BCU5 | 2002

Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 audio tapes

2 audio CDs

Monograph

CME Certified

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How to use this supplement

This booklet supplements the audio program and contains edited comments, clinical trial schemas, graphics and references. **BreastCancerUpdate.com** includes a full transcription of the audio program and an easy-to-use representation of each page of this booklet, allowing users to link immediately to relevant full-text articles, abstracts, trial information and other web resources indicated throughout this guide in **red underlined text.** This regularly updated web site also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

Breast Cancer Update: A CME Audio Series and Activity

Statement of Need /Target Audience

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances.
To bridge the gap between research and patient care, Breast Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

Issue 5, 2002 of Breast Cancer Update consists of discussions with four oncology research leaders on a variety of important issues, including trastuzumab-related cardiac effects, the use of trastuzumab for metastatic disease, the use of adjuvant ovarian ablation with tamoxifen, clinical use of the estrogen downregulator, fulvestrant, the implications of the ATAC trial results on clinical practice, the effect of chemotherapy in older women and the current clinical trials being conducted by the NSABP.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Review the role of trastuzumab in the treatment of metastatic disease
- Discuss the potential cardiac effects of trastuzumab
- Explain the rationale for adjuvant ovarian ablation
- Compare the mechanism of action for fulvestrant to that of tamoxifen and anastrozole
- Describe how ER status is currently measured and defined
- Explain the clinical implications of the ATAC trial results
- Review the effect of adjuvant chemotherapy in older women
- Discuss postmenopausal ovarian function
- Discuss the current clinical trials being conducted by the NSABP

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Designation Statement

The Postgraduate Institute for Medicine designates this educational activity for a maximum of 3 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Faculty Disclosure Statements

The Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted in this supplement to fully inform participants.

Editor's Note

Predicting the Results of Clinical Trials

Every five years, breast cancer research leaders make a pilgrimage to Oxford, where Sir Richard Peto presents the most recent results from an international meta-analysis of virtually every known randomized clinical trial in early breast cancer. This massive undertaking painstakingly incorporates a case-by-case "data cleaning" of each individual trial. In 1990, I was privileged to attend the second trialists' meeting. At breakfast that day, rumors circulated that the soon-to-be-knighted statistician and his team worked all night to have the data ready on time. Looking a bit haggard, but with a bemused expression, Peto appeared and began his day-long presentation.

Always one to push researchers to think creatively, Peto distributed a survey prior to the meeting asking the attendees to predict the results of the meta-analysis. At each critical presentation point, he first reviewed the trialists' predictions followed by the actual findings, many of which were very different than expected. In particular, most of the researchers predicted that — with five more years of follow-up — the differences in the Kaplan Meier plots for disease-free and overall survival for adjuvant tamoxifen would narrow. With a broad smile, Peto disproved these predictions, and indeed, with the additional follow-up, the curves for adjuvant tamoxifen compared to placebo were even farther apart — a trend that persisted in subsequent overviews.

Seasoned clinical researchers know the hazards of predicting randomized trial results, and many cite the lofty, but unfulfilled, expectations in the early 1990s for high-dose chemotherapy with stem cell support. In the accompanying audio program, George Sledge reminded me of this lesson and cautioned clinicians about moving too fast to adopt trastuzumab as adjuvant therapy, until randomized trial data are available.

Another speaker on this program, Tony Howell, noted that many clinicians and researchers assumed that the anastrozole-tamoxifen arm of the ATAC trial would yield the greatest benefit. This prediction was invalidated by the initial ATAC trial results, which demonstrated anastrozole's superiority.

The entire culture of cancer therapy is now focused on evidence-based medicine, and Craig Henderson — a champion of this philosophy in breast cancer — verbalizes in the enclosed interview his struggle to make sense of the age-based efficacy of chemotherapy demonstrated in the Overview. In the 1980s, the triumvirate of Craig Henderson, Richard Peto and Michael Baum played a critical role in educating the research community and practicing clinicians about the need for trials with an adequate numbers of events. Simultaneously, sentinel figures like Bernie Fisher and Charles Coltman provided the leadership within cooperative groups to make this happen.

Echoing the challenge of advancing the field through large well-designed studies, Terry Mamounas' interview traces the background and design of the current and planned NSABP clinical trials. Dr Mamounas discusses the encouraging results of the capecitabine-docetaxel trial by O'Shaughnessy et al demonstrating a survival advantage in metastatic disease compared to docetaxel alone. These results led the NSABP to design two clinical trials that incorporate this combination — a

neoadjuvant study comparing AC → docetaxel to AC → capecitabine / docetaxel and a study of capecitabine / docetaxel in women with a local recurrence of breast cancer.

Shortly after my interview with Dr Mamounas, a relevant and important new data set became available, namely the initial results of BCIRG 001. These findings, presented at the May 2002 ASCO meeting in Orlando by Dr Jean-Marc Nabholtz, demonstrated an advantage in node-positive patients for TAC (docetaxel, doxorubicin, cyclophosphamide) in the adjuvant setting (see table on page 5).

Prior to the ASCO meeting, we surveyed 20 medical oncologists to determine their predictions of this study's results and how they integrated clinical trial information into their practices. Whether the very existence of an ongoing randomized study encourages physicians to utilize the experimental arms in a nonprotocol setting is of particular interest.

It would be interesting to compare the current practices of clinicians, in this regard, to those of 10 or 15 years ago. My guess is that lessons learned from our previous failures to predict clinical trial results have led to a wave of conservatism, and experienced practitioners now are very cautious about changing their practices until clear-cut advantages are demonstrated in well-designed and conducted randomized studies.

— Neil Love, MD

Select publications

Sir Richard Peto and the Early Breast Cancer Trialists' Collaborative Group

Collins R, Gray R, Godwin J, Peto R. **Avoidance of large biases and large random errors in the assessment of moderate treatment effects: The need for systematic overviews.** *Stat Med* 1987;6:245-250. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women.** *N Engl J Med* 1988;319:1681-1691. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Effects of radiotherapy and surgery in early breast cancer: An overview of the randomized trials.** *N Engl J Med* 1995;333:1444-1455. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation in early breast cancer: Overview of the randomised trials.** *Lancet* 1996;348:1189-1196. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Polychemotherapy for early breast cancer: An overview of the randomised trials.** *Lancet* 1998;352:930-942. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women.** *Lancet* 1992;339:1-15 & 71-85. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomised trials.** *Lancet* 1998;351:1451-1467. **Abstract**

Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2000;355(9217):1757-70. **Abstract**

Application of Clinical Research Data: Adjuvant Chemotherapy

BCIRG-001: A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin And Cyclophosphamide (TAC) Versus 5-Fluorouracil in Combination with Doxorubicin And Cyclophosphamide (FAC) as Adjuvant Treatment of Operable Breast Cancer Patients with Positive Axillary Lymph Nodes
Closed Protocol

ARM 1 | TAC (docetaxel, doxorubicin, cyclophosphamide 75/50/500 mg/m^2) q3w x 6

ARM 2 | FAC (5-fluorouracil, doxorubicin, cyclophosphamide 500/50/500 mg/m^2) q3w x 6

Patients with ER/PR-positive tumors received tamoxifen 20 mg/day x 5 years.
Patients undergoing breast-conserving surgery received radiation therapy, while those who had a mastectomy received radiation therapy per center guidelines.

Disease-free survival (DFS) and overall survival for 1,491 patients after a median follow-up of 33 months (TAC n=745; FAC n=746)

	RR TAC/FAC	% Reduction	*p*-value
DFS	0.68	32%	0.0011
by nodal status			
1-3	0.50	50%	0.0002
4+	0.86	No difference	0.33
by hormonal status	0.62	38%	0.005
ER-	0.6	32%	0.02
ER+			
Overall Survival	0.76	24%	0.11
by nodal status			
1-3+	0.46	54%	0.006
≥4+	1.08	No difference	0.75

Nabholtz JM et al. *Proc ASCO* 2002;**Abstract 141.**

Comment: Although adjuvant trials often initially demonstrate benefits in higher-risk patients, where there are more events, BCIRG 001 demonstrated a significant disease-free and overall survival benefit for TAC in women with 1-3 positive nodes, but not in women with four or more positive nodes. In contrast to retrospective analyses from the Intergroup and NSABP trials with paclitaxel, TAC improved disease-free survival regardless of the hormone receptor status.

Select publications

TAC vs FAC in the adjuvant and metastatic setting

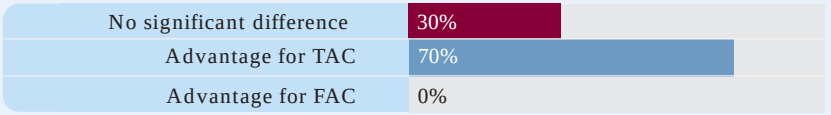
Mackey JR et al. **Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first-line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 137.**

Nabholtz JM et al. **Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer.** *J Clin Oncol* 2001;19(2):314-21. **Abstract**

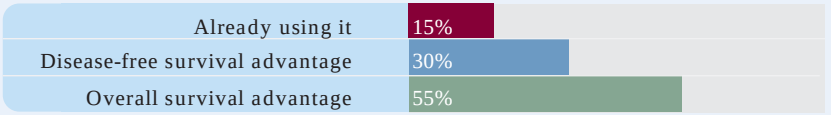
Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

Medical oncologists' survey conducted prior to the ASCO meeting: Predictions of results of BCIRG 001

What do you expect the initial results of BCIRG 001 to demonstrate?



What results would BCIRG 001 have to show in order for you to incorporate TAC into your practice as adjuvant therapy?

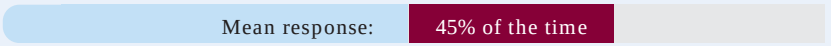


Comment: While most oncologists predicted that the TAC arm of this study would be superior, relatively few were utilizing this combination prior to these results being presented. An overall survival benefit is more highly valued than a disease-free survival benefit in terms of changing clinical practice.

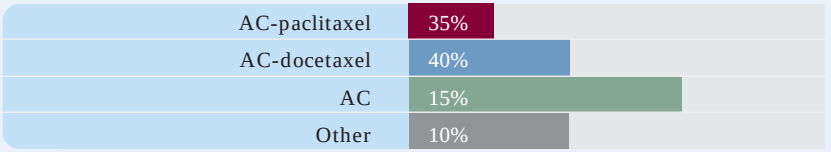
Adjuvant chemotherapy practice patterns

When you prescribe adjuvant chemotherapy, how often do you incorporate a taxane?

How often do your patients treated with adjuvant chemotherapy receive CMF or AC as their sole chemotherapy?



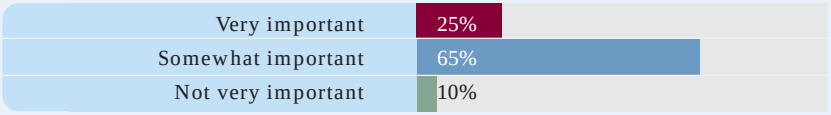
Which adjuvant chemotherapy regimen do you most commonly utilize in breast cancer patients with multiple positive nodes?



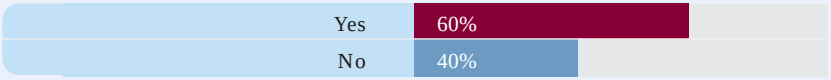
Comment: Even prior to the BCIRG 001 presentation, clinicians were commonly utilizing taxanes as adjuvant therapy, particularly in node-positive patients. Interestingly, most of the available randomized clinical trial data on this subject has come from meeting presentations (ASCO, 2000 NIH Consensus Conference) as opposed to publications in peer-reviewed medical journals.

Adjuvant trials involving capecitabine-docetaxel

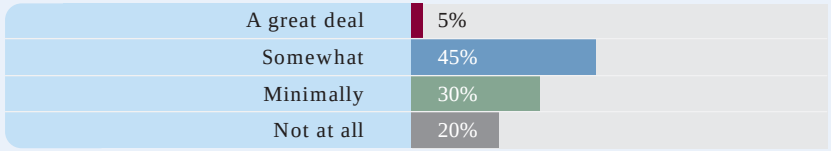
The NSABP is planning an adjuvant study and US Oncology is planning a neoadjuvant study to evaluate AC + docetaxel with or without capecitabine. How much additional significance would you place on an additional BCIRG trial evaluating the same regimen?



Can you recall any instance in the last ten years where you incorporated into your practice an adjuvant regimen that was being evaluated in a randomized trial for which the results were not yet available?



How much does the presence of an ongoing phase III randomized clinical trial tend to lead you to consider using the experimental arm of that study in a nonprotocol setting prior to the results of that trial being available?



Comment: The accumulating evidence suggesting a modest advantage for the addition of taxanes to adjuvant therapy is leading cooperative research groups to consider assessing capecitabine in combination with docetaxel. While two major US cooperative groups are considering trials evaluating this combination in the adjuvant and neoadjuvant setting, clinicians are also interested in other studies evaluating this question.

While more than half of the oncologists surveyed indicated that they have used an experimental arm from an adjuvant randomized trial as nonprotocol therapy, only a small number state that the presence of a randomized study significantly affects their likelihood to utilize an experimental approach prior to its demonstrating an advantage.

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Vice Chairman, Eastern Cooperative Oncology Group Breast Cancer Committee

Member, FDA Oncology Drug Advisory Committee

Member, Department of Defense Breast Cancer Research Program Integration Panel

Edited comments by Dr Sledge

Cardiac effects of trastuzumab

When given in combination with an anthracycline, trastuzumab significantly increases the risk of congestive cardiomyopathy. In the pivotal trial by Slamon et al, the group of women receiving trastuzumab / paclitaxel after a prior anthracycline-containing regimen experienced a smaller yet real risk of cardiac events, including an occasional case of congestive heart failure.

Since anthracyclines may be more effective in women with HER2-positive breast cancer, they are frequently used in this patient population. In 1998, ECOG designed trial E2198 to evaluate these safety issues. Women with HER2-positive (IHC 2+ or 3+), node-positive breast cancer were given four cycles of paclitaxel / trastuzumab followed by four cycles of doxorubicin / cyclophosphamide and then randomized to either stop therapy or receive trastuzumab. The hypothesis, at that time, was that with this schedule, the interaction between trastuzumab and doxorubicin would not occur. Hence, there would be a lower incidence of congestive cardiomyopathy.

However, we have since learned from Dr Brian Leyland-Jones that trastuzumab has a longer half-life than once thought. Although we designed the trial for patients to have discontinued trastuzumab three weeks before receiving doxorubicin, we now know that three weeks is not enough time for trastuzumab to be eliminated from the patient's body.

It is likely that the patients still had circulating trastuzumab in their blood when they received doxorubicin. With that in mind, the results are still reassuring. We assumed that the baseline incidence of congestive heart failure was slightly less than 1%. In our trial, there was a 1.7% incidence of drug-related congestive heart failure. After receiving trastuzumab / paclitaxel, a few patients had a temporary decline in their left ventricular ejection fractions,

which resolved despite subsequent treatment with doxorubicin and cyclophosphamide. There are certain patients in whom one would want to avoid four cycles of trastuzumab / paclitaxel followed by four cycles of doxorubicin / cyclophosphamide. Virtually all of the patients who had cardiac problems in our trial were predisposed to cardiac disease.

E-2198: Phase II Randomized Pilot Study of Paclitaxel Plus Trastuzumab (Herceptin) Followed By Adjuvant Chemotherapy in Women with Node-Positive Stage II or IIIA Breast Cancer with HER2 Overexpression **Closed Protocol**

Protocol: E-2198

Eligibility	Stage II or IIIa (T1-T3, N1-N2, M0) adenocarcinoma of the breast with HER2 overexpression (2-3+ by immunohistochemistry)

ARM 1 | T q 3 weeks x 4 → AC x 4

ARM 2 | T q 3 weeks x 4 → AC x 4 → H q week x 1 year

ER- and/or PR-positive patients receive tamoxifen.
Postmastectomy patients may receive local radiotherapy.

Treatment continues in the absence of disease progression or unacceptable toxicity. Patients are followed every 3 months for 1 year, every 6 months for 2 years, and then annually thereafter.

T=paclitaxel; H=trastuzumab; A=doxorubicin; C=cyclophosphamide

Trastuzumab for patients with metastatic breast cancer

HER2-positive, metastatic breast cancer is a life-or-death situation and therefore quite different than the adjuvant setting. As observed in the ECOG trial and the pivotal trial by Slamon et al, the average survival for these patients when treated with standard chemotherapy was about 17 months, and trastuzumab clearly improved survival. Even though 25% of the patients receiving trastuzumab plus an anthracycline developed a cardiac event, trastuzumab still improved survival in that group. It is reasonable to use trastuzumab in the vast majority of patients with HER2-positive, metastatic breast cancer.

I routinely use trastuzumab as part of my first-line therapy for patients with HER2-positive, metastatic breast cancer. Whether to use trastuzumab alone or in combination with chemotherapy is a separate question. In patients with an impaired performance status, it would be reasonable and appropriate to give trastuzumab alone. My sense is that the majority of community oncologists are using trastuzumab in combination with chemotherapy as first-line therapy for HER2-positive, metastatic breast cancer. Over the last couple of years, there has been a trend to use trastuzumab earlier in the metastatic setting.

Algorithm for assessing HER2 status

Patients with tumors that score 2+ on immunohistochemistry (IHC) are frequently found to be HER2-negative when tested by fluorescence *in situ* hybridization (FISH). In those patients, I routinely have their tumors retested by FISH. On the other hand, I do not obtain a FISH analysis for patients whose tumors score 3+ on IHC from 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 receptors in the mid- to late 1970s. I suspect HER2 testing in the year 2001 was very similar to estrogen receptor testing in the year 1975 or 1976. 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 exactly the same problem.

Number of tumors testing FISH-positive according to their IHC score

Author	IHC Antibody	IHC N	IHC 0	IHC 1+	IHC 2+	IHC 3+
Mass 2000	CTA	529	4.2%	6.7%	23.9%	89.3%
Mass 2001	CTA	451	-	-	31.0%	89.0%
Schaller 2001	A0485	142	0	0	25.0%	100.0%
Lebeau 2001	A0485	79	-	-	25.0%	100.0%
	CB11		-	-	81.8%	100.0%
	TAB250		-	-	66.7%	100.0%
Buehler 2000	A0485	142	0	0	30.5%	100.0%
Tubbs 2001	A0485	145	-	-	12.5%	75.0%
	CB11		-	-	23.5%	85.0%
Hoang 2000	A0485	100	0	0	16.7%	88.9%
	e2-4001		1.6%		5.9%	75.0%
Ridolfi 2000	A0485	117	1.8%		35.9%	100.0%
Seidman 2001	A0485	78	9.1%		82.2%	
	CB11		14.3%		94.4%	
Persons 1997	A0485	100	1.3%		68.2%	

CTA = clinical trial assay (4D5 and CB11 antibodies)

ATAC trial results

Albeit with very early follow-up, the ATAC trial suggests for the first time that an aromatase inhibitor — anastrozole — might be superior to adjuvant tamoxifen. Fascinatingly, the combination of tamoxifen and anastrozole was no better than tamoxifen. There was a marked reduction in the development of contralateral breast cancers in patients receiving adjuvant anastrozole compared to adjuvant tamoxifen. We already knew adjuvant tamoxifen reduced the risk of contralateral breast cancers by up to 50%. Adjuvant anastrozole provided a significant additional benefit on top of that associated with adjuvant tamoxifen. The difference between anastrozole and tamoxifen was striking.

In the ATAC trial, there also appeared to be a lower risk of deep vein thrombosis, endometrial cancer and hot flashes associated with anastrozole than with tamoxifen. From a toxicity standpoint, anastrozole may be better tolerated than tamoxifen. These results represent a fascinating new avenue in terms of therapy, not only in the adjuvant setting, but also in the chemoprevention setting.

ATAC trial: Endometrial subprotocol analysis

	Anastrozole (n=63)	Tamoxifen (n=54)	Combination (n=51)
Endometrial abnormalities	9%	17%	27%
Endometrial thickness at 12 months	4.0 mm	6.5 mm	7.0 mm
Endometrial thickness at 24 months	3.0 mm	7.0 mm	7.0 mm

"Conclusion: These results support the findings from the main trial in which patients treated with anastrozole showed a significantly lower incidence of endometrial cancer (p=0.03), vaginal bleeding (p<0.0001) and vaginal discharge (p<0.0001) compared to those patients treated with tamoxifen."

Derived from Duffy SRG et al. *Proc ASCO* 2002;**Abstract 158.**

Premalignant breast changes in the NSABP P-1 trial (tamoxifen versus placebo)

The NSABP looked at the incidence of premalignant changes in the breast, such as cystic disease, hyperplasias (typical and atypical) and fibroadenomas. In women receiving tamoxifen as a chemopreventative agent, there was a generalized reduction in premalignant changes of the breast, which was age-related. There was a huge reduction in the premalignant and the non-premalignant events for younger women and little or no reduction in many of the events for older women. From a toxicity standpoint, tamoxifen is associated with thromboembolic events and endometrial cancer primarily in older women. Therefore, tamoxifen as a chemopreventative agent is more appealing in younger women.

Adjuvant ovarian ablation/tamoxifen

For a long time, American oncologists have believed that hormonal therapy was of secondary importance in the treatment of breast cancer and that aggressive doses of chemotherapy were more imperative. However, the kinder and gentler approach aimed at the biology of the tumor is also very important. The better we are at shutting off the estrogen receptor pathway, the better the disease-free and overall survival for our patients.

In the late 1980s, an Intergroup trial (INT-0101) was designed to evaluate the role of adjuvant ovarian ablation with or without tamoxifen. It randomized premenopausal women with node-positive, estrogen receptor-positive breast cancer to CAF (the standard chemotherapy at the time), CAF followed by goserelin or CAF followed by goserelin/tamoxifen. Since INT-0101 was designed at a time when tamoxifen was not thought to benefit premenopausal women, an arm consisting of CAF plus tamoxifen was not included. Goserelin had the greatest effect in the youngest group of women — those under the age of 40. This implies that shutting off a woman's ovaries, when chemotherapy has not already done so, is a good thing.

In my own practice, I have tended to offer more ovarian ablation to younger women than I did three or four years ago. The most effective way to reduce the risk of recurrence in premenopausal women is to deprive them of estrogen. In the group of women randomized to CAF, those who became menopausal had a better outcome than the women who did not experience menopause as a result of chemotherapy. There are two plausible explanations for this finding. Either estrogen deprivation related to menopause is beneficial or the patients who became menopausal did so because they had higher CAF serum concentrations. Therefore, menopausal status may simply be a marker of the higher blood levels of cytoxic agents.

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

Management of node-positive, ER-positive patients who do not become menopausal after adjuvant chemotherapy

In some patients, I recommend either surgical or medical ovarian ablation. It would also be reasonable to utilize tamoxifen. In INT-0101, patients who received CAF followed by goserelin/tamoxifen did the best. When inducing premature menopause, it is important to maintain the patient's general health. Therefore, one must pay attention to the serum lipids and bone mineral density. Whether the addition of an aromatase inhibitor will provide the maximum benefit to an LHRH agonist needs to be evaluated in clinical trials.

Anti-vascular endothelial growth factor (VEGF) monoclonal antibody

An upcoming ECOG trial, chaired by Dr Kathy Miller, will randomize patients with metastatic breast cancer to weekly paclitaxel with or without a recombinant humanized monoclonal antibody to vascular endothelial growth factor (rhuMAb-VEGF, bevacizumab). This is the first large trial evaluating an antiangiogenic agent as front-line therapy in metastatic breast cancer. In anthracycline and taxane refractory breast cancer, a trial evaluating capecitabine with or without bevacizumab was recently completed.

In preclinical models, the taxanes have demonstrated antiangiogenic activity. The taxanes kill vascular endothelial cells, affect capillary tubule formation and affect capillary migration. Hopefully, combining an antiangiogenic agent, such as bevacizumab, with a taxane will lead to an additive or synergistic effect. Indeed, in some preclinical models, there was a synergistic effect against endothelial cells when a taxane was combined with anti-VEGF antibodies. Similarly, there is preclinical data suggesting that capecitabine may have some antiangiogenic activity. In the next few years, we will know if antiangiogenic agents contribute significantly to the management of breast cancer.

Breast cancer clinical trials with bevacizumab

Protocol IDs	Schema	Stage
NCI-01-C-0173, NCI-2772	bevacizumab + AT + G-CSF → surgery → bevacizumab	Stage IIIB or IV inflammatory
CWRU-3100, NCI-2722	Arm 1: docetaxel + bevacizumab → surgery → radiation → AC Arm 2: docetaxel → surgery → radiation → AC	Locally advanced
DFCI-01013, NCI-2716	bevacizumab + vinorelbine	Stage IV
GENENTECH-AVF2119g, GUMC-00299*	Arm 1: capecitabine Arm 2: capecitabne + bevacizumab	Previously treated stage IV
CTSU, E-2100	Arm 1: paclitaxel + bevacizumab Arm 2: paclitaxel	Locally recurrent or stage IV

AT=doxorubicin/docetaxel; AC =doxorubicin/cyclophosphamide
* Closed to accrual

Select publications

Adjuvant trastuzumab and cardiac function

Carey LA. **Cardiotoxicity of trastuzumab (Herceptin, H) given with weekly Taxol (T) immediately following 4AC as initial therapy for primary breast cancer (BrCa).** *Proc ASCO* 2002;**Abstract 253.**

Ewer MS. **Trastuzumab (Herceptin) cardiotoxicity: Clinical course and cardiac biopsy correlations.** *Proc ASCO* 2002;**Abstract 489.**

Gerber B et al. **Effectiveness of trastuzumab (Herceptin) in a patient with locally recurrent breast cancer after cardiac failure caused by severe cytotoxic pretreatment.** *Oncology* 2001;61:271-4. **Abstract**

Hortobagyi GN, Perez EA. **Integration of trastuzumab into adjuvant systemic therapy of breast cancer: Ongoing and planned clinical trials.** *Semin Oncol* 2001;28:41-6. **Abstract**

Leyland-Jones B. **Trastuzumab: Hopes and realities.** *Lancet Oncol* 2002;3(3):137-44. **Abstract**

Leyland-Jones B, Smith I. **Role of Herceptin in primary breast cancer: Views from North America and Europe.** *Oncology* 2001;61 Suppl 2:83-91. **Abstract**

Lueck H-JH-J. **Cardiac safety of Herceptin (H) in combination with epirubicin (E) plus cyclophosphamide (C): Interim results of a phase II study in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2001;**Abstract 439.**

Nabholtz JM, Slamon D. **New adjuvant strategies for breast cancer: Meeting the challenge of integrating chemotherapy and trastuzumab (Herceptin).** *Semin Oncol* 2001;28:1-12. **Abstract**

Paik S, Park C. **HER-2 and choice of adjuvant chemotherapy in breast cancer.** *Semin Oncol* 2001;28:332-5. **Abstract**

Perez EA. **The role of adjuvant monoclonal antibody therapy for breast cancer: Rationale and new studies.** *Curr Oncol Rep* 2001;3:516-22. **Abstract**

Rastogi F et al. **Differences in cardiac ejection fractions for breast cancer patients treated with doxorubicin or trastuzumab.** *Proc ASCO* 2002; **Abstract 262.**

Schneider JW et al. **Cardiotoxicity in signal transduction therapeutics: ErbB2 antibodies and the heart.** *Semin Oncol* 2001;28(5 Suppl 16):18-26. **Abstract**

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

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

Sledge GW et al. **Pilot trial of paclitaxel-Herceptin adjuvant therapy for early stage breast cancer (E2198).** *Breast Cancer Res Treat* 2001;**Abstract 4.**

Sparano JA. **Cardiac toxicity of trastuzumab (Herceptin): Implications for the design of adjuvant trials.** *Semin Oncol* 2001;28:20-7. **Abstract**

Tripathy D et al. **Effect of cardiac dysfunction on treatment outcome in the Herceptin (trastuzumab) pivotal trial.** *Breast Cancer Res Treat* 2001;**Abstract 525.**

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Edited comments by Dr Howell

Lack of benefit from anastrozole/tamoxifen compared to anastrozole in the ATAC trial

I believe these findings were entirely predictable. In animal models, such as the immature rat uterus assay, tamoxifen stimulates uterine growth in a low estrogen environment. In a high estrogen environment, tamoxifen acts as an antiestrogen. The lack of benefit from the combination arm may be related to tamoxifen's action as an agonist rather than an antagonist in a low estrogen environment.

A potential explanation for the superiority of anastrozole is suggested by data from Matt Ellis demonstrating that tamoxifen does not seem to be as active as the aromatase inhibitors in low estrogen receptor conditions. In his data, which revealed a correlation between response rates and Allred's estrogen-receptor score, tamoxifen only works with Allred scores above three; whereas, letrozole worked with an Allred score of 3 and 4, as well as the higher scores. That may be another reason why tamoxifen is not as effective as anastrozole. This data may explain why one set of drugs — the aromatase inhibitors — are better than another set of drugs, the SERMs.

Allred score for ER status (0-8)*

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

**Allred Score = % Staining Score + Intensity Score*

Allred DC et al. *Mod Pathol* 1998;11:155-68.

Benefits of aromatase inhibitors in tumors expressing low levels of estrogen receptors

"The observation that tumors with low positive levels of ER expression were responsive to letrozole (Allred scores 3, 4, and 5) validates the concern expressed by Allred et al that a 10% cutoff for ER may be too high and could exclude patients unnecessarily from the benefits of endocrine therapy. A substantial number of patients with tumor ER Allred expression categories in the 3 to 5 range (generally involving 1% to 10% positive cells) might derive benefit from aromatase inhibitor treatment in this and potentially in other treatment settings. These observations further emphasize the need for a concerted effort to re-evaluate the predictive value of ER IHC in the context of the ongoing selective aromatase inhibitor adjuvant studies."

EXCERPT FROM: Ellis M et al. *J Clin Oncol* 2001;19:3808-16. **Abstract**

Defining ER positivity

There is variation in defining estrogen receptor positivity in Europe and across the United States. I agree with Kent Osborne that this variation is extraordinarily disturbing — particularly as our hormonal therapies continue to improve. My feeling is that if there is any receptor present in a tumor, it should be considered positive. Clearly, we can miss a very low positive result quite easily, and the result may be that patients who should receive adjuvant endocrine therapy are not receiving it. We need to get this assay correct for every woman.

Approximately 8% of the women in the ATAC trial had ER-negative breast cancer, and there are women whose estrogen receptor status is still unknown. More than 80% of the women in the ATAC trial had ER- and/or PR-positive tumors, which is reassuring. Even if we include the patients with estrogen receptor-negative and unknown disease, there is still a statistical benefit in terms of disease-free survival. There is a benefit in the intent-to-treat analysis of all patients. Overall, anastrozole has an 18% reduction in the recurrence rate compared to tamoxifen. This increases to 23% for those with known ER-positive disease.

Interlaboratory variance in IHC detection of ER
– Data from 200 laboratories in 26 countries

"There is considerable interlaboratory variability, especially in relation to the detection of breast cancers with low oestrogen receptor positivity, with a false negative rate of between 30% and 60%."

EXCERPT FROM: Rhodes A et al. *J Clin Pathol* 2000;53:125-30.

Correlation between ER status measured by IHC and clinical response

"With minimal training, pathologists in our laboratory were in agreement on discriminating positive from negative tumors in 99% of cases. The optimal cut point in our study was a total IHC score of greater than 2, meaning that even patients whose tumors scored 3 (corresponding to as few as 1% to 10% weakly positive cells) had a significantly improved response, compared with those who had lower scores. ...

...Many hospital and commercial laboratories have converted to assessing ER status exclusively by IHC on archival tissue. They use diverse methodologies, and most have arbitrarily chosen 10% or even 20% positive tumor cells as their cutoff for defining ER positivity, potentially denying a substantial number of patients the benefits of adjuvant hormone therapy."

EXCERPT FROM: Harvey JM et al. *J Clin Oncol* 1999;17:1474-81. **Abstract**

Implications of the ATAC trial in chemoprevention

The 80% reduction in contralateral tumors in the anastrozole arm of the ATAC trial is very exciting. If this translates into preventive therapy, it augurs well for the future prevention of breast cancer. The IBIS-2 prevention trial is in the planning stages, but it may be a three-arm study involving anastrozole, tamoxifen and placebo. We are also discussing the use of a bisphosphonate in IBIS-2. We have so much data on clodronate, and it has a favorable side-effect profile. Therefore, it may be the bisphosphonate of choice for the trial. We plan to begin the study in September or October, and there is enormous enthusiasm for this trial from investigators around the world.

Impact of anastrozole on bone density: Potential role of bisphosphonates

Overall, anastrozole has a much better toxicity profile than tamoxifen. The risks of thromboembolic complications and endometrial cancer are much lower, which makes it an attractive drug. One of the concerns about anastrozole is how to address its potential effects on bone density.

There was an increase in the fracture rate in the anastrozole arm of the ATAC trial. Women in the control arm were given tamoxifen, which prevents fractures; therefore, the increase in the fracture rate with anastrozole was probably not as big as it looks. We estimate that approximately half of the fracture rate in the ATAC trial was due to the negative effects of anastrozole. In terms of monitoring, I think most patients on anastrozole will need serial bone density measurements.

Given the data from Ingo Diel and Trevor Powles on bisphosophonates in the adjuvant setting, in the future we might be treating elderly women with ER-positive breast cancer with a combination of clodronate and anastrozole. Bisphosphonates may not only make anastrozole safe with regard to bone density, they also have an effect on survival. Clodronate is not available commercially in the United States, but many osteoporosis researchers do not believe there is much difference between the bisphosphonates. We need to find the bisphosphonate with the lowest GI toxicity.

Effects of adjuvant clodronate on metastases and mortality in 1,069 patients

	Clodronate	Placebo	Statistical Significance
Bone mets during medication period	12	28	HR 0.44 (95% CI 0.22-0.86) *p*=0.016
Bone mets during study period	63	80	HR 0.77 (95% CI 0.56-1.08) *p*=0.127
Non-osseous mets	112	128	*p*=0.257
Mortality	98	129	*p*=0.047

"Conclusion: Adjuvant clodronate significantly reduces the incidence of bone metastases during the medication period, associated with a significantly reduced mortality."

Derived from Powles TJ et al. *Breast Cancer Res and Treat* 2001;**Abstract 1.**

Adjuvant bisphosphonates in breast cancer

"There are now numerous studies to demonstrate the efficacy of the individual substances in preventing skeletal complications. The reduction in symptoms and signs by approximately 30–40% testifies to the efficacy of the bisphosphonates. Furthermore, in breast carcinoma and multiple myeloma at least, prolongation of the survival time has been demonstrated for subgroups of patients. In comparison to cytotoxic substances, the rate of complications and side effects produced by the bisphosphonates is extremely low and is comparable to that observed for tamoxifen. Not a single study to date has shown any signs of long-term bone toxicity, an effect that previously was feared. That aside, bisphosphonates are used over a period of years in nononcologic indications (Paget disease, osteoporosis)."

EXCERPT FROM: Diel IJ et al. *Cancer* 2000;88:3080-8.

Fulvestrant and sequencing of endocrine therapy

Fulvestrant is a highly potent, estrogen receptor downregulator, which is equivalent as second-line therapy to our best drugs — the aromatase inhibitors. We now have another best drug. Now, women and physicians have a choice between treatments that are clearly equivalent.

New therapies for advanced breast cancer are useful, because we give endocrine agents sequentially. I believe that the first-line treatment for advanced disease in postmenopausal women — even those who have not had adjuvant tamoxifen — is an aromatase inhibitor. At the moment, I see fulvestrant being used after aromatase inhibitors in women who have not received an aromatase inhibitor in the adjuvant setting. It probably does not matter in which order you give them, but we have more data on aromatase inhibitors than fulvestrant.

There is a biological reason why fulvestrant might be better than anastrozole. Anastrozole lowers the serum estradiol levels, but there is still some estradiol present that could potentially stimulate the tumor. Fulvestrant blocks the receptor continuously; thereby preventing stimulation by circulating estradiol.

I do not believe that the fulvestrant injection is a problem. There have not been major problems with injection site reactions. In fact, it could be seen as an advantage, in that women would not have to take pills every day. I do not think women mind an injection if they are receiving an active compound.

Duration of response for fulvestrant compared to anastrozole in postmenopausal women with advanced breast cancer who progressed on previous hormonal therapy.

Updated results of pooled data from two randomized phase III trials with a median follow-up of 22.1 months

	Fulvestrant (n=428)	Anastrozole (n=423)
Median time to progression (TTP)	5.4 months	4.1 months
Objective response (CR+PR)	19.6%	17.3%
Clinical benefit (CR+PR+SD>24 weeks)	43.7%	41.1%
Median duration of response (DOR) for responding patients*	16.7 months	13.6 months
Ratio of average response durations (fulvestrant/anastrozole)**	1.30 (95% CI 1.13 - 1.50) *p*=0.0003	

* No statistical comparison was performed, since these subgroups are treatment-outcome dependent.
** DOR for responders = time from onset of response to disease progression; DOR for nonresponders = 0
Derived from Parker LM, Webster A. *Proc ASCO* 2002;**Abstract 160.**

Fulvestrant: Mechanism of action

Tamoxifen and fulvestrant interact differently with the estrogen receptor. Tamoxifen causes receptor dimerization — binding to the estrogen response element — and activation of AF-1 but inactivation of AF-2. This causes partial estrogen-agonistic and partial antagonistic activity, depending on the cell and the gene promoter contact. In contrast, fulvestrant inactivates both AF-1 and AF-2, completely switching off the receptor, and it increases the turnover of the receptors themselves.

These effects were seen in the preoperative studies, where fulvestrant or tamoxifen was given, and tumor immunostaining for estrogen receptors was examined over a period of two to three weeks. After two weeks, almost as much estrogen receptor in the tamoxifen-treated group stained positive as in the pretreatment sample. In the fulvestrant arm, there was virtually no receptor to be stained.

In vitro effects of complete estrogen blockade

Dick Santen studied MCF-7 cells, which "hunt" prevailing estrogen concentrations. *In vitro*, MCF-7 cells are maximally stimulated by 10^{-9} molar units of estradiol. If these same MCF-7 cells are deprived of estrogen for one month, the dose response curve shifts dramatically to the left, becoming sensitive to 10^{-15} molar units of estradiol. The cells increase their sensitivity quite dramatically.

Estradiol levels are virtually undetectable in women on anastrozole. If Santen's data is transferable to humans, there is the potential for the tumor to adapt to the lower prevailing estradiol concentration, thus circumventing the effect of anastrozole. This data may indicate a tumor's ability to be stimulated by the low concentrations of estrogen that exist in patients treated with anastrozole.

This data from Santen is also very important for the future of endocrine therapy. For women who fail anastrozole therapy, we may be able to add back small doses of estrogen to cause tumor suppression — like high-dose estrogen in the "old days" but with the sensitivity curves shifted to the left.

We studied women who had four endocrine therapies, adding back estradiol in large doses. In this group of 30 patients, one-third responded for a median duration of one year. Thus, we may be able to rechallenge with estradiol and alternate aromatase inhibitors with estrogens. We have not sufficiently thought out endocrine therapy, and there may be more mileage here than we actually know.

Tumor response to long-term estrogen deprivation

"Our data indicate that breast cancer cells can adapt to long-term estradiol deprivation and develop means to re-grow in the presence of very small concentrations of estradiol. Adaptation involves upstream mechanisms with an increase in estrogen receptor level and in basal transcription rates. However, this does not appear to be the primary event mediating hypersensitivity. …Overexpression of growth factor pathways are involved in the hypersensitivity process. …The series of studies presented focus on the ability of breast cancer cells to adapt to various therapies. The possibility that tumors become hypersensitive to estradiol provides a plausible explanation why third-generation aromatase inhibitors are more effective than the first- and second-generation inhibitors. The magnitude of estradiol inhibition is greater with the third-generation inhibitors. In the long run, means to counteract the adaptive process will be necessary to prevent progression of breast cancer cells to a hormone independent state. Further work to explain this adaptive process should result in development of better therapies for patients and perhaps even cure if applied at early stages of disease."

EXCERPT FROM: Santen R et al. *J Steroid Biochem Mol Biol* 2001;79:115-25. **Abstract**

Preoperative fulvestrant

The preoperative EORTC trial evaluates one injection of fulvestrant after the diagnosis of breast cancer but before surgery. The idea is for the fulvestrant injection to cover the operative period as a potent antiestrogen that will lower estrogen receptor levels. We want to test the hypothesis of Bernie Fisher and others that adverse events related to metastases occur during the perioperative period. Hopefully, we can alter that with fulvestrant. The aim is to enroll more than 3,000 women into this study.

EORTC-10963: Phase III randomized neoadjuvant study of ICI 182780 in women with stage I or II primary breast cancer **Protocol**

Eligibility	ER+ or unknown, pre- or postmenopausal, Stage I or II primary operable breast cancer

ARM 1 | Fulvestrant IM on day 1 → surgery between days 8 and 29

ARM 2 | Placebo IM on day 1 → surgery between days 8 and 29

Patients followed q 3 mos x 2 yrs, q 6 mos x 3 yrs, then annually thereafter

Select publications

Use of bisphosphonates in breast cancer

Ali SM et al. **Safety and efficacy of bisphosphonates beyond 24 months in cancer patients.** *J Clin Oncol* 2001;19:3434-7. **Abstract**

Berenson JR. **Zoledronic acid in cancer patients with bone metastases: Results of Phase I and II trials.** *Semin Oncol* 2001;28:25-34. **Abstract**

Bryce CJ et al. **Does short-term, intravenous, low-dose clodronate, administered with adjuvant chemotherapy for premenopausal breast cancer, reduce bone loss in the first year in patients?** *Proc ASCO* 2002;**Abstract 270.**

Chlebowski RT. **Factors influencing the role of bisphosphonates in breast cancer management.** *Semin Oncol* 2001;28:42-8. **Abstract**

Coleman RE. **Should bisphosphonates be the treatment of choice for metastatic bone disease?** *Semin Oncol* 2001;28:35-41. **Abstract**

Coleman RE, Seaman JJ. **The role of zoledronic acid in cancer: Clinical studies in the treatment and prevention of bone metastases.** *Semin Oncol.* 2001;28:11-6. **Abstract**

Diel IJ. **Bisphosphonates in the prevention of bone metastases: Current evidence.** *Semin Oncol* 2001;28:75-80. **Abstract**

Diel IJ, Mundy GR. **Bisphosphonates in the adjuvant treatment of cancer: Experimental evidence and first clinical results. International Bone and Cancer Study Group (IBCG).** *Br J Cancer* 2000;82:1381-6. **Abstract**

Gralow JR. **The role of bisphosphonates as adjuvant therapy for breast cancer.** *Curr Oncol Rep* 2001;3:506-15. **Abstract**

Hillner BE et al. **American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel.** *J Clin Oncol* 2000;18:1378-91. **Abstract**

Hillner BE et al. **Pamidronate in prevention of bone complications in metastatic breast cancer: A cost-effectiveness analysis.** *J Clin Oncol* 2000;18:72-9. **Abstract**

Jagdev SP et al. **The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: Evidence for synergy with paclitaxel.** *Br J Cancer* 2001;84:1126-34. **Abstract**

Nikolic-Tomasevic Z et al. **Tumor 'flare' hypercalcemia--an additional indication for bisphosphonates?** *Oncology* 2001;60:123-6. **Abstract**

Paterson AH. **Adjuvant bisphosphonate therapy: The future.** *Semin Oncol* 2001;28:81-5. **Abstract**

Perez EA. **Metastatic bone disease in breast cancer: The patient's perspective.** *Semin Oncol* 2001;28:60-3. **Abstract**

Powles TJ et al. **A randomised placebo controlled trial to evaluate the effect of the bisphosphonate, clodronate, on the incidence of metastases and mortality in patients with primary operable breast cancer.** *Breast Cancer Res Treat* 2001;**Abstract 1.**

Rosen LS et al. **Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A phase III, double-blind, comparative trial.** *Cancer J* 2001;7:377-87. **Abstract**

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19:10-7. **Abstract**

Saarto T et al. **The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer.** *Br J Cancer* 2001;84:1047-51. **Abstract**

Tripathy D. **Bisphosphonates in oncology: Breast cancer and beyond.** *Semin Oncol* 2001;28:86-91. **Abstract**

Van Poznak C. **How are bisphosphonates used today in breast cancer clinical practice?** *Semin Oncol* 2001;28:69-74. **Abstract**

Vehmanen L et al. **Long-term impact of chemotherapy-induced ovarian failure on bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvant clodronate treatment.** *Eur J Cancer* 2001;37:2373-8. **Abstract**

Fulvestrant (ICI 182,780; Faslodex®)

Cheung KL, Robertson JF. **Fulvestrant.** *Expert Opin Investig Drugs* 2002;11:303-308. **Abstract**

Curran M, Wiseman L. **Fulvestrant.** *Drugs* 2001;61:807-13; discussion 814. **Abstract**

Elkak AE, Mokbel K. **Pure antiestrogens and breast cancer.** *Curr Med Res Opin* 2001;17:282-9. **Abstract**

Erikstein B et al. **ICI 182,780 ('Faslodex') 250 mg monthly intramuscular (IM) injection shows consistent PK profile when given as either 1 x 5ml or 2 x 2.5 ml injections in postmenopausal women with advanced breast cancer (ABC).** *Proc ASCO* 2001; **Abstract 2025.**

Howell A. **Preliminary experience with pure antiestrogens.** *Clin Cancer Res* 2001;7:4369s-4375s; discussion 4411s-4412s. **Abstract**

Howell A et al. **Comparison of efficacy and tolerability of fulvestrant (Faslodex) with anastrozole (Arimidex) in postmenopausal women with advanced breast cancer.** *Breast Cancer Res Treat* 2000;64(1):**Abstract 6.**

Johnston SR. **Fulvestrant (AstraZeneca).** *Curr Opin Investig Drugs* 2002;3(2):305-12. **Abstract**

Jones S. **Fulvestrant ('Faslodex®') versus anastrozole ('Arimidex®') for the treatment of advanced breast cancer in postmenopausal women – safety update on the combined analysis of two multicenter trials.** *Breast Cancer Res Treat* 2001;**Abstract 455.**

Mauriac L. **Fulvestrant ('Faslodex®') is effective in advanced breast cancer in postmenopausal patients with visceral metastases: Comparison with anastrazole.** *Breast Cancer Res Treat* 2001; **Abstract 452.**

Osborne CK. **A double-blind randomized trial comparing the efficacy and tolerability of Faslodex™ (fulvestrant) with Arimidex™ (anastrozole) in postmenopausal (PM) women with advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2000;64(1):**Abstract 7.**

Osborne CK et al. **Selective estrogen receptor modulators: Structure, function and clinical use.** *J Clin Oncol* 2000;18(17):3172-3186. **Abstract**

Parker LM et al. **Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex').** *Proc ASCO* 2002;**Abstract 160.**

Robertson JF. **Estrogen receptor downregulators: New antihormonal therapy for advanced breast cancer.** *Clin Ther* 2002;24 Suppl A:A17-30. **Abstract**

Robertson JFR. **A comparison of the single-dose pharmacokinetics (PK) of 'Faslodex' (fulvestrant) 250 mg when given as either a one x 5-ml intramuscular (IM) injection or two x 2.5-ml injections in postmenopausal (PM) women with advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2000;**Abstract 172.**

Rosenberg Z and RS et al. **Is ICI 182,780 an antiprogestin in addition to being an antiestrogen?** *Breast Cancer Res Treat* 2000;60:1-8. **Abstract**

Vergote I. **Evidence of continued sensitivity to endocrine agents in postmenopausal women with advanced breast cancer progressing on fulvestrant ('Faslodex®') treatment.** *Breast Cancer Res Treat* 2001;**Abstract 446.**

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Implications of ATAC for clinical practice

The most important and exciting data to emerge in breast cancer clinical research this year were the ATAC trial results, which demonstrated a dramatic disease-free survival advantage for anastrozole over tamoxifen as well as a more favorable toxicity profile. These data are from a very large, credible trial, and clearly, I am obligated to discuss these results with my patients. However, I am still uncertain how these data will affect my practice.

There is not yet enough follow-up to determine whether anastrozole will improve survival, and we need more information about its effect on bone mineral density. Trevor Powles' data demonstrating that a bisphosphonate reduces the incidence of bone metastases is compelling. Therefore, one option would be to give a bisphosphonate concurrently with anastrozole. In my practice I still tend to recommend tamoxifen, but I am much more comfortable switching patients to anastrozole if they cannot tolerate tamoxifen.

Management of postmenopausal patients with ER-positive breast cancers

For the 60- to 70-year-old, ER-positive patient I would discuss the very modest benefits of chemotherapy. If a patient chooses chemotherapy, then I would support that as a reasonable option but would not recommend it. These women should receive hormonal therapy.

Even patients who have tumors with a few percent, weakly staining estrogen receptors will have surprisingly large responses to hormonal therapy. If a tumor is predominantly hormone-sensitive, then the added benefit from chemotherapy is going to be very small. Additionally, we know that the older the woman, the smaller the benefit from chemotherapy. In postmenopausal women, the effect from chemotherapy on survival is about one-half to one-third of the effect in premenopausal women. If you take the older women who have ER-positive tumors, the effects from chemotherapy are even less.

The diminishing effect of chemotherapy in older women

We know with certainty that as women get older they derive less benefit from chemotherapy. In younger women, the reduction in the odds of death are slightly higher than 30%, but in 60- to 70-year-old women the reduction is only about 9%. Interestingly, the reverse is seen with tamoxifen — with older women receiving greater benefit than younger patients.

In the 1980s, my initial reaction to this data was that it reflected the effect of chemotherapy on the ovaries. However, Richard Peto analyzed the relationship between menopause and the effects of both chemotherapy and tamoxifen. There is a highly significant linear effect with age and response to chemotherapy and tamoxifen but not with menopause. That did not make sense to me, but it is definitely a real phenomenon, and for 15 years I have been trying to figure it out.

Postmenopausal ovarian function

There is a misconception that once a woman stops menstruating, the ovaries immediately cease to function. That is too simplistic. Ovarian function continues for some time after the onset of amenorrhea, and it is reflected in circulating estrogen levels. One of the best studies to evaluate this issue indicated that, on average, the ovary continues to produce estrogen for four years after cessation of menses and up to ten years in some women. Additionally, more testosterone and androstenedione are being produced by the ovaries in older women. In fact, probably one-half of the androgens in a postmenopausal woman are produced by the ovary, and the other half come from the adrenal gland.

There are data to suggest that chemotherapy reduces both estrogen and androgen levels even in postmenopausal women. Another little pearl that people have forgotten comes from the work of Nissen-Meyer, who conducted one of the earliest oophorectomy trials back in the 1950s, which included postmenopausal women. He demonstrated that postmenopausal women responded to oophorectomy, but only the older postmenopausal patients. The ones who are just a few years after menopause do not respond.

A group of surgeons at the University of Oregon did an oophorectomy series in the 1980s and produced exactly the same results. In the early 1980s, I published a paper demonstrating that premenopausal and very postmenopausal women received the greatest benefit from various hormone therapies, but there was a blip in the perimenopausal years where no type of endocrine therapy worked very well. So, the ovary is not unimportant in postmenopausal women.

Effect of adjuvant chemotherapy in ER-positive patients

In the past year, I have been trying to understand why ER-positive patients did not benefit from the addition of paclitaxel to AC x 4 in the Intergroup adjuvant trial 0148 (CALGB 9344). My initial reaction was that because these patients received tamoxifen, there was little additional effect to be gained from chemotherapy. I evaluated this hypothesis by examining all the trials in the

Overview that gave one, two and five years of tamoxifen plus or minus chemotherapy. If my hypothesis was correct, then adjuvant chemotherapy would have demonstrated greater benefit in those receiving a shorter compared to a longer duration of tamoxifen. That did not prove to be the case.

Currently, my hypothesis is that in both pre- and postmenopausal, ER-positive patients the effect of adjuvant chemotherapy is mediated through the ovary. AC x 4 does not cause a lot of amenorrhea, and I suspect that the taxanes do not give as much ovarian suppression as daily, oral cyclophosphamide. It may be that neither AC x 4 nor paclitaxel x 4 represent optimal treatment if you want to achieve ovarian suppression.

For premenopausal patients, there is an abundance of data demonstrating that chemotherapy regimens that induce amenorrhea — such as the classic Bonadonna CMF regimen — are among the most effective therapies. The Canadian adjuvant FEC trial produced dramatic benefits, and it also used daily, oral cyclophosphamide for 14 days. At the 2001 American Society of Clinical Oncology meeting, Kathy Albain presented the results from an important Intergroup study that randomized ER-positive women — who were no longer menstruating — to tamoxifen plus or minus classic FAC, utilizing that same dosing schedule of cyclophosphamide. FAC-T resulted in a significant disease-free and overall survival advantage compared to tamoxifen alone.

Intergroup 0100: Benefit of chemotherapy plus tamoxifen in postmenopausal ER-positive women

	FAC-T	T	Statistical Significance
5-year disease-free survival	76%	67%	HR=1.43 (95% CI 1.18-1.72) *p*=0.0001
5-year survival	84%	79%	HR=1.29 (95% CI 1.04-1.59) *p*=0.007

"Conclusion: FAC plus T significantly improves long-term DFS, and after prolonged follow-up, offers a definite survival benefit over T for postmenopausal women with node (+), receptor (+) breast cancer."

Derived from Albain K et al. *Proc ASCO* 2001.**Abstract 94.**

FEC versus CMF in node-positive premenopausal women

	FEC (n=351)	CMF (n=359)	Statistical Significance
5-year disease-free survival	63%	53%	*p*=0.009
5-year survival	77%	70%	*p*=0.03

"Conclusion: The results of this trial show the superiority of CEF over CMF in terms of both disease-free and overall survival in premenopausal women with axillary node-positive breast cancer."

Derived from Levine MN et al. *J Clin Oncol* 1998;16(8):2651-8. **Abstract**

Select publications

Adjuvant use of aromatase inhibitors for postmenopausal, ER-positive patients

Pharmacokinetics of anastrozole and tamoxifen alone and in combination during adjuvant endocrine therapy for early breast cancer in postmenopausal women: A subprotocol of the "Arimidex® and Tamoxifen Alone or in Combination" (ATAC) trial.
Br J Cancer 2001;85(3):317-324. **Abstract**

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal women.** *Breast Cancer Res Treat* 2001;69(3):**Abstract 8.**

Baum M et al. **Sequential power calculations in a recruitment phase of a multicentre trial — the experience of the 'Arimidex (anastrozole), tamoxifen alone or in combination' (ATAC) study.**
Proc ASCO 2002;**Abstract 185.**

Brodie A. **Aromatase inhibitors in breast cancer.** *Trends Endocr Metab* 2002;13(2):61-65. **Abstract**

Buzdar AU. **Anastrozole (Arimidex) —- an aromatase inhibitor for the adjuvant setting?**
Br J Cancer 2001;85(2 suppl):6-10. **Abstract**

Duffy SRG et al. **The ATAC ('Arimidex,' tamoxifen, alone or in combination) early breast cancer (EBC) trial in postmenopausal (PM) patients: Endometrial subprotocol results.**
Proc ASCO 2002;**Abstract 158.**

Fallowfield L et al. **Assessing the quality of life (QOL) of postmenopausal (PM) women randomized into the ATAC ('Arimidex,' tamoxifen, alone or in combination) adjuvant breast cancer (BC) trial.**
Proc ASCO 2002;**Abstract 159.**

Goss PE. **Preliminary data from ongoing adjuvant aromatase inhibitor trials.** *Clin Cancer Res* 2001;7(12 suppl):4397s-4401s. **Abstract**

Howell A. **Future use of selective estrogen receptor modulators and aromatase inhibitors.**
Clin Cancer Res 2001;7(12 suppl):4402s-4410s. **Abstract**

Howell A et al. **Where do selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) now fit into breast cancer treatment algorithms?***J Steroid Biochem Mol Biol* 2001;79:227-237. **Abstract**

Ingle JN. **Aromatase inhibition and antiestrogen therapy in early breast cancer treatment and chemoprevention.** *Oncology (Huntingt)* 2001;15:28-34. **Abstract**

Johnson PE, Buzdar A. **Are differences in the available aromatase inhibitors and inactivators significant?** *Clin Cancer Res* 2001;7(12 Suppl):4360s-4368s. **Abstract**

Mamounas EP. **Adjuvant exemestane therapy after 5 years of tamoxifen: Rationale for the NSABP B-33 trial.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):35-39. **Abstract**

Nicholls H. **Aromatase inhibitors continue their ATAC on tamoxifen.** *Trends Mol Med* 2002;8(4):S12-3. **Abstract**

Ragaz J. **Adjuvant trials of aromatase inhibitors: Determining the future landscape of adjuvant endocrine therapy.** *J Steroid Biochem Mol Biol* 2001;79:133-141. **Abstract**

Menopause and the endocrine effects of adjuvant therapy on pre- and postmenopausal patients

Bhatavdekar JM et al. **Endocrine function in premenopausal and postmenopausal advanced breast cancer patients treated with CMF or tamoxifen.** *Neoplasma* 1992;39:123-7. **Abstract**

Bianco AR et al. **Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer.** *Br J Cancer* 1991;63:799-803. **Abstract**

Bines J et al. **Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer.** *J Clin Oncol* 1996;14:1718-29. **Abstract**

Braverman AS et al. **Premenopausal serum estradiol (E2) levels may persist after chemotherapy (CT)-induced amenorrhea in breast cancer (BC).** *Proc ASCO* 2002;**Abstract 164.**

Burger HG. **The endocrinology of the menopause.** *J Steroid Biochem Mol Biol* 1999;69(1-6):31-5. **Abstract**

Burger HG. **The menopause: When it is all over or is it?** *Aust N Z J Obstet Gynaecol* 1994;34(3):293-5. **Abstract**

Burger HG et al. **Hormonal changes in the menopause transition.** *Recent Prog Horm Res* 2002;57:257-75. **Abstract**

Burger HG et al. **Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women.** *J Clin Endocrinol Metab* 1999;84(11):4025-30. **Abstract**

Chakravarti S et al. **Hormonal profiles after the menopause.** *Br Med J* 1976;2(6039):784-7. **Abstract**

Collichio F, Pandya K. **Amenorrhea following chemotherapy for breast cancer: Effect on disease-free survival.** *Oncology (Huntingt)* 1994;8:45-52. **Abstract**

Del Mastro L et al. **Amenorrhea induced by adjuvant chemotherapy in early breast cancer patients: Prognostic role and clinical implications.** *Breast Cancer Res Treat* 1997;43:183-90. **Abstract**

Goldhirsch A et al. **The magnitude of endocrine effects of adjuvant chemotherapy for premenopausal breast cancer patients.** *The International Breast Cancer Study Group.* Ann Oncol 1990;1:183-8. **Abstract**

Johannes CB, Crawford SL. **Menstrual bleeding, hormones, and the menopausal transition.** *Semin Reprod Endocrinol* 1999;17(4):299-309. **Abstract**

Kalantaridou SN, Nelson LM. **Premature ovarian failure is not premature menopause.** *Ann N Y Acad Sci* 2000;900:393-402. **Abstract**

Lower EE et al. **The risk of premature menopause induced by chemotherapy for early breast cancer.** *J Womens Health Gend Based Med* 1999;8:949-54. **Abstract**

Pagani O et al. **Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: Results of the International Breast Cancer Study Group (IBCSG) Trial VI.** *Eur J Cancer* 1998;34:632-40. **Abstract**

Poikonen P et al. **Prognostic effect of amenorrhoea and elevated serum gonadotropin levels induced by adjuvant chemotherapy in premenopausal node-positive breast cancer patients.** *Eur J Cancer* 2000;36:43-8. **Abstract**

Sherman BM et al. **The menopausal transition: Analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women.** *J Clin Endocrinol Metab* 1976;42(4):629-36. **Abstract**

Toma S et al. **Chemotherapy-induced amenorrhea and other clinical and pathological parameters in the prognosis of breast cancer patients.** *J Chemother* 1992;4:321-5. **Abstract**

Utian WH. **Ovarian function, therapy-oriented definition of menopause and climacteric.** *Exp Gerontol* 1994;29(3-4):245-51. **Abstract**

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NSABP B-27 neoadjuvant trial

The main goal of this trial was to determine whether the addition of docetaxel to AC would improve disease-free or overall survival. Additionally, the trial assessed whether the addition of preoperative docetaxel resulted in improved clinical and pathologic response rates and whether postoperative docetaxel improved the outcomes of patients with pathologically positive nodes.

Docetaxel was selected in light of the phase II data demonstrating response rates around 47% in anthracycline-resistant breast cancer. Phase III data, which became available after the trial began, indicated that docetaxel was actually more active than doxorubicin.

Response rates in NSABP B-27

Preoperative doxorubicin/cyclophosphamide followed by docetaxel increased both the clinical and pathologic response rates compared to preoperative doxorubicin/cyclophosphamide alone. The clinical response rate increased from 85% to 91%, with the complete response rate improving from 40% to 65%. Of even greater importance, the pathologic response rate essentially doubled from 13.5% to 25.6% in patients with ER-positive and ER-negative tumors.

The median tumor size in B-27 was 4.5 cm; whereas, the median tumor size in our previous neoadjuvant trial B-18 was about 2.2 cm. Since B-27 involved eight cycles of therapy, there may have been a natural selection to enroll higher-risk patients with larger tumors. Surprisingly, the pathologic response rate (~13%) for doxorubicin/cyclophosphamide was the same in both trials, indicating that a tumor will respond to neoadjuvant chemotherapy regardless of its size.

Sentinel node biopsy in patients on NSABP B-27

In about 400 cases, we performed a sentinel node biopsy off-protocol. We were then able to compare those results to the axillary dissection, which was part of the protocol. We were able to identify the sentinel node in about 85% of the cases. The success rate was higher (~90%) for the cases in which we used radioisotope and blue dye together. The false-negative rate was about 11% for node-positive patients, which is comparable to the results obtained in the multicenter trial by Krag.

Survival in NSABP-27

The disease-free and overall survival analyses require enough observed events, and it may still be another couple of years before we perform the final analyses. Although B-18 did not demonstrate a disease-free or overall survival difference, B-27 may or may not support this result.

NSABP trials

Trial	Schema	Status
NSABP B-27	Eligibility: Palpable, operable breast cancer > 1cm Arm 1: AC x 4 + tam → surgery Arm 2: AC x 4 + tam → docetaxel x 4 → surgery Arm 3: AC x 4 + tam → surgery → docetaxel x 4	**Closed protocol**
NSABP B-30	Eligibility: Node-positive breast cancer Arm 1: AC x 4 → docetaxel x 4 Arm 2: A + docetaxel x 4 Arm 3: AC + docetaxel x 4	**Open protocol**
NSABP B-31	Eligibility: HER2-positive, node-positive breast cancer Arm 1: AC x 4 → paclitaxel x 4 Arm 2: AC x 4 → paclitaxel x 4 + H qw x 1 year	**Open protocol**
NSABP B-32	Eligibility: Clinically node-negative breast cancer Arm 1: Sentinel lymph node biopsy (SLNB) with axillary dissection Arm 2: SLNB → + SN → ax dissection - SN → no ax dissection	**Open protocol**
NSABP B-33	Eligibility: cT1-3 N0-1 M0 postmenopausal breast cancer patients completing > 5 years of tamoxifen Arm 1: Exemestane x 2 years Arm 2: Placebo x 2 years	**Open protocol**
NSABP B-34	Eligibility: Early stage breast cancer Arm 1: Clodronate + chemo/tam at physician discretion Arm 2: Placebo + chemo/tam at physician discretion	**Open protocol**
Proposed NSABP DCIS Trial	Eligibility: Postmenopausal, DCIS, post-lumpectomy Arm 1: Anastrozole Arm 2: Tamoxifen	**Planned protocol**
Proposed NSABP local recurrence trial	Eligibility: Ipsilateral breast tumor recurrence or local/regional recurrence Arm 1: Capecitabine/docetaxel Arm 2: No chemotherapy Hormonal therapy given to ER-positive women	**Planned protocol**

Neoadjuvant capecitabine/docetaxel trial

In light of the B-27 trial results, we are designing a neoadjuvant trial that will compare doxorubicin/cyclophosphamide followed by docetaxel with or without capecitabine. This trial is based on Dr O'Shaughnessy's study, which demonstrated that capecitabine/docetaxel improved survival in patients with metastatic breast cancer. Since B-27 established that preoperative docetaxel almost doubled the pathologic response rate, we want to see if adding capecitabine will further increase the pathologic response.

This trial will also assess many biomarkers, both before and after chemotherapy, with sequential core biopsies. We will attempt to identify molecular biomarkers with DNA microarray and high throughput technology that can predict the response to chemotherapy. We will also measure thymidine phosphorylase to determine if it is upregulated by docetaxel. Based on data from B-18 and B-27, sentinel node biopsy alone will be allowed for patients with a pathologic complete response. We will evaluate whether neoadjuvant chemotherapy can reduce the extent of surgery, not only in the breast but also in the axilla.

Because hand-foot syndrome is associated with higher doses of capecitabine, we plan to decrease the dose to 2 gm/m^2 (in two divided doses for two weeks with one week off). There are some data to suggest that the efficacy is not reduced by this dose reduction. In fact, the majority of the patients in Dr O'Shaughnessy's trial had this dose reduction. In the adjuvant setting, it is reasonable to reduce the dose of a drug from its maximum tolerated dose.

Sequential versus combination chemotherapy in the adjuvant setting

NSABP B-30 is an important trial since it will answer whether sequential chemotherapy is better than combination chemotherapy in the adjuvant setting. Patients with node-positive breast cancer are randomized to doxorubicin/cyclophosphamide followed by docetaxel versus doxorubicin/docetaxel versus docetaxel/doxorubicin/cyclophosphamide. The rationale for selecting docetaxel is related to the issue of cardiac toxicity. Initial phase II trials from Europe reported over a 90% response rate for paclitaxel when given in combination with doxorubicin. However, there was an increase in cardiac toxicity when paclitaxel was given in combination with doxorubicin and cyclophosphamide. Although cardiac toxicity may be attenuated by either changing the length of the infusion or separating paclitaxel from doxorubicin by several hours to a day, these maneuvers may also decrease efficacy.

In phase II trials, docetaxel when given in combination with doxorubicin did not increase cardiac toxicity. This difference in cardiac toxicity may be related to the different vehicles used to dissolve paclitaxel and docetaxel. Paclitaxel is dissolved in cremophor, which is known to increase doxorubicin's area under the concentration curve (AUC). Docetaxel, on the other hand, is dissolved in polysorbate, which does not increase doxorubicin's AUC.

Adjuvant trial of capecitabine as therapy for elderly women

Hy Muss is conducting an adjuvant trial comparing either AC or CMF to capecitabine in elderly women. We do not have convincing data that adjuvant chemotherapy provides a benefit to women over the age of 70. In the Overview Analysis, there was a decrease in the risk reduction with every decade of life. However, there were few women over the age of 70 included in that analysis. Today, many women over the age of 70 have a good performance status and no comorbid conditions.

Yet there is still reluctance, especially in women with ER-positive tumors who will receive adjuvant tamoxifen or perhaps anastrozole, to use adjuvant chemotherapy. We actually need to compare adjuvant hormonal therapy with or without chemotherapy in elderly women with ER-positive breast cancer. If chemotherapy improves survival, then we can look for regimens that are equally effective and less toxic. In women with ER-negative breast cancer, most physicians are comfortable using adjuvant chemotherapy. Therefore, Hy Muss' trial may be more applicable to elderly women with ER-negative breast cancer.

CALGB 49907: A Randomized Trial of Adjuvant Chemotherapy with Standard Regimens, Cyclophosphamide, Methotrexate and Fluorouracil "CMF" or Doxorubicin and Cyclophosphamide "AC", Versus Capecitabine in Women 65 Years and Older with Early Stage Breast Cancer

Eligibility	Breast cancer patients ≥ 65 years of age, node-positive or high-risk node-negative
ARM 1	Capecitabine (2000 mg/m² po in 2 divided doses for 14 days q 3 weeks) x 6 cycles
ARM 2	Standard therapy (CMF vs AC at discretion of treating physician)

Tamoxifen given after completion of chemotherapy for all ER+ or PR+ patients

Adjuvant trastuzumab in HER2-positive, node-positive disease

NSABP B-31 evaluates adjuvant trastuzumab in women with HER2-positive, node-positive breast cancer. It is a two-arm trial comparing doxorubicin / cyclophosphamide followed by paclitaxel with or without trastuzumab. As demonstrated by the trials in metastatic disease, trastuzumab cannot be given concomitantly with anthracyclines because of the potential cardiac toxicity. We are evaluating whether they can be given sequentially. B-31 has very strict criteria for the evaluation of cardiac toxicity. An interim analysis conducted by the Data Safety Monitoring Committee did not find a significant incidence of cardiac toxicity associated with the addition of trastuzumab. In contrast, the NCCTG, because of cardiac toxicity, had to suspend the arm of trial 9831 that administered concomitant trastuzumab and paclitaxel.

In B-31, we conducted an analysis of the first 100 patients' HER2 assays. There was significant inconsistency between the HER2 results obtained from nonreference laboratories and those obtained with FISH at a central laboratory. The protocol now mandates that a reference or central laboratory perform the IHC assay before the patient is enrolled on the trial.

In the metastatic setting, trastuzumab in combination with chemotherapy prolongs median survival by five months. We hope that adjuvant trastuzumab will also be of benefit. In light of the cardiac toxicity, we must, however, be careful not to adopt trastuzumab into the adjuvant setting before we have results from randomized clinical trials. Theoretically, one could justify using trastuzumab in a woman with inflammatory breast cancer; I would still be very hesitant without proven benefit, especially in lieu of the side effects.

Adjuvant clodronate

NSABP B-34 will evaluate adjuvant clodronate, an oral bisphosphonate, in women with node-negative and node-positive breast cancer. Data from Germany as well as the Canadian and UK trials demonstrate that clodronate reduces bone and non-bone metastases and also improves survival. B-34 will randomize 3,000 women to three years of clodronate or placebo. The choice of adjuvant therapy will be left to the investigator's discretion. We chose clodronate for this trial because it is the only bisphosphonate with data in the adjuvant setting.

Clodronate is well tolerated compared to alendronate (Fosamax®). If the B-34 results are positive, hopefully clodronate will be FDA approved. In lieu of the ATAC trial results, it may be reasonable to combine an aromatase inhibitor with a bisphosphonate as adjuvant therapy. Eventually, NSABP plans to compare the bisphosphonates to find the best one. It may, however, be difficult to use an intravenous bisphosphonate in terms of patient acceptability.

Anastrozole in women with DCIS

We are close to initiating a trial in women with DCIS that will compare anastrozole to tamoxifen. This trial will replicate the ATAC trial in women with DCIS. Since these are very low-risk women, it is important to determine whether the risk-benefit ratio will justify the use of an aromatase inhibitor. The additional 50% reduction in contralateral breast cancer, associated with anastrozole in the ATAC trial, justifies the design of this trial in women with DCIS.

Implications of the ATAC trial results

This is the first time that an agent appears to be superior to tamoxifen. Even though the disease-free survival and contralateral breast cancer data are

promising, it is still not known whether this will translate into a survival advantage. In elderly patients in whom one wants to avoid thromboembolic events and endometrial cancer, the ATAC trial results may lead to the adoption of anastrozole as adjuvant therapy. Eventually, anastrozole may be used in most postmenopausal women. In terms of the ongoing NSABP trials, we currently only allow the use of tamoxifen. However, that may have to change. For our new trials, the NCI is already stating that we must allow the use of an aromatase inhibitor. In Europe, the IBIS trial will compare tamoxifen to an aromatase inhibitor as preventative therapy.

Proposed trial of XT in ipsilateral breast tumor recurrence or local regional recurrence

We are planning a trial to determine the value of chemotherapy in patients with ipsilateral breast tumor recurrence (IBTR) or local regional recurrence. These patients have not been studied prospectively, and it is not known whether chemotherapy can improve survival. Patients with IBTR and local regional recurrence have a 50%-60% and 80%-90% risk respectively, of developing systemic disease in the next five years. In ER-positive patients, we will compare hormonal therapy with or without capecitabine / docetaxel. In ER-negative patients, we will compare capecitabine / docetaxel to no treatment. Since most of the patients will have received either an anthracycline or alkylating agent as adjuvant therapy, we chose docetaxel as a noncross-resistant agent. Capecitabine was added to obtain the maximum benefit.

Chemotherapy for local recurrence

"Although there are few retrospective studies to address the care of patients with local-regional recurrent nonmetastatic breast cancer, treatment consisting of complete surgical excision, comprehensive irradiation and systemic therapy is now considered the standard of care by many. The role of chemotherapy is perhaps the most controversial aspect of treating local-regional recurrence after mastectomy."

EXCERPT FROM: Ballo M et al. *Int J Radiat Oncol Biol Phys* 1999;44(1):105-112. **Abstract**

"Local recurrences occur most frequently in the skin, and the optimal treatment consists of complete excision of gross disease followed by irradiation. This approach has improved local control and survival in most series. For systemic management, antihormonal therapy should be administered concurrently with irradiation to all receptor-positive patients. Chemotherapy, using a combined or sequential application of Adriamycin and Taxol, has become a standard treatment in advanced breast cancer, but it may be ineffective in resolving local recurrence."

EXCERPT FROM: Harms W et al. *Int J Radiat Oncol Biol Phys* 2001;49(1):205-10. **Abstract**

Select publications

Neoadjuvant chemotherapy

NSABP. The effect of primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: Preliminary results from NSABP Protocol B-27. *Breast Cancer Res Treat* 2001;**Abstract 5.**

Aapro MS. **Neoadjuvant therapy in breast cancer: Can we define its role?** *Oncologist* 2001;6 Suppl 3:36-9. **Abstract**

Barni S et al. **Cisplatin-epirubicin-vinorelbine: A new neoadjuvant chemotherapy for stage T2-3/N0-2 breast cancer patients.** *Breast Cancer Res Treat* 2001;**Abstract 515.**

Buchholz TA et al. **Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation.** *J Clin Oncol* 2002;20(1):17-23. **Abstract**

Burstein HJ et al. **Preoperative trastuzumab (T) and paclitaxel (P) for HER2 overexpressing (HER2+) stage II/III breast cancer: Clinical, pathological and serological findings.** *Breast Cancer Res Treat* 2001;**Abstract 507.**

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

Colleoni M et al. **Influence of endocrine-related factors on response to perioperative chemotherapy for patients with node-negative breast cancer.** *J Clin Oncol* 2001;19:4141-9. **Abstract**

El-Didi MH et al. **Pathological assessment of the response of locally advanced breast cancer to neoadjuvant chemotherapy and its implications for surgical management.** *Surg Today* 2000;30:249-54. **Abstract**

Fumoleau P et al. **A randomized phase II study of 4 or 6 cycles of Adriamycin/Taxol (paclitaxel) as neoadjuvant treatment of breast cancer.** *Breast Cancer Res Treat* 2001;**Abstract 508.**

Jackisch C et al. **Dose-dense weekly (8 weeks) vs. sequential (24 weeks) neoadjuvant chemotherapy with adriamycin/cyclophosphamide and docetaxel in operable breast cancer (T2-3, N0-2, M0) — Interim analysis of the Geparduo trial.** *Breast Cancer Res Treat* 2001;**Abstract 509.**

Jakesz R. **Comparison of pre- vs. postoperative chemotherapy in breast cancer patients: Four-year results of Austrian Breast & Colorectal Study Group (ABCSG) Trial 7.** *Proc ASCO* 2001; **Abstract125.**

Krag D et al. **The sentinel node in breast cancer — a multicenter validation study.** *N Engl J Med* 1998;339:(14)941-6. **Abstract**

Mamounas EP, Fisher B. **Preoperative (neoadjuvant) chemotherapy in patients with breast cancer.** *Semin Oncol* 2001;28:389-99. **Abstract**

Petit T et al. **Chemotherapy response of breast cancer depends on HER-2 status and anthracycline dose intensity in the neoadjuvant setting.** *Clin Cancer Res* 2001;7:1577-81. **Abstract**

Sanchez-Rovira P et al. **HER2-status as a predictive factor for pathological complete response in primary breast cancer patients treated with gemcitabine-adriamycin-taxol as neoadjuvant treatment.** *Breast Cancer Res Treat* 2001;**Abstract 240.**

Sartor CI et al. **Low rate of ipsilateral breast tumor recurrence for patients with T3/T4 tumors treated with neoadjuvant chemotherapy followed by breast-conserving therapy.** *Breast Cancer Res Treat* 2001;**Abstract 143.**

Singletary SE. **Neoadjuvant chemotherapy in the treatment of stage II and III breast cancer.** *Am J Surg* 2001;182:341-6. **Abstract**

Smith IC et al. **Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel.** *J Clin Oncol* 2002;20(6):1456-66. **Abstract**

Smith IC, Miller ID. **Issues involved in research into the neoadjuvant treatment of breast cancer.** *Anticancer Drugs* 2001;12 Suppl 1:S25-9. **Abstract**

van der Hage JA et al. **Improved survival after one course of perioperative chemotherapy in early breast cancer patients. Long-term results from the European Organization for Research and Treatment of Cancer (EORTC) Trial 10854.** *Eur J Cancer* 2001;37:2184-93. **Abstract**

van der Hage JA et al. **Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer Trial 10902.** *J Clin Oncol* 2001;19:4224-37. **Abstract**

Local recurrence

Bartelink H et al. **Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation.** *N Engl J Med* 2001;345:1378-87. **Abstract**

Buchholz TA et al. **Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy**. *J Clin Oncol* 2001;19:2240-6. **Abstract**

Cowen D et al. **Local and distant failures after limited surgery with positive margins and radiotherapy for node-negative breast cancer.** *Int J Radiat Oncol Biol Phys* 2000;47:305-12. **Abstract**

della Rovere GQ, Benson JR. **Ipsilateral local recurrence of breast cancer: Determinant or indicator of poor prognosis?** *Lancet Oncol* 2002;3:183-7. **Abstract**

Doyle T et al. **Long-term results of local recurrence after breast conservation treatment for invasive breast cancer.** *Int J Radiat Oncol Biol Phys* 2001;51:74-80. **Abstract**

Elkhuizen PH et al. **High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of perioperative chemotherapy: A European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study.** *J Clin Oncol* 2000;18:1075-83. **Abstract**

Freedman GM, Fowble BL. **Local recurrence after mastectomy or breast-conserving surgery and radiation.** *Oncology (Huntingt)* 2000;14:1561-81; discussion 1581-2, 1582-4. **Abstract**

Harms W et al. **Results of chest wall reirradiation using pulsed-dose-rate (PDR) brachytherapy molds for breast cancer local recurrences.** *Int J Radiat Oncol Biol Phys* 2001;49:205-10. **Abstract**

Horiguchi J et al. **Immunohistochemical study on primary and recurrent tumors in patients with local recurrence in the conserved breast.** *Oncol Rep* 2000;7:295-8. **Abstract**

Janni W et al. **Matched pair analysis of survival after chest-wall recurrence compared to mammary recurrence: A long-term follow up.** *J Cancer Res Clin Oncol* 2001;127:455-62. **Abstract**

Janni W et al. **Radiotherapy of the chest wall following mastectomy for early-stage breast cancer: Impact on local recurrence and overall survival.** *Int J Radiat Oncol Biol Phys* 2000;48:967-75. **Abstract**

King TA et al. **Biopsy technique has no impact on local recurrence after breast-conserving therapy.** *Breast J* 2001;7:19-24. **Abstract**

Lohrisch C et al. **Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer.** *J Clin Oncol* 2000;18:2828-35. **Abstract**

Marret H et al. **Histologic multifocality is predictive of skin recurrences after conserving treatment of stage I and II breast cancers.** *Breast Cancer Res Treat* 2001;68:1-8. **Abstract**

McCready DR et al. **Factors associated with local breast cancer recurrence after lumpectomy alone: Postmenopausal patients.** *Ann Surg Oncol* 2000;7:562-7. **Abstract**

Park CC et al. **Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: Influence of margin status and systemic therapy on local recurrence.** *J Clin Oncol* 2000;18:1668-75. **Abstract**

Simmons RM et al. **Recurrence rates in patients with central or retroareolar breast cancers treated with mastectomy or lumpectomy.** *Am J Surg* 2001;182:325-9. **Abstract**

Tartter PI et al. **Lumpectomy margins, reexcision, and local recurrence of breast cancer.** *Am J Surg* 2000;179:81-5. **Abstract**

Voogd AC et al. **Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: Pooled results of two large European randomized trials.** *J Clin Oncol* 2001;19:1688-97. **Abstract**

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
alendronate	Fosamax®	Merck & Co., Inc.
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
bevacizumab	Avastin®	Genentech, Inc.
capecitabine	Xeloda®	Roche Laboratories, Inc.
clodronate	Not available in the United States	
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Myers Squibb Company, Pharmacia Corporation
docetaxel	Taxotere®	Aventis Pharmaceuticals
exemestane phosphate	Aromasin®	Pharmacia Corporation
epirubicin	Ellence®	Pharmacia Corporation
doxorubicin hydrochloride	Adriamycin®	Pharmacia Corporation
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Myers Squibb Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.
zoledronic acid	Zometa®	Novartis Pharmaceuticals

Faculty financial interests or affiliations

George W Sledge Jr, MD
Does not have any financial interests or affiliations to disclose

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Grants/Research Support: AstraZeneca Pharmaceuticals, LP
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Post-test

Questions *(please circle answer)*:

1. The half-life of trastuzumab is

a. 3 hours b. 3 days c. 3 weeks d. Longer than 3 weeks

2. The results from the ECOG trial (E2198) suggest that four cycles of trastuzumab/paclitaxel followed by four cycles of doxorubicin/cyclophosphamide

a. Should not be given under any circumstances
b. Does not increase the risk of congestive cardiomyopathy
c. Slightly increase the risk of congestive cardiomyopathy above baseline
d. Are not effective for metastatic disease

3. Follow up from the NSABP P-1 trial has shown that tamoxifen

a. Caused a generalized reduction in cystic disease
b. Caused a generalized reduction in hyperplasias (typical and atypical) and fibroadenomas
c. Reduced the premalignant and the non-premalignant events for younger women significantly more than for older women
d. All of the above
e. None of the above

4. Bevacizumab is a member of which class of agents?

a. Taxane b. Anthracycline c. Anti-VEGF antibody d. Anti-EGF antibody

5. For a tumor to be considered ER-positive, it must have

a. Any detectable estrogen receptor b. An Allred score of 2
c. At least 10% positive cells d. There is no worldwide standard for ER positivity.

6. True/False: Estrogen deprivation causes MCF-7 cells to become increasingly sensitive to estradiol.

7. Fulvestrant works by

a. Downregulating the estrogen receptor b. Lowering serum estradiol
c. Activating AF-1 but inactivating AF-2 d. None of the above
e. All of the above

8. As a woman becomes older, her chances of benefiting from chemotherapy

a. Increase b. Decrease c. Remain unchanged

9. True/False: For several years after menopause the ovaries produce estrogen.

10. True/False: Chemotherapy regimens that induce amenorrhea are among the most effective therapies for premenopausal women.

Exam Answer Key
1. D, 2. C, 3. D, 4. C, 5. D, 6. True, 7. A, 8. B, 9. True, 10. True

Evaluation Form

BCUS | 2002

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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• Review the effect of adjuvant chemotherapy in older women	5	4	3	2	1
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This program was supported by educational grants from AstraZeneca Pharmaceuticals, LP; Genentech, Inc.; and Roche Laboratories, Inc.

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