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 12/31/04

SOURCE: CTSU correspondence, January 2005.

PHASE III BREAST CANCER TRIALS OPEN THROUGH THE CTSU

Study number	Study description	Accrual to date/goal	As of date
CALGB-40101	Adjuvant AC (four versus six cycles q2wk) versus paclitaxel (four versus six cycles q2wk) for women with node-negative breast cancer	1,396/4,646	12/27/04
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	274/720	12/27/04
E1Z03	Quality of life companion study for NCIC-MA27	NA/1,253	12/22/04
IBCSG-24-02 (SOFT)	Adjuvant tamoxifen versus ovarian function suppression (OFS) + tamoxifen versus OFS + exemestane in premenopausal women with endocrine-responsive breast cancer	101/3,000	12/01/04
IBCSG-25-02 (TEXT)	Adjuvant triptorelin + exemestane versus triptorelin + tamoxifen in premenopausal women with endocrine-responsive breast cancer	206/1,845	12/01/04
IBCSG-26-02 (PERCHE)	OFS + tamoxifen or exemestane ± adjuvant chemotherapy in premenopausal women with endocrine-responsive breast cancer	4/1,750	12/01/04
NCIC-MA20	Regional radiation therapy in early breast cancer	1,146/1,822	01/02/05
NCIC-MA21	Adjuvant sequenced EC + filgrastim + epoetin alpha 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	1,913/2,100	01/02/05
NCIC-MA27	Exemestane versus anastrozole ± celecoxib in postmenopausal women with receptor-positive primary breast cancer	1,666/6,830	01/02/05
NSABP-B-35	Anastrozole versus tamoxifen in postmenopausal patients with DCIS undergoing lumpectomy with radiation therapy	1,389/3,000	01/02/05
NSABP-B-36*	Adjuvant FEC x six cycles versus AC x four cycles, ± celecoxib in women with node-negative breast cancer	327/2,700	01/02/05
NSABP-B-37	Observation or chemotherapy for radically resected locoregional relapse of breast cancer	NA/977	NA
NSABP-B-38	Adjuvant TAC versus dose-dense (DD) AC followed by DD paclitaxel versus DD AC followed by DD paclitaxel + gemcitabine	90/4,800	01/02/05
RTOG-98-04	Whole breast radiation therapy versus observation ± tamoxifen in women with DCIS	485/1,790	12/28/04
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	282/350	12/31/04
SWOG-S0221	Adjuvant continuous-schedule AC + filgrastim versus every two-week AC + pegfilgrastim or filgrastim, followed by paclitaxel given every two weeks versus weekly for 12 weeks in women with node-positive or high-risk node-negative breast cancer	492/4,500	12/31/04
SWOG-S0226	Anastrozole versus anastrozole + fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer	26/690	12/31/04

*Effective 12/17/2004: Temporary suspension to accrual for NSABP-B-36

SOURCES: CTSU correspondence, January 2005; NCI Physician Data Query, January 2005.

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

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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 those data and the centralization of all IRB data on a per-study basis has been helpful. This system should ease the burden of clinical trial participation on investigators in the community and in academic institutions and increase the speed with 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 works, 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 will be 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 debugged, but I hope it works because we need more patients enrolled in these clinical trials. I suspect a large reservoir of oncologists have never filled out the CTSU form — not because it's difficult, but because no one suggested they do it.

— George W Sledge Jr, MD

Controversies in HER2 Testing

The accurate assessment of HER2 status is paramount for the management of patients with metastatic breast cancer and the enrollment of patients into adjuvant trastuzumab trials. Two trials evaluating adjuvant trastuzumab — NSABP-B-31 and NCCTG-N9831 — have reported poor concordance between community and central laboratories' assessments of HER2 status. NSABP subsequently demonstrated that a quality assurance program in which NSABP-approved community laboratories were used could improve the reliability of HER2 testing in the community. Recent studies have also evaluated concordance between different HER2 assays, concordance of HER2 status in the primary lesion, lymph nodes and distant metastases, and the impact of neoadjuvant trastuzumab on HER2 status.

CONCORDANCE BETWEEN COMMUNITY AND CENTRAL LABORATORIES' RESULTS FOR HER2-POSITIVE TUMORS FROM NSABP-B-31

Central laboratory's results	Percent of cases (n=104)
Strongly positive (3+) by the HercepTest® assay	79
Positive for gene amplification by the PathVysion® FISH assay	79
Neither strongly positive (3+) by the HercepTest® assay nor positive for gene amplification	18

QUALITY ASSURANCE PROGRAM FOR NSABP-B-31: 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%

SOURCES: Paik S et al. *J Natl Cancer Inst* 2002;94(11):852-4.

Paik S. Presentation. San Antonio Breast Cancer Symposium, 2002;Abstract 9.

CONCORDANCE RATES BETWEEN CHROMOGEN *IN SITU* HYBRIDIZATION AND FISH IN CORE CUT BIOPSIES OF PRIMARY T2 BREAST CANCER

Samples	N	Concordance rate
IHC score 2+ Differentiation between HER2 positivity or negativity	56	98.2%
IHC score 3+ Differentiation between HER2 positivity	6	100%
All samples (IHC 0/1+, 2+, 3+) Differentiation between HER2 positivity	71	96.6%
All samples (IHC 0/1+, 2+, 3+) Differentiation between HER2 negativity	71	97.9%

SOURCE: Raab GH et al. *Proc ASCO* 2004;Abstract 569.

CONCORDANCE OF HER2 STATUS IN SAMPLES FROM PRIMARY BREAST CANCER AND DISTANT METASTASES IN THE SAME PATIENT

IHC score	Primary breast cancer (n=31)	Distant metastases (n=31)
0 or 1+	80.6%	54.8%
2+	9.7%	25.8%
3+	9.7%	19.4%

CONCORDANCE OF HER2 STATUS IN SAMPLES FROM PRIMARY BREAST CANCER AND REGIONAL LYMPH NODE METASTASES IN THE SAME PATIENT

IHC score	Primary breast cancer (n=10)	Regional lymph node metastases (n=10)
0	80%	80%
1+	10%	10%
3+	10%	10%

SOURCE: Regitnig P et al. *J Pathol* 2004;203(4):8-26.

CONCORDANCE BETWEEN LOCAL AND CENTRAL LABORATORIES' RESULTS FOR THE INITIAL HER2-POSITIVE TUMOR SPECIMENS FROM N9831

Local HER2 testing	Central results		
	Total	FISH-amplified	IHC-positive (3+)
IHC 3+	110	73 (66%)	81 (74%)
FISH-positive	9	6 (67%)	7 (78%)
Total	119	79 (66%)	88 (74%)

CONCORDANCE BETWEEN LOCAL, CENTRAL AND REFERENCE LABORATORIES' RESULTS FOR SUBSEQUENT HER2-POSITIVE TUMOR SPECIMENS FROM N9831

Local HER2 testing	Central HER2 testing	
	FISH-positive	HercepTest® (3+)
FISH-positive	204/240 (85%)	—
HercepTest® (3+)	—	376/473 (79.5%)

Central HER2 testing	Reference HER2 testing	
	FISH-negative	HercepTest® (0, 1+, 2+)
FISH-negative	122/128 (95.3%)	—
HercepTest® (0, 1+, 2+)	—	130/135 (96.3%)

SOURCES: Perez EA et al. Presentation. *ASCO* 2004;Abstract 567.

Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.

FREQUENCY OF HER2 GENE AMPLIFICATION ACCORDING TO HER2 PROTEIN EXPRESSION IN A COHORT OF 6,556 SPECIMENS FROM IMPATH LABORATORIES

IHC score	Percent of cases amplified
0	4.1
1+	7.4
2+	23.3
3+	91.7

SOURCE: Owens MA et al. *Clin Breast Cancer* 2004;5(1):63-9.

HER2 STATUS FOLLOWING PREOPERATIVE TRASTUZUMAB AND PACLITAXEL

HER2 status following preoperative therapy	Baseline HER2 status			
	3+ (n=32)		2+ (n=8)	
	No. of patients	Percent	No. of patients	Percent
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.

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

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 immunohistochemistry or FISH in outside laboratories.** Poster. San Antonio Breast Cancer Symposium, 2002;Abstract 238.

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Regitnig P et al. **Change of HER-2/neu status in a subset of distant metastases from breast carcinomas.** *J Pathol* 2004;203(4):8-26.

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.

QUALITY CONTROL FOR HER2 TESTING

When the NSABP designed the B-31 adjuvant trastuzumab trial, we were reluctant to require central testing for HER2. I always believed that it was not possible for a pathologist to misclassify patients with IHC 3+ overexpression, and the entry criteria for the study required patients' tumors to be IHC 3+. However, we built a safeguard into the protocol, such that we would perform central testing of the initial 100 patients entered into the study.

HER2 status was measured by both IHC and FISH, so HER2-negative tumors were truly negative. We were shocked because the false-positive rate was 18 percent. The Intergroup trial demonstrated essentially the same finding, and these results were a big "wake-up call" for the community.

Based on the false-positive rate, we revised the protocol so that patients had to be tested by an approved laboratory that performs over 100 tests per month or performs fewer tests but demonstrates a concordance rate between IHC and FISH of over 95 percent. The end result was a dramatic improvement in the quality of test results; the false-positive rate dropped from 18 percent to three percent.

— Soonmyung Paik, MD

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

HER2 TESTING ALGORITHM

We initially perform IHC for HER2 testing and then FISH if the IHC result is 2+. We view zero and 1+ results as HER2-negative and 3+ results as HER2-positive. However, we know from concordance data that approximately 10 percent of IHC zero and 1+ cases will be FISH-positive and approximately 10 percent of IHC 3+ cases will be FISH-negative, so that has to be taken into consideration.

We have learned that labs must perform a high volume of FISH testing to be proficient, and community labs have low concordance rates. At the 2004 ASCO meeting, an interesting technique for evaluating the HER2 status was presented, called chromogen *in situ* hybridization (CISH). The concordance rates between this technique and FISH were high, and I believe this new assay will change our current patterns of testing.

— Adam M Brufsky, MD, PhD

INTRAPATIENT STABILITY OF HER2 STATUS

"For most patients with residual tumor after 12 weeks of neoadjuvant treatment, HER2 expression as measured by immunohistochemistry was unchanged. However, a subset of patients whose initial tumors were 3+ was found, on testing after induction therapy, to have lost immunohistochemical expression of HER2.

"The clinical significance of this finding is not known. It may represent downregulation of HER2 expression following anti-HER2 antibody exposure, as reported in preclinical tumor models. It may also represent intrinsic heterogeneity of HER2 expression and tumor response, or an artifact of tumor sampling or testing. It is not clear whether this finding implies resistance or sensitivity to trastuzumab."

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

Chemoprevention and Management of DCIS

Tamoxifen reduced the incidence of breast cancer 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 cancer — 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. *Lancet* 2002;360(9336):817-24.

REDUCTION IN INCIDENCE OF CONTRALATERAL BREAST CANCER WITH ANASTROZOLE VERSUS TAMOXIFEN: 68-MONTH UPDATE FROM THE ATAC TRIAL

	Reduction	95% CI	*p*-value
All patients	42%	12-62	0.01
Hormone receptor-positive patients	53%	25-71	0.001

CI = confidence interval

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

ACTIVE CLINICAL TRIALS COMPARING TAMOXIFEN TO ANASTROZOLE IN WOMEN WITH DCIS

Protocol ID	Eligibility	Randomization	Target accrual
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, ages 40 to 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, December 2004.

INCIDENCE OF INVASIVE BREAST CANCER FOLLOWING RALOXIFENE THERAPY IN WOMEN WITH OSTEOPOROSIS: EIGHT YEARS OF MORE PLUS CORE TRIAL DATA

	Raloxifene	Placebo	Hazard ratio	*p*-value
Cumulative incidence	1.4 per 1,000 women-years	4.2 per 1,000 women-years	0.34 (95% CI, 0.22-0.50)	< 0.001

SOURCE: Martino S. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 22.

OTHER ONGOING OR RECENTLY CLOSED CHEMOPREVENTION TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAP0-0028-150	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
UTSMC-0799-302	High-risk, pre- or postmenopausal, age 35 and over	130	Tamoxifen vs placebo
KUMC-HSC-8919-02	High-risk for ER-negative, premenopausal, age 18 to 55	110	Celecoxib
CHNMC-IRB-02164	High-risk, premenopausal, age 21 to 48	10	Deslorelin + estradiol + testosterone
NU-NCI-00B2	Initiating tamoxifen for risk reduction or sole systemic therapy for breast cancer, premenopausal, age 20 to 45	100	Tamoxifen
CRUK-IBIS-IIB, EU-20227	High-risk, ER/PR-positive (>5% positive cells) in patients with prior DCIS, postmenopausal, age 40 to 70	6,000	Anastrozole vs placebo
CAN-NCIC-MAP2, 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
BCM-H-9315	Known carrier or at risk for BRCA1 or BRCA2 mutation, pre- or postmenopausal, age 18 and over	100	Bexarotene vs placebo
NSABP-P-2 (STAR)	High-risk, postmenopausal, age 35 and over	19,000	Tamoxifen vs raloxifene

SOURCE: NCI Physician Data Query, December 2004.

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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.

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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.

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

Martino S et al. **Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women stratified by baseline serum estradiol level: Results of the continuing outcomes relevant to Evista (CORE) trial.** *Proc SABCS* 2004;Abstract 22.

ATAC TRIAL DATA ON SECOND BREAST CANCERS

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

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

Some might argue that the reduction of contralateral breast cancer in ATAC looks less promising with the updated data than with the original data — it has gone from about a 60 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 longer than tamoxifen. I am very confident that anastrozole will reduce the risk of new receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm-to-benefit ratio.

— Michael Baum, MD, ChM

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 well tolerated.

Aromatase inhibitors have a significant effect in invasive cancer, and it's highly likely they will also impact DCIS. Craig Allred has shown that DCIS is even more likely to be ER-positive than invasive cancer. If that's true, we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

— Patrick I Borgen, MD

NSABP-B-35 was designed shortly before the ATAC study was publicized, so data from ATAC and MA17 were not available to us. It was initiated because of the growing body of evidence that aromatase inhibitors appear to be effective in settings in which tamoxifen is efficacious. Indeed, two large studies in advanced disease showed drugs like anastrozole were either equivalent to or even slightly better than tamoxifen. The dramatic reduction in second or contralateral breast cancer in women who received anastrozole versus tamoxifen seen in the ATAC trial is exciting and emphasizes the importance of our trial.

— Richard G Margolese, MD

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 percent 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

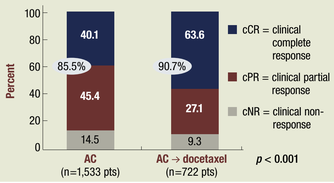
While neoadjuvant chemotherapy may downstage tumors and improve the chance for breast conservation, disease-free and overall survival rates are not altered. At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27 evaluating the addition of docetaxel to neoadjuvant AC. The addition of neoadjuvant docetaxel improved the pathologic complete response rate, but no differences were found in overall or disease-free survival. However, relapse-free survival was significantly improved in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant studies is evaluating a variety of novel neoadjuvant strategies including dose-dense chemotherapy, taxanes, capecitabine/docetaxel (XT) and other combination regimens.

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

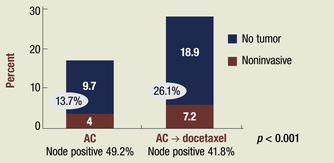
Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)

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

NSABP-B-27 INITIAL RESULTS: CLINICAL RESPONSE



NSABP-B-27 INITIAL RESULTS: PATHOLOGIC RESPONSE IN BREAST



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

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

NSABP-B-27: 68-MONTH UPDATE OF STUDY ENDPOINTS (HAZARD RATIOS COMPARED TO AC)

Variable	AC → T → surg (n=803)	AC → surg → T (n=799)
Overall survival	0.94 (p = 0.57)	1.07 (p = 0.53)
Disease-free survival With cPR after AC (n=378,350)	0.86 (p = 0.10) 0.68 (p = 0.003)	0.91 (p = 0.27) 0.90 (p = 0.40)
Relapse-free survival	0.81 (p = 0.03)	0.91 (p = 0.32)

No significant difference in overall survival or disease-free survival by treatment but improved relapse-free survival in Arm 2 (preoperative docetaxel) vs Arm 1 (AC).
T = docetaxel

NSABP-B-27: 68-MONTH UPDATE: HAZARD RATIOS OF PCR VERSUS NON-PCR

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

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

SOURCE: Bear H. Presentation. SABCS, 2004.

PREOPERATIVE CAPECITABINE OR GEMCITABINE PLUS DOCETAXEL IN SEQUENCE WITH AC

Protocol IDs: NSABP-B-40, CTSU
Accrual: 1,200 (Pending)

Eligibility	Stage II or IIIA operable breast cancer
ARM 1	AC → T 100 mg/m² x 4 → surgery
ARM 2	AC → T 75 mg/m² + capecitabine* x 4 → surgery
ARM 3	AC → T 75 mg/m² + gemcitabine x 4 → surgery
ARM 4	T 100 mg/m² x 4 → AC x 4 → surgery
ARM 5	T 75 mg/m² x 4 + capecitabine* x 4 → AC x 4 → surgery
ARM 6	T 75 mg/m² x 4 + gemcitabine x 4 → AC x 4 → surgery

* Capecitabine dose = 825 mg/m² BID days 1-14 q3wk

SOURCE: NSABP Protocol Summary, November 2004.

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

Protocol IDs: 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)*

* 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

SOURCES: NCI Physican Data Query, January 2005; Livingston R. *Oncology* 2002;16(10 Suppl 12):29-31.

PATHOLOGIC COMPLETE RESPONSE RATES BY TUMOR ER STATUS: PREOPERATIVE TRIALS FROM MD ANDERSON CANCER CENTER

Chemotherapy	No. of pts	Pathologic complete response	
		ER-negative	ER-positive
FAC x 3	532	14.5%	1.2%
FAC x 4	78	27.6%	6.1%
Paclitaxel x 4	81	7.1%	5.7%
Paclitaxel q3wk → FAC x 4	127	30.9%	5.6%
Paclitaxel q1wk → FAC x 4	128	54.5%	14.3%
(A + docetaxel) x 4	72	15.9%	7.1%
Total	**1018**	**20.6%**	**5.0%**

SOURCE: Buzdar AU et al. *Breast Cancer Res Treat,* 2003.

NSABP-B-27: 68-MONTH UPDATED RESULTS

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

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

— Harry D Bear, MD, PhD

NEOADJUVANT CAPECITABINE/DOCETAXEL TRIAL

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

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

Investigators have evaluated the role of serum proteomics in identifying patients at risk of developing a malignancy or segregating patients with cancer from patients with some benign condition. We're trying to take proteomics a step further and determine whether it will predict for response to individual therapies.

— Kathy D Miller, MD

MD ANDERSON NEOADJUVANT/ADJUVANT TRIAL

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

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

We currently have more than 200 patients enrolled in the study. In the first cohort, we gave a somewhat higher dose of capecitabine and saw an increase in morbidity. We reduced the dose of capecitabine and, with the use of this attenuated dose, we are seeing more acceptable toxicity.

Now the big question remains: What is the long-term and short-term efficacy? The data are continuously being monitored, but we won't have definitive information until we have enough patients in the neoadjuvant setting to determine whether the regimens are similar or one is better than the other.

— Aman U Buzdar, MD

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

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

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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.

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

Kaufmann M et al. **International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: Review and recommendations.** *J Clin Oncol* 2003;21(13):2600-8.

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 cancer. 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 the 2003 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.

IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION

Eligibility: Postmenopausal, ER/PR-positive T2 (≥2 cm), T3, T4b NO-2, MO breast cancer patients

Efficacy data (N=330)	A	T	C
Objective clinical tumor response[†]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after three months of treatment[†]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after two weeks of treatment[2‡]	76%	59%	64%

A = anastrozole; T = tamoxifen; C = combination

* 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 two weeks with only marginal changes between two 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.

‡ 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.

LETROZOLE VERSUS 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.

NEOADJUVANT ENDOCRINE THERAPY VERSUS CHEMOTHERAPY FOR POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER

Response	Chemotherapy*	Anastrozole	Exemestane
Clinical objective response	76%	75.6%	81.5%
Mammographic objective response	61.9%	62.1%	71%
Qualified for breast-conserving therapy	23.9%	33.3%	34%

* Chemotherapy = doxorubicin + paclitaxel

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

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 pathological response (pCR)	23%
Partial pathological 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 patients with hormone-dependent, locally-advanced breast cancer.** *Anticancer* 2004;24(2C):1315-8.

ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL BREAST CANCER PATIENTS (N=87)

	A	T	A + T	*p*-value
Overall objective response (clinical)	70%	44%	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

A = anastrozole; T = tamoxifen

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.

CLINICAL RESPONSE TO NEOADJUVANT LETROZOLE

Duration of therapy	Median reduction in tumor volume	95% CI
0-3 months (n=42)	52%	37-62
3-6 months (n=42)	57%	26-100
6-12 months (n=22)	66%	22-100
Duration of therapy	**Number of complete responses**	**Percent**
3 months (n=42)	4	9.5
6 months (n=42)	12	29
12 months (n=22)	8	36

SOURCE: Renshaw L et al. **Is there an optimal duration of neoadjuvant letrozole therapy?** *Proc SABCS* 2004;Abstract 405.

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

Dowsett M et al. **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.

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.

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.

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

Renshaw L et al. **Is there an optimal duration of neoadjuvant letrozole therapy?** *Proc SABCS* 2004;Abstract 405.

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

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.

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 larger 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

I believe the IMPACT trial demonstrates the poor utility of clinical response as an endpoint in neoadjuvant trials. In many respects, reduction in tumor volume is more valuable. If reduction in tumor volume had been evaluated for the patients in the IMPACT trial, I suspect the trial would have demonstrated that anastrozole was superior, as evidenced by the fact that more patients with larger tumors had breast-conserving surgery.

For surgeons who want to shrink larger tumors and be able to perform breast-conserving surgery, it's not just response but the degree of response that is important. In our neoadjuvant studies, the reduction in tumor volume was much better with all of the aromatase inhibitors (including anastrozole) compared to tamoxifen.

— J Michael Dixon, MD

ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN THE NEOADJUVANT SETTING

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

— Michael Baum, MD, ChM

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 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, MB, 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.

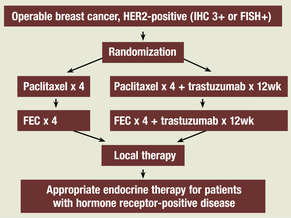
RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

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

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

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

MD ANDERSON 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; FEC = 5-fluorouracil, epirubicin and cyclophosphamide

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

PHASE III RANDOMIZED TRIAL 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: 75 (Open)

Eligibility	**T3 or T4, any N patients with HER2-positive disease* are randomly assigned to neoadjuvant therapy**
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. 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, January 2005.

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

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease.** *Proc ASCO* 2004;22(Suppl 4);Abstract 520.

Carey LA et al. **Responag 4AC as initial therapy for primary breast cancer (BrCa).** *Breast Cancer Res Treat* 2002;76(Suppl 1):109;Abstract 424.

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Moluçon C et al. **Pathological complete response with neoadjuvant (NA) chemotherapy (trastuzumab (T) and docetaxel (D)) in HER2 positive (3+) locally advanced (LA) breast cancer (BC) patients.** *Breast Cancer Res Treat* 2003;82(Suppl 1):59;Abstract 253.

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

MD ANDERSON PREOPERATIVE TRIAL OF TRASTUZUMAB AND CHEMOTHERAPY

All of the patients enrolled in the trial received four courses of every three-week paclitaxel followed by 12 weeks of FEC. We used epirubicin instead of doxorubicin because it has a better cardiac safety profile. One half of these patients also received weekly trastuzumab for 24 weeks. Every patient had a baseline cardiac scan and then repeat scans at 12 and 24 weeks.

In our previous experience with this chemotherapeutic regimen, about 21 percent of unselected patients had pathologic complete remissions. Pathologic complete remission is defined as having no tumor left in the breast or in the lymph nodes after therapy. We were hoping the addition of trastuzumab to chemotherapy would elevate the pathologic complete response rate from 21 percent to 41 percent — a 20 percent improvement.

The trial was interesting because we knew what the pathologic outcome was as soon as the patient completed surgery. As soon as we had results from 34 patients, we were able to see that 65 percent of the patients in the trastuzumab arm had no tumor, whereas only 25 percent of the patients who received chemotherapy alone were tumor-free.

This was much higher than we had anticipated or hoped. The clinical response rate was even more striking, as 87 percent of the patients had clinical complete remission in the trastuzumab arm compared to about 50 percent in the chemotherapy-alone arm.

We observed a slightly increased incidence of reduced ejection fractions in patients enrolled in the trastuzumab arm compared to the patients in the chemotherapy-alone arm. All of these changes were observed on cardiac scan. What was also surprising was that in almost all of the patients who had drops in their cardiac ejection fractions, the LVEFs returned to normal after therapy was completed.

We discussed these data with our institutional Data Monitoring Committee, which looked at them independently and came to the conclusion that the findings were so striking that even if we continued the trial to reach accrual, the results would be similar. Thus the trial was stopped early.

— Aman U Buzdar, MD

Despite the early closure of this randomized trial, its findings are provocative. If we think about the number of papers reporting on various regimens of preoperative chemotherapy, never stratified by HER2, they've always shown pathologic complete response rates of 15 to 20 percent, especially in hormone receptor-negative tumors. This literature just became irrelevant because we now know that we can triple the pathologic complete response rate in HER2-positive tumors by adding trastuzumab.

However, this trial has some caveats. Let's assume the adjuvant trastuzumab trials are positive and that, in general, they share a common design feature of an anthracycline followed by trastuzumab plus a taxane. In the metastatic setting, trastuzumab is less active if the tumor is resistant to chemotherapy, so perhaps we should have administered trastuzumab first before chemotherapy. This would have allowed a safety analysis for concurrent use of up-front chemotherapy.

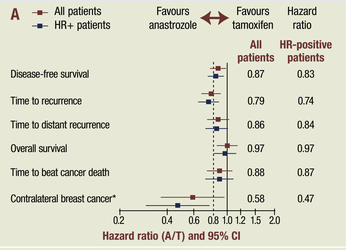
Additionally, if 200 women were treated, the trial may have shown an improvement in the rate of breast-conserving surgery, which is the only rationale for preoperative treatment outside a clinical trial. Furthermore, because few oncologists have experience with the regimen utilized, I'm not sold on this regimen as a widespread nonprotocol option.

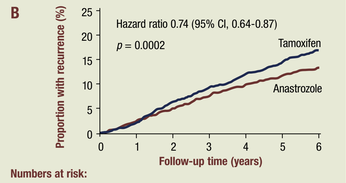
— Harold J Burstein, MD, PhD

Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial

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. At the recent 2004 San Antonio meeting, data were presented from the third analysis at 68 months. An advantage to anastrozole in disease-free survival continued to be present with about one in four relapses on tamoxifen avoided with anastrozole.

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





Numbers at risk:

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

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

A = anastrozole; T = tamoxifen; HR = hormone receptor
* Odds ratio calculated instead of hazard ratio

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

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.
† From 68-month analysis: HR in ER/PR-positive (0.84), ER-positive/PR-negative (0.43)

SOURCES: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of times 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(Suppl 1):7;Abstract 4.

† Howell A. Presentation. San Antonio Breast Cancer Symposium, 2004.

ATAC TRIAL 68-MONTH ANALYSIS: ADVERSE EVENTS*

	Anastrozole (%)	Tamoxifen (%)	Odds ratio (anastrozole vs tamoxifen)	*p*-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/ arthralgia	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001
Hysterectomy	1.3	5.1	—	<0.0001

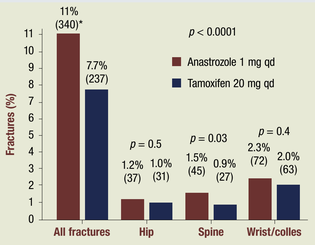
AE = adverse events; SAE = serious adverse events

* Adverse events on treatment or within 14 days of discontinuation
† Fractures occurring before recurrence (includes patients no longer on treatment)

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

Howell A. Presentation. San Antonio Breast Cancer Symposium, 2004.

ATAC TRIAL: BONE FRACTURE ADVERSE EVENTS AT THE UPDATED ANALYSIS



* Numbers in parenthesis refer to numbers of patients with a fracture

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

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Baum M et al; 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.** *Lancet* 2002;359(9324):2131-9.

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;82(Suppl 1):7;Abstract 4.

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Locker GY et al; ATAC Trialists' Group. **Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in postmenopausal women with early breast cancer from a US healthcare system perspective: The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial.** *Breast Cancer Res Treat* 2004;88(Suppl 1):7;Abstract 2085.

CONCLUSIONS FROM THE ATAC TRIALISTS' GROUP

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

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

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The ATAC trial has reached a very important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy was completed.

I believe this is probably the most important of the three analyses, and this latest analysis allows me, as a practicing clinician, to change my mind and change practice. I speak not only as a practicing clinician but also as the past principal investigator of the trial. A *Lancet* article was published in parallel with the 2004 San Antonio presentation and, as a group, we have stuck our necks out and now would say that anastrozole is the preferred initial treatment for postmenopausal women with hormone receptor-positive disease.

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

We are familiar with Kaplan-Meier curves, which are useful for the statistical analysis but don't truly reflect what's going on as the hazard ratios do. A high and narrow peak for relapse occurs at two years, which then comes down again. Then a second, much flatter peak for relapse occurs at about five years.

In the hazard rate analysis plot from the ATAC trial, we're seeing two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial — not only to help make therapeutic decisions, but also to give a fascinating biological insight.

The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile you've lost those patients who will relapse and ultimately die in those first two years.

— Michael Baum, MD, ChM

ADJUVANT AROMATASE INHIBITORS AS INITIAL THERAPY IN POSTMENOPAUSAL WOMEN

Since the third-generation aromatase inhibitors are better than tamoxifen, my postmenopausal patients with ER-positive disease who have not yet started adjuvant hormonal therapy will initially receive an adjuvant aromatase inhibitor — preferably anastrozole. We started using adjuvant anastrozole instead of tamoxifen after the first presentation of the ATAC trial results.

Even if tamoxifen and anastrozole had been therapeutically equivalent, anastrozole would still be preferable because it was better tolerated. For us, the issue of osteopenia was always secondary. We already had experience with the bisphosphonates and monitoring patients for osteoporosis because chemotherapy and ovarian ablation produce premature menopause and accelerated bone resorption. We felt quite comfortable in switching our front-line adjuvant therapy to anastrozole.

— Gabriel N Hortobagyi, MD

Sequential Adjuvant Hormonal Therapy Following Tamoxifen

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, EU-20149, ABCSG-8 and ARNO 95 — 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 continue tamoxifen versus switching to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy demonstrated significant therapeutic advantages to switching to an aromatase inhibitor.

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

Protocol IDs: CRC-TU-TEAM, EU-20149, IES (Intergroup Exemestane Study)
Accrual: 4,724 (Closed)

Eligibility	Postmenopausal women who have received two to three years of adjuvant tamoxifen
ARM 1	Tamoxifen x 2-3y
ARM 2	Exemestane x 2-3y

RESULTS OF UPDATED SURVIVAL ANALYSIS*

Variable	Hazard ratio (exemestane vs tamoxifen)	95% confidence interval	*p*-value
Disease-free survival	0.73	0.62-0.86	0.0001
Breast cancer-free survival	0.70	0.58-0.83	0.00005
Time to contralateral breast cancer	0.50	0.26-0.97	0.04
Overall survival	0.83	0.67-1.02	0.08

* Updated analysis with 615 disease-free survival events and 339 deaths at a median follow-up of 37.4 months

SOURCES: Coombes C. Presentation. San Antonio Breast Cancer Symposium, 2004.

NCI Physician Data Query, January 2005.

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 ID: CAN-NCIC-MA17
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 5y
ARM 2	Placebo x 5y

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

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

* Disease-free survival

SOURCES: NCI Physician Data Query, January 2005.

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.

ANASTROZOLE VERSUS TAMOXIFEN AFTER TWO YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: ABCSG-8, ARNO 95 (Combined)
Accrual: 3,224 (Closed)

Eligibility	Postmenopausal women with hormone-sensitive breast cancer previously treated with adjuvant tamoxifen for two years
ARM 1	Tamoxifen x 3y
ARM 2	Anastrozole x 3y

COMBINED RESULTS FROM 3,224 WOMEN ENROLLED IN THE ABCSG TRIAL 8 AND THE ARNO 95 TRIAL*

Variable	Hazard ratio (anastrozole vs tamoxifen)	95% confidence interval	*p*-value
Event-free survival†	0.60	0.44-0.81	0.0009
Distant recurrence-free survival	0.61	0.42-0.87	0.0067
Overall survival	0.76	0.52-1.12	0.16

* Analysis with 177 events, 104 deaths at median follow-up of 28 months

† Includes locoregional disease, contralateral breast cancer and distant recurrences

SOURCE: Jakesz R. Presentation. San Antonio Breast Cancer Symposium, 2004.

ITA TRIAL: ANASTROZOLE VERSUS TAMOXIFEN IN WOMEN ALREADY RECEIVING ADJUVANT TAMOXIFEN (MEDIAN FOLLOW-UP TWO YEARS)

Protocol ID: 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 2-3y
ARM 2	Tamoxifen x 2-3y

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."

SOURCE: Boccardo F. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 3.

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Coombes RC et al. **The Intergroup Exemestane Study: A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen — Updated survival analysis.** *Breast Cancer Res Treat* 2004;Abstract 3.

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

Jakesz R et al. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** *Breast Cancer Res Treat* 2004;Abstract 2.

SWITCHING PATIENTS FROM ADJUVANT TAMOXIFEN TO AROMATASE INHIBITORS

I now feel confident that women who have been on tamoxifen for two or three years should switch to an aromatase inhibitor. We now have excellent data for both exemestane and anastrozole from three trials. Boccardo's small ITA trial was the first to report, then the large IES study and the joint Austrian-German study that was presented in San Antonio. Overwhelming evidence indicates that a switch is beneficial.

In patients on tamoxifen for one or four years, I think I would still switch. You can wait forever for refinements. No one is ever going to do a trial of a switch at one year or a switch at four years. We just have to stretch the available evidence and be sensible about it, and I think it would be reasonable to switch.

In women who have already received five years of tamoxifen, the MA17 trial is a well-conducted trial. It shows proof of principle that you can influence the natural history of breast cancer after five years of tamoxifen. I've gone on record that I'm bitterly disappointed that they closed the trial and then switched the placebo group to letrozole, because they are now treating the placebo group with experimental therapy — five years on tamoxifen, an average of two and a half years on placebo, and then letrozole. That is an unproven treatment and I don't think we'll ever really learn the long-term benefit and toxicity.

I think we're going way beyond the data. What worries me is that I don't think we can correct this situation. We'll always be left with an area of uncertainty; however, to their eternal credit, the MA17 and NCIC groups have redeemed themselves by being prepared to do a second randomization for duration, which would be at five years of the aromatase inhibitors.

— Michael Baum, MD, ChM

Our group presented the combined analysis of the Austrian and German trials, which compared switching to anastrozole after two years of tamoxifen versus continuing tamoxifen for five years in the adjuvant setting in postmenopausal patients with receptor-positive disease. This is a very clean study with 100 percent hormone receptor positivity.

The results showed a 40 percent reduction in risk of relapse for those who switched to anastrozole, meeting our stopping boundaries for the trial. In terms of side effects and toxicity, we have observed what all the aromatase inhibitor trials have shown — a benefit of aromatase inhibitors in terms of gynecological side effects but more fractures compared to the tamoxifen group.

Although the IES study is more mature, the effects are very comparable in magnitude, however, we have to be cautious making indirect comparisons between trials. Personally, I was hoping that exemestane would be better in terms of bone because of its steroidal nature, but this does not appear to be the case. A significant increase in osteoporosis and an overall low rate of fractures still occur; therefore, the preclinical potential benefit of the steroidal aromatase inhibitor does not materialize in the clinic. For a clinical situation, I think it's fair to say these trials are very comparable.

In terms of selection of an aromatase inhibitor in a postmenopausal woman, I follow the data and use anastrozole up front anastrozole or exemestane after two to three years and letrozole after five years. This is what I believe a clinical trialist has to do. I believe that what has changed since the last San Antonio Breast Cancer Symposium is that we should now consider it mandatory to discuss these options with patients.

— Michael Gnant, MD

For postmenopausal patients who are on tamoxifen for any length of time, our practice today is to switch to an aromatase inhibitor. At one time we would leave patients on tamoxifen if they were already on tamoxifen, because no evidence indicated that crossing over was beneficial. But the result of all three of the crossover trials that came out this past year indicate no justification to continue tamoxifen.

— Gabriel N Hortobagyi, MD

Adjuvant Endocrine Therapy 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 and 2004 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.

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

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

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

ABCSG-05 TRIAL RESULTS: FIVE-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

RT = radiation therapy

Although the data for survival are less mature than for relapse-free survival, the hazard ratio estimate for overall survival favored endocrine therapy ($p = 0.195$).

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

Jakesz R et al. *J Clin Oncol* 2002;20(24):4621-7.

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

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

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

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

SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL

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

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

OFS = ovarian function suppression using triptorelin for five 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 (Open)

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

GnRH = triptorelin for five years, but oophorectomy or ovarian irradiation is allowed after six months

SOURCE: www.ibcsg.org

PERCHE: PREMENOPAUSAL ENDOCRINE RESPONSIVE CHEMOTHERAPY TRIAL

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

Eligibility	Premenopausal women with ER ≥10% and/or PgR ≥10%; patients for whom chemotherapy is considered to be a randomized option (lower risk)
ARM 1	OFS + T or E x 5y
ARM 2	OFS + T or E x 5y + any chemotherapy

OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; T = tamoxifen; E = exemestane

SOURCE: www.ibcsg.org

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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 — low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are small. For 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

For premenopausal women with node-positive, ER-positive disease, I use tamoxifen and chemotherapy. While the standard of care is tamoxifen, you wouldn't be wrong to give goserelin followed by tamoxifen or anastrozole; however, I don't use goserelin because of the menopausal symptoms. Until we see the study data, I am not comfortable using an aromatase inhibitor with an LHRH agonist. I prefer using aromatase inhibitors in women who undergo a prophylactic oophorectomy. A German study is comparing goserelin plus anastrozole to goserelin plus tamoxifen. They have already presented data demonstrating that bisphosphonates can eliminate the risk of osteoporosis associated with aromatase inhibitors.

— Gershon Locker, MD

ABCSG-12: LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONIC ACID

This trial is basically attempting to establish the value of aromatase inhibitors for premenopausal patients with hormone receptor-positive breast cancer. The study will also look at the severity of treatment-induced bone loss and attempt to determine whether we can prevent or treat it.

The main difference between ABCSG-12 and the SOFT and TEXT trials is that cytostatic chemotherapy is only allowed in our trial as neoadjuvant therapy. This may be criticized, but we have previously established that at least some of these patients can be treated without chemotherapy and, clearly, this has an advantage in terms of avoiding toxicity. Eighty percent of patients on this trial have node-negative disease.

The bone substudy for ABCSG-12 closed 18 months ago and we now have results from 401 patients. We presented similar data two years ago that were criticized for being too early. These current data are far more mature and the results are beyond any doubt. Unlike the postmenopausal setting where we know that tamoxifen protects bone via estrogenic agonistic effects, in the premenopausal setting tamoxifen is not able to balance the impact of ovarian suppression. In this study, we observed 11 percent bone loss when goserelin plus tamoxifen was used. At least 40 percent more bone loss occurred with an aromatase inhibitor in the same situation.

The other important piece of data from this trial indicates that the bone loss from hormonal therapy can be prevented with the application of zoledronic acid twice a year. Absolutely no difference between baseline bone density and the 36-month measurements occurred in the two groups treated with the bisphosphonate.

— Michael Gnant, MD

Research To Practice: Adjuvant Endocrine Therapy

Extensive resources have been allocated to evaluate new breast cancer treatment interventions; however, 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 also by performing 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 are from a national telephone survey initiated in 2004 of 150 randomly selected United States-based medical oncologists.

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 with regard to 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 AND NODAL/HER2 STATUS

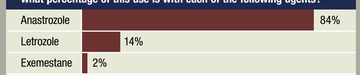
Which endocrine therapy would you most likely recommend to a 65-year-old woman with an ER-positive tumor?

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	—	—	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(1).

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;1(1).

SWITCHING ADJUVANT THERAPY AFTER TWO TO THREE YEARS OF TAMOXIFEN

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

	No side effects with tamoxifen	Complains of 20-pound 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;1(2).

SEQUENCING ADJUVANT THERAPY AFTER FIVE YEARS OF TAMOXIFEN

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

	Has just completed 5 years of tamoxifen	Completed 5 years of tamoxifen 1 year ago	Completed 5 years of tamoxifen 3 years ago
Continue tamoxifen	—	—	—
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;1(2).

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

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(2).

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AROMATASE INHIBITORS AS INITIAL ADJUVANT THERAPY IN POSTMENOPAUSAL WOMEN

What we are seeing in this survey is the trend to switch from tamoxifen to aromatase inhibitors as initial adjuvant therapy. Clearly, the transition has been quick because of the clear efficacy of the aromatase inhibitors. The current aromatase inhibitor trials in postmenopausal women demonstrate approximately a 25 to 50 percent relative reduction in the risk of recurrence with aromatase inhibitors compared to tamoxifen, which translates into a two to five percent absolute difference in overall events, including local and distant recurrences and new contralateral lesions. Efficacy drives oncologists' opinions and, in this survey, most are going with the more efficacious treatment; however, some physicians will still utilize tamoxifen.

I generally lean toward aromatase inhibitors, and I think patients are receptive to that decision. Many patients come in asking about them. Aromatase inhibitors already have a reputation, among both patients and physicians, as not only more effective but also less toxic. All of the studies comparing adjuvant aromatase inhibitors to tamoxifen are reporting compositely better tolerability with the aromatase inhibitors.

The side effects of vaginal discharge, vaginal bleeding, hot flashes and uterine cancer are more common with tamoxifen, whereas arthralgias and myalgias are more common with aromatase inhibitors. As women become older — late sixties, seventies and eighties — the risk of deep vein thrombosis and stroke while on tamoxifen becomes significant, and this is clearly not observed with aromatase inhibitors.

— Debu Tripathy, MD

With the majority of postmenopausal patients, I tend to use an aromatase inhibitor, generally anastrozole, in the adjuvant setting. If a contraindication or resistance to using an aromatase inhibitor exists, my second option is tamoxifen. I'm surprised that so many postmenopausal women are currently receiving an aromatase inhibitor as first-line adjuvant hormonal therapy. That is a huge shift from what we saw just a couple years ago.

— Robert W Carlson, MD

SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN

I discuss aromatase inhibitors with all truly menopausal patients I see in the adjuvant setting. Depending on the patient's situation, I will discuss starting with an aromatase inhibitor, switching to one at two to three years, or completing tamoxifen at four and a half years and then switching to letrozole. The conversation comes up for virtually all menopausal patients, and in most cases I urge them to consider switching.

— Clifford Hudis, MD

Some physicians believe that an ideal approach to adjuvant endocrine therapy is to start with tamoxifen and then switch to an aromatase inhibitor. The problem with that approach is, what are you going to tell the woman who was on tamoxifen in the first five years and relapsed because she wasn't on anastrozole in those first five years?

And what are you going to tell the woman who had a deep vein thrombosis or a stroke in those first five years, who wouldn't have had a deep vein thrombosis or a stroke had she been on anastrozole? Admittedly, the woman who doesn't have a fracture will be happy, but if she's going to receive anastrozole later on, she might have a fracture later on.

— Gershon Locker, MD

ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

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

— Joyce O'Shaughnessy, MD

Optimizing Adjuvant Chemotherapy: Ongoing Trials and Recent Results

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 is 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 dose-dense scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

PHASE III TRIAL OF ADJUVANT TAC VS FAC

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

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

KPS = Karnofsky performance status; T = docetaxel

Of the first 224 patients enrolled, those experiencing febrile neutropenia (≥Grade II fever with Grade IV 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.

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 toxicities	50.4%	20%	27%	26.5%

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

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

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)

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

PHASE III TRIAL OF ADJUVANT TAC VS 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/m^2) q3wk x 6
ARM 2	FAC (500/50/500 mg/m^2) q3wk x 6

KPS = Karnofsky performance status; T = docetaxel

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

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

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

SOURCES: Martin M et al. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 43.

www.bcirg.org/Internet/Studies/BCIRG+001.htm, January 2005.

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

THREE-YEAR RESULTS OF CALGB-9741

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

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

ONGOING PHASE III TRIALS OF ADJUVANT CHEMOTHERAPY

Protocol ID	Target accrual	Eligibility	Randomization
US Oncology 01-062	1,810	Node-positive or high-risk node-negative	AC x 4 → docetaxel x 4 AC x 4 → (docetaxel + capecitabine) x 4
SWOG-S0221	4,500	Node-positive or high-risk node-negative	[AC + PEG-G (d2)] q2wk x 6 → [paclitaxel + PEG-G (d2)] q2wk x 6 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → [paclitaxel + PEG-G (d2)] q2wk x 6 [AC + PEG-G (d2)] q2wk x 6 → paclitaxel qwk x 12 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → paclitaxel qwk x 12
NSABP-B-38	4,800	Node-positive	TAC q3wk x 6 AC q2wk x 4 → paclitaxel q2wk x 4 AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4
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 → [paclitaxel + G (d2-13)*] q3wk x 4 AC q3wk x 4 → [paclitaxel + 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

A = doxorubicin; C_{oral} = oral cyclophosphamide; C = cyclophosphamide; E = epirubicin; G = filgrastim; PEG-G = pegfilgrastim
* 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; US Oncology Protocol 01-062, June 2002.

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Vogel CL et al. **The role of growth factor support following neutropenic events in early stage breast cancer (BC) patients treated with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC): A sub-analysis of BCIRG 001.** *Proc ASCO* 2004;Abstract 677.

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 schedule.

This trial, which accrued more than 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. It has a solid basis.

— Larry Norton, MD

SWOG-S0221: DOSE-DENSE VERSUS CONTINUOUS CHEMOTHERAPY

In this study, AC is administered in either a dose-dense manner with pegfilgrastim or what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment.

Data suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of vasculogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

— G Thomas Budd, MD

USE OF ADJUVANT TAC

Taxanes clearly offer benefit in the adjuvant setting. 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

INTEGRATING DOSE DENSITY INTO CLINICAL TRIALS

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

— Clifford Hudis, MD

NSABP TRIAL B-38

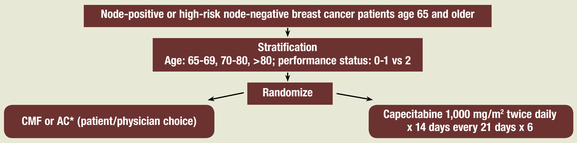
NSABP-B-38 will compare two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It's a good trial design because in addition to determining whether one of the two standard combinations is superior, it examines an agent new to the adjuvant setting — gemcitabine. At the 2004 ASCO meeting, Kathy Albain reported results from a trial in metastatic breast cancer 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

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 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 AGE 65 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.

Objectives
- Primary: Relapse-free survival
- Secondary:
  - Overall survival
  - Toxicities
  - Quality of life
  - Comorbidity and functional status
  - Adherence to capecitabine

Comparing capecitabine to IV therapy: key issues
- Oral agent
- Targets tumor tissue (potential therapeutic index gain)
- Known efficacy in metastatic setting
- Known toxicity: No cardiac damage
- Major drug interaction is with warfarin
- Potential better quality of life
- Less reliance on caregiver

SOURCES: NCI Physician Data Query, October 2004; Budman DR. *Breast Cancer Update Grand Rounds* 2004(8).

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

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

Type of cancer	Percent of US cancer cases occurring in patients age 65 and older	Percent of enrolled patients age 65 and older
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.

UNDERREPRESENTATION 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.

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.

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

One of the exciting trials we have ongoing in North America is CALGB-49907. This is a trial that essentially compares standard chemotherapy — four cycles of AC or CMF with oral cyclophosphamide — to six cycles of capecitabine for elderly patients. Physicians can select the standard chemotherapy for patients randomly assigned to that arm. We're excited about the trial and like to believe it's an equivalence study, as some background data suggest that oral capecitabine is as good as standard therapy. It would be nice if we had an oral regimen because I think people would rather be at home than in our clinics all the time.

What's nice about this trial is we have a quality-of-life endpoint, and we're collecting data from approximately the first 300 patients. We also are using a very clever computerized pill bottle for the patients receiving capecitabine. The bottle has a computer chip in the lid and every time the patient opens the bottle to take a dose, the computer chip registers it. We're also going to collect tumor blocks to see if we can predict how these older patients do with chemotherapy.

— Hyman B Muss, MD

EFFICACY OF CAPECITABINE IN THE ELDERLY

"A recent randomized phase II trial, comparing single-agent capecitabine and CMF as first-line therapy in patients with metastatic breast cancer who were 55 years and older (median age 69 years), demonstrated the response rate to capecitabine alone (25 percent) at a dose of 2510 mg/m² per day for 14 days, every three weeks was superior to intravenous CMF (16 percent). Grade 3 or 4 hand-foot syndrome was seen in 16 percent of patients on capecitabine and none on CMF, Grade 3 or 4 diarrhea in 8 percent with capecitabine and 3 percent with CMF, and Grade 3 or 4 hematological toxicity in 20 percent with capecitabine and 47 percent with CMF. In another Phase II randomized trial comparing capecitabine in the same dose and schedule as above with paclitaxel 175 mg/m² every three weeks, the response rate was 36 percent for 22 patients on capecitabine and 21 percent for 22 patients on paclitaxel. These data suggest that the efficacy of capecitabine in patients with metastatic disease is similar to CMF or paclitaxel."

— CALGB-49907 PROTOCOL

RATIONALE FOR CALGB-49907

Why would the CALGB want to conduct this trial? Capecitabine has the advantage of oral administration, and it targets tumor tissue. My major interest for the last 15 years has been clinical pharmacology and drug development, and this is an interesting drug because it's changing the way we think in oncology. We are trying to target tissue and diminish toxicity rather than just using an active drug. Capecitabine has known efficacy and doesn't cause cardiac damage, which is a major issue as patients get older.

— Daniel R Budman, MD

ACCRUAL AND IMPORTANCE OF CALGB-49907

Hyman Muss has made some changes to try to make the eligibility more streamlined and easier for physicians and patients to participate in the study. Unfortunately, we ran into toxicity problems in two patients in the capecitabine arm. These cases were evaluated by the data monitoring committee and one case was thought to be related to an enzyme deficiency. The other case was thought to be an unfortunate late toxicity in which the patient didn't contact the physician in a timely fashion.

New rules have been written into the trial to ensure toxicity problems do not occur again. We strongly believe that this trial will address a very good question: How does an oral agent compare to traditional intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

— Jeffrey Abrams, MD

Clinical Trials of Adjuvant Trastuzumab

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 CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Status	Target accrual	Eligibility	Randomization	Primary endpoint	Key issues
BCIRG-006	Closed*	3,150	N+ or high-risk N-HER2+ (FISH+)	AC x 4 → docetaxel 100 mg/m² q3wk x 4 AC x 4 → docetaxel 100 mg/m²‡§ q3wk x 4 + H qwk x 12 → H q3wk† remainder of one year Carboplatin + docetaxel 75 mg/m²‡ q3wk x 6 + H qwk x 12 → H q3wk† remainder of one year	Disease-free survival§	Nonanthracycline/ H combination H in combination with chemotherapy
NSABP-B-31	Open	2,700	N+ HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel q3wk‡ x 4 AC x 4 → paclitaxel q3wk‡ x 4 + H qwk x 52	CHF-rate Overall survival	Combined analysis with N9831 Every three-week or weekly taxane with concurrent H
NCCTG-N9831	Open	3,300	N+ or high-risk N-HER2+ (IHC 3+ or FISH+)	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 52 AC x 4 → paclitaxel qwk x 12 + H qwk x 52	Cardiac tolerability Disease-free survival	Combined analysis with B-31 Weekly taxane with concurrent or sequential H Effect of three-month delay between doxorubicin and H on cardiotoxicity
BIG-01-01, HERA	Closed	4,482	N+ or N- HER2+ (IHC 3+ or FISH+) Any chemo + XRT	H q3wk†‡ x 12 months H q3wk†‡ x 24 months Observation	Disease-free survival§	Duration of H Value of H versus no H following adjuvant chemo

N = node; H = trastuzumab (Herceptin®)

* Enrollment completed March 2004; interim analysis is planned for the first quarter of 2006.

† Every 3 weeks at 6 mg/kg

‡ Protocol amended to allow weekly or every three-week H

§ BCIRG-006 will evaluate pathologic and molecular markers predictive of efficacy, the value of cardiac biochemical and genetic markers for cardiac events, and the correlation between the shed HER2 extracellular domain and relapse. Cardiac monitoring is comparable to NSABP-B-31 and NCCTG-N9831. Two out of three planned interim cardiac safety analyses have been completed and passed the review of the Data Monitoring Committee without safety concerns.

‖ Three interim cardiac safety analyses identified no safety concerns.

SOURCES: NCI Physician Data Query, January 2005.

Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7.

ASSESSMENT OF TRASTUZUMAB-ASSOCIATED CARDIAC EVENTS: NSABP-B-31 TREATMENT AND MUGA SCHEDULE

	Cardiac events (CE)
	4.28%
	minus 0.78%
Cardiotoxicity uniquely attributable to trastuzumab (ARM 1 CE - ARM 2 CE)	= 3.5% CI, 1.6-5.3%

Protocol-defined acceptance of <4% congestive heart failure in anticipation of 25% reduction in death and reversible cardiac effects from trastuzumab; LVEF declines requiring cessation of trastuzumab were reversible in the vast majority of patients; therefore, trial accrual continued.

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

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STATUS OF THE ADJUVANT TRASTUZUMAB TRIALS

NSABP-B-31 has accrued nearly 2,000 patients, but it has been the slowest of the trials to accrue, in part because it had the every three-week paclitaxel regimen, which was somewhat of a barrier until we allowed the weekly regimens. Additionally, B-31 is a two-arm rather than a three-arm trial. In the other trials, patients had a two-out-of-three chance of receiving trastuzumab, whereas patients in our trial had a one-out-of-two chance. The HERA and BCIRG-006 studies have finished accruing patients, and the N9831 US Intergroup trial is within eight to 12 months of completing accrual. At our current rate, B-31 would require another two and a half years to complete accrual. We are optimistic about the possibility of combining N9831 and B-31 for a joint analysis, which will substantially accelerate the reporting time. We are close to having our first interim analysis of B-31; the analysis is based on deaths because survival was our primary endpoint.

— Charles E Geyer Jr, MD

CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB

I predict we will see a five to seven percent reduction in recurrence at five years and an impact on disease-free survival in the adjuvant trastuzumab trials. The adjuvant trials are limited to patients with node-positive or high-risk, node-negative disease because the expected benefit must outweigh the known three to five percent short-term risk of cardiotoxicity associated with trastuzumab.

The most common trial design is AC followed by a taxane with or without trastuzumab. BCIRG-006 includes a carboplatin in combination with docetaxel arm because of the synergy seen *in vitro* and the possibility that omitting the anthracycline may mitigate cardiotoxicity. These studies have approximately 3,000 to 5,000 patients and are designed to detect small variations in outcome — approximately a five percent difference in recurrence and possibly a two percent survival benefit.

The adjuvant trials are evaluating one year of trastuzumab therapy, except for the European HERA study that randomly assigns patients to observation versus one year or two years of trastuzumab. The natural history of breast cancer suggests that longer-term biological therapy is more beneficial, so I believe more than one year of trastuzumab will be necessary for optimal effect.

— Debu Tripathy, MD

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 carefully selected patient population. All patients must have FISH-positive disease; 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

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 percent was noted when patients had received six 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."

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

Trials of Hormonal Therapy in Metastatic Disease

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/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/PR-positive metastatic breast cancer	250 mg monthly	690
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole alone in postmenopausal women with ER/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/PR-positive recurrent or 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, January 2005.

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 (Open)

Eligibility	Postmenopausal women with ER/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
Hoffmann-La Roche Inc
Tel: 41-61-688-0638

SOURCE: NCI Physician Data Query, January 2005.

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

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

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

Study Contact:
Martine Piccart-Gebhart, MD, PhD
European Organisation for Research and Treatment of Cancer
Tel: 32-2-541-32

SOURCE: NCI Physician Data Query, January 2005.

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 with Stage IIIb or IV, ER/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
GlaxoSmithKline
Tel: 800-563-6537

SOURCE: NCI Physician Data Query, January 2005.

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

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

Eligibility	Postmenopausal women with Hormone receptor-positive breast cancer that has progressed on a nonsteroidal aromatase inhibitor
ARM 1	Fulvestrant
ARM 2	Exemestane

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

SOURCES: NCI Physician Data Query, January 2005.

http://hcp.cancerline.com

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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 initiate fulvestrant to determine whether the results of that strategy differ from the results of fulvestrant alone without estradiol suppression.

— John F R Robertson, MD

It remains unclear when 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 fulvestrant's 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 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

FULVESTRANT VERSUS AROMATASE INHIBITORS IN THE METASTATIC SETTING

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

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

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

— Gabriel N Hortobagyi, MD

Sequencing of Hormonal Therapies in Metastatic Disease

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/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

Median follow-up 15.1 months	Fulvestrant (n=428)	Anastrozole (n=423)	*p*-value
Complete response rate[1]	4.7%	2.6%	—
Partial response rate[1]	14.5%	13.9%	—
Objective response rate[1]	19.2%	16.5%	0.31
Clinical benefit rate*[1]	43.5%	40.9%	0.51
Estimated median time to progression[1]	5.5 months	4.1 months	0.48
Median follow-up 22.1 months	**(n=84)**	**(n=73)**	***p*-value**
Median duration of response in patients responding[1]	16.7 months	13.7 months	—
Median follow-up 27.0 months	**(n=428)**	**(n=423)**	***p*-value**
Death rate[2]	74.5%	76.1%	—
Median time to death[2]	27.4 months	27.7 months	0.81

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

SOURCES: [1] Robertson JF et al. *Cancer* 2003;98(2):229-38.

[2] Pippen J et al. Poster. San Antonio Breast Cancer Symposium, 2003;Abstract 426.

RETROSPECTIVE ANALYSIS OF THE PROPORTION OF PATIENTS RESPONDING FOR 1, 1.5 AND 2 OR MORE YEARS IN TWO PHASE III STUDIES OF FULVESTRANT VERSUS ANASTROZOLE

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

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

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

SOURCE: Jones SE et al. *Breast Cancer Res Treat* 2004;Abstract 6047.

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

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

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

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

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

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

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

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

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

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

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

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

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SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

I generally use an aromatase inhibitor in a postmenopausal patient progressing after completion of tamoxifen, but I also present the option of fulvestrant. I think both are reasonable and legitimate options that are equivalent; however, I think most patients prefer oral therapy and it is less expensive. Some patients prefer an intramuscular injection once a month. Some patients may not be compliant with oral medication. For them, fulvestrant is a good option.

— Debu Tripathy, MD

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

— Adam M Brufsky, MD, PhD

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

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

— Gershon Locker, MD

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 data from 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 clearly can 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

Patient Perspectives on Endocrine Therapy for 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 prefer oral therapy. In a recent telephone survey of 256 women with metastatic breast cancer, a majority stated that they preferred oral endocrine therapy, assuming equal efficacy and side effects; however, about a third of the patients preferred parenteral administration. Patients cited a variety of reasons for this preference, including concerns about compliance, 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 one third of their patients with metastatic disease on bisphosphonates would prefer parenteral administration of endocrine therapy. This suggests that these 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
Dislike of oral medications	34
Concerns about compliance	35
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 OF 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 Inactive	 72% 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 OF 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	1st-line	2nd-line	3rd-line	4th-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* Study, 2004;1(2).

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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PATIENT PREFERENCES FOR ORAL VERSUS INTRAVENOUS THERAPIES

I generally use an aromatase inhibitor in a postmenopausal patient progressing after completion of tamoxifen, but I also present the option of fulvestrant. I think both are reasonable and legitimate options that are equivalent.

As physicians, I think our viewpoint is different than that of patients. To us, an oral treatment appears to be more convenient because the patient does not have to come in to the office and it is less expensive; however, some patients prefer an intramuscular injection once a month. Some patients may not be compliant with oral medication. For them, fulvestrant is a good option.

Many reasons were cited by women who prefer to receive an injection. One is that they like the interaction with the nurses and feel more cared for coming in and seeing not only the staff but also other patients.

Another reason is the perception that an intravenous or intramuscular drug is more effective. I see many patients from Asia and Latin America who really believe that injectable drugs are better. That may also be true in the United States.

— Debu Tripathy, MD

I use an aromatase inhibitor rather than fulvestrant in patients with ER-positive metastatic disease. I have more experience with the aromatase inhibitors and my perception is that patients prefer pills versus two injections, which is how we administer fulvestrant.

It's possible that as many as 50 percent of patients would prefer injections because, psychologically, they prefer to "be a breast cancer patient" once a month as opposed to every day.

— Gershon Locker, MD

Many doctors, certainly in the United Kingdom, believe that patients don't like needles, but we weren't convinced about this. I've just completed a study on patient preferences for oral versus injectable therapies. We interviewed 200 women with advanced disease about their preferences and found that about 25 percent of our sample said they'd prefer an injection, assuming efficacy was equivalent.

The primary reasons for people preferring injections or pills were all related to convenience, but second on the list were issues related to adherence and the belief that injections actually were more powerful medicine than pills. In places like Germany and parts of France and Italy, a strong correlation exists between perceived efficacy and route of administration — pills aren't seen as accounting to much at all, while an injection is seen as a very powerful thing.

We need to recognize that we live in a world of choice and options, and we need to ask individual patients about their treatment preferences rather than make assumptions based on a mix of data, a few patients we've seen in the past or our own personal preferences.

— Lesley Fallowfield, PhD

In general, I believe most people prefer taking a pill to receiving an intramuscular injection. I would guess that 60 percent of patients would prefer a pill and 40 percent an injection.

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

Most physicians probably 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 J Robert, MD

Chemotherapy for Metastatic Disease

Clinical trials of chemotherapeutic agents and regimens in the metastatic setting 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. 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[1]: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193[2]: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	**Docetaxel**	**Capecitabine/docetaxel**	**Doxorubicin**	**Paclitaxel**	**Doxorubicin/paclitaxel**
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months	18.9 months	22.2 months	22.0 months

SOURCES: [1] O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23.

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

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

Accrual: 529 (Closed)

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

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

TTP = time to progression

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

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

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

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

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

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

ACTIVE PHASE III TRIALS OF COMBINATION CHEMOTHERAPY REGIMENS IN METASTATIC BREAST CANCER

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

SOURCE: NCI Physician Data Query, January 2005.

PHASE II TRIAL OF CAPECITABINE AND WEEKLY PACLITAXEL IN TAXANE-NAÏVE PATIENTS WITH METASTATIC BREAST CANCER: EFFICACY AND TOXICITY

Response*	Percent
Complete response	0
Partial response	50
Stable disease	30
Clinical benefit	65

* N = 54 evaluable patients

Grade III/IV adverse events (>5%)	No. of patients Grade III/IV	Percent Grade III/IV
Hand-foot syndrome	10/0	18.2
Neutropenia	3/4	12.7
Nausea	3/0	5.5
Leukopenia	1/2	5.5
Diarrhea	3/0	5.5

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

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

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

— Joanne L Blum, MD, PhD

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):2321-7.*

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 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/m^2 resulted in a significant improvement in overall survival, time to disease progression, and response rate compared with docetaxel 100 mg/m^2 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.*

Research To Practice: Chemotherapy in Metastatic Disease

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 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 vary. 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.

CHEMOTHERAPY FOR ASYMPTOMATIC PATIENTS WITH METASTASES: PRIOR AC → DOCETAXEL

The patient is a woman treated two years ago with adjuvant AC → docetaxel for an ER-negative, HER2-negative tumor who now has rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient and your second-line treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	6%	3%	6%	4%	2%	2%
Docetaxel	8%	6%	7%	6%	4%	6%
Paclitaxel	13%	6%	16%	5%	14%	4%
Carboplatin + taxane	13%	4%	10%	4%	2%	1%
Capecitabine	24%	22%	26%	24%	35%	25%
Gemcitabine	18%	18%	17%	21%	16%	24%
Vinorelbine	6%	25%	7%	20%	8%	23%
Carboplatin	—	1%	—	1%	—	1%
AC	2%	3%	1%	4%	—	—
AC + paclitaxel	1%	—	1%	—	—	—
Doxorubicin	—	1%	—	1%	—	—
Other chemotherapy	3%	7%	4%	6%	3%	2%
No chemotherapy	6%	4%	5%	4%	16%	12%

CHEMOTHERAPY FOR SYMPTOMATIC PATIENTS WITH METASTASES: PRIOR AC → DOCETAXEL

Same patient but with bone and lung metastases and is very symptomatic.

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	11%	10%	11%	10%	6%	3%
Docetaxel	1%	2%	1%	2%	6%	4%
Paclitaxel	9%	1%	10%	1%	23%	2%
Carboplatin + taxane	33%	2%	32%	2%	9%	—
Capecitabine	4%	23%	5%	25%	20%	37%
Gemcitabine	9%	28%	9%	28%	16%	24%
Vinorelbine	2%	21%	3%	21%	7%	25%
AC	3%	1%	2%	1%	1%	—
AC + docetaxel	3%	—	3%	—	—	—
AC + paclitaxel	3%	—	3%	—	—	—
Cyclophosphamide	1%	—	1%	—	—	—
Other chemotherapy	21%	12%	20%	10%	12%	4%
No chemotherapy	—	—	—	—	—	1%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

TREATMENT OF CHEMOTHERAPY-NAÏVE PATIENTS WITH RECEPTOR-NEGATIVE DISEASE

The patient is a 57-year-old woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with metastases. What are your first- and second-line treatment recommendations in the following clinical scenarios?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	4%	4%	14%	5%
Docetaxel	16%	17%	7%	15%
Paclitaxel	18%	8%	3%	10%
Platinum + taxane	4%	5%	17%	8%
Capecitabine	14%	19%	—	11%
Gemcitabine	—	18%	—	15%
Vinorelbine	—	16%	—	10%
AC	15%	5%	22%	9%
AC + docetaxel	13%	—	27%	1%
Other chemotherapy	10%	5%	10%	16%
No chemotherapy	6%	3%	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(2).

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

The patient is a 57-year-old woman who previously received adjuvant AC → paclitaxel who has an ER-negative, HER2-negative tumor with metastases. What are your first- and second-line treatment recommendations in the following clinical scenarios?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	9%	2%	41%	7%
Docetaxel	29%	14%	10%	5%
Paclitaxel	8%	4%	1%	1%
Platinum + taxane	6%	3%	24%	4%
Capecitabine	20%	19%	1%	17%
Gemcitabine	9%	26%	6%	31%
Vinorelbine	7%	18%	—	21%
AC	—	2%	1%	1%
AC + docetaxel	3%	—	4%	—
Other chemotherapy	2%	8%	12%	13%
No chemotherapy	7%	4%	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(2).

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CAPECITABINE/PACLITAXEL TRIAL IN METASTATIC DISEASE

We are currently investigating capecitabine, 1,650 mg/m^2 total daily dose, for 14 days with paclitaxel 80 mg/m^2, days one and eight of a three-week cycle in patients with metastatic breast cancer. The regimen has been extremely well tolerated and the side effects we have seen have been those we expected from paclitaxel — some alopecia, fluid retention, Grade I neuropathy, skin and nail changes — but capecitabine doesn't seem to add much to the toxicity and the clinical benefit is extraordinary. We have had some patients on this trial for one to two years.

In the taxane-naïve subset, we found this regimen to be exceedingly effective and well tolerated. It's been more difficult to accrue patients who have taken a taxane, so we don't have that data yet. However, this is an ideal trial for patients who have received docetaxel in the past and progressed.

We have seen long, durable responses with capecitabine/paclitaxel, and it is more tolerable than capecitabine/docetaxel. Capecitabine has also been combined with vinorelbine, which is also a very well-tolerated regimen.

— Joanne L Blum, MD, PhD

SELECTION OF CHEMOTHERAPY IN THE METASTATIC SETTING

I think I am consistent with the responses to the survey in that I am remarkably inconsistent and do not follow a single regimen. Little evidence exists to suggest that any one chemotherapy regimen provides a meaningful advantage in terms of response rates, duration of response, survival and so on, relative to other combinations or single agents.

I tend to discuss what she expects from her treatment, how much toxicity she is willing to tolerate and when she would be willing to do so; however, in an asymptomatic woman I try to minimize toxicity. Why should I make a woman sick when she feels well?

In the asymptomatic patient with chemotherapy-naïve disease, I often start with an agent such as capecitabine regardless of her age; however, I can't be critical of the choices that have been made. My second-line therapy tends to be a taxane.

— Robert W Carlson, MD

There are several combinations for which good data exists, including capecitabine/docetaxel and paclitaxel/gemcitabine. The doxorubicin/docetaxel combination improved response rate but didn't improve overall survival. Since George Sledge's ECOG trial 1193, demonstrated sequential therapy was as good as combination treatment in terms of overall survival, I tend to use sequential single agents for the vast majority of my patients.

In a patient who is chemo-naïve and needs a rapid response, I would consider an anthracycline-based combination regimen. It would probably be doxorubicin/docetaxel, but it could also be doxorubicin/paclitaxel. If a patient had dose-dense AC/paclitaxel in the adjuvant setting, I'd be very interested in incorporating a gemcitabine-based combination or a capecitabine-based combination. I use a lot of capecitabine. I think it's a great drug. It's generally well-tolerated when given at non-package-insert doses.

For the patient who's had adjuvant AC → T, I frequently use capecitabine or vinorelbine as first-line therapy. For someone who's chemo-naïve, my first choice would probably be weekly paclitaxel followed by either vinorelbine or capecitabine.

I seldom use early-line doxorubicin up front in my asymptomatic patients, because I think it causes a lot of fatigue and alopecia. Weekly paclitaxel also results in alopecia, but I prefer to use weekly paclitaxel more than doxorubicin in the metastatic setting.

— Maura N Dickler, MD

Targeting the HER Pathways

The human epidermal growth factor receptor (HER) family has four members: HER1, HER2, HER3 and HER4. These four receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target the different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

ECOG-1100: INTERIM EFFICACY DATA FROM PHASE I/II STUDY OF TRASTUZUMAB AND GEFITINIB IN PATIENTS WITH HER2-OVEREXPRESSING METASTATIC BREAST CANCER

Parameter	Prior chemotherapy (n=8)	No prior chemotherapy (n=28)
Complete response	0	1
Partial response	0	1
Stable disease (24 weeks)	0	7
Progressive disease	8*	11
Time to progression	2.5 months 95% CI, 1.9-2.8 months	2.9 months 95% CI, 2.3-5.9 months

* All patients progressed within 12 weeks.

Conclusion: "At a planned interim analysis, the PFS did not meet predetermined statistical endpoints required for study continuation. Moreover, the observed TTP appears shorter than that previously reported for trastuzumab alone, suggesting the possibility of an antagonistic interaction between trastuzumab and gefitinib. Preliminary correlative studies using HER2-overexpressing br ca cell lines and eTag fluorescent antibody-based assays suggest that treatment with both trastuzumab and gefitinib but not each alone induce phosphorylation of HER3 (erbB3). Whether this is a plausible mechanism of escape that can explain the poor efficacy of the combination is under active investigation. These results do not support the further use of this combination and have implications for other trials using trastuzumab and EGFR TK inhibitors simultaneously." [Citations omitted]

SOURCE: Arteaga CL et al. **ECOG1100: A phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib ('Iressa') in patients (pts) with HER2-overexpressing metastatic breast cancer (met br ca).** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 25.

COMPLETE DISAPPEARANCE OF ER+/HER2+ BREAST CANCER XENOGRAFTS WITH THE COMBINATION OF GEFITINIB, TRASTUZUMAB AND PERTUZUMAB

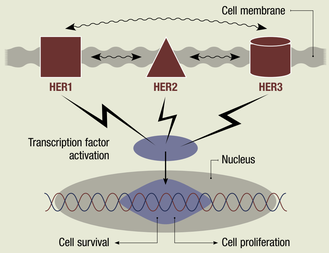
Blockade of HER family signaling	
Agent	**Dimer pair**
Gefitinib	HER1/HER2 HER1/HER3
Trastuzumab	HER2/HER2
Pertuzumab	HER1/HER2 HER2/HER3

Effect of HER family inhibitor on tamoxifen-stimulated growth	
Agents	**Complete response**
Tamoxifen + pertuzumab	5/18
Tamoxifen + pertuzumab + trastuzumab	12/18
Tamoxifen + pertuzumab + trastuzumab + gefitinib	18/20

Conclusion: "Growth factor receptor inhibitors cooperate through distinct, yet complementary, mechanisms to convey a potent HER2 signaling blockade. Combination treatment blocks crosstalk with ER to restore Tam antagonist effect on ER, and together with Tam eradicate MCF7/HER218 tumors. Because growth of these tumors seems to depend mainly on ER and EGFR/HER2 pathways, complete targeted disruption of these pathways can achieve remarkable antitumor activity deserving a clinical trial."

SOURCE: Arpino G et al. **Complete disappearance of ER+/HER2+ breast cancer xenografts with the combination of gefitinib, trastuzumab, and pertuzumab to block HER2 cross-talk with ER and restore tamoxifen inhibition.** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 23.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (HER) SIGNALING



The HER signal transduction pathways are complex. The HER1, HER2 and HER3 receptors are all members of the HER family. HER1 is also known as the epidermal growth factor receptor. The various components of the HER pathways interact with each other. It is these interactions, or "crosstalk," that may provide multiple approaches for interfering with these signals and inhibiting cancer.

ADDITIONAL TRIALS OF COMBINED BLOCKADE OF THE HER RECEPTOR NETWORK REPORTED AT SABCS 2004

Author/abstract no.	Phase of trial	N	Eligibility	Agent(s)
Blackwell KL/302[1]	NR	58	Trastuzumab-refractory metastatic breast cancer	Lapatinib
Burris III HA/3043[2]	I	26	Advanced or metastatic breast cancer	Lapatinib + trastuzumab
Pegram MD/3039[3]	I	9	Recurrent or metastatic breast cancer	Bevacizumab + trastuzumab

SOURCES: [1] Blackwell KL et al. **Determining molecular phenotypes of metastatic breast cancer that respond to the small molecule inhibitor of ErbB1 and ErbB2, lapatinib (GW572016).** *Proc SABCS* 2004;Abstract 302.

[2] Burris III HA et al. **A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib (GW572016) in combination with trastuzumab.** *Proc SABCS* 2004;Abstract 3043.

[3] Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** *Proc SABCS* 2004;Abstract 3039.

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Arteaga CL et al. **ECOG1100: A phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib ('Iressa') in patients (pts) with HER2-overexpressing metastatic breast cancer (met br ca).** *Proc SABCS* 2004;Abstract 25.

Badache A, Hynes NE. **A new therapeutic antibody masks ErbB2 to its partners.** *Cancer Cell* 2004;5(4):299-301.

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Burris III HA et al. **A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib (GW572016) in combination with trastuzumab.** *Proc SABCS* 2004;Abstract 3043.

Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab**. *Proc SABCS* 2003; Abstract 24.

Nahta R et al. **The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells.** *Cancer Res* 2004; 64(7):2343-6.

Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** *Proc SABCS* 2004;Abstract 3039.

Spector N et al. **The ErbB2 pathway in breast cancer: Best approaches for maximum efficacy.** *Proc SABCS* 2004;Abstract MS3-4.

Yarden Y et al. **Molecular approach to breast cancer treatment.** *Semin Oncol* 2004;31(5 Suppl 10):6-13.

OVERVIEW OF HER2 BIOLOGY

The human epidermal growth factor receptor (HER) family includes four members — HER1, HER2, HER3 and HER4. These receptors interact with and provide signals to cells concerning their biologic behavior. Unlike HER2, the other receptors have ligands that bind to them directly. The most probable explanation for HER2's lack of direct ligand binding is that HER2 is the "driver" of signaling for all members of the HER family. For example, ligands bind to HER1, but rely on HER2 to transmit and amplify their signal. The HER family is analogous to a stereo system with a compact disc, tape and DVD player — each playing different types of media. The CDs, tapes and DVDs are like ligands. The cell can "listen" to several types of ligands, but central to the function of the stereo system is the amplifier. HER2 is equivalent to the amplifier. When the HER2 receptor is overexpressed, the "volume" is turned all the way up on the stereo. This causes breast cancer cells to proliferate rapidly.

— Mark D Pegram, MD

ECOG-1100: INTERIM ANALYSIS

The interim analysis of ECOG-1100 suggests no benefit from combining trastuzumab with gefitinib. In addition, the time to progression in patients treated with the combination was shorter than reported with trastuzumab alone, although not a straight comparison. These data highlight the fact that robust preclinical data do not always predict clinical trial results. I know this combination is being used *ad hoc* in the community, and that needs to be re-examined. This analysis has prompted some questions in the ECOG Breast Core Committee. For example, could we have anticipated these results, avoiding the need for a two-year Phase II study? I speculate that if we had done this in a presurgical setting, like Dr Chang's neoadjuvant trial with single-agent trastuzumab, we might have concluded that this longer study would not be worthwhile.

In an effort to identify the rational partners of trastuzumab, how do we make certain these combinations are at least equivalent or better than trastuzumab alone? At ECOG, partly because of the ECOG-1100 data, we are contemplating a clinical trial plan to identify trastuzumab partners that would not interfere with the overwhelming choice in the community for patients with HER2-positive, metastatic breast cancer, which is basically trastuzumab and chemotherapy. The choice of a partner would be driven by basic science and safety, using time to progression as an endpoint. We have explored the possibility of using bevacizumab as our next partner with trastuzumab.

— Carlos Arteaga, MD

PAN-HER2 INHIBITION

Work by Kent Osborne's group with mouse xenografts indicates that you may need a complete blockade of the HER2 pathway in order to elicit cure. In the mouse xenografts, which are MCF-7 transfected with HER2, Osborne's group found that when they utilized a pan-HER2 blockade of trastuzumab, gefitinib and pertuzumab, tumors actually regressed completely and never came back when the combination was stopped. This is extremely exciting and I think that we're moving into an era where, unless you can block the HER family completely, you are going to provide the cell an escape mechanism.

— Jenny C Chang, MD

PRECLINICAL DATA SUPPORTING SYNERGY OF HER2-TARGETED ANTIBODIES

"Trastuzumab (herceptin) and pertuzumab (Omnitarg, 2C4) are recombinant humanized monoclonal antibodies that target different extracellular regions of the HER-2 tyrosine kinase receptor. …

"Combination drug treatment reduced levels of total and phosphorylated HER-2 protein and blocked receptor signaling through Akt but did not affect mitogen-activated protein kinase. These results suggest that combining HER-2-targeting agents may be a more effective therapeutic strategy in breast cancer rather than treating with a single HER-2 monoclonal antibody."

— Nahta R et al. Cancer Res *2004;64(7):2343-6.*

Research To Practice: HER2-Positive Disease

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%	—
HER2-positive only with FISH confirmation	22%	96%	48%
HER2-negative	—	—	52%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(1).

TREATMENT FOR *DE NOVO* ER-NEGATIVE, HER2-POSITIVE METASTATIC DISEASE

How would you generally treat a woman presenting de novo with ER-negative, HER2-positive metastatic disease?

Regimen	Asymptomatic bone mets	Asymptomatic liver mets	Moderate pain/ bone mets	Very symptomatic visceral mets
Trastuzumab only	21%	2%	—	—
Trastuzumab + chemotherapy	67%	90%	94%	94%
Chemotherapy alone	12%	8%	6%	6%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(1).

TRASTUZUMAB AND CHEMOTHERAPY USE FOR HER2-POSITIVE METASTATIC DISEASE AFTER ADJUVANT AC

The patient is a 57-year-old woman treated two years ago with adjuvant AC for an ER-negative, HER2-positive tumor. What is your first-line treatment for this patient and your second-line treatment if she had objective progression over several months but was clinically the same?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Chemotherapy alone	10%	14%	4%	12%
Trastuzumab alone	17%	2%	3%	1%
Trastuzumab + chemotherapy	69%	81%	93%	87%
Capecitabine + docetaxel	1%	3%	6%	5%
Docetaxel	16%	10%	14%	3%
Paclitaxel	22%	9%	15%	4%
Carboplatin + taxane	19%	5%	51%	1%
Capecitabine	4%	7%	—	6%
Gemcitabine	—	13%	—	16%
Vinorelbine	6%	29%	3%	46%
Carboplatin	—	1%	1%	1%
Other chemotherapy	1%	4%	3%	5%
No therapy	4%	3%	—	—

CONTINUATION OF TRASTUZUMAB AFTER PROGRESSION

For this patient, if you would use first-line trastuzumab (with or without chemotherapy), would you continue it upon disease progression?

	Rising tumor markers, asymptomatic bone metastases	Symptomatic bone and lung metastases
Percent continuing trastuzumab upon disease progression	95%	92%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

CLINICAL USE OF ADJUVANT TRASTUZUMAB

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

	Age 55	Age 75
Trastuzumab off protocol	5%	5%
Trastuzumab clinical trial	76%	51%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

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Robert NJ 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.** *Proc ASCO* 2004;Abstract 573.

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.

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HER2-TESTING ALGORITHM

We routinely order IHC on pathology specimens. For patients with metastatic breast cancer, if the IHC is 3+ I do not generally follow up with FISH, provided the tumor stains 3+ in 75 to 100 percent of cells.

I sometimes order FISH in IHC 0 cases — not in the adjuvant setting when I'm trying to decide between tamoxifen and an aromatase inhibitor, but in metastatic disease, I test everybody. I believe every patient with metastatic disease needs one FISH assay in her lifetime. These are not perfect tests by any means, and it is worthwhile to make sure you are comfortable with the results.

— Joyce O'Shaughnessy, MD

I try to find any excuse to order a FISH. If the IHC assay is 3+, I don't, but if it is 2+, I order FISH. A minuscule number of tumors are 1+ and FISH-positive but sometimes, for a young patient who has aggressive disease and not many alternatives, I order FISH if the IHC is slightly positive. I will not do that for IHC 0 tumors.

— Gershon Locker, MD

TREATMENT ALGORITHMS FOR PATIENTS WITH HER2-POSITIVE METASTATIC DISEASE

I generally use trastuzumab alone for asymptomatic patients with HER2-positive disease. If you recommend chemotherapy to an asymptomatic patient, that patient may become symptomatic.

For a highly symptomatic patient who received adjuvant AC, I would recommend a taxane plus trastuzumab. I don't think it matters which taxane. I would either use docetaxel every three weeks or weekly paclitaxel, and I would not argue that either is right or wrong.

— Clifford Hudis, MD

I use a combination with weekly paclitaxel as my preferred partner for trastuzumab. Docetaxel is a reasonable option. In a symptomatic patient I would probably use a platinum/taxane combination. I do not often use combination chemotherapy because most of my patients are not that symptomatic, but for the ones who are, I use a platinum/taxane combination.

Second line, I tend to prefer trastuzumab, but I admit we do not know what the independent contribution of trastuzumab is in that situation. All of the retrospective data does not tell us whether chemotherapy alone would have had the same types of responses that are seen in that setting.

Theoretically, I think trastuzumab still retains the possibility of synergy with other chemotherapy drugs and, therefore, I think a biological rationale exists for continuing it. Also, patients who have not developed toxicities with trastuzumab for some time have a very low risk of additional complications, such as cardiomyopathy, over time. For those reasons, I think it is reasonable to continue trastuzumab. The downside is the cost. It depletes resources, and that is a big issue, especially in fixed-cost medical systems.

— Debu Tripathy, MD

NONPROTOCOL USE OF ADJUVANT TRASTUZUMAB

I find it somewhat surprising but very reassuring that physicians are not prescribing adjuvant trastuzumab off protocol without high-level evidence that the benefits exceed the long-term toxicities — especially with regard to cardiac toxicity.

This might be a result of the "Bezwoda effect" and physicians' experiences with high-dose chemotherapy. Years ago, many community physicians took information that was a little bit disconnected, put it together and concluded that high-dose therapy was superior to standard full-dose therapy. When they eventually were burned by fraudulent trial results, I think many of them paused and thought, "How many women died because of my recommendation, albeit well intentioned, about how to treat their breast cancer?"

— Robert W Carlson, MD

Partial Breast Irradiation for Primary Breast Cancer

The delivery of larger doses of radiation therapy (RT) to the lumpectomy cavity and a margin of surrounding tissue after breast-conserving surgery, via brachytherapy or external beam radiation techniques, may provide several advantages to appropriately selected patients. Partial breast irradiation (PBI) may improve the documented underutilization of breast-conserving surgery by allowing RT to be completed in four or five days, instead of six to seven weeks, eliminate the acute and chronic toxicities associated with whole breast irradiation (WBI), improve cosmesis and confer societal economic benefits. Before PBI can be routinely incorporated into clinical practice, several issues must be addressed, including appropriate patient selection, optimal fractionation schedules and PBI techniques. Importantly, it must be established that long-term rates of locoregional control are similar to those achieved with WBI. A matched-pair analysis has demonstrated comparable outcomes for women treated with limited-field radiation or WBI. Several Phase III clinical trials evaluating these issues are ongoing worldwide.

PUBLISHED PBI RESULTS: BRACHYTHERAPY

Institution	N	Follow-up (months)	Local recurrence (%)
WBH – LDR patients	120	82	0.9
WBH – all patients	199	65	1.2
WBH – HDR patients	59	52	2.1
Ochsner Clinic	51	75	2.0
NIO – Hungary	45	60	4.4
University of Kansas	24	37	0
Tufts – New England Medical Center	32	33	3
NIO – Hungary Phase III	181	30	1.1
Florence, Italy	90	27	4.4
MGH	48	23	0

WBH = William Beaumont Hospital; LDR = low dose-rate brachytherapy; NIO = National Institute of Oncology; HDR = high dose-rate brachytherapy; MGH = Massachusetts General Hospital

SOURCE: Vicini F. **Partial breast irradiation: Current status.** Presentation. San Antonio Breast Cancer Symposium, 2003.

RANDOMIZED PHASE III STUDY OF CONVENTIONAL WHOLE BREAST RADIATION THERAPY VERSUS PBI FOR WOMEN WITH STAGE 0, I OR II BREAST CANCER

Protocol ID: Pending NSABP Protocol B-39
Projected Accrual: 3,000

Eligibility	**Stages 0-II breast cancer, ≤3-cm tumor size, <4 positive axillary lymph nodes and clear surgical margins**
ARM 1	**Whole breast radiation therapy**
ARM 2	**PBI* prior to adjuvant chemotherapy**

* Interstitial brachytherapy or MammoSite® balloon catheter or 3D conformal external beam irradiation. The PBI technique utilized will be at the physician's discretion and will be based on technical considerations, radiation oncology facility technique credentialing and patient preference.

SOURCE: NSABP Protocol Summaries, November 2004.

ACTIVE PARTIAL BREAST IRRADIATION TRIALS

Trial	Schema	Projected accrual
MammoSite® Registry Trial[1]	MammoSite® primary treatment MammoSite® boost treatment	1,300
National Institute of Oncology (Budapest, Hungary)[2]	External beam whole breast radiation therapy PBI (brachytherapy or external beam radiation therapy)	570
European Institute of Oncology (Milan, Italy)[2]	External beam whole breast radiation therapy PBI (intraoperative)	824
University College of London (London, England)[2]	External beam whole breast radiation therapy PBI (intraoperative)	1,666

SOURCES: [1] American Society of Breast Surgeons Patient Registry Protocol, December 2003.
[2] Vicini F. **Partial breast irradiation: Current status.** Presentation. San Antonio Breast Cancer Symposium, 2003.

FIVE-YEAR ACTUARIAL TREATMENT OUTCOMES FROM MATCHED-PAIR ANALYSIS OF PATIENTS TREATED WITH WHOLE BREAST VERSUS LIMITED-FIELD RADIATION THERAPY

Outcome	Whole breast % (95% CI)	Limited-field % (95% CI)	*p*-value
Ipsilateral recurrence	1 (0-2.4)	1 (0-2.8)	0.65
Regional failure*	1 (0-1.5)	1 (0.1-2.1)	0.54
Distant metastasis	5 (2.2-8.4)	3 (0.5-5.9)	0.17
Disease-free survival	91 (86.5-94.7)	87 (81.5-92.1)	0.30
Overall survival	93 (89.7-96.7)	87 (82.1-92.7)	0.23
Cause-specific survival	97 (95.0-99.8)	97 (93.8-99.9)	0.34
Contralateral breast failure	4 (1.0-6.4)	1 (0-2.4)	0.03

* Regional failure is defined as the recurrence of cancer in a regional nodal site before or simultaneously with the diagnosis of local recurrence or distant metastasis.

SOURCE: Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-11.

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Vicini F. **Partial breast irradiation: Current status.** *Breast Cancer Res Treat* 2003;Abstract MS2-1.

PARTIAL BREAST IRRADIATION

One of the advantages of PBI is that it can be completed quickly before systemic therapy is initiated. William Beaumont is one of the few institutions that offers interstitial brachytherapy, MammoSite® and conformal external beam radiation therapy.

Each technique has its advantages and none of them is applicable to all clinical scenarios. Treatment must be individualized based on factors such as the patient's access to a radiation facility and the location of the lesion within the breast.

At our institution, of the patients who receive PBI, approximately 60 percent are treated with the MammoSite®, 30 percent with conformal external beam radiation therapy and a small percentage with interstitial brachytherapy. Reducing the amount of time required and the amount of toxicity associated with radiation therapy may increase the rate of breast conservation. I believe an additional 10 to 20 percent of women making this decision would select breast-conserving therapy if PBI were an option.

— Frank A Vicini, MD

Intraoperative radiation therapy is an idea whose time has arrived. The procedure is gaining acceptance, and many competing technologies exist. I believe three-dimensional conformal, multicollimator, high-tech radiation therapy is absurd. No matter how carefully you plan your fields, you are not hitting the target.

A number of studies using MRI have demonstrated how off target this approach is. Even if the surgeon puts clips around the cavity during surgery, the cavity collapses and the clips migrate; therefore, no matter how expensive and high tech, I don't think this approach will work.

I'm interested in conforming the tissue to the source rather than the other way around. The approach I developed with Carl Zeiss is called Intrabeam. It is an elegant, simple device that a surgeon can utilize after wide local excision. In approximately 25 minutes, you can give a boost to the tumor bed and a centimeter beyond in all directions.

— Michael Baum, MD, ChM

NSABP PBI TRIAL

We are developing a trial to compare partial breast radiation therapy versus whole breast radiation therapy. The eligibility criteria will be broad and will include totally resected DCIS and invasive breast tumors up to three centimeters in size. We want to conduct this study now because there may only be a small window of opportunity before partial breast radiation therapy is widely adopted.

In this study, PBI can be administered by brachytherapy catheters, the MammoSite® device or conformal external beam radiation therapy. The physician and the hospital will determine which method to utilize, and it needs to be declared before randomization, although it can be changed if a patient is not eligible for a certain procedure.

All three options are done in 10 fractions over five days, as opposed to the five or six weeks it takes to administer whole breast radiation therapy, with or without a boost.

PBI may offer subtle advantages. Data suggest if we delay radiation therapy we may increase local recurrence; however, when we delay systemic therapy we increase systemic recurrence, so we choose to use systemic therapy first. PBI takes only five days and is then followed by adjuvant chemotherapy. By moving radiation therapy earlier into the treatment schedule, we may decrease local recurrences.

— Eleftherios P Mamounas, MD, MPH

Management of the Axilla

A series of classic randomized trials, including NSABP-B-04, formed the basis for level I and II axillary-node dissection becoming a standard of care for women with invasive breast cancer. The emergence of sentinel lymph node biopsy (SLNB) as an initial staging procedure led to a new generation of trials evaluating the need for axillary dissection in women with pathologically negative or positive nodes. Recently reported results from NSABP-B-32 and the ALMANAC trial support the use of SLNB for women with clinically node-negative disease. Preliminary data indicate that SLNB has a nine to 10 percent false-negative rate. SLNB can also significantly reduce postoperative arm morbidity.

PHASE III PROGNOSTIC STUDY OF SENTINEL NODE AND BONE MARROW MICROMETASTASES IN WOMEN WITH STAGE I OR IIA BREAST CANCER

Protocol IDs: ACOSOG-Z0010, GUMC-00152
Accrual: 5,300 (Closed)

Eligibility	Stage I or IIA breast carcinoma within 60 days of planned sentinel lymph node biopsy
Protocol	Bilateral anterior iliac crest bone marrow aspiration to test for micrometastases → lumpectomy + sentinel lymph node biopsy
	Sentinel node + → ACOSOG-Z0011

All patients receive whole breast radiation therapy (excluding a supraclavicular field) five days a week for a maximum of eight weeks and systemic adjuvant therapy as indicated.

Patients with no sentinel node identified intraoperatively and patients with sentinel node metastases identified by H&E who chose not to be registered to ACOSOG-Z0011 undergo axillary lymph node dissection.

SOURCE: NCI Physician Data Query, January 2005.

PHASE III RANDOMIZED STUDY OF SENTINEL NODE DISSECTION WITH OR WITHOUT CONVENTIONAL AXILLARY DISSECTION IN WOMEN WITH CLINICALLY NODE-NEGATIVE BREAST CANCER

Protocol ID: NSABP-B-32
Accrual: 5,611 (Closed)

Eligibility	Clinically node-negative breast cancer
ARM 1	Sentinel lymph node biopsy with axillary dissection
ARM 2	Sentinel lymph node biopsy → positive → axillary dissection → negative → no axillary dissection

If no sentinel node is identified, patients undergo axillary dissection. Patients with cytologically negative but histologically positive sentinel nodes undergo axillary dissection.

PRELIMINARY TECHNICAL RESULTS OF NSABP-B-32

Sentinel node identification rate (Both arms, n=5,210)	97%
Percent of identified sentinel nodes that were positive (Both arms, n=5,058)	26%
SNB overall accuracy (Arm 1 only, n=2,461)	97.2% (95% CI, 96.5-97.8)
SNB negative predictive value (Arm 1 only, n=1,811)	96.1% (95% CI, 95.2-97.0)
SNB sensitivity (Arm 1 only, n=720)	90.3% (95% CI, 88.1-92.4)
SNB false-negative rate (Arm 1 only, n=720)	9.7% (95% CI, 7.6-11.9)

SNB = sentinel node biopsy

SOURCES: NCI Physician Data Query, December 2004.

Julian TB et al. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 14.

PHASE III RANDOMIZED STUDY OF AXILLARY LYMPH NODE DISSECTION IN WOMEN WITH STAGE I OR IIA BREAST CANCER WHO HAVE A POSITIVE SENTINEL NODE

Protocol IDs: ACOSOG-Z0011, GUMC-00153
Accrual: 1,900 (Closed)

Eligibility	Stage I or IIA breast carcinoma amenable to lumpectomy with a positive sentinel node
ARM 1	Axillary lymph node dissection involving removal of at least level I and II nodes, followed by whole breast radiation therapy (exclusive of a third supraclavicular field) 5 days a week, for a maximum of 7 weeks
ARM 2	Breast radiation therapy only (as in Arm 1)

Patients in both arms may receive adjuvant systemic therapy at the discretion of the treating physician.

SOURCE: NCI Physician Data Query, January 2005.

ALMANAC TRIAL COMPARING SENTINEL NODE BIOPSY TO CONVENTIONAL AXILLARY TREATMENT IN PATIENTS WITH CLINICALLY NODE-NEGATIVE INVASIVE BREAST CANCER

Accrual: 1,031 (Closed)

Eligibility	T1-3, N0, invasive breast cancer
ARM 1	Standard axillary procedure (clearance or sampling)
ARM 2	Sentinel node biopsy → positive → radiation or surgery to axilla → negative → observation

	Standard axillary procedure	Sentinel node biopsy	*p*-value
Nodal positivity[1]	23%	26%	—
Arm swelling (patient reported)[2]*			
3 months – mild	12%	4%	<0.001†
3 months – moderate or severe	3%	1%	
6 months – mild	14%	4%	
6 months – moderate or severe	3%	0.5%	
Sensory loss (patient reported)[1]*			
1 month	62%	18%	<0.0001†
3 months	54%	20%	
6 months	43%	16%	
Sensory loss (physician assessed)[2]*			
1 month	42%	14%	<0.0001†
3 months	38%	14%	
6 months	37%	14%	
Drain usage[2]*	79%	17%	<0.001†
Mean days of hospital stay[2]*	5.4 days	4.1 days	<0.001‡
Return to normal activities in 6 months[2]*	93%	96%	<0.001‡

* Intention to treat; † Chi-square; ‡ Mann-Whitney test

SOURCES: [1] ALMANAC trialists'. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 15.

[2] Mansel RE et al. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 18.

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CURRENT STATUS OF SENTINEL LYMPH NODE BIOPSY

We now have clear data that sentinel lymph node biopsy is the staging procedure of choice for clinically node-negative breast cancer. Over 4,000 cases have been published with a mean follow-up of at least two years and the incidence of isolated axillary failure is one tenth of one percent, which is very low. Additionally, we now have two randomized trials evaluating the incidence of nodal positivity in women staged by sentinel node biopsy versus axillary dissection.

Sentinel node biopsy provides staging accuracy equivalent to axillary dissection, and the morbidity is clearly less — not only the immediate postoperative morbidity but also two years later in measurable differences in pain, paresthesia, arm motion and lymphedema. Additionally, we now know long-term local tumor control is good.

— Monica Morrow, MD

NSABP-B-32 SENTINEL NODE STUDY

The preliminary specificity and sensitivity data from NSABP-B-32 shows a nine to 10 percent false-negative rate for detecting positive nodes with the sentinel node resection. One can say that surgeons with more experience have a lower rate or that if we examine two or three sentinel nodes, we can lower that rate. However, if we examine four to five nodes, aren't we really talking about an axillary node dissection?

When we examined some of the older NSABP data to determine how many nodes were necessary to establish positive nodes in the axilla, the number was between six and eight. Any number of nodes below that had a high false-negative rate, while any number above that was superfluous.

I don't believe questioning the accuracy of axillary node dissection is particularly helpful. In this randomized prospective trial with over 5,500 women, the false-negative rate with sentinel node biopsy is nine to 10 percent and that's the inescapable conclusion of this trial.

— Norman Wolmark, MD

THE ALMANAC TRIAL

The ALMANAC data show a significant decrease in arm mobility problems and lymphedema with sentinel node biopsy; however, the data actually overestimate the morbidity experienced by the sentinel node group because 20 percent of those patients actually underwent axillary node dissection for a positive sentinel node or they received axillary radiation. I believe the numbers were skewed against sentinel node biopsy and that the associated morbidity is probably much lower than these data suggest, which are already much lower than the results seen in the axillary node dissection group.

— Harry D Bear, MD, PhD

I was the primary investigator for the quality of life study in the ALMANAC trial, and it was probably the first time since I've been working in this area that we've actually had quality of life as the primary endpoint in a surgical trial. In fact, anxiety was not affected and the quality-of-life benefits were superior in women who were randomly assigned to sentinel lymph node biopsy because they experienced less arm morbidity.

Another important aspect of this study is that, although physicians care deeply about their patients, often the focus of attention when reviewing clinical trial data is predominantly on life-threatening adverse events. For women actually experiencing any of our treatments — surgery, chemotherapy or hormone manipulation — non-life-threatening, but nevertheless significant, side effects can dramatically impair quality of life. Lymphedema usually doesn't kill anybody, but it definitely affects one's ability to function adequately in the home and professional world and in care-taking roles. The ALMANAC trial has at least given us clear indications that the sentinel lymph node procedure should become the standard of care.

— Lesley Fallowfield, PhD

Antiangiogenic Therapy

The importance of angiogenesis in cancer biology has been recognized for decades. One of the first stimulating factors identified was the vascular endothelial growth factor (VEGF). At the 2002 San Antonio Breast Cancer Symposium, Kathy Miller and colleagues reported on the first Phase III randomized trial in breast cancer evaluating the anti-VEGF monoclonal antibody bevacizumab. This ECOG study compared capecitabine alone to capecitabine combined with bevacizumab in heavily pretreated patients with metastatic breast cancer and found a modest response rate advantage to the combination but no improvement in the primary endpoint of time to progression. Another key ECOG study is evaluating bevacizumab combined with paclitaxel in the first-line setting. The hope is that a more significant advantage may be seen in earlier-stage disease, as was observed in the recently reported trial in colorectal cancer in which a marked survival advantage was observed for bevacizumab plus irinotecan and 5-FU/leucovorin (IFL) compared to IFL alone. The first interim efficacy analysis from the ECOG-2100 trial is expected to be reported in early summer of 2005.

EFFICACY OF IFL (IRINOTECAN, 5-FU, LEUCOVORIN) WITH OR WITHOUT BEVACIZUMAB IN METASTATIC COLORECTAL CANCER

Efficacy	Bevacizumab/ IFL (n=402)	IFL/placebo (n=411)	Hazard ratio	*p*-value
Overall survival	20.3 months	15.6 months	0.66	<0.001
Progression-free survival	10.6 months	6.2 months	0.54	<0.001
Response rate	44.8%	34.8%	—	0.004

Following the submission of these results, the FDA granted approval in Feb 2004 for the use of bevacizumab as a first-line treatment for metastatic colorectal cancer.

SOURCE: Hurwitz H et al. *N Engl J Med* 2004;350(23);2335-42.

PHASE III RANDOMIZED TRIAL OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER

Protocol IDs: E-2100, CTSU
Target Accrual: 316-650 (Closed)

Eligibility	Locally recurrent disease not amenable to resection with curative intent or metastatic disease
ARM 1	Paclitaxel qwk x 3 + bevacizumab q2wk
ARM 2	Paclitaxel qwk x 3

In both arms, treatment repeats q4wk x 18 in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, January 2005.

PHASE III RANDOMIZED STUDY OF BEVACIZUMAB WITH CAPECITABINE VERSUS CAPECITABINE ALONE IN WOMEN WITH PREVIOUSLY TREATED METASTATIC BREAST CANCER

Protocol IDs: Genentech-AVF2119g, GUMC-00299, MSKCC-01008, UAB-0028, UAB-F001009003
Accrual: 462 (Closed)

Eligibility	Metastatic breast cancer previously treated with one or two chemotherapy regimens for metastatic disease or no prior chemotherapy for metastatic disease if previously treated with an adjuvant anthracycline and taxane regimen and relapsed within 12 months
ARM 1	Capecitabine (days 1-14) q3wk
ARM 2	Capecitabine (days 1-14) q3wk + bevacizumab (day 1) q3wk

Treatment repeats for up to 35 courses in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, January 2005.

EFFICACY AND TOXICITY OF CAPECITABINE PLUS BEVACIZUMAB VERSUS CAPECITABINE ALONE

	Capecitabine	Capecitabine + bevacizumab
Efficacy	**n=230**	**n=232**
Objective response rate	19.1%	30.2%
Duration of response	6.7 months	4.96 months
Progression-free survival	4.2 months	4.9 months
Toxicity	**n=215**	**n=229**
Hypertension (Grade III)	0.5%	17.9%
Thromboembolic	5.6%	7.4%
PE	1.4%	1.3%
DVT	2.3%	6.1%
Bleeding	11.2%	28.8%
Grade ≥III	1.4%	0.4%
Proteinuria	7.4%	22.3%
Cardiac (Grade III or IV)	0.9%	3.1%

SOURCE: Miller K. Presentation. San Antonio Breast Cancer Symposium, 2002.

CLINICAL TRIALS EVALUATING THE ANTI-VEGF BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH METASTATIC BREAST CANCER

Chair	Protocol ID	Status	Accrual	Study arms
Miller	E-2100, CTSU	Closed	316-650	Bevacizumab q2wk + paclitaxel qwk x 3 vs paclitaxel qwk x 3; treatment repeats q4wk x 18
Wedam	NCI-01-C-0173, NCI-2772	Closed	23	(Bevacizumab + AT + G-CSF q3wk) x 7 → surgery → bevacizumab q3wk x 8
Overmoyer	CWRU-3100, NCI-2722	Open	60	Bevacizumab q2wk, wks 1-8 + T qwk, wks 1-6 vs T qwk, wks 1-6 Patients with stable or responsive disease → surgery → AC x 4
Burstein	DFCI-01013, NCI-2716	Closed	56	Bevacizumab q2wk + vinorelbine qwk; treatment repeats q8wk x 4

A = doxorubicin; C = cyclophosphamide; T = docetaxel

SOURCE: NCI Physician Data Query, January 2005.

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CLINICAL TRIALS OF BEVACIZUMAB IN WOMEN WITH METASTATIC BREAST CANCER

I believe the differences in the trial results of bevacizumab in breast cancer and colon cancer were attributable to when patients were treated during the course of the disease — rather than some inherent difference in the biology of the cancers.

Our breast cancer ECOG trial evaluating bevacizumab with capecitabine enrolled patients with advanced disease that was refractory to anthracycline and taxane therapy. Those patients could have received up to two other chemotherapy regimens for metastatic disease if they had received both an anthracycline and a taxane as adjuvant therapy.

Dr Hurwitz's trial of bevacizumab with IFL was conducted in patients with metastatic colon cancer who had not received previous chemotherapy for metastatic disease but could have undergone adjuvant chemotherapy. Likewise, our ECOG-2100 breast cancer trial enrolled patients with breast cancer who had not received chemotherapy for metastatic disease but could have received adjuvant chemotherapy.

Patients were randomly assigned to weekly paclitaxel with or without bevacizumab. The primary endpoint for ECOG-2100 is time to progression.

— Kathy D Miller, MD

IDENTIFYING A TARGET FOR BEVACIZUMAB

I don't view bevacizumab as negative in breast cancer. The capecitabine trial was asking a great deal of bevacizumab in advanced breast cancer, and it showed an increased response rate. Fortunately, an ongoing first-line trial in advanced disease will further elucidate the role of this agent in breast cancer. We're also excited about the potential of bringing bevacizumab into the adjuvant breast cancer setting.

We haven't identified a target for bevacizumab — one that we could use to restrict its use to a subset of the population — but clearly that's a goal. It's often pointed out that if we had conducted the trastuzumab trials on the entire population of patients with breast cancer, we would not have seen an effect. Fortunately, the target could be measured. If we find a target for bevacizumab, the effects may be impressive.

— Norman Wolmark, MD

FUTURE DIRECTIONS WITH BEVACIZUMAB

In an anthracycline- and taxane-refractory setting, adding bevacizumab to capecitabine just about doubles the response rate but does not appear to improve time to progression or overall survival. There is clearly a biologic impact in that setting, but it's not clear that it translates to clinical benefit.

It will be interesting to see whether or not bringing that therapy sooner up front in the metastatic breast cancer setting, as is being done in E-2100, will provide a real clinical benefit, as opposed to simply the response rate benefit we're seeing.

The possibility of adjuvant bevacizumab is certainly reasonable to look at. Approximately 30 to 50 percent of patients with breast cancer appear to have primary tumors that overexpress VEGF compared to surrounding normal tissue. In fairly large, albeit retrospective analyses, this population of patients had a higher rate of relapse. So there's a clear biologic hypothesis and rationale for exploring this strategy of utilizing bevacizumab in the adjuvant setting.

A major issue is whether we have the safety data to bring bevacizumab into this setting. Should we wait until we have the results of E-2100? Should we start looking at pilot approaches in the adjuvant setting now? Should we start planning adjuvant trials? We're certainly considering these questions in the Eastern Cooperative Oncology Group.

— George W Sledge Jr, MD

Adjuvant Bisphosphonates

A number of biologic effects in bone suggest that bisphosphonates have the potential to retard or prevent the clinical onset of metastatic disease. Three randomized adjuvant trials have yielded conflicting results on this question, although the use of these agents is now considered standard in patients with known lytic bone metastases. A new generation of adjuvant trials is currently evaluating whether bisphosphonates will reduce the rate of bone and nonbone metastases and prolong survival. Another promising research strategy actively being discussed is the combination of a bisphosphonate and an aromatase inhibitor, which would not only offer potential reduction in relapse rate but would mitigate bone loss. A data set from Austria presented at the 2002 and 2004 San Antonio Breast Cancer Symposia demonstrated that bone loss from anastrozole in premenopausal women receiving an LHRH agonist was prevented by the use of zoledronic acid.

PHASE III TRIALS OF ADJUVANT CLODRONATE FOR EARLY STAGE BREAST CANCER

Author	Reduction in skeletal metastases	Reduction in nonskeletal metastases	Survival advantage
Diel et al	Yes	Yes	Yes
Powles et al	Yes during Rx only	No	Yes
Saarto et al	No	No	Decreased survival in clodronate arm

DERIVED FROM: NSABP-B-34 Protocol background.

ONGOING AND RECENTLY CLOSED ADJUVANT BISPHOSPHONATE TRIALS IN BREAST CANCER

Study	N	Randomization
NSABP-B-34 (Closed)	3,323	Clodronate qd x 3y Placebo qd x 3y
SHEFF-AZURE, BIG-1-04	3,300	Chemo and/or hormonal therapy + concurrent zoledronic acid q3-4wk x 6 → q3mo x 8 → q6mo x 5 Chemo and/or hormonal therapy alone
CALGB-79809	400	Zoledronate q3mo (months 1-24) + daily calcium + vitamin D (months 1-36) Daily calcium + vitamin D (months 1-36) + zoledronate q3mo (months 13-36)
CPMC-IRB-14069	120	Zoledronate q3mo x 4 + daily calcium + vitamin D Placebo q3mo x 4 + daily calcium + vitamin D
NCCTG-N02C1	220	(Oral risedronate qwk + daily calcium + vitamin D) x 1y (Oral placebo qwk + daily calcium + vitamin D) x 1y

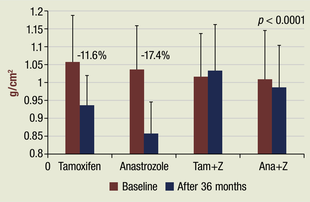
SOURCE: NCI Physician Data Query, January 2005.

ANASTROZOLE OR TAMOXIFEN IN COMBINATION WITH GOSERELIN (± ZOLEDRONIC ACID) AS ADJUVANT TREATMENT FOR HORMONE RECEPTOR-POSITIVE PREMENOPAUSAL BREAST CANCER

Protocol ID: ABCSG-12 (Open)

Eligibility	Premenopausal women with Stage I/II ER/PR-positive breast cancer, <10 positive lymph nodes
ARM 1	Surgery → goserelin + tamoxifen x 3y
ARM 2	Surgery → goserelin + tamoxifen + zoledronic acid x 3y
ARM 3	Surgery → goserelin + anastrozole x 3y
ARM 4	Surgery → goserelin + anastrozole x 3y + zoledronic acid x 3y

CHANGES IN BONE MINERAL DENSITY OF THE LUMBAR SPINE (L1-L4) CAUSED BY ANASTROZOLE OR TAMOXIFEN IN COMBINATION WITH GOSERELIN (± ZOLEDRONIC ACID) IN ABCSG-12



Tam = tamoxifen; Z = zoledronic acid; Ana = anastrozole

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

EFFECTS OF ADJUVANT CLODRONATE ON METASTASES AND MORTALITY IN 1,069 PATIENTS

	Clodronate	Placebo	Statistical significance
Bone metastases during total study period	63	80	HR 0.77 (95% CI, 0.56-1.08) $p = 0.127$
Bone metastases during medication period	12	28	HR 0.44 (95% CI, 0.22-0.86) $p = 0.016$
Nonosseous metastases	112	128	$p = 0.257$
Mortality	98	129	HR 0.77 (95% CI, 0.59-1.00) $p = 0.047$

Conclusion: Adjuvant clodronate may reduce the incidence of bone metastases during the medication period and is associated with a significant reduction in mortality.

DERIVED FROM: Powles T et al. *J Clin Oncol* 2002;20(15):3219-24.

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ADJUVANT BISPHOSPHONATES: RESEARCH BACKGROUND

In our trial, patients receiving clodronate had fewer subsequent bone and nonbone metastases. When we started our study, we selected patients with tumor cells in the bone marrow because we were convinced this was the best prognostic factor for bone metastases. Today we know it's a good prognostic factor for nonbone metastases because it reflects the early hematogenous spread of breast cancer cells from the primary tumor. We only had 300 patients, which is a small number for an adjuvant trial, so the effect we observed on nonbone metastases could have been by chance. We hypothesize that perhaps, if you increase the amount of bisphosphonates on the bone surface, you may have an apoptotic effect on adjacent cells. Evidence indicates that these agents have this effect on osteoclasts and also have an antiadhesive and antiangiogenic effect.

— Ingo Diel, MD

"Our results indicate that clodronate reduced the occurrence of bone metastases in patients with primary operable breast cancer, although this was only significant during the medication period. Furthermore, we have noted a significantly improved overall survival. These results need further evaluation by large clinical trials of adjuvant clodronate (such as the National Surgical Adjuvant Breast and Bowel Project B-34 trial, which has started accrual) and other bisphosphonates used for longer treatment periods to establish the clinical role of anti-osteolytic bisphosphonate therapy for patients with primary operable breast cancer."

— Powles T et al. J Clin Oncol *2002;20(15):3219-24.*

NSABP ADJUVANT CLODRONATE TRIAL

NSABP-B-34 is evaluating adjuvant clodronate, an oral bisphosphonate, in women with node-negative and node-positive breast cancer. Data from Germany and the Canadian and UK trials demonstrate that clodronate reduces bone metastases and improves survival. B-34 randomly assigned women to three years of clodronate or placebo. The choice of adjuvant therapy was left to the investigator's discretion. We chose clodronate because it is the only bisphosphonate with data in the adjuvant setting. If the B-34 results are positive, hopefully clodronate will be FDA approved. In lieu of the ATAC trial results, it may be reasonable to combine an aromatase inhibitor with a bisphosphonate as adjuvant therapy. Eventually, the NSABP plans to compare the bisphosphonates to find the best one. It may, however, be difficult — in terms of patient acceptability — to use an intravenous bisphosphonate in the adjuvant setting.

— Eleftherios P Mamounas, MD, MPH

BONE MINERAL DENSITY RESULTS FROM THE ADJUVANT TRIAL ABCSG-12

"From the results of this randomized trial [ABCSG-12] we conclude that cancer treatment-induced bone loss (CTIBL) is frequent in premenopausal patients receiving combination endocrine treatment. Severity of CTIBL increases with treatment duration. When anastrozole is used in combination with goserelin, CTIBL is significantly more severe than in the tamoxifen/goserelin group. Zoledronic Acid (4mg q6mo) can effectively counteract CTIBL in both settings."

— Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2004.

NEW SWOG ADJUVANT BISPHOSPHONATE TRIAL

Within SWOG, we are about to start an adjuvant bisphosphonate trial that will follow up on the NSABP clodronate versus placebo trial. While we cannot predict the results of the NSABP's trial, we believe clodronate will be the winner. Our trial will compare adjuvant clodronate to a more potent oral bisphosphonate and an IV bisphosphonate. We want to see whether these agents can prevent bone metastases and impact disease-free and overall survival.

— Julie R Gralow, MD

Predicting Prognosis in Women with Early Breast Cancer

Tools that accurately predict the prognosis of women with early breast cancer are invaluable to both clinicians and patients when making decisions about adjuvant therapy. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. The Adjuvant! online computer program, developed by Dr Peter Ravdin, also allows for the prediction of outcomes in women with early breast cancer. In a presentation at ASCO 2004, the predictions from Adjuvant! were found to be very comparable to actual outcomes observed in patients from British Columbia. These and future tools that can predict outcomes should aid in the decision-making process about adjuvant therapies.

ONCOTYPE DX 21-GENE RECURRENCE SCORE ASSAY

16 cancer and 5 reference genes from 3 studies

Proliferation
Ki67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

HER2
GRB7
HER2

Estrogen
ER
PGR
BCL2
SCUBE2

GSTM1

Reference
ACTB (β-actin)
GAPDH
RPLPO
GUS
TFRC

CD68

Invasion
MMP11 (stromolysin 3)
CTSL2 (cathepsin L2)

BAG1

Recurrence Score =

+0.47 x HER2 group score
-0.34 x ER group score
+1.04 x Proliferation group score
+0.10 x Invasion group score
+0.05 x CD68
-0.08 x GSTM1
-0.07 x BAG1

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

SOURCES: Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Paik S. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 16.

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

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

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

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

	Number of eligible patients			
	Tam	Tam+MF	Tam+CMF	Total
All B20	770	763	766	2299
GHI-B-20	227 (29.5%)	203 (26.6%)	221 (28.9%)	651 (28.3%)

Tam = tamoxifen

GHI-B20 study subjects were similar to all B-20 patients. Loss of cases due principally to blocks never collected.

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

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

Chemotherapy = MF or CMF; RS = recurrence score

SOURCES: Paik S. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 24.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Paik S. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 16. Available at www.sabcs.org; accessed December 22, 2004

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

ARM 1	Placebo - Eligible
ARM 2	Tamoxifen - Eligible

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

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

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

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

SOURCE: Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

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

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

OS = overall survival; BCSS = breast cancer-specific survival;
T = tamoxifen; C = chemotherapy; . = event-free survival

* *p*-values are nonsignificant; † $p < 0.05$

SOURCE: Olivotto IA et al. **An independent population-based validation of the adjuvant decision-aid for stage I-II breast cancer.** *J Clin Oncol* 2004;22(14 Suppl):Abstract 522.

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Goldhirsch A et al. **Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer.** *J Clin Oncol* 2003;21(17):3357-65.

Olivotto IA et al. **An independent population-based validation of the adjuvant decision-aid for stage I-II breast cancer.** *J Clin Oncol* 2004;22(14 Suppl):Abstract 522.

Paik S. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 24.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Paik S. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 16. Available at www.sabcs.org; accessed December 22, 2004.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Paik S et al. **Risk classification of breast cancer patients by the Recurrence Score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade.** *Breast Cancer Res Treat* 2004;88(1 Suppl 1);118;Abstract 104.

Piccart MJ et al. **Multi-center external validation study of the Amsterdam 70-gene prognostic signature in node negative untreated breast cancer: Are the results still outperforming the clinical-pathological criteria?** San Antonio Breast Cancer Symposium, 2004;Late Abstract 38.

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.

MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE IN PATIENTS WITH ER-POSITIVE, NODE-NEGATIVE BREAST CANCER

Based on literature review and known prognostic factors in breast cancer, approximately 185 genes were selected for a multigene panel and tested in two data sets. Twenty-one genes appeared to predict for outcome, and they were then confirmed in a subset of patients from the NSABP-B-20 tamoxifen-only arm.

NSABP-B-14 tested this multigene panel prospectively in 668 patients with ER-positive, node-negative breast cancer biopsies, and the panel predicted recurrence risk far better than age, tumor size or tumor grade. This assay assigns patients a recurrence score from zero to 100 to assist in deciding on treatment alternatives.

— Melody A Cobleigh, MD

Previously, gene-expression profiling required frozen material; however, perhaps less than one percent of breast cancers biopsies are stored in that fashion. A breakthrough came when it was discovered that the RNA wasn't missing in paraffin blocks, it was just fragmented. As a result of this discovery and other new technologies, a multigene assay was developed that is predictive of breast cancer recurrence despite adjuvant tamoxifen therapy.

This assay was validated in NSABP-B-20 and B-14, and we now have a predictor that scores a woman's risk of relapse between one and 100. Apparently, it is as powerful as tumor grade in its predictive ability, but the assay is reproducible while tumor grade is not.

— Matthew J Ellis, MB, PhD

THE 21-GENE ASSAY PREDICTS BENEFIT FROM ADJUVANT CHEMOTHERAPY AND TAMOXIFEN

We evaluated patients treated with adjuvant chemotherapy in NSABP-B-20 to determine if the 21-gene assay predicts for response to chemotherapy. The results were actually quite striking.

The absolute benefit from chemotherapy was zero in the patients at low and intermediate risk, but the absolute benefit in the 10-year distant recurrence rate was 28 percent and the relative risk reduction was 75 percent in the group of patients at high risk.

The women enrolled in NSABP-B-20 received tamoxifen at the same time as chemotherapy. Theoretically, the benefit from chemotherapy in the patients with an intermediate risk might have been reduced by tamoxifen.

In the women enrolled in the NSABP-B-14 trial, we can actually identify patients who don't gain any benefit from adjuvant tamoxifen — patients with low levels of estrogen receptor as determined by messenger RNA levels.

— Soonmyung Paik, MD

PROGRAM FOR THE ASSESSMENT OF CLINICAL CANCER TESTS

Dr Soon Paik presented validation data from NSABP-B-14 demonstrating that a new multigene RT-PCR assay could identify gene expression profiles predictive of recurrence in patients with node-negative, ER-positive breast cancer who previously received adjuvant tamoxifen. On multivariate analysis, this assay was a significantly more powerful predictor than other conventional clinical features. On the other hand, Dr Esteva presented data from an MD Anderson trial in which the same assay did not fare so well. Esteva's data examined a more diverse group of patients who had not received any adjuvant therapy.

The Program for the Assessment of Clinical Cancer Tests is planning to study this new technology. The simplest way to validate it would be to study it prospectively, but that would take years to accomplish and by the time the study was completed, newer technology would be available. Another possibility is to prospectively study whether this or a similar assay can be used to select patients at low risk who can be spared chemotherapy, or patients at high risk who need intensive chemotherapy. Clearly, multiple approaches need to be considered, and the final trial design is still being developed.

— G Thomas Budd, MD

Impact of CME on Practice Patterns in Breast Cancer

Surgeon and medical oncologist has the daunting task of keeping up-to-date with the expanding knowledge base in breast cancer medicine. Relatively little is known about the effect of continuing medical education (CME) on oncology practice patterns. As part of the *Breast Cancer Update* Patterns of Care Study, 200 medical oncologists were surveyed about their participation in various CME activities, and the influence of listening to the *Breast Cancer Update* audio series on treatment patterns. Compared to nonlisteners, listeners of the *BCU* audio series were more likely to recommend: dose-dense adjuvant chemotherapy with AC → T, switching a postmenopausal patient who was not tolerating adjuvant therapy to anastrozole fulvestrant as second-line therapy for a woman with asymptomatic ER-positive metastatic disease, and trastuzumab monotherapy for a patient with asymptomatic HER2-positive metastatic disease. Future studies should continue to assess the impact of various CME activities on treatment patterns in medical oncology.

TIME SPENT IN CONTINUING EDUCATION ACTIVITIES

How much time in a typical month do you spend doing the following?

	Mean time spent (hours)
Reading any type of medical educational materials	15.7
Specifically reading medical journals	10.8
Searching for and reading oncology information on the Internet	4.4
Listening to any type of medical educational programs on tape or CD	3.4
Specifically listening to interviews with cancer research leaders	2.5

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

WHICH OF THE FOLLOWING JOURNALS DO YOU READ OR SKIM EACH MONTH?

Listened to *Breast Cancer Update* in past 6 months?	Yes	No
Journal of Clinical Oncology	99%	96%
New England Journal of Medicine	90%	80%
Journal of the American Medical Association	60%	54%
Cancer	38%	34%
Journal of the National Cancer Institute	33%	23%
The Lancet	24%	16%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

A 65-YEAR-OLD WOMAN ON TAMOXIFEN FOR TWO YEARS FOR A 1.2-CM, ER-POSITIVE, HER2-NEGATIVE TUMOR AND THREE POSITIVE LYMPH NODES

How would you manage this patient's adjuvant endocrine therapy?

	Scenario 1: The patient is tolerating tamoxifen without difficulty		Scenario 2: The patient is having significant vasomotor symptoms		Scenario 3: The patient has gained 20 pounds	
Listened to *Breast Cancer Update* in past 6 months?	Yes	No	Yes	No	Yes	No
Stop tamoxifen, switch to exemestane	30%	37%	34%	41%	29%	41%
Stop tamoxifen, switch to anastrozole	12%	11%	41%	22%	38%	26%
Stop tamoxifen, switch to letrozole	10%	15%	11%	15%	15%	18%
Continue tamoxifen	48%	37%	14%	22%	18%	15%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

A 35-YEAR-OLD WOMAN WITH A 1.2-CM, ER-NEGATIVE, HER2-POSITIVE, GRADE II TUMOR

What chemotherapy, if any, would you recommend?

Listened to *Breast Cancer Update* in past 6 months?	Node-negative		3 positive nodes	
	Yes	No	Yes	No
AC	43%	70%	4%	—
Dose-dense AC (with growth factors)	11%	4%	4%	4%
Dose-dense AC → T (with growth factors)	4%	4%	53%	28%
AC → T (not dose-dense)	8%	—	8%	8%
AC → docetaxel	15%	11%	21%	41%
TAC	1%	4%	8%	11%
FAC/FEC	14%	7%	2%	8%
No chemotherapy	4%	—	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

ASYMPTOMATIC 57-YEAR-OLD WOMAN WITH ER-POSITIVE, HER2-NEGATIVE METASTASES TO BONE AND NO PRIOR SYSTEMIC THERAPY

What endocrine therapy would you likely recommend, if any?

Listened to *Breast Cancer Update* in past 6 months?	1st-line		2nd-line	
	Yes	No	Yes	No
Fulvestrant	—	—	39%	23%
Anastrozole	50%	46%	4%	7%
Letrozole	36%	41%	9%	14%
Tamoxifen	11%	10%	22%	23%
Exemestane	3%	3%	26%	33%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

MEDICAL MEETING ATTENDANCE

How many of the meetings below have you attended in the past year?

	Mean
Major scientific meetings (eg, ASCO, San Antonio)	1.2
Local CME meetings, grand rounds, etc	5.5
Pharmaceutical meetings and advisory boards	4.5

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

A 57-YEAR-OLD WOMAN WITH AN ER-NEGATIVE, HER2-POSITIVE TUMOR AND ASYMPTOMATIC BONE METASTASES

What systemic therapy strategy would you recommend?

Listened to *Breast Cancer Update* in past 6 months?	Yes	No
Trastuzumab alone	26%	7%
Trastuzumab plus chemotherapy	68%	86%
Chemotherapy alone	6%	7%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

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Butler WM et al. **Breast cancer care: Changing community standards.** *J Healthc Qual* 2004;26(5):22-8.

Du XL et al. **Discrepancy between consensus recommendations and actual community use of adjuvant chemotherapy in women with breast cancer.** *Ann Intern Med* 2003;138(2):90-7.

Ebell MH, Shaughnessy A. **Information mastery: Integrating continuing medical education with the information needs of clinicians.** *J Contin Educ Health Prof* 2003;23(Suppl 1):53-62.

Stancic N et al. **Continuing medical education: What delivery format do physicians prefer?** *J Contin Educ Health Prof* 2003;23(3):162-7.

INTEGRATION OF NEW STANDARDS OF CARE INTO CLINICAL PRACTICE

I think general consistency exists across the country in terms of the actual implementation of generally accepted guidelines or standards of care. The question is: How long does it take for a new standard to be introduced into practice? I believe it takes a couple of years, but I think it also depends on what the new finding is. If it involves a great deal more technology or difficulty, it may take longer than if it is easy to do and not much more expensive, although exceptions occur.

I believe that meetings that are attended by a large number of people or are covered in the press to a great extent have a big impact. I strongly suspect that the majority of oncologists in the United States first hear about a new oncologic research finding from the meeting at which it was presented or through summaries of the meetings. In our group, somebody will go to the ECOG, NSABP or ASCO annual meeting and come back and tell us what is going on.

Another important part of the equation is continuing educational sessions and print and audio programs. These sources may not be the first time that someone hears new information, but they may be the second or third time, and that may be the point at which practice changes. Continuing medical education has an important role in reinforcing and expanding on data that a physician may have first encountered during a presentation or scanned in a paper.

— Gershon Locker, MD

NCCN TREATMENT GUIDELINES AND ASCO TECHNOLOGY ASSESSMENTS

As clinicians, we have the challenge of tracking data as it evolves and deciding when the evidence surpasses the threshold at which the data should change our clinical practice patterns. The difficulty in doing that task on an ongoing basis has led a number of professional societies to establish expert panels to establish clinical guidelines.

The National Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus approach, and the ASCO Technology Assessment uses a somewhat more formal process in its deliberations. An evidence-based consensus develops recommendations that are based on high-level evidence, whenever high-level evidence exits. Scientifically sound interpretation and cautious extrapolation of existing data are used when necessary, and expert judgment may be used to derive recommendations where evidence is lacking. The latter is very important, because it allows us to establish a guideline across a continuum of disease states, even those specific decision points or treatment modalities for which we may not have any clinical trial data to directly apply.

The ASCO Technology Assessment methodology evaluates a narrow treatment option applied to a narrowly-defined subset of patients. The studies are rated for strength of evidence. The recommendations from the technology assessment must be based on the strength of the evidence, and in the absence of evidence, no positive or negative recommendation can be made.

— Robert W Carlson, MD

CONTINUING MEDICAL EDUCATION

"Traditional continuing medical education (CME) has been disconnected from the actual practice of medicine and has not focused on providing the most useful information in the most efficient way.

"...physicians will learn best when learning is in the context of patient care, answers their questions, does not take too much time, and is directly applicable to their work. ...

"It makes most sense, then, to provide new information in a manner that can be rapidly assimilated and at a time when it can be used immediately. In other words, CME has to be integrated into the practice of medicine, presented at the 'point of care.'"

— Ebell MH, Shaughnessy A. J Cont Ed Health Professions *2003;23(Suppl 1):53-62.*