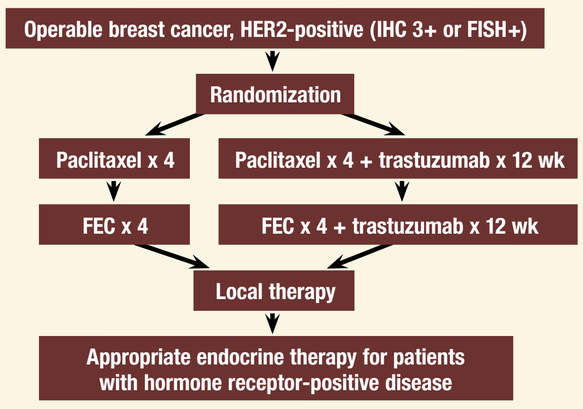
RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

	Neoadjuvant regimen	Number of patients	Pathologic complete response rate
Burstein 2003	Trastuzumab qwk x 12 + paclitaxel q3wk x 4	40	IHC 3+: 19% IHC 2+: 13%
Carey 2002	AC x 4 → (trastuzumab + paclitaxel) qwk x 12	22	22%
Bines 2003	Trastuzumab week 1 → qwk x 14 + (docetaxel qwk x 6 → 2 wk off) x 2	33	12%
Moluçon 2003	Trastuzumab qwk x 17 + docetaxel q3wk x 6	18	28%
Wenzel 2004	(Trastuzumab + epirubicin + docetaxel) qwk x 6	14	7%
Hurley 2003	Trastuzumab qwk x 11 + (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%

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. 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. Wenzel C et al. *J Cancer Res Clin Oncol* 2004;130:400-4.

RANDOMIZED TRIAL OF NEOADJUVANT TRASTUZUMAB AND CHEMOTHERAPY



PATHOLOGIC COMPLETE RESPONSE RATES FOR NEOADJUVANT THERAPY

	Trastuzumab + P + FEC	P + FEC	*p*-value
Overall (n=23,19)	65.2%	26.3%	0.016
Hormone receptor-positive (n=13,11)	61.5%	27.2%	—
Hormone receptor-negative (n=10,8)	70.0%	25.0%	—

P = paclitaxel; F = 5-fluorouracil; E = epirubicin; C = cyclophosphamide

SOURCE: Buzdar AU et al. Presentation. ASCO, 2004.

PHASE III RANDOMIZED STUDY OF NEOADJUVANT DOCETAXEL AND CARBOPLATIN WITH VERSUS WITHOUT TRASTUZUMAB IN WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Protocol IDs: UCLA-9911084, AVENTIS-GIA-11156, GENENTECH-H2269s
Projected Accrual: 400 (Open)

Eligibility	**T3 or T4, any N Patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy as follows:**
ARM 1	**[Trastuzumab days 1, 8 and 15 q21d x 4] + [(docetaxel + carboplatin) q3wk x 4]**
ARM 2	**(Docetaxel + carboplatin) q3wk x 4**

* Patients who do not have HER2-positive disease receive neoadjuvant chemotherapy only, as in arm 2.

Note: Within 4-6 weeks after surgery, patients with responding disease receive 4 additional courses of docetaxel and carboplatin as during neoadjuvant chemotherapy. All patients with HER2-positive disease also receive trastuzumab IV once weekly for 12 weeks and then every 3 weeks for 40 weeks (total of 52 weeks of trastuzumab therapy).

Study Contact:
Helena Chang, MD, PhD
Jonsson Comprehensive Cancer Center, UCLA
Tel: 310-794-5624

SOURCE: NCI Physician Data Query, October 2004.

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Limentani SA et al. **Dose dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support.** *Breast Cancer Res Treat* 2003;82(Suppl 1):55;Abstract 240.

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

NEOADJUVANT TRASTUZUMAB/PACLITAXEL TRIAL

This study is novel for several reasons. It is the first trial evaluating neoadjuvant trastuzumab, and much interest exists in defining the response rate. Also, we performed cardiac analyses during the neoadjuvant trastuzumab/paclitaxel therapy and again during the adjuvant AC. Our results are very similar to George Sledge's — a significant number of women had a 10 to 20 percent decline in their ejection fractions. Fortunately, none of the patients developed any symptoms of congestive heart failure, and the changes in ejection fraction appear to reverse with time. The decline in ejection fraction occurred either during or at the end of adjuvant AC in three of the four women, and did not change much during the trastuzumab/paclitaxel therapy. Most of us believe these kinds of changes in ejection fraction are consistent with what occurs with AC alone, but because this is not a randomized trial, we do not know if the addition of trastuzumab influences the ejection fraction.

— Harold J Burstein, MD, PhD

NEOADJUVANT TRASTUZUMAB

The neoadjuvant data for trastuzumab exemplify a totally different set of circumstances. With chemotherapy alone, clinical response rates are in the 70 to 90 percent range. It is not surprising then that trastuzumab combinations show those same response rates. Because the pathologic complete response rate is a surrogate for survival, we are interested in that. The CALGB neoadjuvant trastuzumab trial was designed to determine the efficacy of dexrazoxane, trastuzumab in combination with paclitaxel, and trastuzumab following surgery. First, the patients are randomly assigned to receive doxorubicin/cyclophosphamide with or without dexrazoxane. This part of the trial will determine whether the introduction of a cardioprotectant can have a long-term effect on controlling cardiotoxicity. In the second phase of the study, the patients will receive paclitaxel with or without trastuzumab. Then, the patients will undergo surgery and continue on trastuzumab or observation alone.

— Debu Tripathy, MD

NONPROTOCOL USE OF NEOADJUVANT AND ADJUVANT TRASTUZUMAB

Before our neoadjuvant trastuzumab data were available, we did not offer neoadjuvant trastuzumab to any patient outside the context of a clinical trial. However, now that the data are in the public domain, I think it is our responsibility to share the information and discuss the issue with our patients. As long as the patient and the physician understand that uncertainties exist regarding the data, the cardiac safety and the long-term outcome, I believe it is a reasonable approach.

At our institution, based on the recommendation of the Data Monitoring Committee, we stopped the control arm of the study. Currently, all patients are being offered chemotherapy with trastuzumab in the neoadjuvant setting. We want to expand our experience, determine whether these data are reproducible and acquire long-term safety data.

On the other hand, if a woman with high-risk node-positive disease comes to MD Anderson seeking adjuvant trastuzumab — which we debate within our group once a month — we are divided on the issue. Some physicians within our group believe that a woman at high risk should be offered this therapy in the nonprotocol neoadjuvant or adjuvant setting whereas others want to be conservative and not offer it.

My experience is that patients who have four or more positive nodes tend to not do well, especially if they have HER2-positive disease. I think we have to discuss these options and let the patients know about these treatments because "the genie is out of the bottle." After appropriate discussion, if the patient agrees and accepts the uncertainties and the limitations of the available data, I am inclined to offer this therapy.

— Aman Buzdar, MD

Adjuvant Endocrine Therapy Trials in Postmenopausal Patients

The ATAC trial reported initial results in December 2001, demonstrating an advantage in disease-free survival (DFS) with the third-generation aromatase inhibitor anastrozole compared to tamoxifen. An advantage was also seen in safety and tolerability with regard to thrombotic events and endometrial cancer, although fractures and arthralgias were more common in women treated with anastrozole. At the 2003 San Antonio Breast Cancer Symposium, further data were presented demonstrating an even greater advantage to anastrozole compared to tamoxifen in women with ER-positive, PR-negative tumors. The first overall survival analysis from the ATAC trial will be presented at this meeting, and other trials evaluating letrozole and exemestane as up-front therapy in postmenopausal patients are maturing and are likely to have initial data available in the near future.

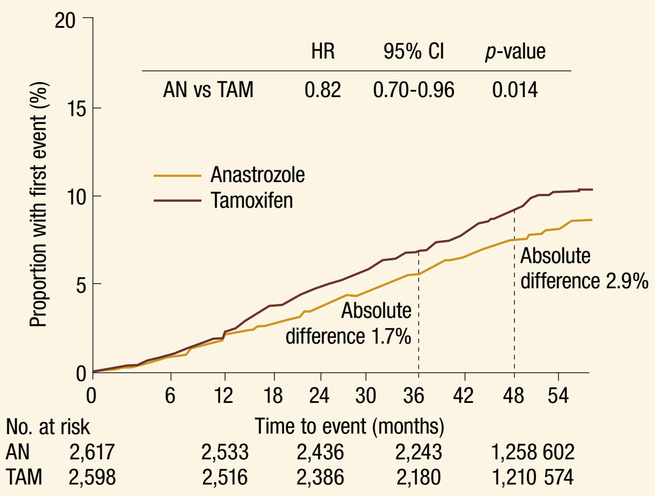
RECURRENCE RATES IN THE ATAC TRIAL ACCORDING TO ESTROGEN AND PROGESTERONE RECEPTOR STATUS

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

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

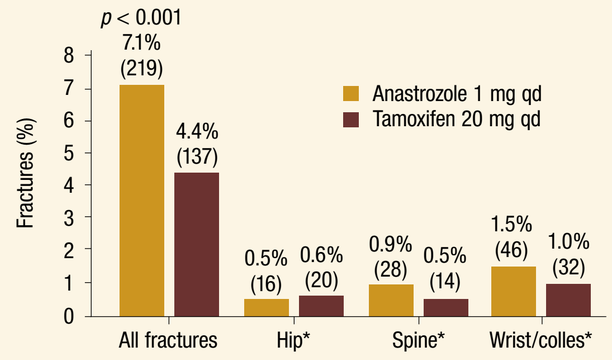
SOURCE: Dowsett M, on Behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6.

PROBABILITY OF FIRST EVENT IN RECEPTOR-POSITIVE POPULATION IN THE ATAC TRIAL



DERIVED FROM: Buzdar A. Presentation. San Antonio Breast Cancer Symposium, 2002.

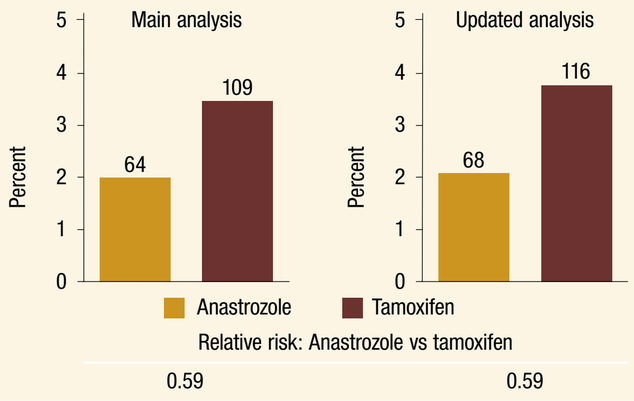
ATAC TRIAL: BONE FRACTURE ADVERSE EVENTS AT THE UPDATED SAFETY ANALYSIS



Numbers in brackets refer to numbers of patients with a fracture
* *p*-value not available (only predefined adverse events were analyzed)

SOURCE: Locker G. Poster. Lynn Sage Breast Cancer Symposium, 2003.

ATAC TRIAL: VENOUS THROMBOEMBOLIC EVENTS



SOURCES: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10.
The Lancet 2002;359:2131-9.

PHASE III STUDY OF EXEMESTANE VERSUS ANASTROZOLE WITH OR WITHOUT CELECOXIB

Protocol IDs: CAN-NCIC-MA27, CALGB-CAN-NCIC-MA27, ECOG-CAN-NCIC-MA27, NCCTG-N0434, SWOG-CAN-NCIC-MA27
Target Accrual: 6,830 (Open)

Eligibility	Postmenopausal, ER/PR-positive Invasive breast cancer
ARM 1	Exemestane x 5 years + celecoxib x 3 years
ARM 2	Exemestane x 5 years + placebo x 3 years
ARM 3	Anastrozole x 5 years + celecoxib x 3 years
ARM 4	Anastrozole x 5 years + placebo x 3 years

Study Contact:
Paul Goss, MD, PhD
NCIC-Clinical Trials Group
Tel: 617-724-3200

SOURCE: NCI Physician Data Query, October 2004.

PHASE III STUDY OF ADJUVANT LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH OPERABLE, HORMONE RECEPTOR-POSITIVE BREAST CANCER

Protocol IDs: IBCSG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98
Accrual: 5,180 (Closed)

Eligibility	Postmenopausal, ER- and/or PR-positive Node-positive or node-negative
ARM 1	Tamoxifen x 5 years
ARM 2	Letrozole x 5 years
ARM 3	Tamoxifen x 2 years → letrozole x 3 years
ARM 4	Letrozole x 2 years → tamoxifen x 3 years

SOURCE: NCI Physician Data Query, October 2004.

SELECT PUBLICATIONS

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;Abstract 30.

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;83(Suppl 1):6.

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

Coombes RC et al. **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.

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;Abstract 770.

Dowsett M, on behalf of the ATAC Trialists Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;83(Suppl 1):7.

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.

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;Abstract 98.

ATAC ADJUVANT TRIAL: SUBGROUP ANALYSIS OF PATIENTS WITH ER-POSITIVE, PR-NEGATIVE DISEASE

The ATAC trial enrolled 9,366 patients, and the first report demonstrated a significant benefit for the patients with hormone receptor-positive disease who were treated with anastrozole compared to tamoxifen. The hazard ratio for disease-free survival in this group was 0.78. The 47-month analysis had a similar hazard ratio. Because the ATAC trial was designed in 1994 and initiated in 1996, it didn't require the patients to have ER- and/or PR-positive disease for enrollment.

Hence, a very small proportion of patients had ER- and PR-negative disease, and a larger cohort had ER- or PR-unknown disease. We retrospectively analyzed the histological blocks from those patients for their ER and PR status to obtain a more comprehensive view of the influence of the ER and PR status on the outcomes of the trial. We asked whether the PR status had any impact on the relative benefit associated with anastrozole and tamoxifen in patients with ER-positive disease.

In the patients with ER- and PR-positive disease, which consisted of approximately 5,700 patients, anastrozole was more beneficial than tamoxifen, with a hazard ratio of 0.82. In the patients with ER-positive and PR-negative disease, a very substantial difference was noted, with a hazard ratio of 0.48, indicating that patients treated with adjuvant anastrozole had half as many relapses as patients treated with adjuvant tamoxifen. The comparison between patients with ER- and PR-positive disease to patients with ER-positive and PR-negative disease was borderline for statistical significance. Although this was a retrospective subgroup analysis, I hope that other aromatase inhibitor trials will perform the same analyses to substantiate this finding.

— Mitchell Dowsett, PhD

We don't know why the ER-positive, PR-negative phenotype behaves so differently, but Dowsett and Osborne have formulated a hypothesis that involves contrasting the effect of tamoxifen versus anastrozole on the classical nuclear versus nonclassical membrane estrogen receptor pathways. When the nuclear pathway is intact, estrogen activates the estrogen receptor, which induces the synthesis of the progesterone receptor; however, we can hypothesize that pathway is not functioning in ER-positive, PR-negative tumors. If the membrane pathway is activated, it can lead to the activation of growth factor receptors and induce cell growth.

Tamoxifen is an antagonist in the nuclear pathway (hypothetically, the nonfunctioning pathway in the ER-positive, PR-negative subset) and it's an agonist in the membrane pathway, which may result in stimulating growth factors and tumor growth. On the other hand, aromatase inhibitors reduce estrogen levels to nearly zero and are antagonists on both pathways. This may explain the striking additional benefit of anastrozole seen in the ER-positive, PR-negative subset, which is the phenotype for 20 percent of breast cancer patients.

The HER2 assays have not yet been performed in the ATAC trial, but some have speculated that the subset of patients with the ER-positive, PR-negative phenotype may also be HER2-positive. However, we've known for years that only 10 or 15 percent of HER2-positive tumors are ER-positive and, while most of those are PR-negative, I don't believe that small subset could be entirely responsible for these intriguing results.

— D Craig Allred, MD

TIME COURSE OF BONE FRACTURES IN ATAC

"Six-monthly fracture rates… remained fairly constant for both A (anastrozole) (range 0.93 to 1.57) and T (tamoxifen) (0.58 to 1.37), with the greatest difference between A and T seen at 18 and 24 mths. After 24 mths, the 6-monthly fracture rates seen with A reached a plateau. Overall osteoporotic fractures, encompassing sites of hip + spine + wrist, showed similar patterns. Anastrozole leads to an increased fracture incidence compared with T, a drug known to have a positive effect on bone. Importantly, the fracture rate in the A-treated group appeared to have stabilized after reaching a peak at 2 years."

— Locker GY et al. **Proc ASCO** *2003;Abstract 98.*

Sequential Adjuvant Hormonal Therapy Following Tamoxifen

27TH ANNUAL
San Antonio Breast Cancer Symposium
8

Since the first International Breast Cancer Overview presented at the 1985 NIH Consensus Conference, tamoxifen was considered the mainstay of adjuvant hormonal therapy for women with early breast cancer. However, the selection of optimal adjuvant hormonal therapy for postmenopausal women is currently controversial. Recent trials — NCIC-MA17, ITA and EU-20149 – have evaluated the role of aromatase inhibitors as follow-up therapy to adjuvant tamoxifen. NCIC-MA17 randomly assigned postmenopausal women who had completed 4.5 to 6 years of adjuvant tamoxifen to five years of placebo or adjuvant letrozole. ITA and EU-20149 randomly assigned postmenopausal women who had completed two to three years of adjuvant tamoxifen to two to three years of continued tamoxifen, or two to three of anastrozole and exemestane, respectively. These trials of sequential adjuvant hormonal therapy demonstrated significant therapeutic advantages for women receiving aromatase inhibitors following adjuvant tamoxifen. The results from these and other ongoing trials will better define optimal adjuvant hormonal therapy regimen.

RANDOMIZED PHASE III STUDY OF LETROZOLE VERSUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER WHO HAVE COMPLETED AT LEAST FIVE YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA.17, SWOG-CAN-MA17, SWOG-JMA17
Accrual: 5,187 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive breast cancer previously treated with adjuvant tamoxifen for 4.5 to 6 years
ARM 1	Letrozole x 5 y
ARM 2	Placebo x 5 y

DISEASE-FREE SURVIVAL (DFS) AND RECURRENCES OR A NEW CONTRALATERAL PRIMARY TUMOR (MEDIAN FOLLOW-UP 2.4 YEARS)

	Letrozole (n=2,575)	Placebo (n=2,582)	*p*-value
Estimated 4-year DFS	93%	87%	<0.001
Recurrences, or a new contralateral primary	75 (2.9%)	132 (5.1%)	<0.00008

SOURCES: NCI Physicians Data Query, October 2004.

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.

ITA TRIAL: ANASTROZOLE (A) VERSUS TAMOXIFEN (T) IN WOMEN ALREADY RECEIVING ADJUVANT TAMOXIFEN (MEDIAN FOLLOW-UP 24 MONTHS)[1]

Protocol IDs: ITA (Italian Tamoxifen Arimidex®)
Accrual: 448 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive primary breast cancer previously treated with adjuvant tamoxifen for two to three years
ARM 1	Anastrozole x 2-3 y
ARM 2	Tamoxifen x 2-3 y

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen n=225	1.0		1.0	
Anastrozole n=223	0.36 (95% CI 0.21-0.63)	0.0004	0.35 (95% CI 0.18-0.69)	0.002

"These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."

A = anastrozole; T = tamoxifen

SOURCE: [1] Boccardo F. Presentation. SABCS, 2003;Abstract 3.

PHASE III TRIAL OF EXEMESTANE VERSUS TAMOXIFEN FOLLOWING TWO TO THREE YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: CRC-TU-TEAM, EU-20149
Accrual: 4,742 (Closed)

Eligibility	Postmenopausal women with ER/PR-positive breast cancer who have received two to three years of adjuvant tamoxifen
ARM 1	Tamoxifen x 2-3 y
ARM 2	Exemestane x 2-3 y

UNADJUSTED HAZARD RATIOS FOR THE EXEMESTANE GROUP COMPARED TO THE TAMOXIFEN GROUP

Endpoints	Unadjusted hazard ratio (95% CI)	*p*-value
Disease-free survival	0.68 (0.56-0.82)	<0.001
Estrogen receptor-positive (ER+) ER+, progesterone receptor-positive ER+, progesterone receptor-negative	0.64 (0.52-0.79) 0.66 (0.51-0.87) 0.58 (0.38-0.90)	
Breast cancer-free survival	0.63 (0.51-0.77)	<0.001
Time to contralateral breast cancer	0.44 (0.20-0.98)	0.04
Overall survival	0.88 (0.67-1.16)	0.37

INCIDENCE OF SIGNIFICANTLY DIFFERENT ADVERSE EVENTS BETWEEN GROUPS

Type of event	Exemestane any Grade	Tamoxifen any Grade	*p*-value
Visual disturbances	7.4%	5.7%	0.04
Osteoporosis	7.4%	5.7%	0.05
Gynecologic symptoms	5.8%	9.0%	<0.001
Arthralgia	5.4%	3.6%	0.01
Diarrhea	4.3%	2.3%	<0.001
Vaginal bleeding	4.0%	5.5%	0.05
Cramps	2.8%	4.4%	<0.001
Thromboembolic events	1.3%	2.4%	0.007

SOURCE: Coombes C et al. **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.

ANASTROZOLE VERSUS TAMOXIFEN AFTER TWO YEARS OF ADJUVANT TAMOXIFEN

Protocol ID: ABCSG-08, ARNO-95
Accrual: 3,123 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive breast cancer previously treated with adjuvant tamoxifen for 2 years
ARM 1	Anastrozole x 3 y
ARM 2	Tamoxifen x 3 y

SOURCES: www.abcsg.at. Jakesz R et al. Presentation. SABCS, 2004.

SELECT PUBLICATIONS

Baum M et al; The ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *The Lancet* 2002;359(9324):2131-9.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;83(Suppl 1):60;Abstract 3.

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

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

SEQUENTIAL ADJUVANT ENDOCRINE THERAPY

For postmenopausal patients who are on tamoxifen for any length of time, our practice today is to switch to an aromatase inhibitor. There was a time when we would leave patients on tamoxifen if they were already on tamoxifen, because there was really no evidence that crossing over was beneficial. But, after all three of the crossover trials came out this past year, there was really no justification in our minds to continue tamoxifen.

– Gabriel N Hortobagyi, MD

We have completed accrual to an adjuvant trial (IBCSG-18-98) comparing five years of tamoxifen, five years of letrozole, two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen in postmenopausal patients with endocrine-responsive disease. This trial accrued 8,028 patients. A lifelong treatment strategy for patients with an increased risk of breast cancer recurrence might be reasonable. I think maintaining the cells under control and suppressing new tumors requires a sequential approach that includes endocrine therapy for tumors that are endocrine responsive.

– Aron Goldhirsch, MD

ADJUVANT LETROZOLE FOLLOWING FIVE YEARS OF ADJUVANT TAMOXIFEN

"We found a significant improvement in disease free survival, including a substantial reduction in the rate of distant metastasis in the letrozole group as compared with the placebo group; the rate of death due to breast cancer was almost halved. Letrozole was equally effective in women with node-negative disease and those with node-positive disease. The reduction in the rates of recurrent and new disease in the letrozole group confirms the continuous dependence of hormone-receptor-positive breast cancer on estrogen. …

"On the basis of these findings, postmenopausal women with hormone-receptor-positive tumors who have completed about five years of adjuvant tamoxifen therapy should be considered for letrozole treatment. However, our results, which necessitated the discontinuation of the study, leave the optimal duration of treatment undefined and the question of long-term toxicity unanswered."

— Goss PE et al. N Engl J Med *2003;349(19):1793-802.*

BIOLOGICAL RATIONALE FOR THE SEQUENCING OF ADJUVANT HORMONAL THERAPY

If the ATAC trial data from the patients with ER-positive and PR-negative disease were confirmed, it would be difficult to substantiate the use of adjuvant tamoxifen followed by adjuvant letrozole in that group of patients. The relapse rate was too high with adjuvant tamoxifen to suggest such a sequential strategy, and it may be best to use an aromatase inhibitor early in that group of patients. In the patients with ER/PR-positive disease, in whom the relapse rates for tamoxifen and anastrozole were more similar, one could argue for the use of such a sequential strategy. However, I suspect even in that group of patients it is best to accept the gain associated with the aromatase inhibitors as initial adjuvant therapy, rather than allow a few patients to relapse and have to treat their metastatic disease.

— Mitchell Dowsett, PhD

ADJUVANT EXEMESTANE FOLLOWING TWO TO THREE YEARS OF ADJUVANT TAMOXIFEN

"We found that switching patients to adjuvant treatment with exemestane after two to three years of tamoxifen therapy was associated with a statistically and clinically significant improvement in disease-free survival, which included a reduction in the incidence of metastic disease. This strategy also reduced the risks of contralateral breast cancer, endometrial cancer, and intriguingly, other primary cancers. At the time of this report, the observed number of deaths over the relatively short follow-up period precludes the detection of a statistically significant difference in overall survival."

— Coombes C et al. N Engl J Med *2004;350(11):1081-92.*

Adjuvant Endocrine Therapy Trials in Premenopausal Patients

Tamoxifen has an established role as adjuvant systemic therapy for premenopausal women with estrogen receptor-positive breast cancer. A number of major current clinical trials are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. A related and important issue is the impact of chemotherapy-related ovarian suppression in these patients. While it will be many years before data on disease-free and overall survival are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate. These data will be updated at this year's meeting.

RANDOMIZED ADJUVANT TRIAL OF TAMOXIFEN AND GOSERELIN VERSUS CYCLOPHOSPHAMIDE, METHOTREXATE AND FLUOROURACIL IN PREMENOPAUSAL PATIENTS

Protocol ID: ABCSG-05
Projected Accrual: 1,034 patients (Closed)

Eligibility	Patients with Stage I or II ER-/PR-positive breast cancer
ARM 1	Surgery (+RT) → goserelin q28d x 3 years + tamoxifen x 5 years
ARM 2	Surgery (+RT) → CMF on days 1, 8 q28d

ABCSG-05 TRIAL RESULTS: 5-YEAR FOLLOW-UP

	Goserelin + tamoxifen (n=511)	CMF (n=523)	*p*-value
Breast cancer-specific deaths	41 (8%)	51 (10%)	0.900
Relapses	88 (17%)	109 (21%)	0.0176
Local recurrences	24 (5%)	42 (8%)	0.0029
Cancer in opposite breast	3 (1%)	12 (3%)	0.0001

SOURCES: Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2002.

Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002;20(24):4621-27.

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

Protocol ID: ABCSG-AU12
Target Accrual: 1,250 (Open)

Eligibility	Premenopausal 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. San Antonio Breast Cancer Symposium, 2002;Abstract 12.

SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL

Protocol ID: IBCSG 24-02
Target accrual: 3,000 patients (Open)

Eligibility	Premenopausal Estradiol (E_2) in the premenopausal range either after CT or without CT ER ≥10% and/or PgR ≥10%
ARM 1	Tamoxifen x 5 y
ARM 2	OFS + tamoxifen x 5 y
ARM 3	OFS + exemestane x 5 y

CT = chemotherapy; OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

SOURCE: www.ibcsg.org

TEXT: TAMOXIFEN AND EXEMESTANE TRIAL

Protocol ID: IBCSG 25-02
Target accrual: 1,845 patients (Open)

Eligibility	ER ≥10% and/or PgR ≥10% Candidates to begin GnRH analogue from the start of adjuvant therapy
ARM 1	GnRH ± CT + tamoxifen x 5 y
ARM 2	GnRH ± CT + exemestane x 5 y

CT = chemotherapy; GnRH = triptorelin x 5 years, but oophorectomy or radiation is allowed after 6 months

SOURCE: www.ibcsg.org

PERCHE: PREMENOPAUSAL ENDOCRINE RESPONSIVE CHEMOTHERAPY TRIAL

Protocol ID: IBCSG 26-02
Target Accrual: 1,750 patients (Open)

Eligibility:	Premenopausal ER ≥10% and/or PgR ≥10% Patients for whom CT is considered to be a randomized option (lower risk)
ARM 1	OFS + TEXT or T or E x 5 y
ARM 2	OFS + TEXT or T or E x 5 y + any CT

CT = chemotherapy; OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; TEXT = randomized trial comparing tamoxifen versus exemestane; T = tamoxifen; E = exemestane

SOURCE: www.ibcsg.org

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Davidson N et al. **Chemohormonal therapy in premenopausal bide-positive receptor-positive breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 2003;Abstract 15.

de Haes H et al. Zoladex Early Breast Cancer Research Association Trialists' Zoladex Early Breast Cancer Research Association Group. **Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast cancer: The Zoladex Early Breast Cancer Research Association Trialists Group.** *J Clin Oncol* 2003;21(24):4510-6.

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Kaufmann M et al. **Zoladex Early Breast Cancer Research Association (ZEBRA) Trialists' Group. Survival analyses from the ZEBRA study: Goserelin (Zoladex) versus CMF in premenopausal women with nodepositive breast cancer.** *Eur J Cancer* 2003;39(12):1711-7.

Love RR et al. **Her-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer.** *J Clin Oncol* 2003;21(3):453-7.

Love RR et al. **Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer.** *J Clin Oncol* 2002;20(10):2559-66.

Nystedt M et al. **Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: A prospective randomized study.** *J Clin Oncol* 2003;21(9):1836-44.

OVARIAN SUPPRESSION IN THE TREATMENT OF PREMENOPAUSAL WOMEN

The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? We probably won't have the data for at least five or 10 years, but these are very important trials in which community oncologists can participate to answer these critical questions.

Currently, I consider ovarian suppression for two groups of patients. The first group consists of patients at high risk — multiple positive nodes, high-risk tumors — and women less than 35 or 40 years of age who may not go into menopause with chemotherapy. The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are very small. In these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it.

— Harold J Burstein, MD, PhD

ABCSG-AU12: LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONATE

The ABCSG-12 trial has four arms comparing goserelin/tamoxifen to goserelin/anastrozole with or without zoledronic acid. We included zoledronic acid because it's the most potent bisphosphonate pharmacokinetically, and we were concerned about the risk of osteoporosis with the aromatase inhibitors. Chemotherapy is only permitted as neoadjuvant therapy.

We did not include a tamoxifen-only arm because we tried to build upon our own results with goserelin/tamoxifen, which is now a national standard in Austria. I also believe tamoxifen-only treatment in premenopausal women is debatable because reasonable evidence indicates that you need to include some cytotoxic treatment.

The early results of ABCSG-12 demonstrate that the combination of goserelin/anastrozole, and goserelin/tamoxifen to a lesser degree, leads to significant deterioration in bone mineral density in premenopausal women and that this can be completely counteracted by zoledronic acid. Even though tamoxifen has an agonistic effect on bone, when combined with goserelin it results in a net reduction in bone density. The bone deterioration is more pronounced with anastrozole/goserelin, but the difference is not significant at this time. The main message is that zoledronic acid was able to completely prevent bone loss regardless of which hormone combination the patients received.

— Michael F Gnant, MD

The ABCSG trial 12 demonstrated increased bone density from zoledronate at six months and one year among patients treated with an LHRH agonist plus tamoxifen or anastrozole. We need to follow that study because these were early data from only about 100 patients, and it's a much larger trial than that.

I'm regularly asked, "Should I automatically administer a bisphosphonate when starting an aromatase inhibitor?" I prefer to monitor bone density because some patients won't need a bisphosphonate at all. Most of the patients aren't going to lose significant bone mineral density quickly, so you can do a baseline study, monitor patients and institute bisphosphonates at an appropriate time based on the WHO criteria for osteoporosis and osteopenia.

— Julie R Gralow, MD

Research To Practice: Adjuvant Endocrine Therapy

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While extensive resources have been allocated to evaluate new breast cancer treatment interventions, relatively minimal investment has been made to determine how these advances are implemented in practice. Continuing medical education has the potential to be a useful component in the clinical research continuum, not only by informing clinicians about available trials and emerging research findings, but by implementing outcomes assessments to evaluate how research advances are being implemented in clinical practice. The data presented here from the *Breast Cancer Update* Patterns of Care Study is from a national telephone survey of 150 randomly selected United States-based medical oncologists initiated in May 2004.

One of the key aspects of this initiative was the use of hormonal therapy. The most important databases currently affecting nonprocotol use of adjuvant endocrine therapy were derived from trials of aromatase inhibitors in postmenopausal patients, both as initial therapy and after two to three, or five years of tamoxifen. In premenopausal women, controversy continues on the use of ovarian ablation/suppression, particularly in women who continue to menstruate after receiving adjuvant chemotherapy.

CHOICE OF ADJUVANT ENDOCRINE THERAPY BASED ON TUMOR SIZE, NODAL AND HER2 STATUS

Which endocrine therapy would you likely recommend to a 65-year-old woman with an ER-positive tumor?

Therapy	2.2-cm, N2+ HER2-neg	2.2-cm, N- HER2-neg	0.8-cm, N- HER2-neg	2.2-cm, N10+ HER2-pos
Tamoxifen	34%	33%	43%	23%
Anastrozole	59%	61%	45%	75%
Letrozole	7%	6%	2%	2%
Exemestane	0%	0%	0%	0%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

USE OF ADJUVANT AROMATASE INHIBITORS FOR INITIAL THERAPY

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is with each of the following agents?

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SWITCHING ADJUVANT THERAPY AFTER 2-3 YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER-positive, HER2-negative, Grade II tumor and 3 positive lymph nodes on tamoxifen for 2 years. How would you manage this patient's endocrine therapy?

	No side effects with tamoxifen	Complains of 20 lb weight gain	Complains of moderate hot flashes
Continue tamoxifen	45%	17%	16%
Stop tamoxifen	—	—	—
Stop tamoxifen and switch to anastrozole	12%	35%	36%
Stop tamoxifen and switch to letrozole	11%	16%	12%
Stop tamoxifen and switch to exemestane	32%	32%	36%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SEQUENCING ADJUVANT THERAPY AFTER 5 YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER-positive, HER2-negative, Grade II tumor and 3 positive lymph nodes who has completed 5 years of tamoxifen therapy. How would you manage this patient's endocrine therapy?

	Has just completed 5 years of tamoxifen	Is 1 year post-5 years of tamoxifen	Is 3 years post-5 years of tamoxifen
Continue tamoxifen	—	—	—
Start anastrozole	16%	14%	4%
Start letrozole	77%	58%	19%
Start exemestane	1%	—	—
Use no further hormonal therapy	6%	28%	77%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Which endocrine therapy would you recommend for a woman in average health with a 1.2-cm, ER-positive, HER2-negative Grade II tumor and negative lymph nodes?

	Age 35	Age 45
Tamoxifen	73%	76%
Aromatase inhibitor + LHRH agonist or ovarian ablation	4%	4%
Tamoxifen + LHRH agonist or ovarian ablation	14%	9%
LHRH agonist or ovarian ablation	2%	2%
Other	5%	7%
Would not recommend endocrine therapy	2%	2%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

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AROMATASE INHIBITORS AS INITIAL ADJUVANT THERAPY IN POSTMENOPAUSAL WOMEN

The results of the ATAC trial are quite compelling. Even if you assume, for the sake of argument, that the curves will come together with further follow-up, the safety profile of anastrozole is still clearly better than that of tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures. Because the safety profile of anastrozole is better than that of tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as a neutral choice, but as a better choice. I discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but I would certainly recommend anastrozole as opposed to tamoxifen.

— Gabriel N Hortobagyi, MD

"Many more years will be required to fine-tune the risk-benefit assessment of adjuvant aromatase inhibitors, but the use of these agents should be discussed with patients who are suitable candidates, and they should be informed about the limitations of the current data. In my opinion, women whose risk of recurrence is high are reasonable candidates for the inclusion of an aromatase inhibitor in plans for adjuvant treatment, whereas women with a low risk of recurrence might give more weight to long-term safety and be better served by tamoxifen therapy."

— Martine J Piccart-Gebhart, MD, PhD
N Engl J Med 2004;350:1140-1142

SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN

It may be reasonable to offer an aromatase inhibitor to patients who completed a five-year course of adjuvant tamoxifen for as long as five or 10 years previously. However, with every year that passes, the absolute risk of recurrence decreases; therefore, the risk-to-benefit ratio changes. Every year the risks become more important relative to the benefit.

— I Craig Henderson, MD

Over the past couple of decades, tamoxifen has had a huge impact on the management of breast cancer, but its use in the adjuvant setting may be declining. Several studies have demonstrated the superiority of aromatase inhibitors over tamoxifen, including the ATAC trial, the NCIC-CAN-MA17 trial in which women received letrozole after five years of tamoxifen and two trials in which women were switched to an aromatase inhibitor after two or three years of tamoxifen. The Intergroup study utilizing exemestane, and Boccardo's trial utilizing anastrozole in node-positive breast cancer demonstrated an advantage to switching early from tamoxifen to the aromatase inhibitor. When I use endocrine therapy in newly diagnosed patients, I select anastrozole. If I'm going to switch therapy after two or three years of tamoxifen, I use exemestane, but after five years of tamoxifen, I choose letrozole.

— Nicholas J Robert, MD

Off protocol in a postmenopausal woman, I generally use adjuvant anastrozole up front or, if the patient has been on tamoxifen for two or three years, I switch her to exemestane. After five years of tamoxifen therapy, I offer patients letrozole. The issue here is that because patients generally do well after five years of tamoxifen, we have to carefully weigh the potential benefit and side effects of further adjuvant therapy. A patient with a small tumor may not need it; however, in a patient with multiple positive nodes, it probably is indicated.

— Adam M Brufsky, MD, PhD

AROMATASE INHIBITORS AND OVARIAN SUPPRESSION

I'm very enthusiastic about the research strategy of evaluating LHRH agonists with aromatase inhibitors. Extrapolating from the data in postmenopausal breast cancer, which suggest that anastrozole may have superior efficacy compared to tamoxifen, this seems like a rational strategy to transfer to premenopausal women. The two issues are whether or not it is actually going to be efficacious, and what the cost is in terms of side effects. I wouldn't utilize this strategy outside the context of a clinical trial.

— Nancy Davidson, MD

Optimizing Adjuvant Chemotherapy: Recent Trial Results

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Two taxane-containing regimens have demonstrated improved efficacy in recent studies — dose-dense, every two-week AC → paclitaxel with growth factor support, and TAC (docetaxel, doxorubicin and cyclophosphamide). Because of the relatively high rate of febrile neutropenia, growth factor support was required for the TAC regimen.

Indirect comparison of these databases suggests similar efficacy and tolerability, and both have demonstrated an overall survival advantage in randomized trials. Another taxane-containing regimen — AC followed by docetaxel — is commonly utilized in the adjuvant setting but has only been reported in a major randomized trial in the neoadjuvant setting. While the benefits in terms of disease-free and overall survival observed in CALGB-9741 are clear, it is unclear whether the advantage observed from the dose-dense every two-week scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

PHASE III RANDOMIZED TRIAL COMPARING ADJUVANT TAC TO FAC

Protocol IDs: GEICAM-9805
Accrual: 448 (Closed)

Eligibility	Operable, high-risk breast cancer Node-negative, age 18 to 70 years; KPS* ≥80%
ARM 1	TAC (75/50/500 mg/m²) q3wk x 6
ARM 2	FAC (500/50/500 mg/m²) q3wk x 6

* Karnofsky performance status
T = docetaxel

Of the first 224 patients enrolled, those experiencing febrile neutropenia (≥ Grade 2 fever with Grade 4 neutropenia) were treated with granulocyte colony-stimulating factor (G-CSF) in all subsequent cycles. In the following 224 patients enrolled, a protocol amendment mandated the use of prophylactic G-CSF for those receiving TAC.

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

ADJUVANT TAC VERSUS FAC (GEICAM-9805): INTERIM SAFETY ANALYSIS

	TAC		FAC	
	Before protocol amendment* (n=109)	After protocol amendment* (n=115)	Before protocol amendment* (n=111)	After protocol amendment* (n=113)
Febrile neutropenia	23.8%	3.5%	0.9%	1.7%
Other Grade III/IV toxities	50.4%	20%	27%	26.5%

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

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

SECONDARY PROPHYLAXIS WITH G-CSF AND INCIDENCE OF FEBRILE NEUTROPENIA PER CYCLE OF TAC OR FAC: A RETROSPECTIVE SUBGROUP ANALYSIS FROM BCIRG-001

	TAC (n=4,278)		FAC (n=4,348)	
Cycles administered with G-CSF as secondary prophylaxis	18.7%		2.9%	
Febrile neutropenia per cycle	–G-CSF 6.0%	+G-CSF 3.1%	–G-CSF 0.5%	+G-CSF 0.3%

n = number of cycles; –G-CSF = without granulocyte colony-stimulating factor; +G-CSF = with granulocyte colony-stimulating factor

SOURCE: Vogel CL et al. *Proc ASCO* 2004;Abstract 677.

PHASE III TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS FAC

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

Eligibility	Stage T1-3, N1, M0; age ≤70; KPS* ≥80%
ARM 1	TAC (75/50/500 mg/m²) q3wk x 6
ARM 2	FAC (500/50/500 mg/m²) q3wk x 6

* Karnofsky performance status
T = docetaxel

SOURCES: http://www.bcirg.org/Internet/Studies/BCIRG+001.htm, February 2004. Vogel CL et al. *Proc ASCO* 2004;Abstract 677.

ADJUVANT TAC VERSUS FAC: DISEASE-FREE SURVIVAL (DFS) AND OVERALL SURVIVAL (OS) AFTER A MEDIAN FOLLOW-UP OF 55 MONTHS (BCIRG-001)

N=1,491	Hazard ratio* TAC/FAC (95% CI)	*p*-value
DFS Adjusted for nodal status 1-3 nodes (n=923) ≥4 nodes (n=568)	 0.72 (0.59-0.88) 0.61 (0.46-0.82) 0.82 (0.63-1.08)	 0.0010 0.0009 0.1629
Hormone receptor-positive Hormone receptor-negative	0.73 (0.57-0.94) 0.66 (0.47-0.93)	0.0132 0.0163
OS Adjusted for nodal status	 0.70 (0.53-0.91)	 0.0080

* Hazard ratios less than one indicate values in favor of TAC.
CI = confidence interval

SOURCE: Martin M et al. Presentation. SABCS, 2003;Abstract 43.

THREE-YEAR RESULTS OF CALGB-9741

Parameters	Dose-dense scheduling	Conventional scheduling	Response rate (*p*-value)
Disease-free survival	85%	81%	0.74 (0.010)
Overall survival	92%	90%	0.69 (0.013)

Complications during treatment	Dose-dense scheduling	Conventional scheduling
Patients with dose delay	37.5%	39.0%
Patients tranfused (RBC)	7.8%	1.9%
Patients hospitalized for febrile neutropenia	2.0%	4.3%

RR = relative reduction or risk reduction

SOURCE: Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9.

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CALGB-9741: ADJUVANT DOSE-DENSE CHEMOTHERAPY

This study, designed with input from all members of the breast Intergroup and coordinated by the CALGB, had a two-by-two factorial design. The two parameters were dose-density — giving drugs every two weeks with G-CSF instead of every three weeks — and combination versus sequential therapy. The doses were derived from previous clinical trial experience. The only difference was the schedules. This trial, which accrued over 2,000 patients, shows improved efficacy, decreased death rates and reduced toxicity. I believe in dose-dense therapy because I've seen its evolution in the laboratory and the clinic for 25 years, and it has a solid basis.

— Larry Norton, MD

Unlike some other trials, analysis of CALGB-9741 was time-driven, not event-driven. I'm glad we didn't have an event trigger because we'd still be waiting for this important data, and results are only relevant for a certain period of time. The study stipulated an analysis at 36 months and, consistent with trends in adjuvant therapy in general and adjuvant therapy trials in particular, the actual number of events at 36 months was far less than expected — 315 events for event-free survival rather than the expected 515 events. The data revealed a statistically significant advantage to every two-week versus every three-week therapy but no difference between sequential versus concurrent AC.

— Clifford A Hudis, MD

I believe the dose-dense approach is an advance in treatment. It's amazing that chemotherapy every two weeks rather than every three weeks can be less toxic, but that's been my experience. With dose-dense therapy, dose delays do not occur, the patients feel fine and are thrilled to finish therapy earlier, and neutropenic fever is rare. The one toxicity that concerns me is neurotoxicity because it's less objective. We can harm patients by continuing paclitaxel when significant neurotoxicity is present.

— Melody A Cobleigh, MD

Currently, the weight of the evidence supports dose-dense AC followed by paclitaxel regimen, but TAC may be as efficacious. Data from the TAC/FAC adjuvant study have been updated and demonstrate a survival benefit when 5-FU is replaced with a taxane. AC followed by docetaxel in a sequential manner is probably tolerated better and may be just as efficacious, but, we only have surgical data from NSABP-B-27, not long-term results.

— Julie R Gralow, MD

USE OF ADJUVANT TAC

Taxanes clearly offer benefit in the adjuvant setting, and I typically utilize the six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are similar. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741.

— Denise A Yardley, MD

My first choice for treatment of younger patients with node-positive disease is TAC, which most of my patients choose. My second choice is the dose-dense regimen because the Phase III data shows a benefit, but I am concerned about the reported 13 percent incidence of blood transfusions. I've spoken with physicians who say it's not that high in actual practice, so it may not be a real effect, rather just a result of limited data.

My third choice is AC followed by docetaxel, because in NSABP B-27 we saw a higher pathologic complete response rate, although not a survival benefit. I don't use anthracycline-based regimens like FEC or CAF because I prefer a regimen that includes a taxane. Although data support using these regimens in the pre- or postmenopausal patient, I'm convinced the taxanes provide an additive benefit.

— Sandra Swain, MD

Ongoing Clinical Trials of Adjuvant Chemotherapy

The encouraging results of CALGB-9741 have led to a new generation of Phase III randomized trials evaluating dose-dense chemotherapy. NSABP-B-38 is a new trial comparing every two-week dose-dense AC → paclitaxel to the other major taxane-containing regimen evaluated in large Phase III adjuvant trials, TAC (docetaxel, doxorubicin, cyclophosphamide) and a third experimental arm including dose-dense AC → paclitaxel/gemcitabine. The follow-up Intergroup trial to CALGB-9741 is SWOG-S0221, comparing a dose-dense metronomic regimen of AC to every two-week dose-dense AC → paclitaxel. A second randomization compares weekly to every two-week paclitaxel. Another strategy being investigated in current trials is the addition of capecitabine to docetaxel, which is included in ongoing US Oncology and MD Anderson studies.

PHASE III TRIAL COMPARING AC FOLLOWED BY EITHER DOCETAXEL (T) OR CAPECITABINE PLUS DOCETAXEL (XT)

Protocol ID: US Oncology 01-062
Accrual: 1,810 (Open)

Eligibility	Node-positive or high-risk node-negative operable breast cancer
ARM 1	AC x 4 → docetaxel x 4
ARM 2	AC x 4 → (docetaxel + capecitabine) x 4

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

SOURCE: US Oncology Protocol 01-062, June 2002.

PHASE III STUDY OF AC FOLLOWED BY DOCETAXEL (T) VERSUS AT VERSUS ATC

Protocol IDs: NSABP-B-30, CTSU
Target Accrual: 5,300 (Closed)

Eligibility	Stage I, II or IIIA breast cancer with at least one positive axillary lymph node
ARM 1	(Doxorubicin + cyclophosphamide) q3wk x 4 → docetaxel q3wk x 4
ARM 2	(Doxorubicin + docetaxel) q3wk x 4*
ARM 3	(Doxorubicin + cyclophosphamide + docetaxel) q3wk x 4*

* Note: Primary prophylaxis with growth factors at investigators' discretion will be given

SOURCE: NCI Physician Data Query, February 2004.

PHASE III ADJUVANT TRIALS INCORPORATING DOSE-DENSE SCHEDULES

Protocol ID	Target accrual	Eligibility	Randomization
SWOG-S0221	4,500	Node-positive or high-risk node-negative	[AC + PEG-G (d2)] q2wk x 6 → [P + PEG-G (d2)] q2wk x 6 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → [P + PEG-G (d2)] q2wk x 6 [AC + PEG-G (d2)] q2wk x 6 → P qwk x 12 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → P qwk x 12
NSABP-B-38	4,800	Node-positive	TAC q3wk x 6 AC q2wk x 4 → paclitaxel q2wk x 4 AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4
CAN-NCIC-MA21	1,500	Node-positive or high-risk node-negative	[E + 5-FU (d1-8) + C_{oral} (d1-14)] q4wk x 6 [EC + G (d2-13)*] q2wk x 6 → [P + G (d2-13)*] q3wk x 4 AC q3wk x 4 → [P + G (d2-13)*] q3wk x 4
CALGB-40101	4,646	High-risk node-negative	AC q2wk x 4 AC q2wk x 6 Paclitaxel q2wk x 4 Paclitaxel q2wk x 6

C = cyclophosphamide; E = epirubicin; G = filgrastim; PEG-G = pegfilgrastim; A = doxorubicin; C_{oral} = oral cyclophosphamide; P = paclitaxel; T = docetaxel;
* Epoetin alpha is administered weekly in patients with a hemoglobin <13 g/dL.

SOURCES: NCI Physician Data Query, September 2004. Protocol Summaries, NSABP Group Meeting, June 2004.

COMPARISON OF TWO COMBINATION CHEMOTHERAPY REGIMENS WITH OR WITHOUT CELECOXIB IN TREATING WOMEN WITH BREAST CANCER

Protocol ID: NSABP-B-36, CTSU
Accrual: 2,700 (Open)

Eligibility	T1-3 node-negative breast cancer
ARM 1	AC q3wk x 4 → oral celecoxib BID x 3 years → oral placebo BID x 3 years
ARM 2	FEC q3wk x 6 → oral celecoxib BID x 3 years → oral placebo BID x 3 years

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

SOURCE: NCI Physician Data Query, September 2004.

PHASE III RANDOMIZED STUDY OF THREE DIFFERENT ADJUVANT CHEMOTHERAPY REGIMENS

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

Eligibility	Node-positive breast cancer, with known ER status and PR status known only if ER-negative
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

T = docetaxel
Note: Beginning 3-12 weeks after the last dose of chemotherapy, patients with ER-positive and/or PR-positive tumors receive tamoxifen or an aromatase inhibitor.

SOURCE: NCI Physician Data Query, October 2004.

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Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients: Results from GONO — MIG1 study.** *Breast Cancer Res Treat* 2003;Abstract 12.

NEW STRATEGIES FOR ADJUVANT THERAPY

I believe the adjuvant trials studying the combination of capecitabine and docetaxel are wonderful trials to evaluate extremely active drugs in the adjuvant setting. We have several outstanding agents with high response rates in the metastatic setting, such as capecitabine, vinorelbine and gemcitabine, which haven't been evaluated in the adjuvant setting. I support the strategy of moving these agents into the adjuvant course of treatment.

— Hyman B Muss, MD

SWOG-S0221: DOSE-DENSE VERSUS CONTINUOUS CHEMOTHERAPY

In this study, AC is administered in either a dose-dense manner with pegfilgrastim versus what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment. Data suggests six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of vasculogenesis occurs between cycles and hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

— G Thomas Budd, MD

NSABP-B-30: AC FOLLOWED BY DOCETAXEL (T) VERSUS AT VERSUS ATC

Many investigators believed that docetaxel was the most active agent in metastatic disease and that it should be investigated in the adjuvant setting, which is why we included it in all three arms of B-30. We also wanted to compare the various durations of treatment. The AC followed by docetaxel arm is a six-month treatment, while the other arms are shorter in duration. NSABP data showed four cycles of AC was effective, and we felt that four cycles of AT or TAC would be effective. Perhaps with hindsight, based on the TAC data, it would have been better to go with six cycles of TAC, but there's really no data showing six is superior to four cycles. We added growth factors, and it is up to the investigators whether they use the long- or shorter-acting growth factor.

— Sandra Swain, MD

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 A Hudis, MD

NSABP TRIAL B-38

NSABP-B-38 will compare two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It's a good trial design because in addition to determining whether one of the two standard combinations is superior, it examines an agent new to the adjuvant setting — gemcitabine. At the 2004 ASCO meeting, Kathy Albain reported on a metastatic trial that showed an advantage for gemcitabine/paclitaxel versus paclitaxel alone. While the every two-week schedule is a bit of a leap, it was necessary to make it comparable to the dose-dense paclitaxel schedule.

— G Thomas Budd, MD

CALGB-49907: Adjuvant Chemotherapy in Elderly Women

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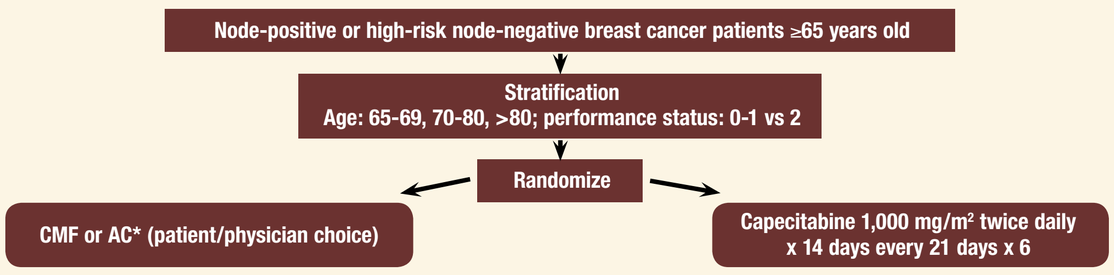
Relatively few randomized trials of adjuvant chemotherapy have included substantial numbers of elderly women, so a relative paucity of research data exists with regard to the risks and benefits of this intervention. This is particularly problematic in older women with estrogen receptor-negative tumors who will not receive endocrine therapy. Another common clinical dilemma is the elderly woman with an estrogen receptor-positive tumor for whom the incremental benefits and risks of chemotherapy in addition to endocrine treatment must be considered. An important related trial is being led by Dr Hyman Muss. CALGB-49907 randomly assigns elderly women with primary breast cancer to either the orally administered fluoropyrimidine prodrug capecitabine, or AC or CMF chemotherapy. In addition to evaluating disease-free and overall survival, a number of key quality-of-life endpoints are being evaluated.

CALGB-49907: ADJUVANT CMF OR AC VERSUS CAPECITABINE IN WOMEN 65 YEARS AND OLDER



* Patients whose LVEF is not within lower limits of normal must receive CMF, not AC. All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor for five years.

SOURCE: NCI Physician Data Query, October 2004.

SUMMARY OF EFFICACY: SINGLE-AGENT CAPECITABINE VERSUS STANDARD CHEMOTHERAPY IN METASTATIC DISEASE

Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF) as first-line therapy (n=93)		
	Capecitabine	**CMF**
Response rate (95% CI)	30% (19-43)	16% (5-33)
Complete response	5%	0%
Median time to disease progression (95% CI)	4.1 months (3.2-6.5)	3.0 months (2.4-4.8)
Median survival	19.6 months	17.2 months
Capecitabine versus paclitaxel as second-line therapy (n=41)		
	Capecitabine	**Paclitaxel**
Response rate (95% CI)	36% (17-59)	26% (9-51)
Complete response	14%	0%
Median time to progression (95% CI)	3.0 months (1.4-6.6)	3.1 months (2.5-6.5)
Median duration of response	9.4 months	9.4 months

CI = confidence interval

DERIVED FROM: Biganzoli L et al. **Moving forward with capecitabine: A glimpse of the future.** *Oncologist* 2002;7(Suppl 6):29-35.

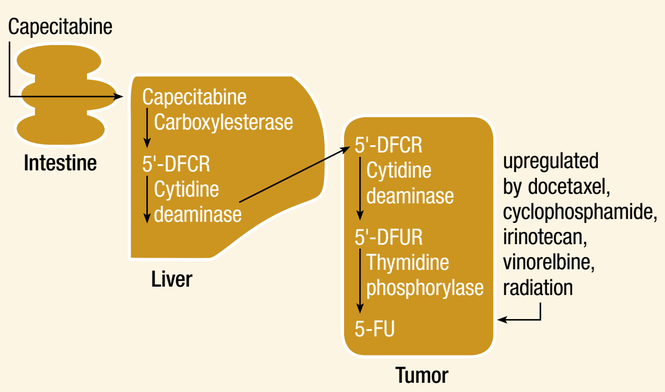
PROPORTION OF ELDERLY PATIENTS (AGE ≥65) IN SWOG TRIALS AS COMPARED WITH THE PROPORTION OF ELDERLY PATIENTS WITH CANCER*

Type of cancer	Percent of US cancer cases occurring in patients age ≥65	Percent of enrolled patients age ≥65
Breast	49%	9%
Brain	44%	19%
Colorectal	72%	40%
Leukemia	63%	27%
Lung	66%	39%
Myeloma	70%	25%
All types	63%	25%

* The differences between the two groups were significant ($p < 0.001$) for all types of cancer listed.

SOURCE: Hutchins LF et al. **Underrepresentation of patients 65 years of age or older in cancer-treatment trials.** *N Engl J Med* 1999;341(27):2061-7.

ENZYMATIC CONVERSION OF CAPECITABINE TO 5-FLUOROURACIL



RATES OF OFFERING AND ACCEPTING CLINICAL TRIAL PARTICIPATION IN WOMEN

Mean age (years)	Offered protocol	Consented when offered
50.4	51%	56%
76.5	35%	50%

SOURCE: Kemeny M et al. **Barriers to clinical participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

UNDER-REPRESENTATION OF ELDERLY WOMEN IN RECENT CALGB ADJUVANT TRIALS

Trial regimens	Total accrued	Age 70 and older
CLB-8541 CAF in three different doses	1,572	150 (10%)
CLB-9344 AC ± T	3,170	182 (6%)
CLB-9741 A → T → C vs AC → T in a q2wk vs q3wk schedule	2,005	162 (8%)

C = cyclophosphamide; A = doxorubicin; F = fluorouracil; T = paclitaxel

SOURCE: CALGB-49907 Protocol.

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Kemeny MM et al. **Barriers to clinical trial participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

Mandelblatt JS et al. **Predictors of long-term outcomes in older breast cancer survivors: Perceptions versus patterns of care.** *J Clin Oncol* 2003;21(5):855-63.

O'Shaughnessy JA et al. **Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12(9):1247-54.

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72.

CALGB-49907: CAPECITABINE VERSUS CA/CMF IN THE ELDERLY

CALGB-49907 is an Intergroup trial also available through the Cancer Trials Support Unit (CTSU) of the NCI that compares capecitabine with CA or CMF. Patients are randomly assigned to standard therapy — either CA or CMF — and the physician chooses which of these two regimens to use. The goal is to determine whether capecitabine is equally effective as standard adjuvant therapy.

Women eligible for this trial are 65 years and older with node-positive or high-risk, node-negative breast cancer. Women with ER-positive tumors can receive tamoxifen or anastrozole as their endocrine therapy.

Capecitabine is a reasonably safe drug, but patients need to be informed about side effects and toxicity. We are gathering excellent quality-of-life data and collecting adherence data with an electronic pill bottle. We are also evaluating some incredible laboratory science including genes that might tell us about toxicity, such as levels of thymidine phosphorylase, thymidylate synthase and dihydropyrimidine dehydrogenase (DPD). In addition, we'll be storing all the blocks for future work.

Although it's a little early for me to predict how to compare these regimens, I believe patients may perceive that capecitabine is a little easier to take because it is oral and not associated with alopecia.

— Hyman B Muss, MD

In addition to the more familiar ER, PR and HER2 markers, we are looking at some interesting predictive and prognostic markers and other biological markers. We are also examining how these drugs are metabolized in the elderly population. The data from the metastatic setting provided the rationale for selecting capecitabine for this trial. In addition to the convenience of an oral regimen, the trials comparing capecitabine to single-agent paclitaxel and to CMF demonstrated benefits from capecitabine in time to progression. However, capecitabine is not a benign drug, so we are closely monitoring patients.

— Maria Theodoulu, MD

CAPECITABINE IN ELDERLY PATIENTS

We did a small, randomized Phase II trial comparing intravenous CMF and full-dose capecitabine as front-line therapy in elderly patients aged 55 years or older in the metastatic setting. The response rate with capecitabine was 30 percent compared to 16 percent with intravenous CMF.

In a randomized Phase II trial of patients pretreated with an anthracycline, comparing paclitaxel every three weeks to capecitabine, the response with capecitabine was 36 percent compared to 26 percent with paclitaxel. The confidence intervals were widely overlapping, so we couldn't conclude that capecitabine is superior.

What we can say from these two studies is that it's certainly unlikely that capecitabine is worse than CMF or paclitaxel. It's interesting how quickly capecitabine has moved to trials in the adjuvant setting. In women over age 65, the role of chemotherapy is unknown. For women over 70, in particular, the overview analysis includes so few patients in that age group that I think it's very reasonable to compare capecitabine to AC or CMF.

— Joyce O'Shaughnessy, MD

CALGB-49907: QUALITY-OF-LIFE SUBPROTOCOL

Capecitabine is an obvious choice to study in the adjuvant setting. I'm most interested in Hyman Muss' Intergroup study comparing capecitabine versus AC or CMF in women over age 65. Based on the chemistry of capecitabine, it wouldn't surprise me if it proves to be equivalent in efficacy with a superior toxicity profile. In addition, it has the advantage of being an oral regimen.

US Oncology and MD Anderson each have adjuvant studies evaluating the combination of capecitabine and docetaxel, but these trials are not mature and it will be some time before we know the results.

— Daniel R Budman, MD

Dose-Dense Adjuvant Chemotherapy

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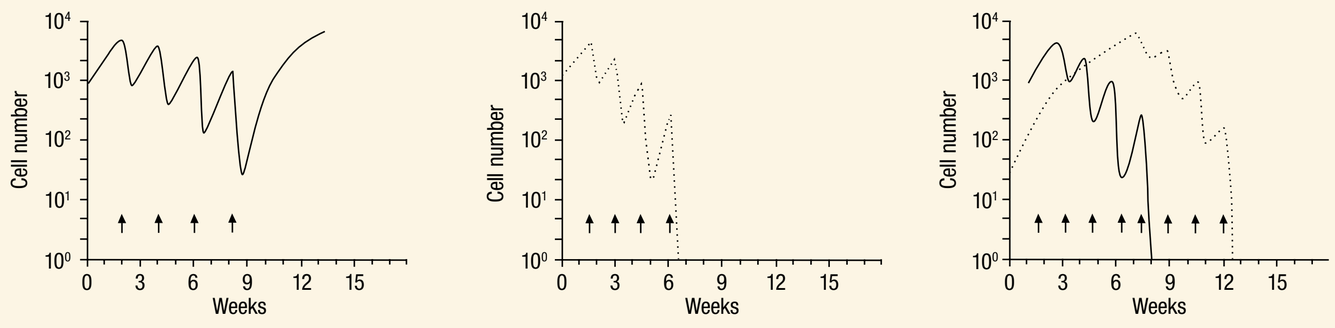
A number of randomized trials have failed to demonstrate an advantage to dose-intensive chemotherapy. Dose-dense chemotherapy involves the use of shorter dosing intervals, facilitated by hematopoietic growth factor support (ie, filgrastim, pegfilgrastim). This strategy is based on theoretical mathematical modeling by Norton and others, suggesting a potential benefit to retreatment before tumor regrowth occurs. In December 2002, results of CALGB-9741 were reported at the San Antonio Breast Cancer Symposium, demonstrating a disease-free and overall survival advantage to two dose-dense chemotherapeutic regimens involving doxorubicin, cyclophosphamide and paclitaxel given every two weeks with filgrastim support. A number of ongoing randomized trials are incorporating the dose-dense strategy and also are evaluating the role of pegfilgrastim.

LOG CELL KILL IN GOMPERTZIAN GROWTH NEEDED FOR IMPACT OF ADJUVANT CHEMOTHERAPY



SOURCE: Reproduced with permission from Norton L. **Theoretical concepts and the emerging role of taxanes in adjuvant therapy**. *The Oncologist* 2001;6(56):30-35.

PHASE III ADJUVANT TRIAL OF STANDARD VERSUS ACCELERATED FEC

Protocol ID: GONO-MIG1
Accrual: 1,214 (Closed)

Eligibility	Node-positive or high-risk node-negative operable breast cancer
ARM 1	FEC21 q3wk (600/60/600 mg/m²) x 6
ARM 2	FEC14 q2wk (600/60/600 mg/m²) x 6 + filgrastim

Change in hazard of death with FEC14 q2wk compared to FEC21 q3wk

	FEC14 q2wk	Hazard ratio (HR)
Overall population	-18%	HR = 0.82 (95% CI = 0.6-1.12), p = 0.22
<50 years	-49%	HR = 0.51 (95% CI = 0.27-0.94)
50-59 years	-29%	HR = 0.71 (95% CI = 0.40-1.25)
>60 years	+48%	HR = 1.48 (95% CI = 0.80-2.75)

SOURCE: Venturini M et al. *Breast Cancer Res Treat* 2003;Abstract 12.

PHASE III ADJUVANT TRIAL OF DOSE DENSE SEQUENTIAL CHEMOTHERAPY VERSUS CONVENTIONALLY DOSED CHEMOTHERAPY

Protocol ID: AGO
Accrual: 1,284 (Closed)

Eligibility	High-risk breast cancer (>4 positive nodes), age <65
ARM 1	E (150 mg/m²) → T (225 mg/m²) → C (2500 mg/m²) q2wk + G-CSF
ARM 2	E (150 mg/m²) → T (225 mg/m²) → C (2500 mg/m²) q2wk + G-CSF + Epo
ARM 3	EC (90/600 mg/m²) x 4 → T (175 mg/m²) q3wk

E = epirubicin; T = paclitaxel; C = cyclophosphamide; Epo = epoetin alpha

Endpoint	E → T → C* (n=599)	EC → T (n=570)	p-value
Relapse or death	94 (15.7%)	127 (22.3%)	0.0009
Death	43 (7.2%)	60 (10.5%)	0.03

* Epo arm resulted in less transfusion but similar survival

SOURCE: Mobus VJ. Presentation. ASCO, 2004;Abstract 513.

A PHASE III RANDOMIZED STUDY OF DOSE-DENSE VERSUS CONVENTIONAL SCHEDULING AND SEQUENTIAL VERSUS COMBINATION ADJUVANT CHEMOTHERAPY

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741 (Closed)

ARM 1	A q3wk x 4 → T q3wk x 4 → C q3wk x 4
ARM 2	A q2wk x 4 → T q2wk x 4 → C q2wk x 4*
ARM 3	AC q3wk x 4 → T q3wk x 4
ARM 4	AC q2wk x 4 → T q2wk x 4*

* Filgrastim (G-CSF) is administered on days 3-10 after each dose of doxorubicin, paclitaxel and cyclophosphamide.

A = doxorubicin; T = paclitaxel; C = cyclophosphamide

SOURCE: Citron ML et al. *J Clin Oncol* 2003; 21(8):1431-9.

THREE-YEAR RESULTS OF CALGB-9741

Parameters	Dose-dense scheduling	Conventional scheduling	Response rate (p-value)
Disease-free survival	85%	81%	0.74 (0.010)
Overall survival	92%	90%	0.69 (0.013)

Complications during treatment	Dose-dense scheduling	Conventional scheduling
Patients with dose delay	37.5%	39.0%
Patients tranfused (RBC)	7.8%	1.9%
Patients hospitalized for febrile neutropenia	2.0%	4.3%

RR = relative reduction or risk reduction

SOURCE: Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9.

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CALGB-9741: DOSE-DENSE CHEMOTHERAPY

At a median follow-up of three years, dose-dense treatment was associated with a 26 percent proportional reduction in relapse and a 31 percent proportional reduction in mortality. We had expected 515 relapses based on CALGB-8541, the CAF dose-intensive trial; however, only 315 patients had a recurrence. The four-year disease-free survival was 82 percent for dose-dense therapy and 75 percent for the every three-week regimens. I was surprised by the magnitude of the difference — seven percent at four years is significant. We'll have to see whether the survival benefit is lost or confirmed with further follow-up. Most patients received the optimal doses of their drugs in all arms, which may be related to the low ANC requirement and the fact that less than eight percent of treatment cycles were delayed. This assured us that the benefits of dose density could not be attributed to a lower dose or further dose delays in the conventional regimens — the arms were balanced in that regard.

— Marc Citron, MD

HAZARD RATES OF RECURRENCES

Some criticize the data from CALGB-9741 because the magnitude of benefit over time may not be as large as it is now. That's fair, because it could fluctuate, but the positivity won't go away. We saw the same phenomenon in CALGB-9344. If you plot the hazard function and compare paclitaxel to no paclitaxel, sometimes the curves are close together and sometimes the curves are further apart, but the aggregate benefit is clear and consistent.

— Clifford A Hudis, MD

DOSE-DENSE THERAPY TARGETS INHIBITION OF REGROWTH

A paper in *Seminars in Oncology* in the mid-1980s indicated that the primary problem in Gompertzian growth is not cell kill, but rather regrowth between cycles. While therapy gets us closer to the cure limits, you have to get below a small number of cells to prevent regrowth, and you regrow faster away from that limit. There's a rebound effect, and the key is to inhibit that regrowth.

One of the simplest ways to address regrowth is to move the doses of therapy close enough together to have less regrowth between cycles. This is extremely powerful in Gompertzian kinetics, as long as you can drive the tumor toward that cure limit. In the adjuvant setting, when you're probably close to the cure limit, you can have dramatic benefits by giving the doses closer together in time.

— Larry Norton, MD

DOSE-DENSE STUDY OF FEC

At the 2003 San Antonio Breast Cancer Symposium, Venturini et al presented data from a trial comparing FEC every two weeks versus every three weeks. It's one of the few studies that, like CALGB-9741, truly tested dose density because every patient received the same doses of the same drugs for the same number of cycles and the only variable was the interval between treatments. I commend Venturini and his colleagues because that approach is the key to demonstrating the value of dose-dense therapy.

We hoped Venturini's trial would confirm CALGB-9741 as a general principle, but their event rate was lower than expected and the study lost its power. In CALGB-9741, we also had fewer events than expected. Fortunately, our trial was large enough to demonstrate the benefit of dose density at 36 months. They presented the data showing a trend in favor of the dose-dense therapy, stating that while the trial was not positive, the range of possibilities included positivity.

Consistent with CALGB-9741, they were able to show that dose-dense therapy was faster with fewer episodes of febrile neutropenia. Although I was disappointed that their study didn't have the power to confirm the CALGB data, I'm confident that their data was consistent with ours.

— Clifford A Hudis, MD

Research To Practice: Adjuvant Chemotherapy

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One of the most important factors affecting the use of adjuvant chemotherapy in clinical practice has been the use of computerized web- and PDA-based models estimating risk of relapse and death with and without specific adjuvant chemotherapy and hormonal therapy regimens. About half of practicing oncologists in the United States currently use these models to assist in clinical decision-making, and a particularly common scenario is the patient with an ER-positive, node-negative tumor for whom the incremental benefit of chemotherapy is a key issue. In terms of selection of regimens, the most important recent research databases are the CALGB-9741 trial evaluating dose-dense adjuvant chemotherapy and multiple trials addressing the inclusion of taxanes, including CALGB-9344, NSABP-B-28 and BCIRG-001. The patterns of care survey demonstrates that taxane-containing regimens are commonly utilized in patients with node-positive and high-risk node-negative tumors. Dose-dense AC → T is the most frequently utilized regimen in this setting, and pegfilgrastim is more commonly utilized than filgrastim for growth factor support.

USE OF COMPUTER MODELS IN CLINICAL PRACTICE

In which of the following situations do you* tend to use computer models to estimate breast cancer patients' risk of relapse and/or mortality?

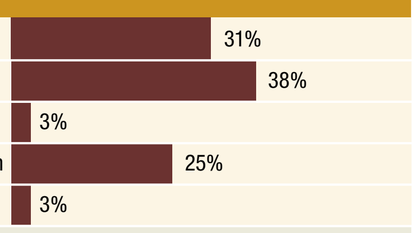
To review risk estimates with patients	98%
To decide whether to use chemotherapy in node negative cases	81%
To decide whether to use endocrine therapy in node negative cases	44%
To select type of chemotherapy to use	19%
To select type of endocrine therapy to use	10%
Other situations	5%

* 25% of oncologists surveyed use the Adjuvant! model, 12% use the Mayo clinic model, 22% use both models and 41% of physicians do not use either model.

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

CHOICE OF GROWTH FACTORS FOR DOSE-DENSE ADJUVANT CHEMOTHERAPY

When using dose-dense chemotherapy*, which growth factor(s) do you use?



* 64% of oncologists report having utilized dose-dense adjuvant chemotherapy in a nonprotocol setting.

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE DISEASE

The patient is a woman in average health with a 1.2-cm, ER-positive, HER2-negative (as confirmed by FISH), Grade II tumor and 3 positive lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend?

	Age 35	Age 55	Age 65	Age 75
AC x 4 q3wk	3%	4%	7%	11%
AC x 4 q2wk with pegfilgrastim	3%	3%	2%	2%
AC x 4 q2wk with filgrastim	1%	1%	—	—
FAC or FEC x 6	2%	3%	4%	7%
AC x 4 followed by paclitaxel x 4 q3wk	7%	8%	13%	7%
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	38%	33%	26%	11%
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	7%	7%	5%	3%
AC x 4 q3wk followed by weekly paclitaxel x 12	2%	1%	3%	5%
AC x 4 followed by docetaxel x 4 - no growth factors	15%	17%	16%	8%
AC x 4 followed by docetaxel x 4 - with growth factors	11%	10%	10%	6%
CMF	—	—	—	10%
TAC (docetaxel)	9%	9%	7%	2%
Other chemotherapy	2%	2%	2%	2%
Would not recommend chemotherapy	—	2%	5%	26%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ACCURACY OF PHYSICIAN-ESTIMATED RISK OF RELAPSE AND MORTALITY

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH), Grade II tumor and negative lymph nodes. How would you estimate this patient's 10-year risk of relapse and mortality?

Therapy	Estimated 10-year risk of relapse	Actual* 10-year risk of relapse	Estimated 10-year risk of mortality	Actual* 10-year risk of mortality
With no systemic therapy	20%	23%	12%	7%
With hormonal therapy alone	13%	Anastrozole 13% Tamoxifen 15%	8%	Tamoxifen 6%
With both hormonal therapy and chemotherapy (AC x 4)	10%	Anastrozole 11% Tamoxifen 14%	6%	Tamoxifen 5%

* Based on Adjuvant!

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

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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.

USE OF COMPUTERIZED RISK ESTIMATE MODELS

I am really pleased about how many practitioners are actually using computer-based models in their practice. My expectation is that the number is rapidly increasing. I have found that it is difficult to convince practitioners to try these models; however, once they do, I believe that they see the power of the numbers and how the presentation of absolute benefits to the patient can make decision-making an easier and much more objective process.

I use these models for every patient who comes in the door for a discussion of adjuvant therapy. For the past two years I have printed out the results and usually give them to the patient. I love the Adjuvant! model because it helps me to avoid biases. There are all types of factors that influence how physicians think about a specific patient — personality type, type of relationship that is established, referral source — these models totally remove those from the equation.

— Robert W Carlson, MD

NONPROTOCOL ADJUVANT MANAGEMENT OF PATIENTS WITH POSITIVE NODES

Right now, I believe that TAC and dose-dense AC followed by T are among the two best choices for adjuvant chemotherapy in node-positive patients. I use more dose-dense therapy, and by limiting anthracyclines to four courses, perhaps we will have somewhat less cardiotoxicity in the long run. I've occasionally observed cardiotoxicity with some of the six or more cycle anthracycline regimens. This is more of a gut feeling than a scientific observation, and I believe both regimens are excellent. In terms of quality of life and toxicity, my interpretation is that the regimens are not drastically different. You must use growth factors with TAC because the rate of neutropenic fever can be ameliorated with filgrastim or preferably pegfilgrastim.

— Hyman B Muss, MD

The most effective regimens are perceived to be TAC and dose-dense AC followed by paclitaxel. Without a comparative trial, it's difficult to say whether one is better than the other. A direct comparison is required to obtain a clear answer. I am most likely to use dose-dense AC followed by paclitaxel, but I helped to develop that regimen, and we often use what we have the most experience with. I believe Marc Citron and Cliff Hudis were surprised that dose-dense therapy wasn't more toxic; they feel that the dose-dense regimen is less toxic than the every three-week regimen, and the data support that.

— I Craig Henderson, MD

I've heard doctors state that they don't want to use a more aggressive dose-dense regimen unless the patients are at very high risk. Frankly, the dose-dense regimen is less toxic, more effective and faster. If CALGB-9741 had demonstrated that the regimens had equal efficacy, there would be real arguments for using a dose-dense regimen just from the toxicity point of view.

— Larry Norton, MD

RATIONALE FOR THE EFFECTIVENESS OF DOSE-DENSE SCHEDULING

The results of CALGB-9741 support the basic hypothesis I've had since the late 1980s, which is if you achieve a critical concentration necessary for cell kill, you're more likely to get an effective result in direct proportion to the amount of time, or area under the curve, that the tumor cells are exposed. That may sound a little simple-minded, and the explanation is probably more complex, but I think the exposure of cells to effective concentrations of chemotherapy over a longer period of time is the key to why dose-dense therapies work better.

A second reason, which may be very important, is the antiangiogenic hypothesis. We now have good preclinical data that demonstrate that with continuous exposure, certain classes of agents — cyclophosphamide, the vincas and the taxanes — result in much better cell kill and tumor regressions than intermittent exposure. There is solid evidence in preclinical systems that an antiangiogenic effect is the primary reason for that cell kill.

— Robert B Livingston, MD

Clinical Trials of Adjuvant Trastuzumab

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Randomized trial data from the advanced disease setting demonstrate that in women with HER2-overexpressing breast cancer, the combination of trastuzumab and chemotherapy — using either doxorubicin/cyclophosphamide or paclitaxel — results in improved progression-free and overall survival compared to the same chemotherapy given without trastuzumab. These encouraging results have led to a new generation of adjuvant trials evaluating a variety of chemotherapeutic regimens combined with trastuzumab. While no efficacy endpoints have been met, closely evaluated cardiac monitoring has not yet revealed dysfunction that would preclude continuing these trials. Almost all clinical research leaders currently advocate using adjuvant trastuzumab only in a clinical trial setting.

PHASE III RANDOMIZED STUDY OF ADJUVANT AC AND DOCETAXEL WITH OR WITHOUT TRASTUZUMAB VERSUS TRASTUZUMAB, DOCETAXEL, AND EITHER CARBOPLATIN OR CISPLATIN

Protocol ID: BCIRG-006
Accrual: 3,150 patients (Closed)

Eligibility	Node-positive or high-risk node-negative HER2-overexpressing (FISH-positive) breast cancer
ARM 1	AC x 4 → docetaxel x 4
ARM 2	AC x 4 → docetaxel x 4 + H (qwk x 12 weeks) → H (qwk x 40 weeks)
ARM 3	(Docetaxel + C) x 6 + H (qwk x 18 weeks) → H (qwk x 34 weeks)

C = cisplatin or carboplatin; H = trastuzumab;
AC = doxorubicin/cyclophosphamide

Patients with ER- and or PR-positive disease receive oral tamoxifen for five years beginning three to four weeks after the completion of chemotherapy. Patients may undergo radiotherapy beginning three to eight weeks after completion of chemotherapy.

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF TRASTUZUMAB IN WOMEN WITH HER2-POSITIVE PRIMARY BREAST CANCER

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 4,482 patients (Open)

Eligibility	Node-negative or node-positive HER2-positive breast cancer
ARM 1	H q3wk x 1 y
ARM 2	H q3wk x 2 y
ARM 3	No H

H = trastuzumab

Previously treated with at least 3 months or 4 courses of approved neoadjuvant or adjuvant chemotherapy with or without radiotherapy. Concurrent systemic adjuvant hormonal therapy for patients with ER-positive disease is allowed.

Study Contact:
Martine J Piccart-Gebhart, MD, PhD, Chair
Breast International Group
Tel: 32-2-5413206

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

Protocol IDs: NCCTG-N9831, CLB-49909, E-N9831, SWOG-N9831
Projected Accrual: 3,300 patients (Open)

Eligibility	Node-positive or high-risk node-negative HER2-overexpressing breast cancer
ARM 1	AC x 4 → T qwk x 12
ARM 2	AC x 4 → T qwk x 12 → H qwk x 52
ARM 3	AC x 4 → (T + H) qwk x 12 → H qwk x 40

T = paclitaxel; H = trastuzumab; AC = doxorubicin/cyclophosphamide

All postmenopausal patients with ER/PR-positive disease receive tamoxifen or an aromatase inhibitor for five years. Patients may undergo radiotherapy at the completion of chemotherapy.

Study Contact:
Edith A Perez, MD, Chair
North Central Cancer Treatment Group
Tel: 904-953-7283

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF AC FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

Protocol ID: NSABP-B-31
Projected Accrual: 2,700 patients (Open)

Eligibility	HER2-positive, node-positive breast cancer
ARM 1	AC x 4 → paclitaxel q3wk x 4 or paclitaxel qwk x 12
ARM 2	AC x 4 → (paclitaxel q3wk x 4 or paclitaxel qwk x 12) + H (qwk x 1 y)

H = trastuzumab; AC = doxorubicin/cyclophosphamide

Patients with ER/PR-positive disease receive tamoxifen for five years. Lumpectomy patients undergo radiotherapy at completion of chemotherapy and concurrent with trastuzumab.

Study Contact:
Edward Romond, MD, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 859-323-8043

SOURCE: NCI Physician Data Query, October 2004.

N9831: EFFECT OF ADJUVANT AC ON LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH HER2-POSITIVE BREAST CANCER (n=1,458)

Reduction in LVEF	n (%)
Patients with >15%	37 (2.5)
Patients with ≤15% and LVEF below LLN	42 (2.9)
Patients with ≤15% and LVEF remains at or above LLN	745 (51.1)

LVEF= left ventricular ejection fraction (measured by MUGA or ECHO)
LLN = lower limit of normal

SOURCE: Perez EA et al. *J Clin Oncol* 2004;22(18):3700-4.

NSABP-B-31 CARDIAC SAFETY ANALYSIS

	AC → paclitaxel	AC → paclitaxel/ trastuzumab	Percent increase
Cardiac events/n (%)	4/510 (0.78%)	23/538 (4.28%)	3.50%

SOURCE: Geyer CE Jr. Presentation. San Antonio Breast Cancer Symposium, 2003.

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Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20(5):1215-21.

Slamon D, Pegram M. **Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials.** *Semin Oncol* 2001;28(1 Suppl 3):13-9.

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Tan-Chiu E, Piccart M. **Moving forward: Herceptin in the adjuvant setting.** *Oncology* 2002;63(Suppl 1):57-63.

INTERGROUP 9831 TRIAL

N9831 is a randomized Phase III clinical trial building on several issues: (1) the relative importance of anthracyclines in the adjuvant management of patients with HER2-positive breast cancer, (2) the value of taxanes in patients eligible to receive adjuvant therapy, (3) the specific value of taxanes for patients with HER2-positive breast cancer, and (4) the value of weekly paclitaxel therapy for patients with breast cancer.

We were comforted by the data presented from CALGB-9741. That trial administered dose-dense chemotherapy with growth factor support once every two weeks, and in our trial we are using an even more dose-dense approach by administering paclitaxel on a weekly basis. The AC in our trial is still being given once every three weeks. Although we thought about potentially changing it to once every two weeks, we hypothesized that the advantage seen in CALGB-9741 may be due to the paclitaxel schedule. We also didn't want to introduce another factor that could impact cardiac toxicity.

— Edith A Perez, MD

HERA TRIAL OF ADJUVANT TRASTUZUMAB

The HERA trial is a relatively pragmatic study. Patients initially receive an approved adjuvant chemotherapy regimen, and then they are randomly assigned to trastuzumab monotherapy for either one or two years or no trastuzumab. It's my responsibility and that of Brian Leyland-Jones, who co-chairs the Trans-HERA Committee, to collect the tumor blocks from that trial and perform biomarker analyses.

— Mitchell Dowsett, PhD

BCIRG-006 ADJUVANT TRASTUZUMAB TRIAL

For the first time in a large randomized adjuvant study of patients with HER2-positive tumors, a non-anthracycline-containing synergistic combination will be put to the test in a very carefully selected patient population. All of the patients must have FISH-positive disease; therefore, I think the trial will define the standard of care for the adjuvant treatment of patients with HER2-positive breast cancer. The other important component of this trial is safety. It doesn't appear that cardiac safety is going to be a major issue in the adjuvant trastuzumab trials.

— Mark D Pegram, MD

NSABP-B-31: ADJUVANT AC FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB

After the NSABP designed the adjuvant trial B-31, the Intergroup designed a similar trial so that the data could be analyzed together. I think that's great because it will be a stronger analysis. I hope we'll see a benefit with trastuzumab, which has been a miracle drug in the metastatic setting. If this trial is positive, there will still be a lot of scheduling questions to be answered, such as, "How long do you really need trastuzumab and can it be administered every three weeks rather than weekly?"

— Sandra Swain, MD

CARDIAC SAFETY ANALYSIS IN NSABP-B-31

"… a 3.5 percent increase in cardiac events among patients receiving AC followed by Herceptin and Taxol compared to AC followed by Taxol alone was identified.

"The increase in cardiac events was within protocol limits, justifying continuation of accrual. Abnormal LV function and symptoms, if present, improved with cessation of Herceptin in the vast majority of patients. A peak decline in median LVEF of 3% was noted when patients had received 6 months of Herceptin.

"Clearly, additional follow-up will be needed to fully define the short and long term cardiac events of Herceptin in this setting. And these results support continued accrual into ongoing adjuvant trials, but indicate use as adjuvant therapy outside of clinical trial would clearly be premature."

— Charles E Geyer Jr, MD. Presentation. San Antonio Breast Cancer Symposium, 2003.

Trials of Hormonal Therapy in Metastatic Disease

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The recent emergence of the estrogen receptor downregulator fulvestrant and steroidal and nonsteroidal aromatase inhibitors have complicated the treatment algorithm for women with ER-positive metastatic disease. A number of ongoing clinical trials are attempting to evaluate endocrine strategies in women progressing on the usual first-line therapy (nonsteroidal aromatase inhibitors). Other studies are evaluating the combination of aromatase inhibitors with fulvestrant, based on the theoretical advantage of utilizing fulvestrant in a lower estrogen environment. Biologic agents are also being evaluated in combination with endocrine interventions. These include trials of trastuzumab with aromatase inhibitors and trials of tyrosine kinase inhibitors plus endocrine therapies.

ONGOING CLINICAL TRIALS OF HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN WITH METASTATIC DISEASE

Study	Trial design	Fulvestrant dosing/scheduling	Targeted accrual
SAKK	Phase II trial of monthly fulvestrant in postmenopausal women after progression on tamoxifen and a nonsteroidal aromatase inhibitor	250 mg monthly	93
EFECT	Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women after progression on a nonsteroidal aromatase inhibitor	500 mg day 0, 250 mg days 14, 28 and then monthly	660
SoFEA	Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER- and/or PR-positive breast cancer who progressed on anastrozole or letrozole	250 mg monthly	750
SWOG S0226	Phase III randomized study of anastrozole with or without fulvestrant as first-line therapy in postmenopausal women with ER- and/or PR-positive metastatic breast cancer.	250 mg monthly	690
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole in postmenopausal women with ER- and/or PR-positive metastatic breast cancer or premenopausal women on goserelin	500 mg day 0, 250 mg days 14, 28 and then monthly	558
ECOG 4101	Phase II trial of fulvestrant + gefitinib vs anastrozole + gefitinib in postmenopausal women with ER- and/or PR-positive metastatic breast cancer	250 mg monthly	148

SOURCES: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®).** Poster. Lynn Sage Breast Cancer Symposium, September 2003. NCI Physician Data Query, October 2004.

PHASE II/III RANDOMIZED STUDY OF ANASTROZOLE WITH OR WITHOUT TRASTUZUMAB IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE HER2-OVEREXPRESSING METASTATIC BREAST CANCER

Protocol IDs: ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, ROCHE-1100, ROCHE-BO16216E
Target Accrual: 202 patients (Open)

Eligibility	Postmenopausal women with ER- and/or PR-positive, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer
ARM 1	Anastrozole qd + trastuzumab qwk
ARM 2	Anastrozole qd

In both arms, treatment continues for at least two years in the absence of disease progression or unacceptable toxicity. During the extension phase of this study, patients in either arm who do not develop disease progression may continue receiving treatment in the arm to which they were originally randomly assigned. Patients in Arm 2 who develop disease progression may receive treatment in Arm 1 during the extension phase in the absence of further disease progression.

Study Contact:
Bernd Langer, PhD, Protocol Chair
Hoffman La Roche Inc
Tel: 41-61-688-0638

SOURCE: NCI Physician Data Query, October 2004.

PHASE II TRIAL EVALUATING A TYROSINE KINASE INHIBITOR IN COMBINATION WITH AN AROMATASE INHIBITOR

Protocol ID: EORTC-10021, IDBBC-10021
Target Accrual: 108 (Open)

Eligibility	Postmenopausal, ER/PR-positive, metastatic or locally recurrent breast cancer
ARM 1	Anastrozole + gefitinib
ARM 2	Anastrozole + placebo

Study Contact:
Emiel Rutgers, MD, PhD, FRCS
European Organization for Research and Treatment of Cancer
Tel: 31-20-512-2551

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF LETROZOLE WITH OR WITHOUT LAPATINIB IN POSTMENOPAUSAL WOMEN WITH STAGE IIIB OR IV BREAST CANCER

Protocol IDs: GSK-EGF30008, UCLA-0311034-01
Target Accrual: 760 (Open)

Eligibility	Postmenopausal women Stage IIIb or IV, ER- and/or PR-positive breast cancer No prior endocrine therapy for advanced disease
ARM 1	Letrozole + lapatinib
ARM 2	Letrozole + placebo

Study Contact:
Trial Lead Organizations
Acurian Pre-Screening Evaluation Contact
GlaxoSmithKline
Tel: 800-563-6537

SOURCE: NCI Physician Data Query, October 2004.

FULVESTRANT AND EXEMESTANE IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE ADVANCED BREAST CANCER

Protocol IDs: 9238IL/0048, NCT00065325
Target Accrual: 486 (Open)

Eligibility	Postmenopausal women Hormone receptor-positive breast cancer that has progressed on a prior aromatase inhibitor other than exemestane
ARM 1	Fulvestrant
ARM 2	Exemestane

Study Contact:
AstraZeneca Cancer Support Network
AstraZeneca Pharmaceuticals LP
Tel: 866-992-9276

SOURCE: NCI Physician Data Query, October 2004.

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Schiff R et al. **Breast cancer endocrine resistance: How growth factor signaling and estrogen receptor coregulators modulate response.** *Clin Cancer Res* 2003;9(1 Pt 2):447S-54S.

TRIALS COMBINING FULVESTRANT WITH AN AROMATASE INHIBITOR

A number of studies are beginning to evaluate combining fulvestrant with aromatase inhibitors. SWOG-S0226 will compare anastrozole to anastrozole plus fulvestrant as first-line therapy in postmenopausal women. In the UK, the SoFEA study will enroll patients who have had disease progression while on an aromatase inhibitor. Those patients will be randomly assigned to fulvestrant, exemestane, or fulvestrant plus anastrozole.

The rationale behind that trial is the data suggesting that estrogen-deprived MCF-7 cells become supersensitive to lower doses of estradiol and, hence, are stimulated again. The third arm of that trial will keep the estradiol levels low and then come in with fulvestrant to determine if that strategy is different from fulvestrant alone without estradiol suppression.

— John F R Robertson, MD

It remains unclear where fulvestrant should be utilized in the sequence of hormonal therapies for metastatic disease. Several new North American trials and the SoFEA trial should help to clarify its role in our armamentarium of hormonal therapies. The SoFEA trial will provide an indication of whether fulvestrant is better than exemestane as second-line therapy and also whether it's necessary to suppress the levels of estrogen. It's possible that by discontinuing the aromatase inhibitor, sufficient estrogen will be produced to circumvent the effects of fulvestrant.

— Anthony Howell, MD

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

The SoFEA trial will randomly assign 750 patients who have failed therapy with a nonsteroidal aromatase inhibitor to exemestane, fulvestrant alone or fulvestrant plus anastrozole. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone.

— Mitchell Dowsett, PhD

TRIALS COMBINING TRASTUZUMAB WITH HORMONAL THERAPY

Although controversial, some physicians use the combination of trastuzumab and hormonal therapy as first-line treatment off protocol for women with HER2-positive, hormone receptor-positive metastatic disease. I don't use that strategy. Hormonal therapy is the mainstay of treatment and can produce prolonged responses. It's important to know whether a patient has hormone-sensitive disease. I would not cloud the issue by adding trastuzumab until the ongoing clinical trials indicate a definite advantage for the combination compared to the sequential approach.

A worldwide trial, which has been accruing very slowly, is comparing anastrozole with or without trastuzumab. Approximately 20 percent of tumors are FISH-positive, and of those, perhaps 40 percent are ER-positive — that is less than 10 percent of the overall breast cancer population. The eligibility criteria carve away another few percent. Hence, about seven percent of the overall patient population could potentially be eligible for such trials. It's not surprising that accrual is difficult for these types of trials.

— Charles L Vogel, MD

Sequencing of Hormonal Therapies in Metastatic Disease

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As in postmenopausal women with early breast cancer, the sequencing of hormonal therapies in women with metastatic disease has become a topic of considerable interest. Postmenopausal women may now receive not only tamoxifen but also aromatase inhibitors in the adjuvant setting, and the optimal sequencing of hormonal agents for the treatment of metastatic disease is unknown. Fulvestrant, an estrogen receptor downregulator, is a recent addition to the hormonal therapy armamentarium. As second-line therapy in postmenopausal women with advanced breast cancer, fulvestrant and anastrozole have similar efficacy. Fulvestrant has also been compared to tamoxifen as first-line therapy in women with advanced ER- and/or PR-positive disease, and the benefits were comparable. Retrospective analyses of subsequent hormonal agents administered following fulvestrant have demonstrated significant response rates. Future clinical trials are required to determine the optimal sequencing of hormonal therapy options.

COMBINED ANALYSIS OF TWO PHASE III MULTICENTER TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

	Fulvestrant (n=428)	Anastrozole (n=423)	*p*-value
Complete response rate	4.7%	2.6%	—
Partial response rate	14.5%	13.9%	—
Objective response rate	19.2%	16.5%	0.31
Clinical benefit rate*	43.5%	40.9%	0.51
Estimated median time to progression	5.5 months	4.1 months	0.48
Median duration of response in those responding	16.7 months	13.7 months	—
Death rate (median follow-up, n=27.2 months)	74.5%	76.1%	—
Median time to death	27.4 months	27.7 months	0.81

* Clinical benefit = complete response + partial response + stable disease ≥24 weeks

SOURCES: Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. SABCS, 2003;Abstract 426.

RETROSPECTIVE ANALYSIS OF DURATION OF RESPONSE TO FULVESTRANT VERSUS ANASTROZOLE

	Fulvestrant 250 mg, n (%)	Anastrozole 1 mg, n (%)	*p*-value
Total patients with OR	82 (19.2)	70 (16.5)	0.3070
Patients with OR ≥1 year	43 (10.0)	30 (7.1)	0.1627
Total patients with CB	186 (43.5)	173 (40.9)	0.5059
Patients with CB ≥1 year	82 (19.2)	59 (13.9)	0.0692

SOURCE: Jones SE. *Proc ASCO* 2004;Abstract 737.

RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY IN PATIENTS ENROLLED IN A PHASE III TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE THERAPY

	Clinical benefit (CB) with second-line agent	
	No. of patients	%
First-line fulvestrant (n=70)		
Patients who derived CB (n=35)	20	57
Patients who did not derive CB (n=35)	15	43
First-line tamoxifen (n=52)		
Patients who derived CB (n=31)	19	61
Patients who did not derive CB (n=21)	12	57

SOURCE: Howell A. Poster. SABCS, 2002.

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

	All patients		Patients with ER- and/or 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[1]	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate[2]	54.3%	62.0%	57.1%	62.7%
Median time to progression[3]	6.8 months	8.3 months	8.2 months	8.3 months
Estimated median survival[4]	36.9 months	38.7 months	39.3 months	40.7 months

[1] Objective response indicates a complete or partial response; $p = 0.45$ for all patients; $p = 0.64$ for patients with ER- and/or PR-positive tumors

[2] 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- and/or PR-positive tumors

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

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

SOURCE: Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13.

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

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

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

SOURCE: Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79:207-11.

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Henderson IC. **A rose is no longer a rose.** *J Clin Oncol* 2002;20:3365-8.

Howell A. **Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies.** Poster. SABCS, 2002;Abstract 251.

Lonning PE et al. **Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial.** *J Clin Oncol* 2000;18(11):2234-44.

Perey L et al. **Fulvestrant ('Faslodex') as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing phase II SAKK trial.** Poster. SABCS, 2002;Abstract 249.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. SABCS, 2002;Abstract 426.

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

Vergote I. **Evidence of continued sensitivity to endocrine agents in postmenopausal women with advanced breast cancer progressing on fulvestrant treatment.** Poster. SABCS, 2001;Abstract 446.

SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

In postmenopausal women whose disease relapses while on adjuvant tamoxifen, I use fulvestrant because I've seen some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (eg, aromatase inhibitors and megestrol acetate).

A few reports have evaluated the response to fulvestrant in patients who received an aromatase inhibitor. A small Swiss study reported that about one third of patients derive clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor.

At ASCO 2003, a compassionate-use trial reported on about 60 patients treated with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had more than a 50 percent clinical benefit rate in those patients.

— Stephen E Jones, MD

Women with breast cancer whose disease fails while on tamoxifen can clearly respond to fulvestrant, and the response rate is equivalent to that seen with anastrozole. Also, in women with disease that has failed anastrozole, subsequent therapy with fulvestrant leads to a substantial clinical benefit rate of approximately 40 percent. Patients who cross over from fulvestrant to an aromatase inhibitor also show response rates of approximately 40 percent.

Surprisingly, the magnitude of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One rule of thumb in the past has been that the magnitude and duration of response to the most recent hormonal therapy predicted for the likelihood of response to subsequent hormonal therapies. A small retrospective study suggests that may not be the case with fulvestrant.

— Robert W Carlson, MD

In Trials 20 and 21, anastrozole and fulvestrant were equivalent as second-line therapy after tamoxifen failure, but fulvestrant had a significantly longer duration of response in the North American study. In the first-line study, tamoxifen was slightly superior to fulvestrant, which was a very surprising result. In the ER/PR-positive group, fulvestrant was slightly (but not significantly) better than tamoxifen. In other words, it's a drug that is equivalent to anastrozole as second-line therapy and nearly equivalent to tamoxifen as first-line therapy.

We have to ask, "Why wasn't fulvestrant better than tamoxifen?" That's what we expected. The answer may be in the dosing of fulvestrant, because it takes about six months to achieve steady-state levels. Clinical trials will evaluate loading-dose schedules of fulvestrant. Our modeling analyses indicate these approaches will increase the dose of the drug sooner, and then we will be able to investigate whether that is the reason fulvestrant was not better than tamoxifen in the first-line trials.

— Anthony Howell, MD

Many of my patients have received adjuvant tamoxifen, so I typically use first-line aromatase inhibitors and administer fulvestrant upon progression. Subsequently, we may readminister tamoxifen, utilize progestins or try another aromatase inhibitor. Many of our patients with hormone receptor-positive metastatic disease can be maintained on hormonal therapies for several years before we have to treat them with chemotherapy.

— Julie R Gralow, MD

In patients progressing on tamoxifen, tamoxifen binds the estrogen receptors and may actually stimulate growth of the tumor — it certainly is no longer inhibiting it. Treating these patients with an aromatase inhibitor will be ineffective until all the tamoxifen is gone, which takes a couple of months. Fulvestrant, on the other hand, competes with tamoxifen for binding, thus the response may be quicker with fulvestrant than with an aromatase inhibitor in that setting.

— C Kent Osborne, MD

Patient Perspectives on Metastatic Disease

Two large randomized clinical trials have demonstrated essentially equivalent efficacy and tolerability of anastrozole and fulvestrant in postmenopausal patients with progressive metastatic disease on tamoxifen; however, oncologists in practice generally utilize nonsteroidal aromatase inhibitors prior to fulvestrant because of the perception that patients would prefer oral therapy. In a recent telephone survey of 256 women with metastatic breast cancer, a majority stated that they preferred oral therapy, assuming equal efficacy and side effects. However, about a third of the patients preferred parenteral therapy, with regard to both chemotherapy and endocrine therapy, and cited a variety of reasons for this preference, including concerns about compliance, a dislike of oral therapy, support received from the oncology office and convenience. In a tandem survey of oncologists and oncology nurses, these professionals estimated that more than a third of their patients with metastatic disease on bisphosphonates would prefer parenteral administration of antitumor therapy. This suggests that decisions in this palliative setting should be individualized based on patient preference.

DEMOGRAPHICS OF PATIENTS PARTICIPATING IN SURVEY

Median age (years)	55
Median time since initial diagnosis (years)	6.75
Median time since diagnosis of metastases (years)	2.58
Offered clinical trial participation	46%
Participated in clinical trials (of those offered)	61%

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

CURRENT AND PRIOR THERAPIES OF PATIENTS PARTICIPATING IN SURVEY

Therapy	Percent of patients who received
Intravenous chemotherapy	88%
Oral chemotherapy	32%
Oral hormonal therapy	84%
Fulvestrant	23%
LHRH agonist	13%

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

PATIENT PREFERENCES FOR ORAL VERSUS INTRAMUSCULAR ENDOCRINE THERAPY

Patient preference	Percent of patients preferring
Oral endocrine therapy	55%
Intramuscular endocrine therapy	36%
Neutral	9%

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

PATIENT PREFERENCES FOR ORAL VERSUS INTRAVENOUS CHEMOTHERAPY

Patient preference	Percent of patients preferring
Oral chemotherapy	64%
Intravenous chemotherapy	28%
Neutral	8%

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

REASONS CITED BY PATIENTS FOR PREFERRING PARENTERAL THERAPY

Reasons cited	Percent of patients
Concerns about compliance	35%
Dislike of oral medications	34%
Belief that parenteral therapy is more effective	52%
Emotional support received during parenteral therapy	53%
Convenience	78%

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

LIFESTYLE DEMOGRAPHICS IN PATIENTS WITH METASTATIC BREAST CANCER

Variable	
Travel time to oncologist's office (median)*	25 minutes
Average time spent in oncologist's office (median)	2 hours
Activity Level	
Active	72%
Inactive	28%
Find conversations with other patients in waiting or treatment room rewarding	70%

* Patients who spent 15 minutes or less traveling to the oncologist's office were more likely to prefer parenteral therapy (45%) than patients traveling more than 15 minutes (24%).

SOURCE: *Breast Cancer Update* Survey of Metastatic Breast Cancer Patients, 2004.

SEQUENCING ENDOCRINE THERAPY BY MEDICAL ONCOLOGISTS

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen four years previously?

Therapy	First-line	Second-line	Third-line	Fourth-line
Tamoxifen	8%	12%	10%	12%
Anastrozole	44%	10%	4%	—
Letrozole	48%	6%	2%	4%
Exemestane	—	34%	30%	6%
Fulvestrant	—	38%	36%	14%
Megestrol acetate	—	—	4%	16%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

HEALTHCARE PROFESSIONALS' PREDICTIONS ABOUT PATIENT PREFERENCES FOR METHOD OF ENDOCRINE THERAPY ADMINISTRATION

	Oral endocrine therapy	Intramuscular endocrine therapy	Neutral
Medical oncologists (n=50)	51%	33%	16%
Oncology nurses (n=50)	41%	43%	16%

* Note that these professionals were presented with a scenario of a patient with metastatic breast cancer receiving intravenous bisphosphonates.

SOURCE: *Breast Cancer Update* Survey of Medical Oncologists and Oncology Nurses, 2004.

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Carlson RW, Henderson IC. **Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole.** *Breast Cancer Res Treat* 2003;80(Suppl 1):19-26.

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;1;22(9):1605-13.

Ingle JN. **Sequencing of endocrine therapy in postmenopausal women with advanced breast cancer.** *Clin Cancer Res* 2004;10(1 Pt 2):362S-7S.

Mouridsen H et al. **Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2003;21(11):2101-9.

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

SEQUENCING OF ENDOCRINE THERAPY AND PATIENT PREFERENCES FOR METHOD OF TREATMENT ADMINISTRATION

"A new generation of aromatase inhibitors, including anastrozole, letrozole, and exemestane, have replaced aminoglutethimide for postmenopausal women with metastases. Not only are all of these considerably less toxic than aminoglutethimide, each has been shown to be more effective than megestrol acetate, and two have been shown to be more effective than tamoxifen. ...

"The most recent entrant into the new pantheon of drugs for the treatment of breast cancer is the pure antiestrogen fulvestrant. …Fulvestrant downregulates and degrades the estrogen receptor, causes a reduction in progesterone receptor, and has only estrogen antagonistic effects. This is in contrast to tamoxifen, which has partial agonist effects, and the aromatase inhibitors, which reduce the estrogen available to the cancer cell. ...

"The endocrine cascade has grown much more complex over the past 10 years. …While these new therapies may be confusing to clinicians and patients at this time, they also offer promise of much more effective, nontoxic treatment that will both palliate symptoms and prolong the lives of patients with breast cancer."

— Henderson IC. J Clin Oncol *2002;20(16):3365-8.*

In general, for a postmenopausal woman with disease progression on adjuvant tamoxifen, I would present the options of an aromatase inhibitor or fulvestrant. These are both reasonable and legitimate options, and I believe they are equivalent.

Although I believe most patients would prefer oral therapy, some prefer a monthly injection. Patients may have concerns about compliance with oral medications or they may like the interaction with the nursing staff and may feel more cared for by coming to the office. Others may value the time with other patients that they've met.

Patients may also have the perception that intravenous or intramuscular drugs are more effective. I see many patients from Asia and Latin America who believe injectable drugs are better. That perception may also be true in this country.

— Debu Tripathy, MD

In general, I believe most people prefer taking a pill to receiving an intramuscular injection, although it's probably close. I would guess that 60% of patients would prefer a pill and 40% an injection.

With that being said, I have not found any problems with compliance or acceptability in patients in my practice treated with fulvestrant. I also believe that a monthly intramuscular injection would be an advantage for a patient who can't afford the oral medication. But, in general, I believe an oral medication is preferable for most patients.

Most physicians probably would recommend an oral drug mainly because they perceive that it will be better accepted by patients, but the actual numbers are probably worthwhile to know, and this is something we should spend more time on.

— Nicholas Robert, MD

We were involved in one of the initial studies of fulvestrant. Our major concern was that women wouldn't like the injection; however, the toxicity was not an issue. Many physicians tell me their patients have no problems with the injection. In fact, many women prefer it because they don't have to worry about taking a pill. I believe this varies throughout the country and among the patient population being treated. I use fulvestrant commonly now, mainly in patients who have failed primary endocrine therapy.

— Daniel R Budman, MD

Single-Agent versus Combination Chemotherapy for Metastatic Disease

27TH ANNUAL San Antonio Breast Cancer Symposium 20

Randomized clinical trials of chemotherapeutic agents and regimens not only help better define clinical care but also provide important clues to future adjuvant therapy strategies. A series of recent studies have resulted in encouraging results with new combinations, including capecitabine/docetaxel, capecitabine/paclitaxel, and gemcitabine/paclitaxel. Adjuvant trials are now being planned and conducted utilizing these regimens. However, most breast cancer clinical research leaders support nonprotocol therapy with sequential single-agent chemotherapy in the metastatic setting, and the choice of agents is mainly based on prior adjuvant treatment and toxicity considerations.

PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY FOR METASTATIC BREAST CANCER

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

SOURCES: * O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23.

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

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

Accrual: 529 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer Prior adjuvant anthracycline treatment No prior therapy for metastatic disease**
ARM 1	**Gemcitabine 1250 mg/m² + paclitaxel 175 mg/m² q3wk**
ARM 2	**Paclitaxel 175 mg/m² q3wk**

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

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

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

Efficacy endpoints	No. of responders	Response rate
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 mo	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)
Grade III/IV adverse events	**No. of patients**	**%**
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m² twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m² day 1 every three weeks

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

ACTIVE PHASE III TRIALS OF CHEMOTHERAPY IN METASTATIC BREAST CANCER

Protocol ID	Target accrual	Eligibility	Randomization
EORTC-10001	406-452	Prior taxanes	Vinorelbine Capecitabine
DO03-21-022	NR	≥65 years old No prior chemotherapy for Stage IV No anthracycline resistance	Pegylated liposomal doxorubicin Capecitabine
CA163-048	NR	Prior anthracycline and taxane. No more than 2 prior chemotherapy regimens	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF100151	372	Progression in metastatic disease or relapse within 6 months after adjuvant taxane and anthracycline	GW572016 + capecitabine Capecitabine
CA163-046	NR	2-3 prior chemotherapy regimens; 1 in the metastatic setting Taxane resistant and prior anthracycline	Ixabepilone (BMS-247550) + capecitabine Capecitabine
XRP9881B/3001	NR	Prior anthracycline and taxane	Investigational drug Capecitabine
GSK-EGF30001	570	No prior chemotherapy for Stage IV HER2-negative or unknown	Paclitaxel + GW572016 Paclitaxel + placebo
MDA-ID-99242	160	≤2 prior chemotherapy regimens; 1 in the metastatic setting No taxane for Stage IV and ≥12 months since adjuvant taxane	Docetaxel day 1 q3wk Docetaxel days 1, 8 and 15 q4wk

NR = Not reported

SOURCE: NCI Physician Data Query, October 2004.

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Alba E et al; Spanish Breast Cancer Research Group. **Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: A Spanish Breast Cancer Research Group (GEICAM-9903) phase III study.** *J Clin Oncol* 2004;22(13):2587-93.

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;Abstract 510.

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7.

Moinpour C et al. **Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Quality of life (QoL) and pain palliation results from the global phase III study.** *Proc ASCO* 2004;Abstract 621.

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23.

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

FIRST-LINE CAPECITABINE/PACLITAXEL

"This phase II study supports the concept that the complementary mechanisms of action and non-overlapping major toxicities of capecitabine and taxanes create a highly effective and well-tolerated combination chemotherapy regimen for MBC. Both capecitabine and taxanes are effective when used as monotherapy, and preclinical studies in tumor xenograft models demonstrate synergistic antitumor activity when the drugs are used in combination. …The high clinical activity of capecitabine plus paclitaxel documented in this phase II study is consistent with that reported from the recent large international phase III trial of capecitabine combined with docetaxel, compared with docetaxel alone, in anthracycline-pretreated patients."

— Gradishar WJ et al. J Clin Oncol *2004;22(12):2321-27.*

COMBINATION VERSUS SEQUENTIAL DOXORUBICIN AND PACLITAXEL AS FIRST-LINE THERAPY

"Trial E1193 tested whether the combination of two active drugs, representing what are arguably the two most active classes of agents (anthracyclines and taxanes) used in breast cancer, might prove superior to sequential, single-agent therapy with the same agents. Combination therapy resulted both in a superior overall response rate and a superior TTF, two frequent measures of efficacy in metastatic chemotherapy trials. Despite this superiority, combination therapy failed to improve overall survival. Perhaps more importantly, given the usually fatal nature of the disease, combination therapy did not improve quality of life."

— Sledge GW et al. J Clin Oncol *2003;21(4):588-92.*

GEMCITABINE (G) PLUS PACLITAXEL (T) VERSUS PACLITAXEL AS FIRST-LINE THERAPY

"GT had phase II safety and efficacy in MBC after anthracyclines, so it was compared to T in a phase III study of frontline therapy. …GT provides significant OS advantage over T when both are given on a q3 week cycle, a result to be confirmed in the final planned analysis in late 2004. The TTP benefit predicted OS improvement with longer follow-up. GT should be considered a frontline regimen in MBC."

— Albain KS et al. Proc ASCO *2004;Abstract 510.*

CAPECITABINE/DOCETAXEL VERSUS DOCETAXEL IN HEAVILY PRETREATED PATIENTS WITH METASTATIC BREAST CANCER

"This phase III study demonstrates that capecitabine/docetaxel combination therapy is more effective than a current standard treatment, single-agent docetaxel, and is thus a significant development for patients with breast cancer whose disease has progressed after an anthracycline containing regimen. The addition of capecitabine to docetaxel 75 mg/m² resulted in a significant improvement in overall survival, time to disease progression, and response rate compared with docetaxel 100 mg/m² alone. The addition of capecitabine to docetaxel resulted in a 23% reduction in risk of death compared with docetaxel, with an increase in median survival of 3 months. The survival benefit with capecitabine/docetaxel combination therapy was seen early in the course of treatment and persisted throughout the study."

— O'Shaughnessy J et al. J Clin Oncol *2002;20(12):2812-23.*

SELECTING A COMBINATION REGIMEN: ANTHRACYCLINE/TAXANE VERSUS CAPECITABINE/DOCETAXEL

We typically use a combination regimen of an anthracycline and a taxane, but capecitabine/docetaxel is equally reasonable. We know a survival advantage exists with capecitabine/docetaxel, and no survival advantage exists with an anthracycline/taxane combination; however, that's like comparing apples and oranges, because many of the trials of anthracycline/taxane combinations — including the largest ECOG-1193 trial — included a crossover. The capecitabine/docetaxel trial didn't. Had they conducted the study using the ECOG-1193 model — combination therapy versus each single-agent with a crossover — I believe they would have seen the same results as in ECOG-1193.

— Kathy Miller, MD

Taxanes in the Metastatic Setting

27TH ANNUAL
San Antonio Breast Cancer Symposium 21

Single-agent paclitaxel and docetaxel are the most common first-line chemotherapeutic approaches in previously untreated patients in the first-line metastatic setting. Data presented at last year's San Antonio Breast Cancer Symposium demonstrated improved efficacy with docetaxel compared to paclitaxel on an every three-week schedule. Docetaxel is associated with a significant rate of febrile neutropenia when used at 100 mg/m², and a recent placebo-controlled randomized trial demonstrated that pegfilgrastim dramatically reduces the incidence of this complication. Nanoparticle paclitaxel appears to be as efficacious as docetaxel, but this agent does not require premedication and thus avoids secondary side effects and toxicity.

TAX 311: A PHASE III RANDOMIZED TRIAL OF DOCETAXEL VERSUS PACLITAXEL IN METASTATIC BREAST CANCER

Response rate and duration data

Parameter	Intent-to-treat population		Evaluable population	
	Docetaxel (n=225)	Paclitaxel (n=224)	Docetaxel (n=189)	Paclitaxel (n=205)
Response rate (CR + PR)	32.0%	25.0%	37.0%	25.9%
	$p = 0.10$		$p < 0.05$	
Stable disease	38.2%	39.7%	42.9%	42.9%
Duration of response	7.5 mo	4.6 mo	7.5 mo	4.6 mo
	$p < 0.05$		$p < 0.05$	

Time to progression (TTP) and survival data

Parameter	Docetaxel	Paclitaxel	*p*-value
Median TTP	5.7 months (95% CI 4.6-6.9)	3.6 months (95% CI 3.1-4.2)	<0.0001
Overall survival	15.4 months (95% CI 13.3-18.6)	12.7 months (95% CI 10.6-14.8)	0.03

Toxicity data

Parameter	Docetaxel (n=222)		Paclitaxel (n=222)	
	Overall	Grade 3/4	Overall	Grade 3/4
Neutropenia*	96%	93%	83%	55%
Febrile neutropenia*	15%		2%	
Anemia	77%	10%	61%	7%
Infection*	33%	10%	10%	2%
Stomatitis*	51%	11%	16%	0%
Asthenia*	74%	21%	55%	5%

Secondary G/GM-CSF administered to 23.4% of patients receiving docetaxel and 4.1% of patients receiving paclitaxel

* For the difference in Grade 3/4 toxicities, $p < 0.05$

SOURCE: Jones S et al. **Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 10.

ANTHRACYCLINES WITH OR WITHOUT TAXANES AS FIRST-LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER: COMPREHENSIVE REVIEW OF 2,805 PATIENTS IN SEVEN PHASE III TRIALS

Parameter	Risk ratio	95% CI	*p*-value
Time to progression	1.10	1.00-1.21	0.05
Overall response rate	1.21	1.10-1.32	<0.001
Complete response rate	2.04	1.41-2.94	<0.001
Overall survival	1.05	0.90-1.23	0.58
Neutropenia	1.19	1.11-1.29	<0.001
Febrile neutropenia	2.82	1.39-5.69	<0.001
Cardiotoxicity	3.34	0.90-12.41	Not reported
Neurotoxicity	13.20	1.51-115	Not reported

Conclusions:
- The combination of taxanes and anthracyclines is significantly more active in terms of overall response and complete response rates and slightly but significantly more beneficial in terms of time to progression when compared to standard anthracycline therapy.
- Toxicity (mainly neutropenia and febrile neutropenia) is significantly greater for the combination of taxanes and anthracyclines than standard anthracycline therapy.

SOURCE: Bria E et al. **Impact of taxanes in association with anthracyclines in 1st line chemotherapy for metastatic breast cancer (MBC): Comprehensive review of 2805 patients in 7 Phase III trials.** Presentation. ASCO, 2004;Abstract 659.

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

Efficacy data

Investigator response assessments	All treated patients		First-line patients	
	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%)
	$p < 0.001$		$p = 0.029$	
Independent radiology review	**All treated patients**		**First-line patients**	
	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*

Parameter	ABI-007 (n=229)		Paclitaxel (n=225)		*p*-value
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia	25%	9%	31%	22%	< 0.001
Sensory neuropathy	10%	0%	2%	0%	< 0.001

SOURCE: O'Shaughnessy J et al. **ABI-007 (Abraxane™), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in metastatic breast cancer: A Phase III trial.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 44.

PHASE III STUDY OF PEGFILGRASTIM VERSUS PLACEBO IN PATIENTS RECEIVING DOCETAXEL

Accrual: 928 (Closed)

Eligibility	Stage 1-4 breast cancer, ECOG performance of 0-2, ≥18 years of age
ARM 1	Docetaxel + pegfilgrastim*
ARM 2	Docetaxel + placebo*

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

EFFICACY DATA

Parameter	Placebo** (n=465)	Pegfilgrastim** (n=463)	*p*-value
Febrile neutropenia (FN)	17%	1%	<0.0001
FN-related hospitalizations	14%	1%	<0.0001
FN-related IV anti-infective use	10%	2%	<0.0001
Chemotherapy planned dose on time (cycles 2-4)***	78%	80%	Not reported

** 62% of patients had metastatic disease
*** Placebo arm included patients receiving open-label pegfilgrastim

Summary:
- Pegfilgrastim was well tolerated and resulted in a relative reduction of 94% in FN, 93% in FN-related hospitalizations and 80% in IV anti-infective use.
- 65% of FN occurred during the first cycle in the placebo group.

SOURCE: Vogel CL. Presentation. *Breast Cancer Update* Think Tank on Adjuvant Chemotherapy, August 2004.

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TAX-311: DOCETAXEL VERSUS PACLITAXEL

The TAX-311 trial was completed in 2003 and basically confirmed that docetaxel was probably a more potent taxane, at least the every three-week schedule. I didn't expect the results to be so dramatic. The evaluable patients demonstrated a significant difference in the response rate, time to tumor progression and survival in favor of docetaxel. The survival advantage was surprising — few regimens have a documented survival advantage in patients with metastatic breast cancer. More toxicity was associated with docetaxel, but it was the usual manageable toxicity.

— Stephen E Jones, MD

NANOPARTICLE PACLITAXEL IN THE METASTATIC SETTING

The pivotal trial of nanoparticle paclitaxel in anthracycline-pretreated patients showed it to be as efficacious as docetaxel in terms of response rates. The Phase III trial demonstrated superior efficacy of nanoparticle paclitaxel 260 mg/m² over paclitaxel 175 mg/m² in terms of response rate and time to progression. I believe in the next few years physicians will use nanoparticle paclitaxel for palliation in the metastatic setting in patients whom they want to experience as few side effects as possible. I expect it will be used weekly at 100 mg/m² for three weeks, followed by one week off, as in Joanne Blum's study.

I have treated several patients with this agent and found it to be extremely well tolerated, particularly at the 100 mg/m² dose. I don't premedicate patients receiving nanoparticle paclitaxel, because most patients on weekly taxanes do not have problems with hypersensitivity reactions. In addition, I find weekly dexamethasone is not well tolerated by patients — it tires them and has a crash effect. Avoiding premedication may be one of the reasons we don't see significant side effects with the nanoparticle paclitaxel.

— Joyce O'Shaughnessy, MD

TRIAL COMPARING PEGFILGRASTIM TO PLACEBO IN PATIENTS RECEIVING DOCETAXEL

The objective of this study was to determine if pegfilgrastim significantly reduces febrile neutropenia in patients receiving a chemotherapy regimen associated with an expected rate of approximately 20 percent. Patients were eligible for the trial whether they were receiving docetaxel in the adjuvant or the metastatic setting. In this double-blind, randomized trial, patients received docetaxel plus pegfilgrastim versus a placebo. If a patient developed febrile neutropenia, they were able to subsequently receive pegfilgrastim.

Febrile neutropenia, related hospitalizations and intravenous anti-infective use were all significantly reduced by pegfilgrastim. While the difference in the rates of patients receiving their planned chemotherapy dose on time doesn't look impressive, all the placebo patients who developed febrile neutropenia received pegfilgrastim. Consequently, both groups experienced delivery of planned dose on time.

— Charles L Vogel, MD

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

— Lee Schwartzberg, MD

Research To Practice: Chemotherapy for Metastatic Disease

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The Patterns of Care Study indicates that key factors determining choice of systemic treatment in the metastatic setting are patient age, performance status, site of disease and ER and HER2 receptor assay results. Endocrine therapy alone is generally utilized in patients with good performance status and ER-positive tumors. Trastuzumab, usually in combination with chemotherapy, is widely utilized as first-line therapy for women with HER2-positive disease. A key issue in selection of chemotherapy is the choice between sequential single agents and combinations. Oncologists often use single agents for patients with good performance status, and the decisions regarding sequencing varies. Side-effect profiles alter choices in individual situations. Anthracycline-based regimens are commonly utilized in patients who have not previously received adjuvant chemotherapy. The combination of docetaxel and capecitabine is frequently utilized in women who have previously received chemotherapy.

TREATMENT OF ASYMPTOMATIC CHEMOTHERAPY-NAÏVE PATIENTS WITH RECEPTOR-NEGATIVE DISEASE

The patient is a woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with rising tumor markers and asymptomatic bone metastases. What are your first- and second-line treatment recommendations?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st line	2nd line	1st line	2nd line	1st line	2nd line
Capecitabine + docetaxel	6%	5%	4%	4%	1%	2%
Docetaxel	16%	16%	16%	17%	10%	15%
Paclitaxel	17%	9%	18%	8%	19%	8%
Platinum + taxane	4%	5%	4%	5%	1%	1%
Capecitabine	12%	17%	14%	19%	27%	26%
Gemcitabine	—	16%	—	18%	4%	15%
Vinorelbine	—	16%	—	16%	5%	15%
AC	15%	8%	15%	5%	6%	2%
AC + docetaxel	14%	—	13%	—	3%	—
Other chemotherapy	8%	5%	10%	5%	6%	3%
No chemotherapy	8%	3%	6%	3%	18%	13%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

TREATMENT OF SYMPTOMATIC CHEMOTHERAPY-NAÏVE PATIENTS WITH RECEPTOR-NEGATIVE DISEASE

The patient is a woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with bone and lung metastases and is symptomatic. What are your first- and second-line treatment recommendations?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st line	2nd line	1st line	2nd line	1st line	2nd line
Capecitabine + docetaxel	15%	9%	14%	5%	12%	4%
Docetaxel	4%	15%	7%	15%	15%	18%
Paclitaxel	2%	8%	3%	10%	15%	8%
Platinum + taxane	16%	12%	17%	8%	12%	—
Capecitabine	—	9%	—	11%	12%	21%
Gemcitabine	—	13%	—	15%	4%	17%
Vinorelbine	—	8%	—	10%	5%	23%
AC	23%	8%	22%	9%	15%	3%
AC + docetaxel	30%	1%	27%	1%	6%	—
AC + paclitaxel	4%	1%	4%	1%	1%	—
Other chemotherapy	6%	16%	6%	15%	3%	6%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

TREATMENT OF ASYMPTOMATIC PATIENTS WITH RECEPTOR-NEGATIVE DISEASE AFTER ADJUVANT AC-PACLITAXEL

The patient is a woman treated two years ago with adjuvant AC → paclitaxel for an ER-negative, HER2-negative tumor with rising tumor markers and asymptomatic bone metastases. What are your first- and second-line treatment recommendations?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st line	2nd line	1st line	2nd line	1st line	2nd line
Capecitabine + docetaxel	11%	3%	9%	2%	3%	2%
Docetaxel	29%	14%	29%	14%	15%	12%
Paclitaxel	8%	4%	8%	4%	6%	3%
Platinum + taxane	6%	4%	6%	3%	1%	—
Capecitabine	18%	20%	20%	19%	36%	24%
Gemcitabine	8%	25%	9%	26%	8%	25%
Vinorelbine	8%	14%	7%	18%	11%	18%
Other chemotherapy	5%	12%	5%	10%	3%	2%
No chemotherapy	7%	4%	7%	4%	17%	14%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

TREATMENT OF SYMPTOMATIC PATIENTS WITH RECEPTOR NEGATIVE DISEASE AFTER ADJUVANT AC-PACLITAXEL

The patient is a woman treated two years ago with adjuvant AC → paclitaxel for an ER-negative, HER2-negative tumor who now has bone and lung metastases and is symptomatic. What are your first- and second-line treatment recommendations?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st line	2nd line	1st line	2nd line	1st line	2nd line
Capecitabine + docetaxel	41%	9%	41%	7%	17%	4%
Docetaxel	9%	5%	10%	5%	18%	8%
Paclitaxel	1%	—	1%	1%	7%	1%
Platinum + taxane	24%	2%	24%	4%	9%	—
Capecitabine	1%	16%	1%	17%	17%	30%
Gemcitabine	6%	29%	6%	31%	15%	29%
Vinorelbine	—	22%	—	21%	8%	22%
AC	1%	2%	1%	1%	—	—
AC + docetaxel	4%	—	4%	—	—	—
Other chemotherapy	13%	15%	12%	13%	9%	6%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

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CHEMOTHERAPY IN THE METASTATIC SETTING

I believe that single-agent sequential therapy is still the best way to manage metastatic breast cancer in most patients. It is less toxic, you're not lowering dose — and perhaps efficacy — below a threshold level, and survival is identical. Additionally, other drugs can be offered later. I believe single-agent sequential therapy is the way to go, and I start with capecitabine first in most patients.

I don't believe vast differences exist with regard to responses and confidence intervals; however, there are exceptions, such as the patient with terrible bone pain or in whom another doubling of their liver or pulmonary metastases will be catastrophic. While achieving a faster response is helpful in these cases, these are the minority of patients. When I use combinations, I use agents like capecitabine and docetaxel. In chemotherapy-naïve patients, anthracyclines and taxanes have high response rates, but in the last several years in my practice I have started with a combination regimen in only about 10 percent of patients. Breast cancer is not high-grade lymphoma or acute myeloid leukemia. We have time to work with the patients. This is a tough problem for which all of our therapy is palliative.

— Hyman B Muss, MD

In the metastatic setting, I generally use sequential single agents rather than combination therapy, except when an early response is vital, such as lymphangitic pulmonary disease. The sequence depends on the patient's prior therapy, comorbid conditions and lifestyle, so it's extremely variable.

I usually use a taxane, as most of the patients who are relapsing have not previously been treated with a taxane. I believe docetaxel is superior to paclitaxel, so for a younger or more seriously ill patient, I tend to use docetaxel every three weeks. In an older patient, I prefer weekly paclitaxel. If a patient has received a taxane and progresses, I generally use capecitabine, starting at two grams per meter squared per day for two weeks, then one week off. Some patients do fine, but some develop toxicity during the second week, so I shorten the duration of treatment with subsequent cycles.

I have become more liberal with combination therapy and if a patient is quite ill, I generally use capecitabine/docetaxel. Paclitaxel/gemcitabine is less toxic; however, docetaxel/capecitabine may be superior in terms of survival. Docetaxel has a survival advantage over paclitaxel, paclitaxel plus gemcitabine has a survival advantage over paclitaxel alone, and docetaxel plus capecitabine has been shown to be superior to docetaxel. In my experience the majority of patients I have treated with capecitabine/docetaxel have derived benefit, although they have also experienced significant toxicity.

— G Thomas Budd, MD

In metastatic disease, I believe sequential single-agent chemotherapy is a gentler approach than combination therapy and offers equivalent survival. Capecitabine is probably my favorite drug in this setting because it's oral, very active and extremely well tolerated as long as patients are properly educated about side effects. I prefer capecitabine before an anthracycline or a taxane in a patient who hasn't received either one.

— Melody A Cobleigh, MD

Patients with ER-negative, HER2-negative disease can only benefit from chemotherapy. I use combination chemotherapy when I need a quick response and sequential single agents when I don't. In a patient who has recently received adjuvant AC and a taxane and has relapsed, I would probably use capecitabine as my first choice for a sequential single agent. We don't know which drug is better in this situation, but women tend to like an oral drug and many would choose capecitabine. Interestingly, an ongoing EORTC trial (EORTC-10001) is comparing capecitabine and vinorelbine in these women.

— Martine J Piccart-Gebhart, MD, PhD

Trastuzumab in Combination with Chemotherapy in Metastatic Disease

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A variety of chemotherapeutic agents and regimens have been studied in combination with the humanized monoclonal antibody trastuzumab for the treatment of patients with HER2-positive metastatic disease. The most recent related major study evaluated the combination of docetaxel and trastuzumab, and as with prior similar trials, progression-free and overall survival advantages were observed with the addition of trastuzumab. Additional studies have attempted to define whether continuation of trastuzumab beyond progression is safe and efficacious. While no definitive efficacy data exist, Dr Debu Tripathy demonstrated that this strategy results in disease response without significant excess toxicity compared to chemotherapy alone.

PHASE III STUDY COMPARING TRASTUZUMAB AND PACLITAXEL WITH AND WITHOUT CARBOPLATIN IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

Parameters	TPC regimen	TP regimen	*p*-value
Response rate (RR)	52% (n=89)	36% (n=94)	0.04
Overall response in HER2 IHC 3+	57%	37%	0.03
Time to progression (TTP)	10.7 months	7.0 months	0.016
TTP in HER2 IHC 3+	14.0 months	7.1 months	0.007
Overall Survival (OS)	36 months	32 months	0.496
OS in HER2 IHC 3+	42 months	29 months	0.29

TPC = trastuzumab, paclitaxel, carboplatin; TP = trastuzumab, paclitaxel

"Overall response (OR) and time to progression (TTP) were significantly improved with TPC compared to TP... . Therapy was well-tolerated on both arms of the study. Grade 3-4 neutropenia and thrombocytopenia were more common with TPC, as expected. There was no difference in fever/neutropenia, neuropathy, fatigue, and other toxicities between study arms. There were 2 cases of congestive heart failure, seen in the TP arm."

SOURCE: Robert N et al. **Randomized Phase III study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An update including survival.** Presentation. ASCO, 2004.

PHASE II RANDOMIZED TRIAL OF DOCETAXEL WITH OR WITHOUT TRASTUZUMAB AS FIRST-LINE THERAPY IN WOMEN (N=188) WITH HER2-POSITIVE METASTATIC BREAST CANCER

	Docetaxel + trastuzumab	Docetaxel alone*	*p*-value
Overall response rate	61%	36%	0.001
Median survival	27.7 months	18.3 months	Not reported
Median time to progression	10.6 months	6.1 months	0.0001
Median duration of response	8.3 months	4.2 months	Not reported
Febrile neutropenia	23%	17%	Not reported

* 44 percent of the patients treated with docetaxel alone crossed over to receive trastuzumab

SOURCE: Extra JM et al. **First-line trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone in women with HER2-positive metastatic breast cancer (MBC): Results from a randomised phase II trial (M77001).** *Breast Cancer Res Treat* 2003;82(Suppl):47;Abstract 217.

CALGB-9840: PHASE III STUDY OF WEEKLY VERSUS EVERY THREE-WEEK PACLITAXEL WITH TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE, METASTATIC BREAST CANCER

Efficacy	Weekly paclitaxel	Every three-week paclitaxel	*p*-value
Tumor response (TR)	40% (n=344)	28% (n=373)	0.017
Time to progression (TTP)	9 months (n=350)	5 months (n=385)	0.0008
Overall survival (OS)	24 months (n=350)	16 months (n=385)	0.17
Efficacy*	**Paclitaxel + trastuzumab**	**Paclitaxel only**	***p*-value**
TR in HER2-normal tumors	35% (n=112)	29% (n=111)	0.34
TTP in HER2-normal tumors	7 months (n=113)	6 months (n=115)	0.09
OS in HER2-normal tumors	22 months (n=113)	20 months (n=115)	0.67
Grade 3-4 toxicities**	**Weekly paclitaxel**	**Every three-week paclitaxel**	***p*-value**
Granulocytopenia	5%	15%	0.013
Neurosensory	23%†	12%	0.001

* Combined weekly plus standard schedules

** Selected, based on any incidence >5%, no significant difference with trastuzumab use

† 19% for patients who did not receive 100 mg/m^2 x 6 initially

SOURCE: Seidman A 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+ MBC and randomized for trastuzumab for HER2 normal MBC.** Presentation. ASCO, 2004.

EXTENSION TRIAL OF TRASTUZUMAB BEYOND DISEASE PROGRESSION IN PATIENTS WITH METASTATIC BREAST CANCER: SAFETY AND EFFICACY DATA

Severe toxicities*	Group 1 Chemotherapy alone in initial trial** (n=153)	Group 2 Chemotherapy + trastuzumab in initial trial† (n=93)
Asthenia	11%	10%
Carcinoma†	8%	12%
Pain	6%	10%
Leukopenia	8%	11%
Efficacy	**Group 1 (n=154)**	**Group 2 (n=93)**
Objective Response (CR+PR)	14% (95% CI, 8.3-19.2)	11% (95% CI, 4.5-17.0)
Clinical benefit (CR+PR+SD)	32%	22%
Median duration of response	7.4 months (95% CI, 5.1-12.5)	6.7 months (95% CI, 4.1-10.2)

CR = complete response; PR = partial response; SD = stable disease >6 months

* Adverse events reported as severe in >5% of treated patients

** Both groups received trastuzumab ± chemotherapy in the extension trial

† Indicative of progressive breast cancer; does not indicate a new cancer

SOURCE: Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70.

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TRASTUZUMAB ALONE OR WITH CHEMOTHERAPY

I use trastuzumab alone in a minority of patients — usually elderly women or young women who are not willing to undergo another course of chemotherapy — but I prefer combination therapy. In patients who have had a prior response to chemotherapy and trastuzumab and are now receiving trastuzumab alone but have disease progression, I continue trastuzumab and reintroduce chemotherapy for three to four months. I have seen nice responses in those situations.

If the treatment-free interval was long, I might use the initial chemotherapy, but if it was six months or less I would select a different agent. We have strong data supporting the use of taxanes in combination with trastuzumab. A recent trial comparing docetaxel with or without trastuzumab had striking results favoring the combination. I believe it is a good regimen to choose. If I were to use paclitaxel, I would administer it weekly with trastuzumab. I have also seen impressive anecdotal responses to vinorelbine plus trastuzumab.

— Martine J Piccart-Gebhart, MD, PhD

I discuss the data on combination and single-agent trastuzumab and tell patients that we don't know if it is better to give the combination up front or if there is any harm in giving trastuzumab alone and then adding the chemotherapy at progression. Generally, in a patient with life-threatening disease, I'm going to go for the best response and will recommend giving chemotherapy with trastuzumab. But for patients who have pretty low-volume or quiescent disease and are not symptomatic, or older patients in whom cardiac problems may arise, I think trastuzumab monotherapy is a reasonable option.

— Julie R Gralow, MD

The *in vitro* synergy between the platinums and trastuzumab has recently been put to the test. The results of Dr Nicholas Robert's study were remarkable. In the patients who received carboplatin in addition to trastuzumab/paclitaxel, the response rates and the time to progression were significantly improved.

— Mark D Pegram, MD

TRIAL OF TRASTUZUMAB BEYOND PROGRESSION

"…some patients who experience disease progression may respond to or derive a clinical benefit from additional trastuzumab-based therapy, although the magnitude of the benefit is also consistent with the effect of salvage chemotherapy alone.

"The durations of response in both groups exceeded 6 months, slightly shorter than has been seen on first exposure to trastuzumab when used as a single agent or in combination with chemotherapy. Because HER2-positive cancer is associated with an aggressive clinical course, these results may represent promising activity in this population refractory to prior chemotherapy regimens, including trastuzumab."

— Tripathy D et al. J Clin Oncol *2004;22(6):1063-70.*

SAFETY OF TRASTUZUMAB BEYOND PROGRESSION

"The extension trial described in this report was undertaken to provide trastuzumab therapy to patients whose metastatic breast cancer progressed during treatment with chemotherapy with or without trastuzumab. It was designed primarily to provide additional safety information regarding the addition of trastuzumab to various chemotherapeutic agents. …

"No new specific adverse events were seen with any particular chemotherapy regimen or with prolonged administration of trastuzumab of up to 40 months, suggesting that long-term trastuzumab treatment is well tolerated. No cumulative toxicities emerged over this time frame. …

"Although treatment beyond progression would represent a new paradigm in oncologic therapy, the novel and targeted activity of trastuzumab, including direct antiproliferative activity, synergistic interaction with a number of standard chemotherapy agents, and antiangiogenic activity, may support this approach."

— Tripathy D et al. J Clin Oncol *2004;22(6):1063-70.*

Research To Practice: HER2-Positive Disease

27TH ANNUAL San Antonio Breast Cancer Symposium 24

Availability of the humanized monoclonal antibody trastuzumab makes it critical to accurately determine HER2 tumor status in all patients with metastatic breast cancer. About three fourths of oncologists accept IHC results of 3+ as HER2-positive, but others require FISH confirmation. The 2004 Patterns of Care Study demonstrated that, in the first-line metastatic setting, trastuzumab is generally combined with chemotherapy — usually a taxane. Although no randomized clinical trial data are available addressing the questions of continuation of trastuzumab upon disease progression, this is a common practice pattern both in tertiary care centers and community oncology practice. In the adjuvant setting, trastuzumab is rarely utilized outside the context of a clinical trial.

INTERPRETATION OF HER2 TEST RESULTS

How would you interpret the following HER2 test results?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	78%	4%	0%
HER2-positive only with FISH confirmation	22%	96%	48%
HER2-negative	0%	0%	52%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

TREATMENT OF PATIENTS WITH HER2-POSITIVE ASYMPTOMATIC METASTATIC DISEASE

The patient is a woman who has had no prior systemic therapy who has an ER-negative, HER2-positive tumor with rising tumor markers and asymptomatic bone metastases. What would be your first- and second-line treatments?

	Age 40 (premenopausal)		Age 57		Age 75	
	First line	Second line	First line	Second line	First line	Second line
Chemotherapy alone	7%	17%	6%	17%	8%	18%
Trastuzumab alone	19%	3%	20%	3%	23%	10%
Trastuzumab + chemotherapy	70%	77%	71%	77%	61%	68%
No therapy	4%	3%	3%	3%	8%	4%

If you would use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

	Age 40 (premenopausal)	Age 57	Age 75
Yes, continue	84%	85%	86%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

CHEMOTHERAPY REGIMENS USED WITH TRASTUZUMAB

Which chemotherapy regimen do you generally utilize with trastuzumab?

	First line	Second line	Third line
Docetaxel	40%	26%	10%
Paclitaxel	24%	6%	2%
Carboplatin/docetaxel	8%	16%	5%
Carboplatin/paclitaxel	6%	4%	4%
Vinorelbine	14%	34%	33%
Gemcitabine	6%	4%	22%
Other/none	2%	10%	24%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SCHEDULE OF TRASTUZUMAB

What trastuzumab schedule do you generally utilize?	Percent of physicians
Weekly	88%
Every three weeks	12%
Other	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

CLINICAL USE OF ADJUVANT TRASTUZUMAB

The patient is a woman in average health with a 1.2-cm, ER-positive, Grade II tumor and 3 positive lymph nodes. Tumor is HER2-positive as confirmed by FISH. Would you utilize trastuzumab for this patient? (Percent responding "yes")

	35 years old	65 years old
Trastuzumab off protocol	6%	4%
Trastuzumab clinical trial	75%	70%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

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TREATMENT ALGORITHM FOR PATIENTS WITH HER2-POSITIVE METASTATIC DISEASE

I tend to put patients into three categories — low risk, intermediate risk and high risk. I look at the low-risk category as an opportunity to give trastuzumab by itself. As the risk increases, I add more agents. My double-agent combination has generally been a taxane and trastuzumab, while my three-drug combination has been taxane/platinum/trastuzumab.

If a patient is fairly asymptomatic and doesn't have much disease, I offer her trastuzumab by itself and see how it goes. I have had some patients do very well with trastuzumab monotherapy. We conducted a trial in which patients had the opportunity to have a lead-in induction with trastuzumab. Patients who had stable disease (or better) remained on trastuzumab for eight weeks and then received an additional eight weeks of treatment.

In patients who had evidence of progressive disease, paclitaxel and carboplatin were added to the trastuzumab. It was a small trial of 63 patients, but if you look back and see how the patients fared, we didn't lose any ground during those first eight weeks in patients who didn't benefit from trastuzumab.

For a patient who clearly has visceral metastases and is symptomatic, I use the three-drug combination with a platinum included. The other patients fall in the mix, and we discuss which one to start with and how aggressive to be.

— Howard A Burris III, MD

I have been using carboplatin/docetaxel/trastuzumab frequently, especially in patients with bulky disease and visceral crises. My choice of which chemotherapeutic agent to use is guided by the toxicities a patient is willing to tolerate. A woman with newly diagnosed metastatic disease may feel absolutely violated by the idea of hair loss with the use of a weekly taxane. I also like the vinorelbine/trastuzumab combination. It's well-tolerated and generates good responses.

Once a patient reaches an optimal response on combination therapy, I discontinue the chemotherapy and maintain them on trastuzumab almost indefinitely. Some of my patients have been on monotherapy for three or four years, if only to avoid the possibility of upregulating proliferative mechanisms when trastuzumab is stopped.

Trastuzumab monotherapy is a reasonable option for patients with small-volume, HER2-positive disease who are not open to the idea of chemotherapy. Chuck Vogel demonstrated a 47 percent clinical benefit with trastuzumab monotherapy in chemotherapy-naïve patients with measurable metastatic disease. I tend to use trastuzumab with chemotherapy up front and then apply trastuzumab alone as maintenance treatment.

— Maria Theodoulou, MD

SELECTION AND INTERPRETATION OF HER2 TESTING

Every patient with metastatic breast cancer in my practice has her tumor evaluated for HER2 gene amplification by FISH. Tumors with an IHC score of 3+ should be evaluated by FISH, because they may not have gene amplification. In tumors with an IHC score of 0 or 1+, three percent and seven percent, respectively, will have HER2 gene amplification by FISH. We need to determine HER2 status accurately because it is a matter of life or death.

— Melody A Cobleigh, MD

We recommend an algorithm that starts with immunohistochemistry because it is an easier, less expensive test to do. If the tumor is IHC 0, 1+ or 3+, no further testing is necessary. If the tumor is IHC 2+, reflex FISH testing is recommended. At our facility, the pathologists automatically perform the FISH analysis. We believe perhaps it's not a good idea to do FISH testing for every tumor because the majority will be negative.

— Edith A Perez, MD