2004

21st Annual Miami Breast Cancer Conference

SPECIAL REPORT

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Table of Contents

Editor's Note

Bringing out the vote

Our group has been doing electronic keypad polling at oncology meetings since 1995, and what we have observed over the years has been so interesting that we started to incorporate the results into our print education programs. Last year we produced a supplement to our *Breast Cancer Update* audio program based on the polling data from the Miami Breast Cancer Conference with supporting excerpts from our audio series, and the feedback was so positive that we have done it again. My review of the enclosed findings revealed that several interesting trends continue from prior years:

1. Many physicians have uncertain feelings of equipoise concerning a number of ongoing randomized clinical trials.

The Miami meeting has proven to be a fascinating laboratory in this regard. For example, we noted several years ago that randomly assigning women with node-positive tumors to postmasectomy radiation therapy or not was an uncomfortable position for most physicians. It is interesting that the Intergroup trial evaluating this strategy, which was headed by Lori Pierce, recently had to close because of accrual problems. Other trials presented in this book were supported more enthusiastically.

2. Physicians listen to their patients as well as read the medical literature.

For example, we consistently observe that a significant fraction of meeting attendees believe that tamoxifen causes weight gain (page 6) in spite of the clinical trial evidence contradicting this widely held belief.

3. News travels fast.

While it is likely that a physician attending a three-day meeting on breast cancer might be more informed than the average physician, it is fascinating how quickly key information is communicated. For example, last year — just months after Craig Allred's San Antonio presentation — most attendees were already incorporating ER assay measurements into management of women with DCIS. This year, the fraction of attendees ordering ER/PR measurements exceeded 90 percent (page 8).

4. Second opinions can be helpful.

The most interesting aspect of these data is the diversity of perspectives on challenging situations, which is quite understandable given the lack of solid evidence on which to base many decisions. It is sobering to consider how different a recommendation a patient might receive depending on which physician does the evaluation.

Our mission as a CME group is not to provide dogmatic answers for the many controversies in every stage of breast cancer management, but to heighten awareness of the spectrum of perspectives on these issues. The enclosed report documents the wide diversity of opinions on many key issues.

— Neil Love, MD
NLove@ResearchToPractice.net

Tumor Panel Cases Keypad Results

Tumor Panel Case 1

Part 1:

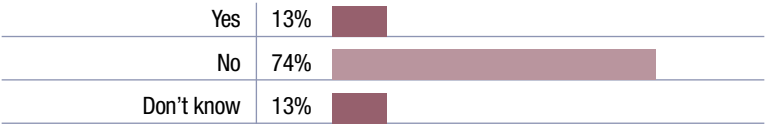
This 63-year-old healthy woman had one prior breast biopsy demonstrating fibrocystic changes. Her mother and sister both had postmenopausal breast cancer.

1.1 ***Would you calculate this patient's risk of developing breast cancer using the Gail model and use this in your decision-making?***

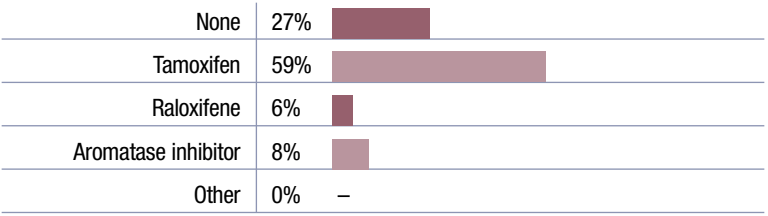
Part 2:

The patient's Gail model risk is 7.5 percent at five years and 28.3 percent lifetime. Genetic testing is negative.

2.1 ***Would you recommend ductal lavage for this patient?***

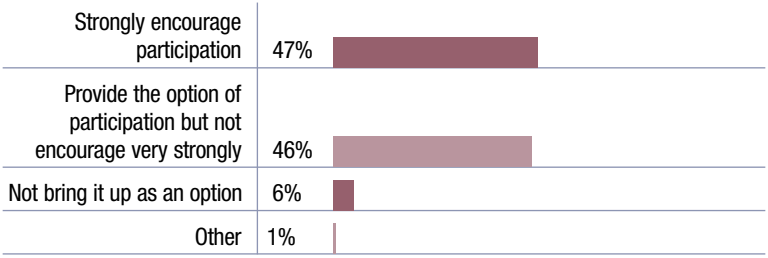


2.2 ***Outside a clinical trial, what chemoprevention, if any, would you recommend?***

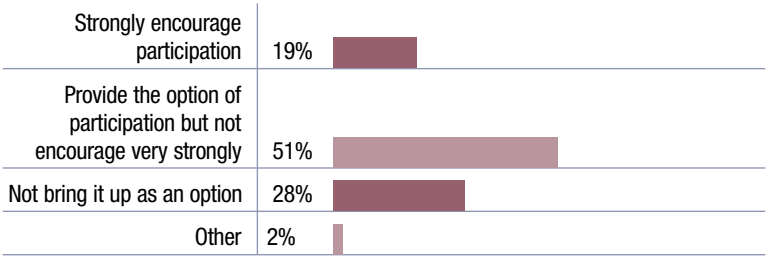


Part 2: *(Continued)*

2.3 ***If this woman were eligible for the STAR trial, comparing tamoxifen to raloxifene, what advice should she be given regarding participation?***



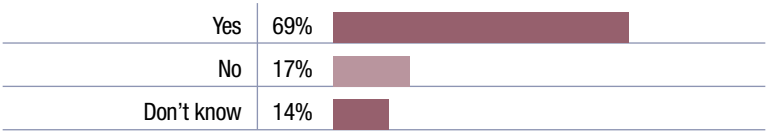
2.4 ***If this woman were eligible for the IBIS-II prevention trial, comparing anastrozole to placebo, what advice should she be given regarding participation?***



Part 3:

No intervention is utilized, and two years later (at age 65) she is found to have a mammographic abnormality in the lower inner quadrant of the left breast. Core biopsy reveals an infiltrating ductal carcinoma (ER-positive, PR-negative, HER2 IHC is 2+).

3.1 ***Should FISH testing be done on the tumor?***



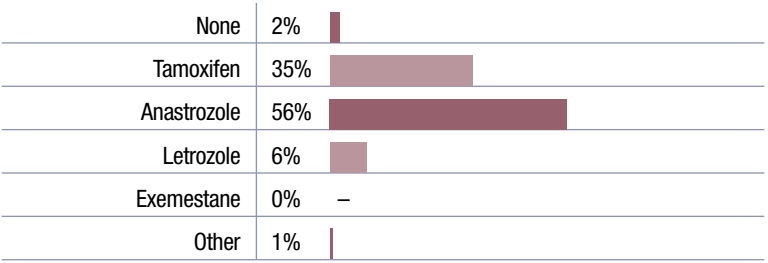
Part 3: *(Continued)*

3.2 ***The patient wishes to have breast conservation but is concerned about travel for radiation therapy. Would you recommend partial breast irradiation (PBI) for this patient (off protocol)?***

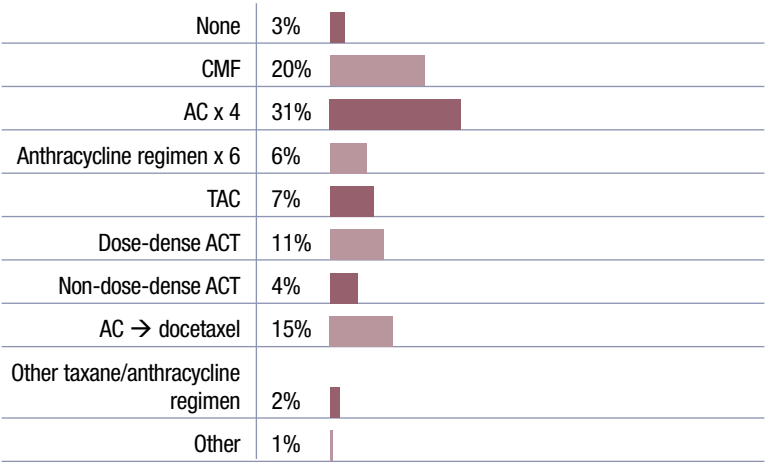
Part 4 Scenario 1:

The tumor proves to be HER2-positive by FISH. The patient undergoes a lumpectomy with sentinel node biopsy demonstrating a 2.2-centimeter IDC. The sentinel node and one other axillary node are both positive.

4.1 ***What endocrine therapy, if any, would you recommend?***



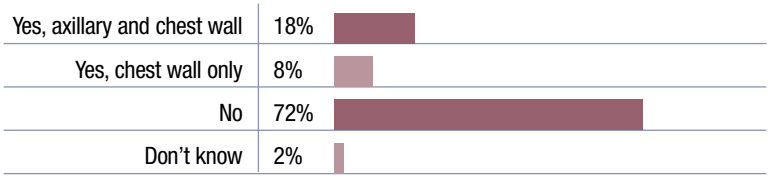
4.2 ***What chemotherapy, if any, would you recommend?***



Part 4 Scenario 2:

The patient opts for modified radical mastectomy with breast reconstruction. She has no residual tumor in the breast, but a sentinel node and one other axillary node are both positive.

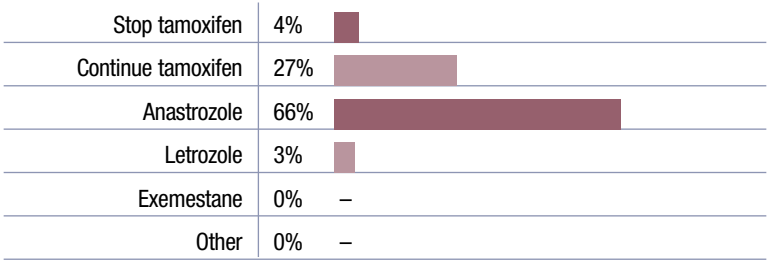
4.3 *Would you recommend radiation therapy?*



Part 5 Scenario 1:

The patient receives four cycles of dose-dense AC → T. After two years on adjuvant tamoxifen, she presents for routine follow-up doing well but complaining of weight gain and inquiring about switching to an aromatase inhibitor.

5.1 *What would you recommend?*

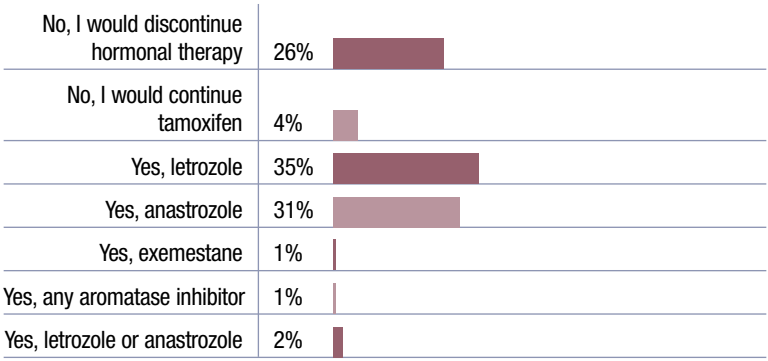


5.2 *Does tamoxifen cause weight gain?*

Part 5 Scenario 2:

The patient receives four cycles of dose-dense AC → T. Just after completing five years of adjuvant tamoxifen, she presents for routine follow-up doing well but asking about switching to an aromatase inhibitor.

5.3 ***Would you recommend an aromatase inhibitor?***



Part 5 Scenario 3:

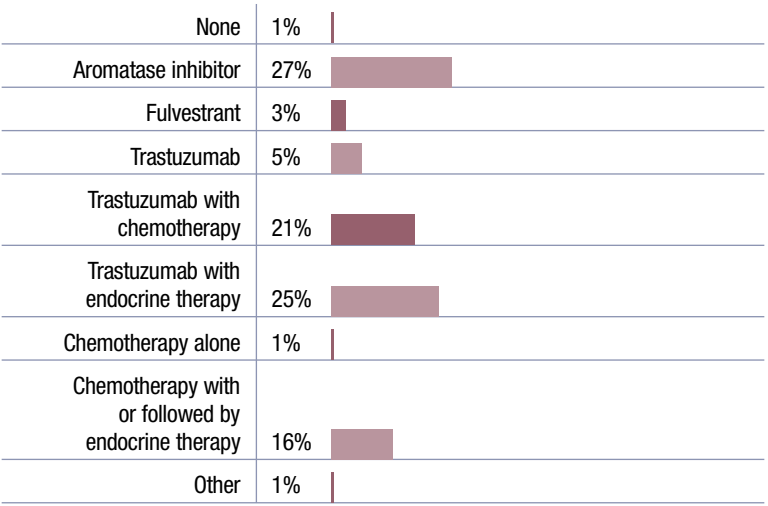
The patient had 10 positive nodes at initial diagnosis and received chemotherapy followed by five years of tamoxifen. It is now five years later.

5.4 ***Would you recommend an aromatase inhibitor?***

Part 6:

After receiving four cycles of dose-dense AC → T and just after completing five years of adjuvant tamoxifen, she presents for routine follow-up doing well but with three skin nodules on her abdomen. Biopsy of one of the nodules is positive for tumor (ER-positive, PR-negative, HER2-positive by FISH). Her CA27.29 is 120, and a bone scan shows several suspicious areas.

6.1 ***What systemic therapy, if any, would you recommend?***

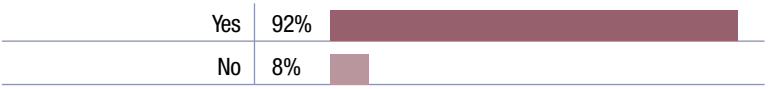


Tumor Panel Case 2

Part 1 Scenario 1:

This 66-year-old woman presents with an abnormal mammogram. Biopsy of the suspicious area demonstrates a 1.4-centimeter focus of comedo DCIS. Margins are clear to 2 millimeters, and no residual calcifications are seen on follow-up mammogram.

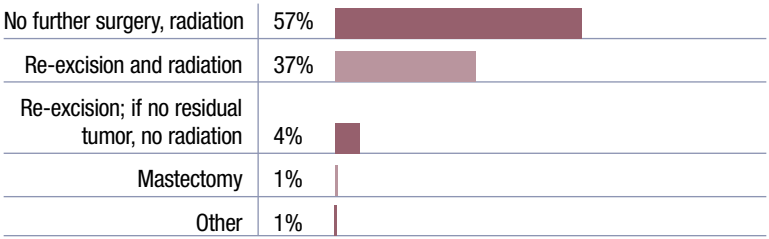
1.1 ***Would you order an ER/PR assay?***



Part 1 Scenario 2:

The specimen was sent for receptor staining, and eight percent of cells stained positively for ER; two percent stained positively for PR. The patient wishes to have breast conservation.

1.2 ***What recommendation do you have concerning local therapy?***

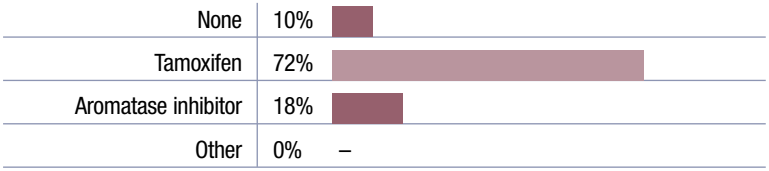


1.3 ***Would you recommend sentinel node biopsy?***

Part 1 Scenario 3:

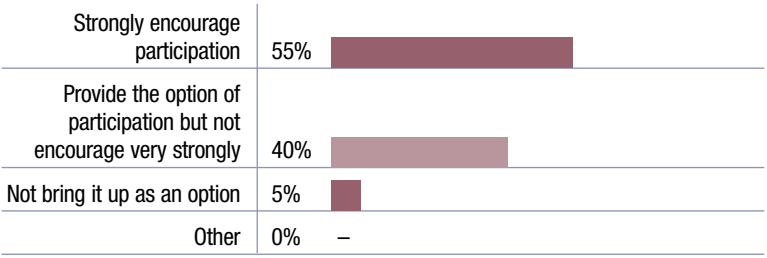
Patient undergoes re-excision of the lesion with no residual tumor. Radiation is planned.

1.4 ***What endocrine therapy, if any, should be suggested?***



Part 1: *(Continued)*

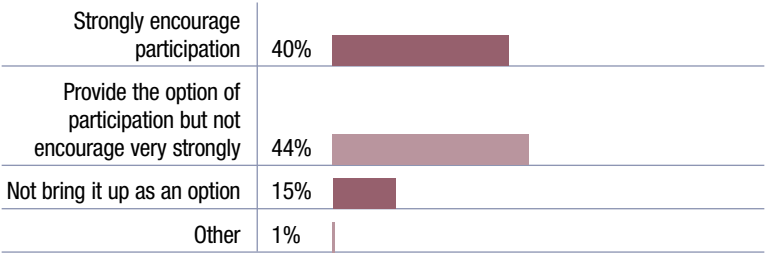
1.5 ***If this woman were eligible for NSABP-B-35, comparing tamoxifen to anastrozole in women with ER-positive DCIS, what advice should she be given regarding participation?***



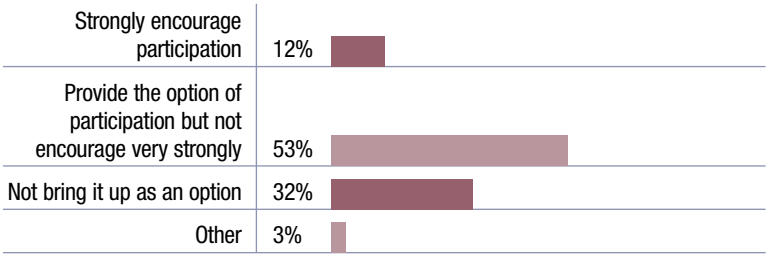
Part 2 Scenario 1:

The patient is treated with tamoxifen and three years later (at age 69), she has a 2-centimeter lesion palpated in the opposite breast. The lesion is excised and proves to be a 2.2-centimeter infiltrating ductal carcinoma (ER/PR-positive, HER2-negative [IHC 1+]). Sentinel node and eight axillary nodes are positive.

2.1 ***If this woman were eligible for CALGB-49907, comparing capecitabine to AC or CMF in elderly women, what advice should she be given regarding participation?***



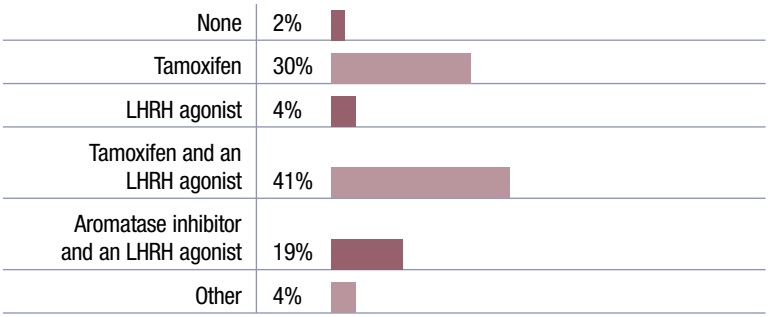
2.2 ***If this woman were eligible for CAN-NCIC-MA21, comparing CEF versus CE + G-CSF → paclitaxel versus AC → paclitaxel, what advice should she be given regarding participation?***



Part 2 Scenario 2:

The same patient is 37 years old. She is treated with dose-dense AC → T and is still menstruating after chemotherapy.

2.3 ***What hormonal therapy, if any, would you recommend?***



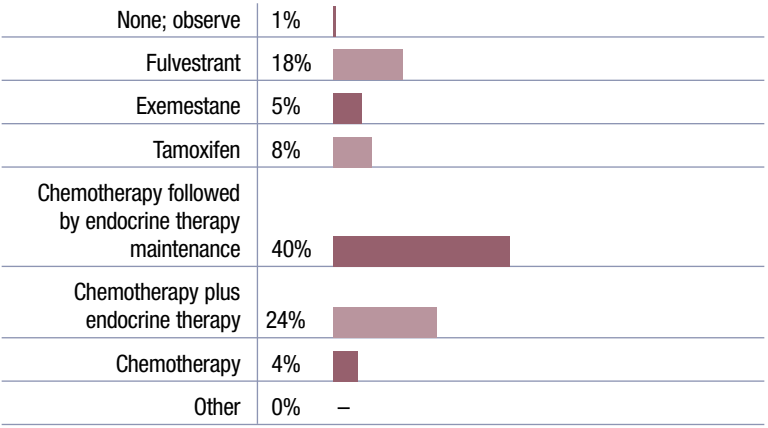
Part 3:

The patient (69 years old) is treated with dose-dense AC → T followed by anastrozole. Four years later she presents with shortness of breath, bilateral pleural effusions and multiple pulmonary nodules. Pleural tap relieves the symptoms, and adenocarcinoma cells are observed. Her CA27.29 is 338.

3.1 ***Would you do a FISH assay for HER2 status?***

Part 3: *(Continued)*

3.2 ***FISH is negative. What systemic therapy, if any, would you recommend?***



Research Leader Commentary and Supporting Graphics from *Breast Cancer Update*

A Breast Cancer Prevention

NSABP-P-1 and IBIS-I Studies: Breast Cancer Events

Trial	No. of patients		Total invasive and noninvasive cancers		
	Placebo	Tamoxifen	Placebo	Tamoxifen	Odds ratio 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

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

Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer

Protocol ID: NSABP-P-2
Projected Accrual: Approximately 19,000 patients will be accrued to this trial (open)

Eligibility	Postmenopausal women at risk (LCIS or ≥ 1.66% five-year probability) for developing breast cancer

ARM 1:	Tamoxifen + placebo x 5 years
ARM 2:	Raloxifene + placebo x 5 years

Quality of life assessed at baseline and six-month intervals to five years, then annually thereafter.

Study Contact:
Norman Wolmark, Chair, Tel: 412-359-3336
National Surgical Adjuvant Breast and Bowel Project
Allegheny General Hospital, Pennsylvania

SOURCE: NCI Physician Data Query, April 2004.

IBIS-II: International Breast Cancer Intervention Study-II

Protocol IDs: CRUK-IBIS-IIB, EU-20227
Target Accrual: 6,000 (open)

Eligibility	Postmenopausal women with increased breast cancer risk

ARM 1:	Anastrozole qd x 5 years
ARM 2:	Placebo qd x 5 years

Study Contact:
Jack Cuzick, PhD, Tel: 44-20-7269-3006
Cancer Research UK Clinical Trials Unit at the University of Glasgow

SOURCE: NCI Physician Data Query, April 2004.

RESEARCH LEADER COMMENTARY

Chemoprevention of breast cancer

NSABP-P-1 demonstrated a proof of principle. Tamoxifen prevented the clinical expression of breast cancers in about 50 percent of women at high risk. Epidemiologists question whether this is true prevention, or whether we're simply treating early at the level of phenotypic expression. That's possible, and I'm certain that there will be other candidates for prevention, such as the aromatase inhibitors. These agents have less toxicity, which will make them ideal agents for testing in the prevention setting.

As the mechanisms for detecting breast cancer improve, we are going to detect more lesions that are "preventable." The prognosis for these women is so good that we don't see why we should treat them. However, in the prevention mode we are treating these women and are very happy to reduce their risk of breast cancer by 50 percent. We are in a conundrum: "Should we treat them or not?"

— Bernard Fisher, MD

Aromatase inhibitors for prevention in postmenopausal women

Considerably fewer vasomotor symptoms and problems with weight gain are associated with aromatase inhibitors than with tamoxifen. While these are anecdotal observations, I have seen these differences in my own practice so often that I'm fairly certain they will prove to be true.

Perfectly healthy women considering prevention have a different level of motivation and tolerance of side effects than breast cancer patients who have been thrust into menopause by chemotherapy. The aromatase inhibitors are very well-tolerated and very safe, and I think if clinical trials demonstrate a positive therapeutic ratio for aromatase inhibitors, healthy women with even the slightest motivation to reduce their breast cancer risk will find them acceptable.

— Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)

ATAC: Research implications for prevention

If we look at the ATAC data, the improvement in terms of contralateral breast cancer risk is impressive. It is over 50 percent better than what we have achieved with tamoxifen. If the prevention trials with the aromatase inhibitors are positive, then the discussion will be easier than it ever was for us with tamoxifen, because tamoxifen was virgin territory. We had to begin with no understanding about chemoprevention. There was a whole process of educating physicians and patients, and that has been done.

The major obstacle for the use of tamoxifen in women at high risk is their fear of endometrial cancer and thrombosis. Some women are concerned about hot flashes and quality-of-life issues, and I think when you eliminate those fears, it'll be much easier to convince women to utilize a chemoprevention strategy.

— Generosa Grana, MD

IBIS-II trial

IBIS-II, a prevention trial, will compare anastrozole to placebo in women at high risk of developing breast cancer. In the United Kingdon, tamoxifen as prevention has not caught on because it has a high rate of morbidity. The IBIS-I study showed a very minimal effect and considerable morbidity with tamoxifen. Anastrozole looks like a better agent than tamoxifen for prevention, so I agree with the direct comparison to placebo.

Based on the ATAC trial data, I would expect anastrozole to dramatically decrease the number of breast cancers that develop. I think anastrozole should be superior to tamoxifen in that setting.

— J Michael Dixon, MD, FRCS

SELECT PUBLICATIONS

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

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

Cuzick J et al. **Overview of the main outcomes in breast-cancer prevention trials.** *Lancet* 2003;361(9354):296-300. **Abstract**

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. **Abstract**

Freedman AN et al. **Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention.** *J Natl Cancer Inst* 2003;95(7):526-32. **Abstract**

Goss PE, Strasser K. **Aromatase inhibitors in the treatment and prevention of breast cancer.** *J Clin Oncol* 2001;19(3):881-94. **Abstract**

Goss PE, Strasser-Weippl K. **Aromatase inhibitors for chemoprevention.** *Best Pract Res Clin Endocrinol Metab* 2004;18(1):113-30.

Peshkin BN et al. **Tamoxifen as chemoprevention in BRCA1 and BRCA2 mutation carriers with breast cancer: a pilot survey of physicians.** *J Clin Oncol* 2003;21(23):4322-8. **Abstract**

Smith RE, Good BC. **Chemoprevention of breast cancer and the trials of the National Surgical Adjuvant Breast and Bowel Project and others.** *Endocr Relat Cancer* 2003;10(3):347-57. **Abstract**

B HER2 Assessment

Comparison of Local HER2 Testing Performed for Study Entry to N9831 and Central FISH

	Central FISH result		
	Not amplified	Amplified	Total
Local HER2 testing			
IHC-positive (3+)	37	73	110
FISH-positive	3	6	9
Total	40	79	119

DERIVED FROM: Roche PC et al. *J Natl Cancer Inst* 2002;94:855-7. **Abstract**

Reproducibility of Community Laboratories' Results for HER2-Positive Status of Tumor Specimens from NSABP-B-31

Central laboratories' 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%

DERIVED FROM: Paik S et al. *J Natl Cancer Inst* 2002;94:852-4. **Abstract**

RESEARCH LEADER COMMENTARY

Importance of accurate HER2 testing

Whenever we have a new therapy requiring a predictive test, how that therapy performs is dependent on how good the test is at identifying the appropriate target. Both the NSABP adjuvant trial and the Intergroup trial indicated that HER2 testing in centers around the country — both community centers and academic centers — appeared to be less than perfect. Approximately 25 percent of the time, the test that was done in the local hospital — nonacademic institutions and academic institutions alike — couldn't be confirmed at a central testing site.

We need to be careful about where the HER2 testing is performed and view results from less-experienced labs with caution. This is especially important in the adjuvant setting where, unlike the metastatic setting, we're committing the patient to a course of therapy and we have no way of knowing if the treatment is working.

Also, when we are banking on results from clinical trials, it is critical that we know the testing is accurate. Currently, there's no established adjuvant role for trastuzumab, but I suspect in the next three to five years we'll learn whether it's an effective adjuvant therapy. Then accurate testing will be important to correctly identify the patients who will receive the maximum benefit from therapy.

— Eric P Winer, MD

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

— Melody Cobleigh, MD

Concordance between local and central laboratory HER2 testing

We were surprised when we found poor concordance between community and central laboratory HER2 testing, in terms of both HER2 protein expression and gene amplification. Perhaps more unexpected, we found poor concordance in terms of FISH testing in a central laboratory compared to the local laboratories. This last fact really came as a surprise to us and many others because the prevalent notion regarding FISH was that it was 100 percent accurate.

I've learned about these tests by spending time with our pathologists and looking at exactly what they see under the microscope with FISH. Although, theoretically, it is a matter of counting dots, it's not as simple as that — many tumors are aneuploid, some tumors have deletions of the chromosomes, and some tumors have clumping of dots in one spot. In other specimens it may be difficult to obtain the appropriate hybridization. There are some technical difficulties involved in FISH analysis.

The data from these 119 cases was so important that we actually changed the eligibility criteria for this large cooperative group trial (NCCTG-N9831). We modified the protocol so that physicians can still conduct HER2 testing based on any technology in their local laboratories. The patient is then enrolled in the study and starts the doxorubicin/cyclophosphamide (AC) portion of the chemotherapy.

During that time, we test the tumor specimens again by the HercepTest™ and the PathVysion™ FISH assay. If we find that neither of those two tests demonstrates HER2 positivity, we send the tumor specimen to another central laboratory to double-check our laboratory at the Mayo Clinic. If the other central laboratory also finds that the tumor is HER2-negative by both assays, then we notify the physician that the patient really should not participate in the trial.

— Edith A Perez, MD

Algorithm for HER2 testing: IHC versus FISH

Considerable controversy remains regarding the optimal method to routinely evaluate HER2 status. I won't treat a patient with metastatic breast cancer until I have a FISH

assay. In the June 2002 issue of the *Journal of the National Cancer Institute,* the NSABP and the Intergroup published their experiences with HER2 assessment, and it really cast doubt on our quality control for immunohistochemistry. Until the College of American Pathologists does something to resolve this problem of quality control, I continue to use FISH.

— Charles Vogel, MD, FACP

I assume that the tumors with a 3+ score on immunohistochemistry (IHC) are truly HER2-positive, and we do not test them further. An IHC score of 3+ is pretty reliable, as long as it is done at a laboratory that performs a lot of assays. If a tumor has a 2+ score on IHC, we test with fluorescence in situ hybridization (FISH). Even in patients with an IHC score of 0 or 1+ and other features of excessively aggressive disease, we may also do a FISH test.

Both the Intergroup and the NSABP study discovered that smaller community hospitals were overscoring tumors as 3+. Close to 20 percent of the 3+ scores were downstaged when they were reviewed centrally. The Intergroup protocol has now been amended to require that the patients wait for final randomization until there is a central review of their HER2 status.

— Debu Tripathy, MD

If one wants to know whether a patient has the HER2 alteration, one should do FISH testing. One should not do a default IHC, and then do FISH, only if the tumor scores 2+. Using that algorithm, patients without the HER2 alteration will be treated with trastuzumab, and other patients with the HER2 alteration may not be treated.

The BCIRG trial we are conducting was designed with FISH as the only criteria for assessing HER2 status. I think the day when FISH testing is the only assay used in the community is coming, and I hope it will be sooner rather than later.

— Dennis Slamon, MD, PhD

Tumors that score 2+ IHC are frequently found to be HER2-negative when tested by FISH. In those patients, I routinely have their tumors retested by FISH. On the other hand, I do not obtain a FISH analysis for tumors that score 3+ on IHC performed at a laboratory where I trust the pathologist.

Since HER2-positive breast cancer has a fairly specific phenotype (i.e., steroid receptor-negative, younger age, early relapse), I will retest those types of patients by FISH if I have a two- to three-year-old IHC score of 0 or 1+. If the patient's tumor is IHC-negative and FISH-positive, I will treat them with trastuzumab despite the fact that we do not have clinical data for that group of patients. Tumors that are FISH-positive are likely to have ample amounts of HER2 receptors on their cell surface.

We lack quality control for both IHC and FISH. This is analogous to the situation encountered with estrogen receptor testing in the mid- to late 1970s. One wonders how many patients died because they did not receive adjuvant tamoxifen as a result of inadequate estrogen receptor testing. If adjuvant trastuzumab provides a benefit like adjuvant tamoxifen, we may encounter the same problem.

— George Sledge, MD

SELECT PUBLICATIONS

Paik S et al. **Real-world performance of HER2 testing — National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94:852-4. **Abstract**

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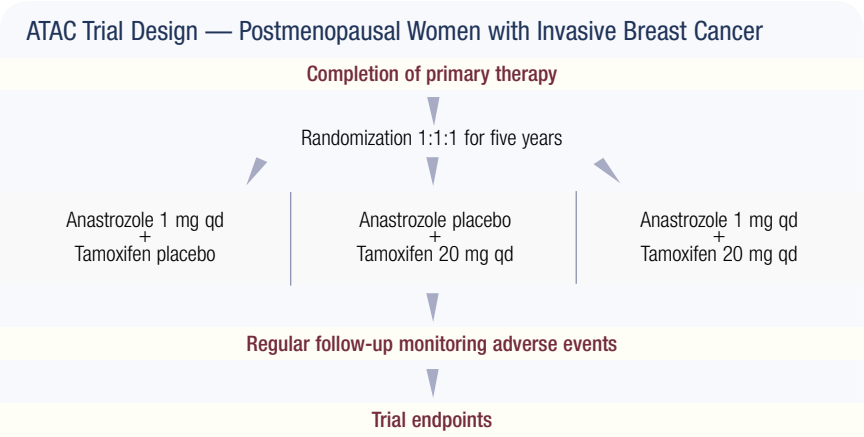
C Adjuvant Endocrine Therapy in Postmenopausal Patients: ATAC

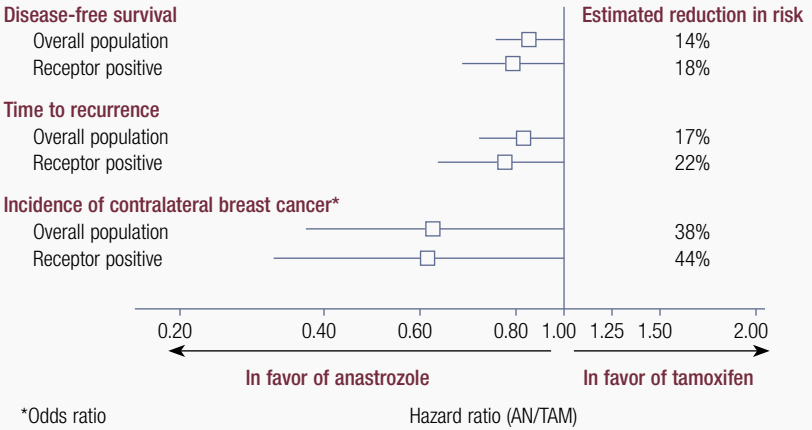


SOURCE: Buzdar A. Presentation, San Antonio Breast Cancer Symposium, 2002.

First Events in Overall Population

	Anastrozole n=3,125 (%)	Tamoxifen n=3,116 (%)
First event	413 (13.2)	472 (15.1)
Locoregional events	84 (2.7)	101 (3.2)
Distant events	195 (6.2)	222 (7.1)
Contralateral (invasive)	20 (0.6)	35 (1.1)
Contralateral (DCIS)	5 (0.2)	5 (0.2)
Deaths without recurrence	109 (3.5)	109 (3.5)

Summary I — Updated Analysis



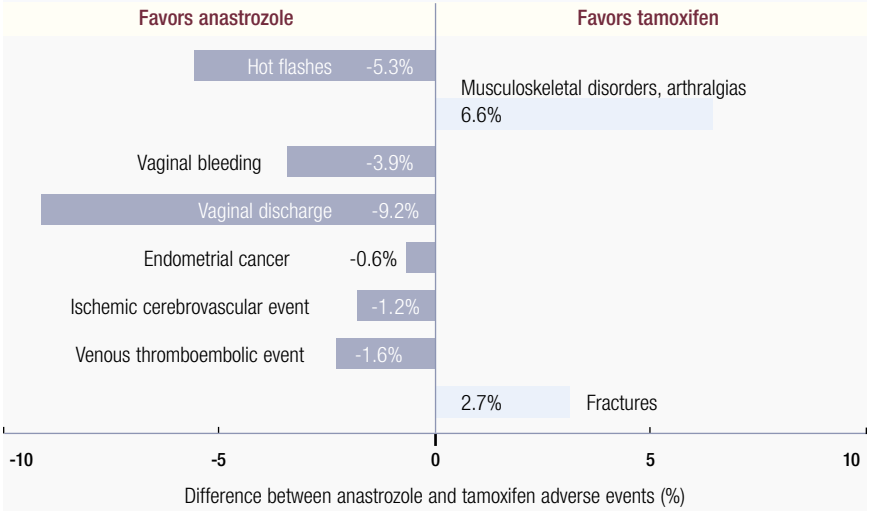
SOURCE: Buzdar A. San Antonio Breast Cancer Symposium, 2002.

Summary II — Absolute Benefits in Favor of Anastrozole

	3 years (%)	4 years (%)
Overall population		
Disease-free survival	1.5	2.4
Recurrences	1.7	2.3
Receptor-positive population		
Disease-free survival	1.7	2.9
Recurrences	1.8	2.6

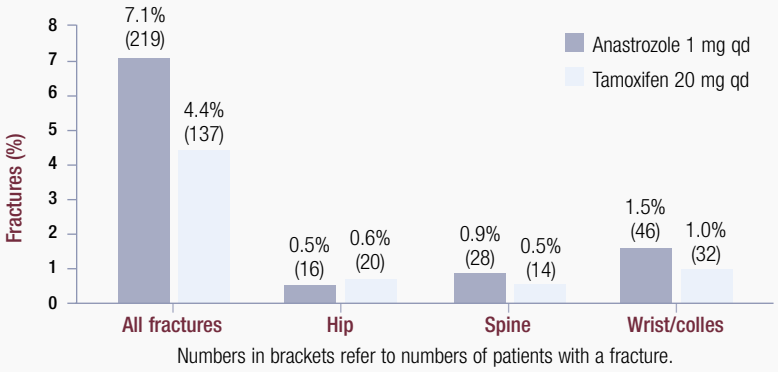
SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. **Abstract**

Significant Differences in Predefined Adverse Events



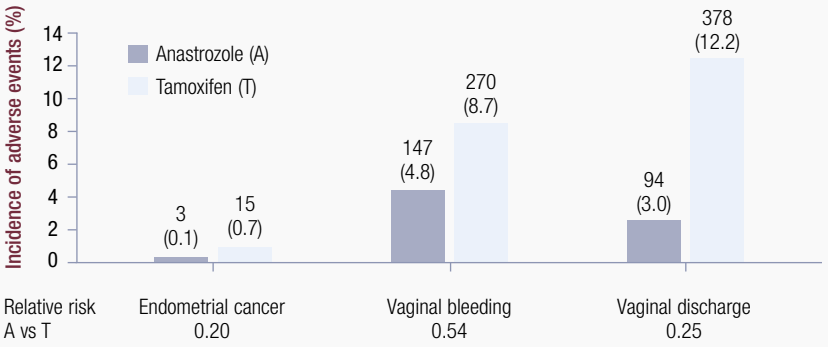
SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. **Abstract**

Bone Fracture Adverse Events



DERIVED FROM: Locker G. Poster presentation, Lynn Sage Breast Cancer Symposium, 2003.

Incidence (%) of Endometrial Cancer, Vaginal Bleeding and Vaginal Discharge in the ATAC Trial



DERIVED FROM: Grana G. Poster presentation, Lynn Sage Breast Cancer Symposium, 2003.

RESEARCH LEADER COMMENTARY

Updated results of the ATAC trial

The ATAC trial is a superb study of more than 9,000 patients. An update of the data was presented by Dr Aman Buzdar in San Antonio and showed that at four years follow-up, anastrozole was superior to tamoxifen with respect to disease-free survival and event rates. In addition, anastrozole is a less toxic drug without the risks of endometrial cancer or thromboembolic disease. Anastrozole was associated with an increased risk of fractures, which is important because fractures are a cause of mortality in the United States; we need a lot more information with regard to bone. This statistically powerful trial gives us another option for adjuvant therapy in estrogen receptor-positive postmenopausal patients, and I discuss both tamoxifen and anastrozole with patients.

— Hyman Muss, MD

Now my default therapy for postmenopausal women with estrogen receptor-positive tumors is anastrozole, unless contraindicated. We have another year of follow-up in the ATAC trial, and I am impressed by the separation of the curves. The safety update is also comforting. The fracture rate isn't racing away, the relative risks are stable, and the other safety profile issues continue to strongly favor anastrozole.

— Michael Baum, MD, ChM, FRCS, FRCR

The initial publication of the ATAC results caused concern because the data represented only about two-and-a-half years of follow-up. Now the median follow-up is four years, there are no new safety concerns and the early efficacy advantages have persisted — in fact, the absolute differences are increasing with time. I believe the data provide strong support for the adjuvant use of anastrozole in postmenopausal patients with hormone receptor-positive, early-stage breast cancer.

— Aman Buzdar, MD, FACP

Side effects and toxicities of anastrozole versus tamoxifen

The biggest problem with tamoxifen is not the risk of thromboembolism or uterine cancer, but managing uterine bleeding. Any woman who has uterine bleeding on tamoxifen goes through a panoply of tests, which causes a great deal of anxiety. At some time during their five years of therapy, a large percentage of women undergo a gynecologic procedure as a result of tamoxifen. What's really unacceptable about tamoxifen is that we overinvestigate some of these symptoms. This may be due to our medicolegal milieu, but it contributes to a miserable lifestyle and a lot of anxiety for women on tamoxifen in the adjuvant and preventative settings.

— Gershon Locker, MD

Implications of the ATAC trial in clinical practice

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

— Gabriel N Hortobagyi, MD

The ATAC trial has had a major impact across the country, and we are seeing more adjuvant anastrozole being used. The ATAC trial results must be discussed with patients, and patients should be aware of the two hormonal therapy options. Many factors go into making a decision about hormonal therapy, including the patient's ability to pay for the drug, her feelings and her history of thromboembolic events.

I am more likely to use adjuvant anastrozole in the patient with higher-risk, node-positive disease. The woman with 10 positive nodes needs every percentage point possible to make sure her cancer doesn't recur. I try to encourage those patients to receive anastrozole.

— Stephen E Jones, MD

ASCO Technology Assessment regarding adjuvant aromatase inhibitors

The ASCO Technology Assessment is a superb document, but it needs to be viewed for exactly what it is. A technology assessment looks at a given therapy, attempts to decide whether that therapy has utility in a given clinical situation and determines what the preponderance of data is within that clinical situation. The ASCO Technology Assessment, in both the first and second versions, states that tamoxifen remains the standard adjuvant therapy to which other therapies should be compared.

Interestingly, several members of the ASCO Technology Panel also sit on the NCCN Practice Guidelines Panel. When the NCCN Practice Guidelines Panel looked at this issue, there was no major dissension in considering anastrozole as an option. The difference between groups occurred because of the different processes.

The ASCO Technology Assessment is strictly evidence-based and cannot go beyond the evidence, so there are no extrapolations beyond five years of anastrozole or the 47 months of follow-up.

In the NCCN Practice Guidelines process, we use a methodology called evidence-based consensus. We establish recommendations based on evidence, but we are also able to use expert consensus in situations where the evidence is lacking. Obviously, 10-year data with adjuvant anastrozole are lacking, but we can come up with expectations about what might happen and make recommendations that extrapolate into the unknown.

The NCCN Practice Guidelines are patient-focused, and they look at the various therapies that are available from a patient's perspective. The NCCN Practice Guidelines Panel believes that women should consider the use of anastrozole, although we don't say it should necessarily be used in preference to tamoxifen.

— Robert W Carlson, MD

2003 NCCN® Practice Guidelines: Adjuvant Hormonal Therapy

"Early evidence from a single, large, double-blind, randomized clinical trial demonstrates that anastrozole provides superior disease-free survival and a favorable toxicity profile compared to tamoxifen as adjuvant therapy for hormone receptor-positive breast cancer in women. Additional follow-up of this trial and additional experience is required before definitive conclusions can be made.

"At the current time, anastrozole may be considered as an option to tamoxifen after discussion of the available data between the physician and patient. These data do not address whether women currently on tamoxifen should be changed to anastrozole. Anastrozole is not appropriate therapy for premenopausal women."

SOURCE: National Comprehensive Cancer Network (NCCN®). **NCCN Clinical Practice Guidelines in Oncology, Breast Cancer — Version 2. 2003.** Available at **http://www.nccn.org/physician_gls/f_guidelines.html**. Accessed July 9, 2003.

The ASCO Technology Assessment that does not support the use of adjuvant anastrozole outside a clinical trial is based on fear of the unknown in the face of the single largest clinical trial ever conducted in the adjuvant setting. We have no comparable trial in the history of medical oncology or breast cancer, and there is no other tumor type with so many well-planned clinical trials conducted. We are in a leadership position in oncology, and we can't advocate doing the best trials and then ignore the results of those trials. Every single trial we do brings with it some of the unknown. We have very compelling data about anastrozole from the ATAC trial, in terms of its therapeutic and safety profile superiority. I would be doing a disservice to my patients who are candidates for adjuvant antiaromatase therapy by not presenting the data. I also present tamoxifen as an option.

— Gabriel N Hortobagyi, MD

Clinical use of adjuvant aromatase inhibitors

Currently, I do not recommend the use of aromatase inhibitors other than anastrozole in the adjuvant setting. I recently published a review in *Cancer* demonstrating differences in the pharmacology and pharmacokinetics among the newer generation of aromatase inhibitors: anastrozole, letrozole and exemestane. Until we have long-term safety and efficacy data on letrozole and exemestane, I don't recommend their use outside of a clinical trial.

Experimental data in mice show possible benefits of exemestane on bone, but this still needs to be proven in patients. In addition, exemestane is a steroidal molecule that, because of its agonistic effect, may have safety issues similar to those associated with tamoxifen. We don't have enough long-term safety or efficacy data, even in metastatic disease, to know whether these androgenic effects will be beneficial or detrimental when exemestane is given to patients for a long period of time.

— Aman Buzdar, MD, FACP

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Duffy SR, Greenwood M. **The endometrial cancer data from the ATAC (arimidex, tamoxifen, alone or in combination) trial indicates a protective effect of anastrozole (arimidex) upon the endometrium.** *Breast Cancer Res Treat* 2003;**Abstract 134**.

Howell A, on Behalf of the ATAC Trialists' Group. **Effect of anastrozole on bone mineral density: 2-year results of the arimidex (anastrozole), tamoxifen, alone or in combination (ATAC) trial.** *Breast Cancer Res Treat* 2003;**Abstract 129**.

Winer EP et al. **American Society of Clinical Oncology Technology Assessment Working Group Update: use of aromatase inhibitors in the adjuvant setting.** *J Clin Oncol* 2003;21(13):2597-9. **Abstract**

D Adjuvant Endocrine Therapy in Postmenopausal Patients: Sequencing Tamoxifen and Aromatase Inhibitors

Phase III Randomized Study of Letrozole versus Placebo in Postmenopausal Women with Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen

Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA17, SWOG-CAN-MA17, SWOG-JMA17

Accrual: 5,187 (closed)

Eligibility	**Postmenopausal patients with ER- and/or PR-positive breast cancer previously treated with adjuvant tamoxifen for 4.5 to 6 years**

ARM 1	Letrozole x 5 years
ARM 2	Placebo x 5 years

Disease-Free Survival and Recurrences (Median Follow-up, 2.4 Years)

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

*Based on <1% of patients having been followed for ≥ 4 years.

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

Randomized Study of Tamoxifen versus Anastrozole in Postmenopausal Women with Breast Cancer Who Have Completed at Least Two Years of Adjuvant Tamoxifen

Protocol ID: ITA
Accrual: 448 (closed)

Eligibility	**Postmenopausal patients with node-positive, ER-negative and/or PR-positive breast cancer previously treated with adjuvant tamoxifen for 2 to 3 years**

ARM 1	Tamoxifen x 2-3 years
ARM 2	Anastrozole x 2-3 years

SOURCE: Boccardo A. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** Presentation, San Antonio Breast Cancer Symposium, 2003.

Efficacy Data Comparing Anastrozole (A) versus Tamoxifen (T) in Women Already Receiving Adjuvant Tamoxifen Treatment[1]

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

"Conclusion: 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."[2]

SOURCES: [1]Boccardo F. Presentation, San Antonio Breast Cancer Symposium, 2003.
[2]Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;**Abstract 3**.

Recent and Ongoing Trials of Sequential Adjuvant Endocrine Therapy

Study	N	Randomization	Status
ABCSG-8	3,500	TAM x 2 y → anastrozole x 3 y TAM x 2 y → TAM x 3 y	Open
NSABP-B-33	3,000	TAM x 57-66 mo → EXE TAM x 57-66 mo → placebo x 2 y	Closed
IBCSG-18-98/ EU-99022/ IBCSG 01-98	5,180	TAM x 5 y Letrozole x 5 y TAM x 2 y → letrozole x 3 y Letrozole x 2 y → TAM x 3 y	Closed
CAN-MA17/ BIG 97-01/	4,800	TAM 4.5-6 y → letrozole TAM 4.5-6 y → placebo x 5 y	Closed
ICCG 96 BIG 97-02	4,400	TAM x 5 y TAM x 2-3 y → EXE 2-3 y	Closed
ARNO-95	1,059	TAM x 2 y → anastrozole x 3 y TAM x 2 y → TAM x 3 y	Closed
Italian (ITA)	445	TAM x 2-3 y → anastrozole x 2-3 y TAM x 2-3 y → TAM x 2-3 y	Closed
GROCTA 4B	380	TAM x 2-3 y → aminoglutethimide x 2-3 y TAM x 2-3 y → TAM x 2-3 y	Closed

TAM = tamoxifen; EXE = exemestane

SOURCES: NCI Physician Data Query, January 2004; German Adjuvant Breast Cancer Group website; Boccardo F. Presentation, Nottingham International Breast Cancer Conference, 2003.

Switching adjuvant therapy in clinical practice

I am usually conservative, especially with my work. The ITA trial is a relatively small trial and the data is still early, so we need to be cautious and avoid over-interpretation of it. However, with that being said, the data speaks for itself and supports an advantage for switching to anastrozole following two to three years of adjuvant tamoxifen. This data also fits in with previous data from a study with aminoglutethimide, the ATAC trial and MA17, all pointing in the same direction.

— Francesco Boccardo, MD

We completed accrual to an adjuvant trial (IBCSG-18-98) comparing five years of tamoxifen, five years of letrozole, two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen in postmenopausal patients with endocrine-responsive disease. This trial accrued 8,028 patients.

A lifelong treatment strategy for patients with an increased risk of breast cancer recurrence might be reasonable. I think maintaining the cells under control and suppressing new tumors requires a sequential approach that includes endocrine therapy for tumors that are endocrine responsive.

— Aron Goldhirsch, MD

Aromatase inhibitors as initial therapy and sequence after tamoxifen

Increasingly, more data are emerging to support the superiority of aromatase inhibitors over tamoxifen. The NCIC-MA17 trial demonstrated the value of letrozole after five years of tamoxifen, and the Italian trial reported in San Antonio indicated that the switch from tamoxifen to anastrozole at two or three years results in a disease-free survival advantage and nearly results in a statistically significant survival advantage ($p = 0.06$).

I believe that if you're going to use an aromatase inhibitor, it is most appropriate to use it up front. The data in this setting are with anastrozole, so if I am going to use an aromatase inhibitor up front, I use anastrozole. The data for switching from tamoxifen at two to three years are with anastrozole, so I use anastrozole in that setting. After five years of tamoxifen, the data are with letrozole, so I use letrozole in those patients. Good clinical scientists treat patients according to the data.

— Anthony Howell, MD, MSc, FRCP

CAN-NCIC-MA17 trial: Efficacy of aromatase inhibitors following five years of adjuvant tamoxifen

Led by the National Cancer Institute of Canada, MA17 randomly assigned over 5,000 postmenopausal women who had received tamoxifen for between four and a half and six years and were free of tumor, to receive letrozole or a placebo. Letrozole reduced the rate of breast cancer events by about 50 percent, including the risk of distant metastases and the risk of ipsilateral or contralateral breast cancer. The differences were so robust

after only two and a half years that the study was closed before completing its planned five-year duration.

The data are exciting because letrozole has the potential to improve the long-term prognosis for the largest demographic group of patients — postmenopausal women with hormone receptor-positive breast cancer. Historically, these women have been offered five years of tamoxifen; now many such patients should consider taking letrozole after completing that therapy.

It's always exciting to close a study early because of such good news, but follow-up trials are needed to address unanswered questions about the best way to use letrozole in this setting. Also, there are concerns regarding the profound estrogen deprivation effects of aromatase inhibitors, particularly osteoporosis. We can study those issues, and potential interventions, but it means that we have to pause before blindly recommending this therapy to everyone.

— Harold J Burstein, MD, PhD

Time since completion of tamoxifen and aromatase inhibitor

MA17 was open to women who had finished tamoxifen within the past three months, but we have no data for women who have been off tamoxifen for a longer period. In practice, I consider letrozole therapy for patients who have finished their five years of tamoxifen therapy within the past year. Beyond year six, women who have had no recurrences have an additional period of time during which they've done well, and that means their moving-forward risk is even lower than it was before. It's difficult to know whether or not the data apply to them.

The whole issue of the timing, duration and sequencing of antiestrogen strategies is very interesting, and everyone is looking forward to the results of the Breast International Group/Femara®-Tamoxifen (BIG/FEMTA) study. This large European trial has four arms: (1) five years of an aromatase inhibitor, (2) five years of tamoxifen, (3) two years of tamoxifen followed by three years of an aromatase inhibitor, and (4) two years of an aromatase inhibitor followed by three years of tamoxifen.

— Harold J Burstein, MD, PhD

A good clinical scientist and clinician will treat patients according to the available data. In the adjuvant setting, the ATAC data support using anastrozole up front, the Boccardo data support switching to anastrozole after two to three years of tamoxifen, and MA17 supports the use of letrozole after five years of tamoxifen.

So at this point, if you are starting adjuvant therapy, you should use anastrozole because we have data on that. If you are going to switch at two to three years, you switch to anastrozole because we have data on that. But if you're going to give treatment after five years, you use letrozole because we have data on that.

— Anthony Howell, MD, MSc, FRCP

In the ITA trial, patients received a total of five years of therapy — either tamoxifen alone or tamoxifen for at least two years followed by anastrozole. Results from the ITA trial confirm the data from the MA17 trial in which patients received five years of adjuvant tamoxifen and then an aromatase inhibitor. It is unknown whether 10 years of

an adjuvant aromatase inhibitor alone would be more effective than five years of adjuvant tamoxifen followed by five years of an adjuvant aromatase inhibitor. Although the ITA trial was a small study, I'm willing to accept it as being fundamentally correct because the results are consistent with those from the MA17 trial. In both trials, a clear advantage was demonstrated for the crossover to an aromatase inhibitor after tamoxifen.

— I Craig Henderson, MD

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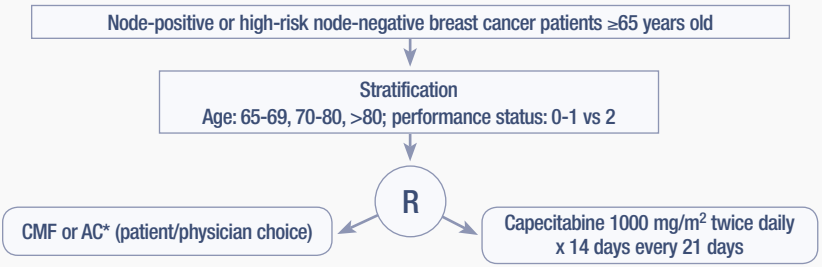
Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;**Abstract 3**.

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

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. **Abstract**

E Adjuvant Chemotherapy in the Elderly

CALGB-49907: Adjuvant CMF or AC versus Capecitabine in Women 65 Years and Older



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

SOURCE: NCI Physician Data Query, January 2003.

RESEARCH LEADER COMMENTARY

CALGB-49907: Adjuvant chemotherapy trial in elderly women

In my adjuvant trial for elderly (≥65 years) women with node-positive breast cancer or high-risk, node-negative breast cancer, patients are randomly assigned to either standard

chemotherapy or capecitabine. Because of the controversies about standard therapy, we gave doctors and patients the option of either CMF with an oral cyclophosphamide regimen or AC.

We have a quality-of-life assessment as part of the trial. We are looking at function and comorbidities, major issues in the management of older women with breast cancer in the adjuvant setting. We are also going to evaluate other issues including the biology of breast cancer and patient compliance. In a companion study with tissue blocks, we will look at HER2 and thymidine phosphorylase, which is related to the effect of capecitabine. This trial in older women may provide clues on how to predict which patients will benefit from which therapies.

— Hyman B Muss, MD

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

In a randomized Phase II trial of patients pretreated with anthracycline, comparing paclitaxel 175 mg/m^2 every three weeks to full-dose capecitabine, 1,250 mg/m^2 BID, two weeks on, one week off, the response with the capecitabine was 36 percent compared to 26 percent with paclitaxel. The confidence intervals were widely overlapping, so we couldn't conclude that capecitabine is superior, but what you can say from these two studies is that it's certainly unlikely that capecitabine is worse than CMF or paclitaxel.

It's interesting how quickly capecitabine has moved to trials in the adjuvant setting. In women over age 65, 75 percent have ER/PR-positive breast cancers. I think the role of chemotherapy in that group of patients is sufficiently unknown. Particularly for women over 70, the overview analysis includes so few patients in that age group that I think it's very reasonable to compare capecitabine to AC or CMF. I'd be a little less comfortable with it in a younger patient population, only because the overview has clearly shown that polychemotherapy is superior to monotherapy.

— Joyce O'Shaughnessy, MD

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

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Lewis JH et al. **Participation of patients 65 years of age or older in cancer clinical trials.** *J Clin Oncol* 2003;21(7):1383-9. **Abstract**

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

F Clinical Trials of Adjuvant Trastuzumab

Trials of Adjuvant Trastuzumab in the Treatment of Breast Cancer

Study name	Target accrual	Arms
BCIRG-006	3,150 (closed)	ARM 1: AC x 4 → docetaxel x 4 ARM 2: AC x 4 → docetaxel x 4 + H (qwk x 12 wk) → H (qwk x 40 wk) ARM 3: (docetaxel + C) x 6 + H (qwk x 18 wk) → H (qwk x 34 wk)
NCCTG-N9831 CLB-49909 E-N9831 SWOG-N9831	3,300 (open)	ARM 1: AC x 4 → paclitaxel qwk x 12 ARM 2: AC x 4 → paclitaxel qwk x 12 + H (qwk x 52 wk) ARM 3: AC x 4 → (paclitaxel + H) qwk x 12 → H qwk x 40 wk
BIG-01-01 EORTC-10011 HERA	3,192 (open)	(Randomization after approved neoadjuvant or adjuvant chemotherapy) ARM 1: H q3wk x 1 y ARM 2: H q3wk x 2 y ARM 3: No H
NSABP-B-31	1,000-2,700 (open)	ARM 1: AC x 4 → paclitaxel x 4 ARM 2: AC x 4 → paclitaxel x 4 + H qwk x 1 y

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

SOURCE: NCI Physician Data Query, April 2004.

RESEARCH LEADER COMMENTARY

Clinical trials of adjuvant trastuzumab

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

— Sandra Swain, MD

The Intergroup adjuvant trial evaluating trastuzumab plus chemotherapy builds on several issues, including the relative importance of anthracyclines in patients with HER2-positive breast cancer, and the value of adjuvant taxanes. Patients randomly assigned to trastuzumab receive it for a year. I believe adjuvant trastuzumab currently should only be used in a clinical trial setting. Clinicians who use this therapy off protocol are essentially shooting in the dark, because we don't understand for how long this therapy should be given, what schedule should be used in combination with chemotherapy, and the potential risks or benefits patients may derive from such treatment. Several major clinical protocols are available, and I hope that every woman diagnosed with HER2-

positive breast cancer asks her physician about participation in a clinical trial that will help answer those questions.

— Edith A Perez, MD

BCIRG-006 is a multinational, randomized, controlled trial for patients with FISH-positive, early-stage breast cancer — either node-positive or high-risk, node-negative disease. Patients are randomized to one of three different treatment arms: AC followed by docetaxel, AC followed by docetaxel/trastuzumab with trastuzumab continued for a total of one year, and trastuzumab/docetaxel with either carboplatin or cisplatin.

For the first time in a large randomized adjuvant study, a non-anthracycline-containing synergistic combination will be put to the test in a very carefully selected patient population. All of the patients must have FISH-positive disease; therefore, I think the trial will define the standard of care for the adjuvant treatment of patients with HER2-positive breast cancer.

The other important component of this trial is safety. There is a data safety monitoring committee and a specific cardiac safety monitoring committee. They are monitoring all of the treatment arms in real time, and they have predefined trigger points that call for an interruption in the protocol if there are any flags for cardiotoxicity in the AC followed by trastuzumab/docetaxel arm.

In fact, the study was designed in such a way that the arm can drop out if we encounter cardiotoxicity problems. We would still have a two-arm study — one arm with conventional chemotherapy and the other arm with trastuzumab/platinum/taxane.

It doesn't appear that cardiac safety is going to be a big issue in the adjuvant trastuzumab trials. Although there was a scare some months ago with the Intergroup trial and one arm was closed temporarily, that arm has reopened and the most recent update, presented by Dr Edith Perez, reveals that the incidence of depressed ejection fractions is the same in all of the arms of the Intergroup trial.

— Mark D Pegram, MD

Cardiac Safety Analysis in NSABP-B-31 Adjuvant Trastuzumab Trial

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

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

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

— Charles E Geyer Jr, MD,

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

Nonprotocol use of adjuvant trastuzumab

Trastuzumab is a fabulous drug that has made a huge difference for a lot of patients with metastatic disease and a very poor prognosis. We don't have any efficacy data for adjuvant trastuzumab, so I think it's unwise to use it in that setting outside of a clinical trial. I'm concerned about the potential cardiac toxicity, and we need the studies to mature in order to analyze the toxicity data. On the other hand, there are cases in which I would consider using trastuzumab, such as inflammatory breast cancer, where more of the patients are HER2-positive and survival is poor.

— Sandra Swain, MD

I try not to use trastuzumab in patients with Stage II and IIIA breast cancer outside of a trial, because it's not an established therapy. In patients with inflammatory breast cancer, I don't know that we're ever going to have a randomized study, and at least 50 percent of the time the tumor is HER2-positive. I would be hard-pressed to criticize a physician who wanted to use a trastuzumab-based regimen in a patient with HER2-positive, inflammatory breast cancer.

I feel patients who are eligible for the randomized adjuvant trials should be encouraged to participate. Outside of those trials, I think that the standard adjuvant treatment is a non-trastuzumab-containing combination.

— Eric P Winer, MD

In the nonprotocol adjuvant setting, it's hard to know the right thing to do. I've evaluated patients with high-risk disease — 10 or more positive nodes — in whom I've considered adjuvant trastuzumab therapy off protocol.

I don't want to say that this is something that is widely done at our center — it's infrequent and uncommon. However, the prospects for a patient with that type of disease are really unacceptable. If you consider that trastuzumab prolongs survival in patients with metastatic disease, biologically there are probably many similarities between high-risk Stage II and advanced disease. Therefore, that would be an interesting patient population to study. Off protocol we have considered such patients for adjuvant trastuzumab therapy.

— Mark D Pegram, MD

The research question that has to be answered is: How do we use it appropriately? Do we use AC followed by paclitaxel and concurrent trastuzumab, or should we be using a non-anthracycline-containing regimen to avoid cardiac toxicity? Those two questions are going to be very important to address in clinical trials.

I have not been using trastuzumab in the adjuvant setting but have used it for locally advanced and inflammatory disease. I'm selective in choosing patients for whom I'll use it. Often, it will be the patient who did not respond well to AC or had very aggressive disease.

— Generosa Grana, MD

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G Sequencing Endocrine Therapy in Metastatic Disease

Efficacy of Fulvestrant Compared to Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy

	Combined analysis[1]		European trial (0020)[3]		North american trial (021)[5]	
	Fulvestrant n=428	Anastrozole n=423	Fulvestrant n=222	Anastrozole n=229	Fulvestrant n=206	Anastrozole n=194
Disease progression			82.4%	83.4%	83.5%	86.1%
Median time to progression	5.4 mo	4.1 mo	5.5 mo	5.1 mo	5.4 mo	3.4 mo
Treatment failures			84.7%	85.6%	79.6%	84%
Objective response	19.2%[2]	16.5%[2]	20.7%	15.7%	17.5%	17.5%
Clinical benefit (CR + PR + SD ≥24 wk)	43.5%[2]	40.9%[2]	99 (44.6%)	103 (45.0%)	87 (42.2%)	70 (36.1%)
Median duration of response in those responding	16.7 mo*	13.6 mo*	15.0 mo	14.5 mo	19.0 mo	10.8 mo
Median time to death			26.5 mo[4]	24.3 mo[4]		

*In addition to reporting median duration of response (DOR) in those responding, a newly developed statistical analysis of DOR was performed, defined for responders as the time from onset of response to disease progression and for nonresponders as zero. In this analysis, DOR was significantly greater (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; p=0.0003) for fulvestrant versus anastrozole.

SOURCES: [1]Parker LM et al. *Proc ASCO* 2002;**Abstract 160**. [2]Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. **Abstract** [3]Howell A et al. *J Clin Oncol* 2002;20:3396-403. **Abstract** [4]Howell A et al. *Proc ASCO* 2003;**Abstract 178.** [5]Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. **Abstract**

Ongoing and Future Clinical Trials of Fulvestrant in the Metastatic Setting

Study	Trial design	Dosing/scheduling of fulvestrant	Status (accrual)
NCCTG-N0032	Fulvestrant after progression on an AI ± tamoxifen	250 mg monthly	Ongoing (57/89)
SAKK	Fulvestrant after progression on tamoxifen and a nonsteroidal AI	250 mg monthly	Ongoing (69/93)
EFECT	Fulvestrant vs exemestane after progression on a nonsteroidal AI	500 mg day 0, 250 mg days 14, 28, and then monthly	Not yet open (0/660)
SOFEA	Fulvestrant vs fulvestrant + anastrozole vs exemestane after progression on anastrozole or letrozole	250 mg monthly	Planned (0/750)
SWOG-S0226	Anastrozole vs fulvestrant	250 mg monthly	Planned (0/690)
FACT	Anastrozole + fulvestrant vs anastrozole in postmenopausal women or premenopausal women on goserelin	500 mg day 0, 250 mg days 14, 28, and then monthly	Planned (0/558)
ECOG-4101	Fulvestrant + gefitinib vs anastrozole + gefitinib	250 mg monthly	Not yet open (0/204)

AI = aromatase inhibitor

DERIVED FROM: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®).** Poster, Lynn Sage Breast Cancer Symposium, September 2003.

RESEARCH LEADER COMMENTARY

Clinical experience with fulvestrant

I've used a fair amount of fulvestrant, and it's very well-tolerated. We've had some very nice responses to fulvestrant, including one of my patients who was enrolled in the original clinical trial of fulvestrant versus anastrozole. She was on fulvestrant for three and a half years, and now she's on anastrozole. The injections have not been an issue for patients, and most women are very grateful that the side-effect profile is close to nil. I think fulvestrant probably crosses the blood-brain barrier and patients do have hot flashes on it, but in general, they're quite mild.

I am a little disquieted by the fact that it can take three to five months to reach a steady state with fulvestrant. A patient with rapidly progressing disease may not benefit from fulvestrant, but fortunately most women with hormone-responsive breast cancer have relatively indolent disease. I'm very interested in the clinical trial in which they are loading fulvestrant 500 mg every two weeks for a couple of doses and then reducing it to 250 mg monthly. That makes sense to me, so I've been trying to load it a little by giving it every three weeks for several injections in an attempt to raise the levels more quickly.

— Joyce O'Shaughnessy, MD

My patients like fulvestrant because it lets them get on with their activities and maintain their quality of life. In my experience, it has been much more likely to result in stable disease rather than produce measurable responses or complete remissions. However, it has stabilized patients with excellent quality of life for long periods of time without having to change therapy.

It'll be interesting to see the trials that move fulvestrant into the front-line setting. All of the hormonal agents, when they first become available, are used in patients with refractory disease.

— Denise A Yardley, MD

Like many of my colleagues, I'm not quite sure where to use fulvestrant, partly because we have limited clinical trial data. My interpretation of the results of the large North American and European trials is that fulvestrant and anastrozole are roughly equivalent agents in terms of survival.

In the North American trial, fulvestrant appeared to have some advantage over anastrozole in response and time to progression. My approach to therapy is to use survival to guide how I treat patients. The trials didn't demonstrate a survival difference, so I don't feel strongly that one agent is better than the other.

I use fulvestrant regularly in my patients with steroid receptor-positive, metastatic breast cancer. I have patients who prefer receiving an injection once a month to taking pills every day. I have other patients who would prefer a pill to a shot. Aside from the acute discomfort of the injection itself, I've found fulvestrant to be an exceptionally well-tolerated medication.

— George W Sledge, MD

In my clinical experience, fulvestrant is very easy to administer and extremely well-tolerated. My patients have not had any problems with the intramuscular injection. One might assume that a pill is more convenient therapy for a patient than an injection, but that is not necessarily so. Convenience is an individual choice. Some patients would rather receive a shot once a month than take a pill every day.

Fulvestrant has been exceptionally well-tolerated and I've seen responses in heavily pretreated patients. Fulvestrant also works after multiple endocrine failures, including tamoxifen and the aromatase inhibitors, even in a third- or fourth-line setting. We now have a very well-tolerated endocrine agent to add to our armamentarium in the metastatic setting.

— Richard M Elledge, MD

Sequencing hormonal agents in postmenopausal women with metastatic disease

In a postmenopausal woman whose disease relapses on adjuvant tamoxifen, I would 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 (e.g., aromatase inhibitors and megestrol acetate).

A couple of reports have looked at the response to fulvestrant in patients who have received an aromatase inhibitor. A fairly small Swiss study reported that about one-third of patients derived clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor. A compassionate-use study, reported at ASCO 2003, reported about 60 patients with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had a more than 50 percent clinical benefit rate in those patients.

— Stephen E Jones, MD

Clinical trials of fulvestrant in the metastatic setting: Fulvestrant versus anastrozole

Fulvestrant has a different mechanism of action than the other hormonal agents because it downregulates both the estrogen and progesterone receptors. It's a well-tolerated parenteral agent — a potential advantage for patients with compliance issues. There is a subset of patients who had an exceptionally long duration of response with fulvestrant, and this is not fully appreciated.

US Oncology participated in one of the trials comparing fulvestrant to anastrozole, and I personally enrolled 27 patients in the study. Five of those patients had responses lasting longer than three years, which is really extraordinary for any endocrine treatment; two of the patients had responses lasting longer than four years. Of those five patients, four have progressed and had their therapy unblinded; all four were on fulvestrant. I would bet the fifth patient, although her treatment remains blinded, is also on fulvestrant.

A reanalysis of the North American and the European fulvestrant trials used a different statistical model called the mean duration of response. In that statistical model, values were assigned to every patient: patients with disease that did not respond were assigned a value of zero and patients with disease that did respond were assigned a number to correspond with the number of months of the response. With those calculations, fulvestrant had a significantly longer duration of response. It was 36 percent longer in the North American trial and 27 percent longer in the European trial.

— Stephen E Jones, MD

The trials of fulvestrant versus anastrozole in patients progressing on tamoxifen were large, well-executed studies — in contrast to other hormone therapy trials done as recently as five years ago. The fulvestrant versus anastrozole trials demonstrated that fulvestrant is a very safe therapeutic agent for cancer. There were virtually no toxicities other than background noise.

The main difference between fulvestrant and anastrozole in the American trial was the increased duration of response in the fulvestrant arm. Not only was there a statistically significant improvement from 10 months to 19 months, but this time difference is clinically and humanly worthwhile in the metastatic setting. It tells us that this agent might give us a bit of a boost in the adjuvant setting.

— Richard M Elledge, MD

I'm concerned that physicians routinely give fulvestrant to patients with hormone receptor-positive metastatic disease who have received multiple chemotherapy regimens

and hormonal therapies, and then judge fulvestrant to be a relatively inactive drug. This is probably not a fair evaluation.

In randomized trials of patients receiving fulvestrant or anastrozole in the metastatic setting, fulvestrant was at least as good as anastrozole, and I find the data quite persuasive. The one striking difference that favored fulvestrant was that there were fewer arthralgias and musculoskeletal complaints and, in our institution, the injection has not been a major issue.

— Eric P Winer, MD

Fulvestrant versus tamoxifen

Much to our surprise, the trial comparing fulvestrant versus tamoxifen did not demonstrate that fulvestrant was superior in the first-line setting. Extrapolating what we know from previous trials of fulvestrant versus anastrozole, and of anastrozole versus tamoxifen, we predicted that fulvestrant would be better than tamoxifen. However, in the study we just didn't see it.

Some have suggested that the dose of fulvestrant was inadequate. While I believe this should be explored, I'm not entirely convinced it is the reason. Another possibility relates to the fact that most patients in the second-line study had been treated with tamoxifen or were coming straight off of tamoxifen. This may have somehow altered the phenotype, perhaps causing fulvestrant to work better in the second-line trial, as opposed to treatment-naïve tumors or those that have not been recently exposed to tamoxifen. After reviewing the data, the reason the first-line trial didn't demonstrate fulvestrant to be superior to tamoxifen is still not clear.

— Richard M Elledge, MD

Data have been presented demonstrating that fulvestrant is active in the first-line setting, but in the first-line study comparing it to tamoxifen, it did not prove to be more active. The primary endpoint was time to treatment failure, and tamoxifen was superior, although not statistically. One question that has been raised in this setting is whether the fulvestrant dose was adequate.

A number of investigators feel that some of the early failures seen in the comparison of fulvestrant and tamoxifen might indicate that patients were not brought up to their steady-state level, and that a loading dose of fulvestrant may be necessary.

This is currently being studied in a clinical trial that gives patients a loading dose in the first month of therapy. I would not recommend the concept of a loading dose in a nonprotocol setting at this time. We already know that when fulvestrant was compared to anastrozole as treatment for progression after tamoxifen, the current dose was adequate.

— Leroy M Parker, MD

Novel hormonal therapy combinations

There is an increasing body of preclinical evidence suggesting that breast cancers that become resistant to tamoxifen or fulvestrant have upregulation of epidermal growth factor receptor (EGFR) and HER2 expression. As those endocrine-sensitive cells become

endocrine-resistant and the EGFR and HER2 upregulate, some of the sensitivity to the endocrine agents may return if those cells are exposed to EGFR inhibitors.

Series of trials are being conducted to evaluate the role of fulvestrant or other hormonal agents in combination with gefitinib. ECOG is initiating a Phase II randomized trial comparing fulvestrant/gefitinib to anastrozole/gefitinib.

The combination of an aromatase inhibitor and fulvestrant is of some interest, but the difficulty with such a study is that fulvestrant eliminates the estrogen receptor. Theoretically, if the estrogen receptor is eliminated, then the cells shouldn't care how much estrogen is present.

— Robert W Carlson, MD

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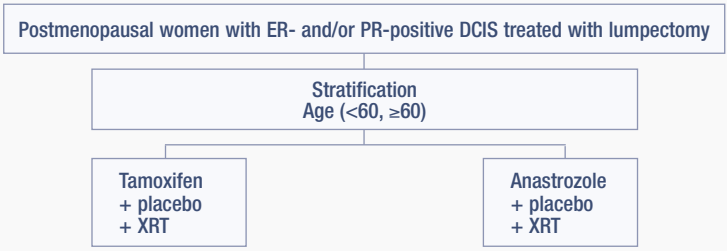
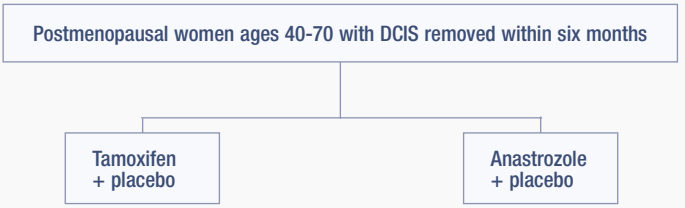
H Ductal Carcinoma In Situ

NSABP-B-35 Trial



SOURCE: NCI Physician Data Query, April 2004.

IBIS-II DCIS Trial



SOURCE: Cancer Research (UK) website, April 2004.

RESEARCH LEADER COMMENTARY

Trends in the diagnosis of DCIS

In 1978, the American College of Surgeons conducted a survey demonstrating that 200 out of 24,000 cases of breast cancer were DCIS — less than one percent. The incidence of DCIS exploded in the mammographic era. By screening women, we discovered microcalcifications and other architectural distortions that we otherwise never would have known were present. Some of those women would have developed invasive breast cancer six to 10 years later. Now, we intercede in the neoplastic continuum five to 10 years earlier. Today, DCIS represents 21 percent of all new cancers. In 2003, we will detect 57,000 cases of DCIS and 211,000 cases of invasive breast cancer.

DCIS is the precursor lesion to invasive breast cancer. Roland Holland, the renowned

Dutch pathologist, examined 100 consecutive invasive breast cancers, which he thoroughly sampled with multiple slides for each. In 98 out of 100 cases, he found a DCIS component in at least one of the slides. This is compelling evidence that DCIS is a precursor lesion. It does not mean all DCIS will develop into invasive breast cancer; rather, all invasive breast cancers were probably born from DCIS.

— Melvin Silverstein, MD

NSABP-B-35 trial : Anastrozole versus tamoxifen in DCIS

NSABP-B-35 is the next protocol in a generation of NSABP DCIS trials: B-17 compared radiotherapy to no treatment, B-24 added tamoxifen to lumpectomy and radiotherapy, and B-35, which opened in January 2003, compares anastrozole to tamoxifen for five years. We're hoping that anastrozole will be superior to tamoxifen, as it was in the ATAC trial; however, that trial was powered to detect small differences in efficacy.

We debated considerably whether ER positivity should be required for eligibility in B-35. Dr Craig Allred reanalyzed data from NSABP-B-24 and demonstrated benefit from tamoxifen only in patients with ER-positive DCIS. Ultimately, we decided to limit eligibility for B-35 to patients with ER-positive DCIS. Only a small subset of women with DCIS — approximately 20 percent — is ER-negative. At the current time, I believe it is overly restrictive and authoritarian to dictate that the community standard require estrogen receptor assay prior to treating DCIS.

— Norman Wolmark, MD

The NSABP study comparing tamoxifen and anastrozole for patients with DCIS is essentially a trial aimed at preventing invasive breast cancer. Aromatase inhibitors have emerged as very good agents in the treatment of metastatic breast cancer, both second- and first-line, and the pivotal results from the ATAC trial demonstrated adjuvant anastrozole was more effective than tamoxifen in reducing recurrence rates and contralateral breast cancers. If patients with DCIS fail, it's usually in the ipsilateral or contralateral breast rather than in the regional nodes or distant sites.

Aromatase inhibitors are very well-tolerated in general. In the ATAC trial, the safety profile of anastrozole was impressive. Patients had fewer thromboembolic events, endometrial cancers and menopausal symptoms than with tamoxifen, but with aromatase inhibitors we need to monitor bone density and fractures.

— Eleftherios P Mamounas, MD, MPH, FACS

The question about aromatase inhibitors as preventive agents is a very important one. I am concerned that the IBIS-II trial — comparing anastrozole to placebo — won't give us the answer we need. We'll know if anastrozole is better than a placebo, but we won't know how SERMs compare to aromatase inhibitors or which is better in terms of overall health. We will not be able to extrapolate these answers from two completely different study populations, and this will leave us with another trial to do. In addition, I would not recommend this trial to a woman at very high risk. With tamoxifen on the market, proven to reduce breast cancer risk, I don't think taking a 50 percent chance of being randomized to a placebo is a good choice. IBIS-II also has a randomization for women with DCIS, but this compares anastrozole to tamoxifen.

I agree that treating DCIS is primarily prevention — it's a lesion that carries a significantly increased risk of invasive breast cancer. We tend to think of it differently because we treat it like cancer, but the question is the same. The NSABP-B-35 trial is asking the same question, randomly assigning women with DCIS to anastrozole versus tamoxifen. It is a good trial, addressing an important question, and I heartily support that study.

— Monica Morrow, MD

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I Adjuvant Endocrine Therapy: Premenopausal Patients

EST-5188, INT-0101: Phase III Randomized Comparison of Adjuvant Therapies in Premenopausal Women with Resected Node-Positive Hormone Receptor-Positive Adenocarcinoma of the Breast — **Closed Protocol**

Eligibility	Node-positive, hormone receptor-positive patients within 12 weeks of surgery

ARM 1	Surgery → CAF
ARM 2	Surgery → CAF + Z
ARM 3	Surgery → CAF + Z + T

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

SOURCE: NCI Physician Data Query, April 2004.

INT-0101 Trial Results: 9.6 Years Follow-up

	DFS	Survival	DFS (patients under age 40)
CAF	57%	70%	48%
CAFZ	60%	73%	55%
CAFZT	68%	76%	64%

SOURCE: Davidson NE. Presentation, ASCO Annual Meeting, 2003;**Abstract 15**.

Randomized Adjuvant Trial of Tamoxifen and Goserelin versus CMF: Evidence for the Superiority of Treatment with Endocrine Blockade in Premenopausal Patients with Hormone-Responsive Breast Cancer

Protocol ID: ABCSG-05
Projected Accrual: 1,099 patients (closed)

Eligibility	Premenopausal, Stage I or II, ER- and/or PR-positive breast cancer

ARM 1	IV CMF x 6*
ARM 2	Goserelin x 3 y + tamoxifen x 5 y

*Patients did not receive tamoxifen after completion of chemotherapy.

DERIVED FROM: Jakesz R et al. *J Clin Oncol* 2002;20:4621-7. **Abstract**

ABCSG-05 Trial Results: Five-year follow-up

	Goserelin + tamoxifen (n=511)	CMF (n=523)	*p*-value (Breslow)
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

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

Ongoing Trials of Adjuvant Endocrine Therapy in Premenopausal Patients

Study	Entry	Intervention	Target accrual
ABCSG-AU12	Stage I, II	Tamoxifen + goserelin ± zoledronate Anastrozole + goserelin ± zoledronate	1,250
IBCSG-24-02 (SOFT trial)	T1-T3, pNO-N2	Tamoxifen Ovarian suppression + tamoxifen Ovarian suppression + exemestane	3,000
IBCSG-25-02 (TEXT trial)	T1-T3, pNO-N2	Triptorelin + tamoxifen Triptorelin + exemestane	1,845
IBCSG-26-02 (PERCHE trial)	T1-T3, pNO-N2	Ovarian suppression + tamoxifen or exemestane Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy	1,750

DERIVED FROM: NCI Physician Data Query, January 2004; and Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;**Abstract 12**.

RESEARCH LEADER COMMENTARY

Intergroup Trial 0101

The design of this trial was CAF chemotherapy versus CAF chemotherapy followed by five years of goserelin versus CAF chemotherapy followed by five years of goserelin and tamoxifen. There is no impact on disease-free survival in the overall population with the addition of goserelin, but there is a trend to suggest that the younger patients may benefit.

Although it seemed like such a large clinical trial at the time it was initiated, a study of 1,500 women doesn't have the power to reveal a significant difference even in younger women and even with all this follow-up.

We don't have any new data over the last year but we have a lot of re-examination of old data. My synopsis is that in ER-positive, premenopausal women, tamoxifen is a good drug. Ovarian suppression or ablation is also beneficial, but we are having a difficult time figuring out how to integrate them.

The one new trial that I've seen over the last year is the Austrian trial comparing CMF chemotherapy to ovarian suppression with tamoxifen in premenopausal ER-positive women. They suggested that the outcome was slightly better with the combined endocrine therapy.

In that trial the women who underwent chemotherapy didn't take tamoxifen because it was not the standard of care when the trial was launched. Today we think of that as a pretty profound deficit with that study and related studies, so we need to come together to investigate this further. There is a trio of trials that we are trying to launch worldwide to look at issues of ovarian suppression in young women.

— Nancy E Davidson, MD

SOFT: Ovarian ablation with tamoxifen or an aromatase inhibitor

The adjuvant ovarian suppression trial that I am most enthusiastic about is the Suppression of Ovarian Function Trial (SOFT). Premenopausal ER-positive women who may or may not have received chemotherapy will be randomly assigned to tamoxifen for five years, ovarian suppression/ablation plus tamoxifen, or ovarian suppression/ablation plus an aromatase inhibitor. This very interesting trial will help us address several issues. Does ovarian ablation or suppression add to tamoxifen? And if this is an important strategy, is it better to use tamoxifen or an aromatase inhibitor in women with ovarian suppression? This trial is an international collaboration put together by the International Breast Cancer Study Group (IBCSG).

— Nancy E Davidson, MD

In premenopausal women, there is a rejuvenation of interest in ovarian ablation in combination with tamoxifen. Is ovarian ablation in addition to tamoxifen or in combination with an aromatase inhibitor superior to tamoxifen alone in a premenopausal woman? Right now that is the $64-million question that is being addressed in the SOFT and the Tamoxifen and Exemestane Trial (TEXT).

— G Thomas Budd, MD

The SOFT and TEXT trials are evaluating whether ovarian ablation, with either an aromatase inhibitor or tamoxifen, is beneficial. Right now we just don't know.

— Sandra Swain, MD

ABCSG-12: Adjuvant anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) for patients with hormone receptor-positive, premenopausal breast cancer

The ABCSG-12 trial has four arms comparing goserelin/tamoxifen to goserelin/anastrozole with or without zoledronic acid. We included zoledronic acid because it's the most potent bisphosphonate pharmacokinetically, and we were concerned about the risk of osteoporosis with the aromatase inhibitors. Chemotherapy is only permitted as neoadjuvant therapy. No postoperative chemotherapy is allowed.

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

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

— Michael F Gnant, MD

SELECT PUBLICATIONS

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Davidson N et al. **Effect of chemohormonal therapy in premenopausal, node(+), receptor (+) breast cancer: An Eastern Cooperative Oncology Group phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 1999;**Abstract 249A, 67A**.

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

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Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002;20(24):4621-7. **Abstract**

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

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

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

J Chemotherapy in Metastatic Breast Cancer

Phase III Trial of Docetaxel/Capecitabine (XT) Combination Therapy versus Docetaxel Monotherapy (T) in Metastatic Breast Cancer

Accrual: 511 patients (closed)

Eligibility	**Metastatic breast cancer patients resistant to or relapsing after anthracycline-based therapy**
ARM 1	Capecitabine 1,250 mg/m^2 BID days 1-14 + docetaxel 75 mg/m^2 IV q3wk
ARM 2	Docetaxel 100 mg/m^2 IV q3wk

"The significantly superior survival, including a 3-month improvement in median survival, achieved with combined docetaxel plus capecitabine and the manageable toxicity should establish this regimen as an important treatment option for patients with anthracycline-pretreated metastatic breast cancer."

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

XT versus T: Post-Study Chemotherapy after Progression

	XT	T
Percent receiving postrandomization chemotherapy	72%	65%
Agent received*		
Capecitabine	3%	18%
5-FU	20%	23%
Vinorelbine	33%	28%
Anthracyclines	11%	11%
Docetaxel	21%	7%

*Reflects combination and single-agent chemotherapy regimens.

Capecitabine versus all other chemotherapies resulted in a 50% decreased risk of death (HR = 0.5, $p < 0.005$).

Vinorelbine-containing chemotherapy versus all other chemotherapy agents did not provide benefit (HR = 1.0, $p = 0.94$).

Median survival was 21.0 months for single-agent capecitabine, 13.5 months for vinorelbine, and 12.5 months for patients receiving any other chemotherapy regimen.

SOURCE: Miles D. Poster 442, San Antonio Breast Cancer Symposium, 2001.

Summary of Efficacy: Single-Agent Capecitabine versus Standard Chemotherapy in Patients with Anthracycline-Resistant Metastatic Breast Cancer

Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF) as first-line therapy

	Capecitabine	CMF
Response rate (95% CI)	30% (19-43)	16% (5-33)
Complete response	5%	0%
Median time to disease progression (95% CI)	4.1 months (3.2-6.5)	3.0 months (2.4-4.8)
Median survival	19.6 months	17.2 months

Capecitabine versus paclitaxel as second-line therapy

	Capecitabine	Paclitaxel
Response rate (95% CI)	36% (17-59)	26% (9-51)
Complete response	14%	0%
Median duration of response	9.4 months	9.4 months
Median time to progression (95% CI)	3.0 months (1.4-6.6)	3.1 months (2.5-6.5)

CI = confidence interval

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

NCCN® Practice Guidelines: Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer*

Preferred agents	Preferred combinations	Other active agents
Anthracyclines	CAF/FAC	Gemcitabine
Taxanes	FEC	Platinoids
Capecitabine	AC	Oral etoposide
Vinorelbine	EC	Vinblastine
	AT	Fluorouracil
	CMF	
	Capecitabine/Docetaxel (XT)	

C = cyclophosphamide, A = doxorubicin, F = fluorouracil, E = epirubicin, T = docetaxel or paclitaxel, M = methotrexate, CI = continuous infusion

*There is no compelling evidence that combination regimens are superior to sequential single agents.

SOURCE: National Comprehensive Cancer Network (NCCN®). **NCCN Clinical Practice Guidelines in Oncology, Breast Cancer — Version 2. 2003.** Available at **http://www.nccn.org/physician_gls/f_guidelines.html**. Accessed July 9, 2003.

Prospective Evaluation of Patient Preferences for Palliative Chemotherapy

Preference for method of administration in 103 patients with metastatic disease

Oral	92/103 (89%)
Intravenous	10/103 (10%)
No preference	1/103 (1%)

SOURCE: Liu et al. *J Clin Oncol* 1997;15:110-5. **Abstract**

RESEARCH LEADER COMMENTARY

Sequencing chemotherapy in the metastatic setting

In terms of sequencing chemotherapy in the metastatic setting, I generally start with an anthracycline in patients who did not receive one in the adjuvant setting. Otherwise, I usually begin with a taxane. Capecitabine is my next chemotherapy choice after anthracyclines and taxanes.

Especially in elderly or frail patients, I always bring capecitabine into the equation. Not only is it oral, but it is also associated with a good quality of life if the dose is somewhat attenuated and we monitor for hand-foot syndrome.

I usually start capecitabine as a single agent at 2,000 mg/m^2 per day in two divided doses for three to five cycles and then a rest. I do not routinely use it with docetaxel, though I recognize that a number of people do and there are good reasons to do so in certain conditions.

— Richard M Elledge, MD

Dr O'Shaughnessy's study of women with metastatic breast cancer demonstrated that the combination of capecitabine/docetaxel — compared to docetaxel alone — resulted in improved response rate, time to progression and survival. The dosing and scheduling of the combination are controversial and remain to be defined. In the XT trial, the drugs were given simultaneously on day one. It's possible that upregulating TP with a taxane should be done before introducing capecitabine, and perhaps lower doses will result in the same benefit. If you want to utilize aggressive therapy, the combination in the XT trial was superior and the quality of life wasn't impaired compared to the sequential approach.

— Vincente Valero, MD

Sequential single-agent versus combination chemotherapy in patients with metastatic breast cancer

The big question associated with the sequential single-agent versus combination chemotherapy trials is the effect of crossover therapy. In Joyce O'Shaughnessy's trial, we don't know what the effect on survival would have been if 60 or 70 percent of the patients treated with single-agent docetaxel were then treated with capecitabine. Maybe

there would not have been a survival difference. Hence, the effect of crossover therapy remains a question in all of these trials comparing doublets to single-agent regimens.

— Stephen E Jones, MD

Capecitabine/docetaxel in the metastatic and adjuvant settings

When Dr Joyce O'Shaughnessy presented the positive data from the capecitabine/docetaxel trial in the metastatic setting, I was surprised by the results. Many of us thought there would be no significant difference. We had compared doxorubicin with and without vinorelbine and didn't see a significant difference, so we expected to see the same results with this study. The data is exciting and I think it warrants examination in the adjuvant setting. If we can treat these patients for three to six months and have them be well for five or 10 years, that's worth studying.

— Kathleen I Pritchard, MD

I use the capecitabine/docetaxel regimen for a select group of women with metastatic disease — those with more extensive disease and with a better performance status. The regimen produces good results but may have significant toxicity, especially at the doses that were initially presented. I tend to start at 1,250 mg/m^2 twice a day for 14 days followed by seven days off as the regular approach. If you select your patient population appropriately, it's tolerable. The hand-foot syndrome is manageable with appropriate dose reductions when it occurs. The hardest symptom complex I encounter with that regimen is the GI toxicity. It's more difficult to manage and less amenable to improvement with dose reductions.

— Generosa Grana, MD

I am a big fan of capecitabine. Maybe it comes from being a "hormonal-therapy person" preferring pills to begin with, because I use it a lot for salvage chemotherapy in women who've already had an anthracycline and a taxane for metastatic disease. In oncology, we tend to remember our successes, but I have seen several very impressive responses with capecitabine in pretty dire circumstances. I have had women on it for a considerable period of time with relatively good quality of life. My personal best was somebody who was on capecitabine for several years.

— Nancy Davidson, MD

SELECT PUBLICATIONS

Miles D et al. **Combination versus sequential single-agent therapy in metastatic breast cancer.** Oncologist 2002;7(Suppl 6):13-9. *Erratum in: Oncologist* 2003;8(1):127. **Abstract**

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