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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** contains an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. The first CD and the website also contain PowerPoint® files of the slides located at the end of the monograph.

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* uses 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.

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 3 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Robertson, Lyman, Budman and Boccardo on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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John F R Robertson, MD, FRCS	Grants/Research Support and Honorarium: AstraZeneca Pharmaceuticals LP
Gary H Lyman, MD, MPH, FRCP	Grants/Research Support: Amgen Inc, GlaxoSmithKline Consultant: Amgen Inc, Ortho Biotech Products LP
Daniel R Budman, MD, FACP	Grants/Research Support: Aventis Pharmaceuticals Inc, Eisai Inc, Eli Lilly and Company, GlaxoSmithKline, Novartis Pharmaceuticals, Roche Laboratories Inc Consultant: Eisai Inc Honorarium: Amgen Inc, Aventis Pharmaceuticals Inc, GlaxoSmithKline, Roche Laboratories Inc
Francesco Boccardo, MD	Grants/Research Support: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company Honorarium: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Eli Lilly and Company, Novartis Pharmaceuticals

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
5-fluorouracil, 5-FU	Various	Various
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Various	Various
epirubicin hydrochloride	Ellence®	Pfizer Inc
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
hydrocortisone	Various	Various
letrozole	Femara®	Novartis Pharmaceuticals
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology

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Editor's Note

Where we are; where we're headed

Some months ago I had the honor of interviewing a legendary figure in breast cancer research. While I had regularly said "hello" to this European-based oncologist in recent years at scientific meetings, this was the first time in about a decade that we sat down for an in-depth chat. I entered the conversation optimistic that this visionary researcher would deliver some new revelation about where we might be headed in clinical research. However, when I asked him about future treatment strategies, he mumbled the same jargon about targeted therapies and tissue predictors of response that I have heard endlessly in my audio interview travels.

Exiting this conversation, I was more than depressed. "Does anyone in the field have truly creative thoughts?" I asked myself. Sometimes cancer research seems like just one more government-based, bean-counting bureaucracy, and I was tempted to join the many patients and physicians who throw up their hands in frustration. But experience has shown me that my disillusionment is always tempered by moments when I am seduced by the prospect that hope is just around the corner. This issue of our series beckons with that promise.

John Robertson is my "go-to guy" when the absence of progress makes me want to give up on current research efforts. John is like a magician who amazes you with new tricks, and this most recent conversation once again suggests that we may be closer to reality, than we are to illusion.

Item number one on John's list is fulvestrant, an estrogen receptor "terminator" that many clinicians consider just one more endocrine option on a long but unexciting list. John is much more optimistic that this fascinating agent might hold a lot more antitumor potential than many appreciate.

In a recent issue of our series, Stephen Jones, one of the more sagacious "Jedis" of the field, shared with us his observation — anecdotal but nonetheless thought provoking — that there was a subset of women with metastatic breast cancer who experienced prolonged responses to fulvestrant.

Steve specifically referred to four of his patients who experienced very prolonged antitumor responses while participating in the initial North American double-blind randomized trial of fulvestrant versus anastrozole. Unblinding of the trial revealed that all four of these women were on fulvestrant. Was this a coincidence or, as Steve postulated, an important clue? I have found Steve to be a very levelheaded observer, and he believes that some important but poorly defined biology explained the unusual courses of these women.

I shared Steve's thought with John, who responded with two hats — the evidence-based trooper who noted the pitfalls of anecdotal observations, and the open-minded investigator who spouts theories to consider. John noted that fulvestrant competitively inhibits the estrogen receptor and, if there is a subset of women with profound and longstanding responses to fulvestrant, it might be those patients with serendipitously minimal circulating estrogen levels.

John further commented that this concept is being tested in the SoFEA study, a new trial that randomly assigns breast cancer patients who are progressing on an aromatase inhibitor to either fulvestrant alone or fulvestrant plus the continuation of the aromatase inhibitor.

I like that one, John! It's simple, but intriguing. Maybe we don't need to escalate the dose of fulvestrant, but rather just obliterate circulating estrogens to see the true value of this agent. In a couple of years, we should know.

John further raised my hopes with new data on the use of serum tumor markers to detect the initial primary appearance of breast cancer and early recurrence after primary local therapy. ASCO tells us that serum tumor marker monitoring after adjuvant therapy is of unproven value. John argues that a couple of semiobscure trials refute this, and that logic suggests that if adjuvant therapy works because systemic agents are more effective with lower tumor burden, then detecting and treating recurrence earlier should also be beneficial.

Who really knows? Breast cancer in the adjuvant setting boils and stews microscopically beneath the surface while both patients and physicians anxiously wait to see if it will rear its very ugly head. Of potential relevance are three trials that have recently reported initial results suggesting that switching from adjuvant tamoxifen to an aromatase inhibitor lowers the recurrence rate. John persuasively argues that what is happening in these studies is that microscopic relapse is being treated earlier and more effectively than waiting for clinically detected disease.

For this issue of our series, I also interviewed Dr Francesco Boccardo, the principal investigator of one of these fascinating new "switching" studies — in this case, anastrozole after two to three years of tamoxifen. Hoping to push this very cautious and reserved researcher to speculation, I plied him with increasing doses of espresso, but no amount of chemical stimulation could loosen his lips about why his study, like the Canadian trial of letrozole after five years of tamoxifen, demonstrated such a provocative advantage.

Just prior to going to press, a similar trial published in the *New England Journal of Medicine* also revealed an advantage for switching to another aromatase inhibitor, exemestane, after two years of tamoxifen. It will be very interesting to see where this all leads and what the mavens say it means.

It is increasingly clear that decreasing the microscopic tumor burden in the adjuvant and postadjuvant settings holds the potential to significantly improve long-term outcomes, and this issue of our series includes comments on several related strategies involving chemotherapy. Dan Budman — who has had a leadership role in the development of the highly targeted oral fluoropyrimidine

prodrug, capecitabine — notes that there are a number of new trial designs integrating this valuable agent into the adjuvant setting.

Perhaps most promising is the combination of capecitabine with a taxane. In a trial of capecitabine and docetaxel (XT) in the metastatic setting, this strategy clearly resulted in improved response rates, and arguably improved survival. A current US Oncology trial evaluates adjuvant XT, while MD Anderson is testing the regimen in both the adjuvant and neoadjuvant settings. This simple approach may result in improved outcome.

Another somewhat basic adjuvant chemotherapeutic strategy that holds great promise relates to dose and schedule. In prior issues of our series, Larry Norton, Cliff Hudis, Mark Citron and Thomas Budd eloquently elaborated on CALGB-9741, a groundbreaking trial that documented significant improvements in disease-free and overall survival when therapy was given every two weeks with growth factor support versus every three weeks.

In this issue, Gary Lyman presents some disturbing patterns-of-care data suggesting that a significant number of patients are having therapy delivered in the exact opposite direction. Gary's data reflect practice patterns in the late 1990s and show that chemotherapy doses at that time were regularly being reduced and delayed. One can only hope that subsequent surveys will document trends toward greater diligence in delivering the planned dose on time. In fact, one of the key trials suggesting a detrimental effect of compromising dose was a classic CALGB study headed by Dan Budman.

Will breast cancer take a tangible step forward because of the strategies discussed in this issue? Or ten years from now, will we be stuck with the "same old, same old?" Can we test these and other innovative ideas in clinical trials in a reasonably expeditious manner and then "deliver the goods" to practice? Will cranky, impatient observers like me back off when breast cancer mortality starts to go south and stays there? Stay tuned.

—Neil Love, MD

Select publications

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

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

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

Lyman GH et al. **Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices.** *J Clin Oncol* 2003;21(24):4524-31. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. **Abstract**

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

Edited comments by John F R Robertson, MD, FRCS

Potential strategies to improve the efficacy of fulvestrant

Fulvestrant 250 mg is an effective dose, as demonstrated by the clinical trials. It is as effective as anastrozole as second-line therapy and equivalent to tamoxifen as first-line therapy in postmenopausal women. In premenopausal women, data suggest that 250 mg of fulvestrant is not effective at downregulating the estrogen receptor. This raises questions about whether a 250 mg dose of fulvestrant leads to complete down-regulation of the estrogen receptor in postmenopausal women. Could a higher dose of fulvestrant achieve more?

Two strategies exist to increase the dose of fulvestrant. The first is a loading dose sequence. The second is the administration of a higher dose of fulvestrant. For example, instead of administering one five-milliliter injection every month in one buttock, using one five-milliliter injection in each buttock, for a total of 500 mg. Future studies are needed to determine the dose-response curve for fulvestrant.

Trials combining fulvestrant with an aromatase inhibitor

Either increasing the fulvestrant dose or decreasing estradiol levels can evaluate the dose-response curve for fulvestrant. A number of studies are beginning to look at decreasing estradiol levels with aromatase inhibitors. In my own unit in Nottingham, we are randomly assigning patients preoperatively to three weeks of fulvestrant, anastrozole or the combination. SWOG-S0226 will compare anastrozole to anastrozole plus fulvestrant as first-line therapy in postmenopausal women (Figure 1.1).

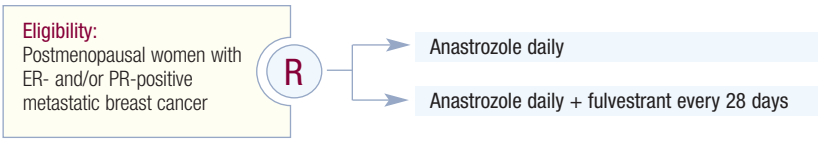
In the UK, the SoFEA study (Figure 1.2) will enroll patients who have had disease progression while on an aromatase inhibitor. Those patients will be randomly assigned to fulvestrant, exemestane or fulvestrant plus anastrozole. The rationale behind that trial is the data suggesting that estrogen-deprived MCF-7 cells become supersensitive to lower doses of estradiol and, hence, are stimulated again. The third arm of that trial will keep the estradiol levels low and then come in with fulvestrant to determine if that strategy is different from fulvestrant alone without estradiol suppression.

Dr Robertson is a Professor of Surgery at the University of Nottingham in Nottingham, England.

Figure 1.1

Phase III Randomized Study of Anastrozole with or without Fulvestrant as First-Line Therapy in Postmenopausal Women with Metastatic Breast Cancer

Accrual: 690 (Approved – Not yet active)
Protocol IDs: SWOG-S0226



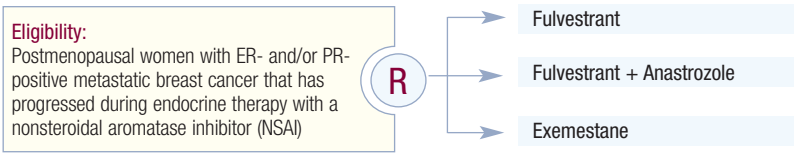
Study Contact:
Rita Mehta, MD, Study Coordinator
Tel: 714-456-5153
Southwest Oncology Group

SOURCES: NCI Physician Data Query, March 2004.

Figure 1.2

Phase III Trial of Fulvestrant with or without Concomitant Anastrozole versus Exemestane Following Progression on Nonsteroidal Aromatase Inhibitors

Accrual: 750 (Proposed)
Protocol IDs: SoFEA



Study Contact:
Stephen Johnston, MD, Principal Investigator
Tel: 0208 722 4062
ICR - Clinical Trials & Statistics Unit

SOURCES: National Cancer Research Network Trials Portfolio. Available at **http://controlled-trials.com/isrctn/trial/%7c/o/44195747.html** April 1, 2004

Duration of response to hormonal therapy

Retrospective data suggest that fulvestrant may have a longer duration of response than anastrozole (Figure 1.3). It's an interesting finding that would support some of the preclinical models. However, as academic clinicians, we need to be rigorous in our review of the data.

Our group has some patients who have had long durations of response to fulvestrant. One woman was on fulvestrant for more than seven years, another for more than five years and another for four and a half years. We've also reported good responders who were treated with other hormonal agents. The only way to test whether patients treated with fulvestrant have longer durations of response is by conducting a randomized trial.

Figure 1.3

Duration of Response (DOR) for Fulvestrant Compared to Anastrozole

"Extended follow-up (median, 22.1 months) was performed to obtain more complete information for DOR. The median DOR, as measured from randomization to progression, in patients who responded to treatment was 16.7 months for the fulvestrant group (n =84) and 13.7 months for the anastrozole group (n=73). In the statistical analysis of DOR, which included all randomized patients, with DOR defined from the onset of response to disease progression for responders and as 0 for nonresponders, the DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group. The ratio of average response durations was 1.30 (95% CI, 1.13–1.50; p<0.01)."

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

Tolerability of fulvestrant injections

I don't believe that fulvestrant injections are a major problem. We have been administering fulvestrant for nearly 10 years and have not had any serious problems with the injection — no patients with sterile abscesses or complaining of buttock pain (Figures 1.4 and 1.5). The clinical trials have demonstrated similar favorable results. In women being treated with a bisphosphonate, fulvestrant provides the opportunity to have their treatment completed during a single visit each month.

Alterations in breast cancer cell phenotype after tamoxifen therapy

We've been collecting tumor samples from patients before tamoxifen therapy, after six weeks and six months of tamoxifen therapy, and at progression. Initially, downregulation of the estrogen and progesterone receptors occurs; then, when the cancers become resistant, quite marked levels of estrogen and progesterone receptors are present. During response to tamoxifen, a downregulation in proliferation occurs, and at progression, an upregulation in proliferation is evident.

We have not seen a huge upregulation of growth factors, like HER2 and EGFR, using older assays. We're about to launch a new study using microarrays on the samples we've collected. We're also going to use the new assays for EGFR and HER2. It will be interesting to see if those pathways are also being upregulated. Studies with tamoxifen-resistant cell cultures have demonstrated an upregulation of growth factors and sensitivity to gefitinib.

Figure 1.4

2003 Survey of US Oncologists: Use and Tolerability of Fulvestrant

What percentage of your patients receiving fulvestrant reported difficulty tolerating the injection?

Mean	3%

83% of physicians stated that none of their patients receiving fulvestrant reported difficulty tolerating the injection.

What percentage of your patients receiving fulvestrant reported significant side effects?

Mean	3%

78% of physicians stated that none of their patients receiving fulvestrant reported significant side effects.

SOURCE: 2003 National Patterns of Care Survey: Medical Oncologists

Figure 1.5

Fulvestrant: A Once-Monthly, Injectable Estrogen Receptor Downregulator

"Although fulvestrant is the first commercially available injectable HT [hormonal therapy], complications such as injection-site pain or reactions were mild to moderate and led to treatment withdrawals in only 0.5% of patients. The rates of overall withdrawals due to a drug-related adverse event were 0.9% for fulvestrant and 1.2% for anastrozole. No evidence of endometrial tissue changes has been reported with fulvestrant or anastrozole. Fulvestrant has been shown to be at least as effective as anastrozole in postmenopausal women with advanced breast cancer, which is noteworthy because most patients had prior tamoxifen treatment."

SOURCE: Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24(Suppl 3):43-57. **Abstract**

Phase II trial of gefitinib in patients with tamoxifen-resistant or ER-negative breast cancer

At ASCO 2003, we presented results from a Phase II trial of gefitinib in patients with metastatic breast cancer who were not heavily pretreated. The two arms of the trial included: (1) patients with tamoxifen-resistant breast cancer who had only been treated with tamoxifen and (2) patients with ER-negative breast cancer who had only received one prior chemotherapy regimen. We reported an 11 percent clinical benefit rate in the patients with ER-negative disease and a 66 percent clinical benefit rate in patients with tamoxifen-resistant breast cancer (Figure 1.6).

Gefitinib has not yet been evaluated in patients with previously untreated breast cancer. However, hormone-sensitive MCF-7 cells that have not been exposed to tamoxifen do not respond to gefitinib. Cell culture data suggest that the growth factor pathways are activated when cells become tamoxifen resistant.

Figure 1.6

Phase II Gefitinib Trial: Response Rates in Evaluable Patients

	Tamoxifen-resistant ER-positive (n=9)	ER-negative (n=18)
Partial response	1	1
Stable disease	5	1
Clinical benefit	6 (66%)	2 (11%)

SOURCE: Robertson JFR Presentation, ASCO 2003. **Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant oestrogen receptor (ER)-positive and ER-negative breast cancer: Results from a phase II study. Abstract 23.**

Response to gefitinib in a patient with tamoxifen-resistant breast cancer

One of the patients I enrolled in the Phase II gefitinib trial had liver metastases, which have been in complete remission for almost 21 months. This postmenopausal woman was treated with a mastectomy a number of years ago. Then, she received tamoxifen for the treatment of liver and bone metastases. She responded well to tamoxifen and then progressed. At that point, she was in her late seventies and we felt it was reasonable to try gefitinib alone rather than chemotherapy. Within three months, she had a complete response in the liver metastases and a partial response in the bone metastases, and she's currently still being treated. She experienced a few side effects — the classic skin rash, lethargy and alopecia. Her skin rash resolved when we reduced the gefitinib dose from 500 mg/day to 250 mg/day and her hair started to grow back while continuing on gefitinib.

Combining hormonal and biologic agents

A study that is about to start will compare tamoxifen to tamoxifen plus gefitinib. Preclinical data have shown that in the same way gefitinib can treat tamoxifen resistance, when it is administered initially, gefitinib seems to prevent resistance. This clinical trial will evaluate whether gefitinib can prevent or delay acquired clinical resistance in patients with metastatic breast cancer. I believe a study should also evaluate the efficacy of gefitinib after fulvestrant. Preclinical data suggest that gefitinib may reverse or prevent tamoxifen resistance; if it also reverses or prevents fulvestrant resistance, then gefitinib may affect a whole group of patients.

If we can establish that gefitinib is useful for either the treatment or prevention of endocrine resistance, it will be a major addition to our armamentarium. The same may potentially be true for trastuzumab. I believe that a trial should be conducted with tamoxifen and trastuzumab or with tamoxifen, trastuzumab and gefitinib. Fulvestrant and trastuzumab is another possible combination.

Utility of tumor markers in patients with breast cancer

The established antigen-based tumor markers are cancer antigen CA 15-3 and

carcinoembryonic antigen (CEA). For a number of years, we've known that cancer can be detected earlier in patients followed with these markers. At least two pilot studies have now shown that not only can cancer be detected, but if early intervention is utilized, outcomes can be affected.

One study from Germany demonstrated that patients with elevated tumor markers and no evidence of metastases on scans, who were randomly assigned to a change in treatment, experienced a delay in the onset of symptomatic metastases. No impact on survival was found, but a marked delay in onset of symptomatic metastatic disease was evident. A study from Italy with a similar design showed not only a delay in the onset of symptomatic metastases, but also an improvement in survival from the time of the primary surgery.

We're hoping to initiate a study that will randomly assign patients to standard follow-up, or routine tumor marker follow-up in addition to standard follow-up as a basis for early intervention. I have called it the "Second Adjuvant Therapy Study," and it will be based on two other studies. The first is a substudy from the ATAC trial. We've been collecting follow-up blood samples from a subpopulation of those patients to determine the patterns of change in tumor markers that indicate whether a patient will develop metastatic disease. Hence, we hope to learn when a patient's treatment should be altered.

The second is a study we've been conducting that is similar to the Italian trial — an early intervention study. We are evaluating the problems that can occur with such a study, because patients are certainly more anxious when they know their tumor markers are elevated without any obvious signs of metastases. Will that anxiety be offset by increased disease control?

Select publications

Ebeling FG et al. **Serum CEA and CA 15-3 as prognostic factors in primary breast cancer.** *Br J Cancer* 2002;86(8):1217-22. **Abstract**

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

Nicolini A et al. **"Tumour marker guided" salvage treatment prolongs survival of breast cancer patients: Final report of a 7-year study.** *Biomed Pharmacother* 2003;57(10):452-9. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. **Abstract**

Robertson JFR et al. **Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant oestrogen receptor (ER)-positive and ER-negative breast cancer: Results from a phase II study.** *Proc ASCO* 2003;**Abstract 23**.

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

Robertson JF et al. **Fulvestrant versus tamoxifen for the first-line treatment of advanced breast cancer (ABC) in postmenopausal women.** *Ann Oncol* 2002;13(Suppl 5):46;**Abstract 1640**.

Edited comments by Gary H Lyman, MD, MPH, FRCP

Survey of dose and schedule of adjuvant chemotherapy in practice

We contracted with over 1,200 non-academic practices of all sizes (but not academic centers) geographically distributed across the country. We asked them to gather information on their last series of patients receiving adjuvant chemotherapy for breast cancer, starting currently and going backward. These were patients who were treated with a mixture of chemotherapy regimens from the mid-1990s until early 2000. We are just beginning to evaluate patients treated more recently. Our report published in the *Journal of Clinical Oncology* focused on approximately six years of data from approximately 20,000 women. The primary area of interest was dose intensity (Figure 2.1).

Figure 2.1

Dose Reduction, Dose Delay and Use of Growth Factor Support

	% of Patients		
Parameter	All patients (N=19,898)	Age < 65 (83%)	Age ≥ 65 (17%)
Lymph node-positive	52.4	50.1	64.0
ER-positive	56.2	56.1	56.7
Doxorubicin-based chemo	54.7	57.5	40.6
Relative dose-intensity <85%	55.5	53.3	66.5
Chemo dose delay ≥ 7 days	24.9	23.9	30.2
Chemo dose reduction ≥ 15%	36.5	34.0	48.9
G-CSF administration	26.4	26.1	27.8

SOURCE: Lyman GH et al. **Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices.** *J Clin Oncol* 2003;21(24):4524-31. **Abstract**.

Dr Lyman is a Professor of Medicine and Oncology at the University of Rochester School of Medicine and Dentistry and Director of Health Services and Outcomes Research of the James P Wilmot Cancer Center at the University of Rochester Medical Center in Rochester, New York.

It was a very eye-opening experience. We found that the majority of women underwent some degree of reduced dose intensity from the published reference standards. In fact, 56 percent of women, across all regimens, are receiving less than 85 percent of targeted dose intensity.

In those patients experiencing dose reductions approximately 40 percent was planned dose reduction, which I believe reflects an intention to "go light" on the first cycle and then raise the doses for subsequent cycles if the patient tolerates therapy well. That seldom occurs, even in patients who don't develop neutropenic complications. It's extremely rare for those cycle-specific dose intensities to be raised during subsequent cycles. Once started low, doses continue to remain low. In the unplanned reductions, we believe 60 to 65 percent are due to physician or patient responses to hematologic toxicities and 40 percent are due to non-hematologic complications.

Utilization of growth factor support

One variable that has changed over time is the use of growth factors. While I can't overemphasize the limitations of retrospective chart reviews, growth factors are not commonly used early in adjuvant therapy of breast cancer, like they might be used in patients with lymphomas or those receiving more intensive regimens.

Approximately, one-fourth of patients in our study received a hematopoetic growth factor during the course of treatment, but 85 percent received it secondarily after toxicity occurred. Only two to three percent of patients received primary prophylaxis and those were probably elderly patients or patients with comorbidities.

Calculation of dose based on body surface area

Every oncologist has a threshold at which they become anxious and begin to adjust weight to ideal, or to some compromise between ideal and actual body weight. In our study, that threshold was extremely variable and particularly dramatic above 2.0 m^2 body surface area (BSA). Many practices have patients with BSAs exceeding 2.75 m^2, or even 3.0 m^2, and calculating dose based on actual weight can arouse anxiety. However, for patients in whom dose was based on actual body weight, there was no greater hematologic toxicity or later dose reduction or treatment delay, at least not in patients with BSAs between 2.0 m^2 and 2.3 m^2.

My oncology group is excited about these findings and about trying to re-evaluate the early data that served as the basis for our approach of dosing based on BSA. In reviewing those early studies, one realizes that a handful of patients were studied, with techniques that we could probably improve upon today. Were going back and trying to redo many of the early pharmacokinetic studies to determine if basing dose on BSA — of all the possible options that are out there — still seems to be the most rational approach. It seems to be how most physicians are currently calculating dose.

Impact of dose and schedule on long-term outcome

The impact of dose intensity on long-term outcome is our primary interest. We debated before we conducted this retrospective survey because we didn't want physicians to dismiss the results as being from "selected" patients.

In breast cancer, we have data from the Budman-Wood study, which randomly assigned patients to three different relative dose intensities of CAF. This study was published initially in the *New England Journal of Medicine* in 1994 and then in the *Journal of the National Cancer Institute* in 1998 with nine years of follow-up (Figure 2.2).

A 50 percent reduction in relative dose intensity demonstrated a significant reduction in disease-free and overall survival at five years. The one-third reduction in dose intensity showed a significant decrease in disease-free survival, but overall survival was not yet significantly different.

Why might that be? Can we actually measure the impact of dose intensity and the impact on outcome in patients with a 10 percent, 15 percent, or even 25 percent reduction in relative dose intensity? This is where it becomes very difficult, because it's largely a power issue. Those studies have not been done prospectively.

Figure 2.2

CALGB-8541: Evaluation of Total Dose and Dose Intensity in Patients with Stage II Breast Cancer: Nine-Year Follow-Up

FAC dose	5-year DFS	5-year OS
600/60/600 mg/m^2	66% ± 2%	78% ± 2%
400/40/400 mg/m^2	61% ± 2%	77% ± 2%
300/30/300 mg/m^2	56% ± 2%	72% ± 2%

"Within the conventional dose range for this chemotherapy regimen, a higher dose is associated with better disease-free survival and overall survival."

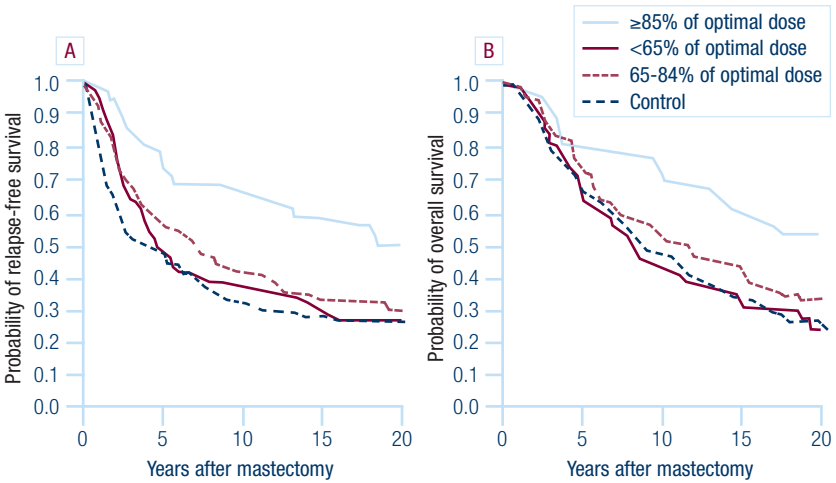
SOURCE: Budman DR et al. *J Natl Cancer Inst* 1998;90:1205–11. **Abstract**

In 1995, Bonadonna retrospectively evaluated his CMF data and found enormous differences between women who received more than 85 percent of CMF dose intensity on a 28-day schedule versus those who received less than 85 percent (Figure 2.3). Patients who received less than 65 percent of standard dose had a disease-free and overall survival no different than that of the control group. The problem with Bonadonna's study is that there are many other potential causes for those reduced dose intensities that might also be related to outcomes.

Retrospective data from the Toronto group and others almost always demonstrated that reducing dose intensity was associated with poorer outcomes, but we really need prospective randomized trials to resolve this issue. Despite the CALGB trial and a smaller French adjuvant trial — which evaluated FEC 100 versus FEC 50 and showed a significant decrease in disease-free and overall survival with the lower-dose epirubicin — the power calculations would indicate that you literally need thousands of patients in each arm of a trial to measure these kinds of small decrements.

Figure 2.3

Adjuvant Cyclophosphamide, Methotrexate and Fluorouracil in Node-Positive Breast Cancer*



*Relapse-free survival (panel A) and overall survival (panel B) according to the percentage of the optimal dose administered.

ADAPTED FROM: Bonadonna G et al. *N Engl J Med* 1995; 332:901-6. **Abstract**

Dose intensity delivered with dose-dense adjuvant chemotherapy

The timing of our survey results fall on the heels of reporting the results of CALGB trial 9741 and other data suggesting dose-dense regimens may provide a therapeutic advantage. We do not yet have data on patients who received dose-dense adjuvant chemotherapy in our survey, but the registry is tabulating that data. In my own experience — both in the trial setting and now in the post-trial setting — these patients seem to do extremely well and require very little compromise in their treatment dose intensity. Of course, they're all receiving growth factor support, so there's an economic issue that hasn't been fully addressed. If the early differences in the arms from CALGB-9741 hold up over time, I think cost will become a secondary issue because dose-dense chemotherapy will result in a significant improvement in long-term outcome.

Algorithm for managing neutropenia during adjuvant therapy

The adjuvant chemotherapy regimens for early-stage breast cancer have not demonstrated an extremely high rate of febrile neutropenia. With AC every 21 days, the rates of febrile neutropenia are quite low but somewhat higher with the addition of a taxane. Severe neutropenia — less than 500 neutrophils at the nadir — is probably more common, although I dare say that many of my colleagues aren't even looking at it today because the occurrence of febrile neutropenia is so low.

In 1998, Jeff Silber's group published back-to-back papers in *the Journal of Clinical Oncology*, in which they developed a model based on retrospective analysis of 100 women receiving adjuvant breast cancer chemotherapy. They identified three factors in multivariate analyses that were significant predictors of future dose reductions, treatment delays or neutropenic events that would have led them to reduce dose intensity in those patients. These factors were absolute neutrophil count nadir less than 500 in the first cycle, a drop in hemoblobin from baseline to the midcycle of the first cycle and in patients who had previously undergone radiation therapy.

Managing patients presenting with afebrile neutropenia

Managing patients who present with afebrile neutropenia is a challenge. A key issue is the threshold neutrophil count at which one feels comfortable treating. In my career, I've gravitated to using from 800 to 1,000 neutrophils as my cutpoint for either delaying or reducing dose.

Typically, I will delay treatment one to three days and repeat counts. I won't delay a full week, which has historically been the "knee-jerk" reaction. Doxorubicin plus cyclophosphamide has a very abbreviated period of neutropenia. It can go quite low, but usually it's not very prolonged, which is probably why these women don't have a very high risk of febrile neutropenia.

In patients with high-risk disease, I do everything possible to avoid reducing their dose. Use of growth factors is an option. Another rational option is to forge ahead with therapy, especially with dose-dense therapy in which we're automatically using growth factor support. I think we're going to find that even women in the 21-day cycles are going to receive growth factors for the future cycles, and they'll probably do fine.

I don't use growth factors universally. I consider age and comorbidities, and if I think chemotherapy presents a real risk of future complications to the woman, I'll add growth factors. In my experience, probably 25 to 30 percent of patients receive growth factor support at some point. I believe the more rational approach is to target it to the highest-risk group of patients and do it preemptively as opposed to waiting until they're hospitalized or already neutropenic. Growth factors are much less effective once the patient is neutropenic.

Nonprotocol selection of adjuvant chemotherapy

In the nonprotocol setting — certainly in the younger node-positive population and even the younger elderly population — my colleagues and I often utilize an

ACT type of regimen. We are still waiting for data to mature, but many of us are convinced that the taxanes add to the long-term outcomes in those patients; until proven otherwise, we believe patients should have the benefit of the doubt and be offered the taxane.

In patients with node-negative disease, I typically utilize AC every three weeks. However, patients and family members are inquiring about dose-dense schedules. Generally, I will comply with their desire for dose-dense AC because that regimen does not appear to be any more toxic than conventional scheduling. Additionally, I am willing to accept that the node-positive data will probably extrapolate, at smaller increments of benefit, to the node-negative population. If a woman asks for the dose-dense approach, I don't have a compelling reason to refuse.

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Edited comments by Daniel R Budman, MD, FACP

Impact of dose reduction on clinical outcome

Dr Lyman's data evaluating delivery of full-dose therapy included tens of thousands of women treated for breast cancer in clinical practices, and evaluated all the permutations of the regimens we currently use. It revealed that over 60 percent of women are not receiving full-dose therapy, which is a major concern because most anticancer drugs have a narrow dose-response curve, so there's a narrow therapeutic index at the upper limits of the conventional dose range.

Several years ago, data from CALGB-8541 demonstrated that in the adjuvant setting, full-dose conventional-range therapy was significantly better in the treatment of node-positive breast cancer (Figure 3.1). The study examined three cohorts of patients, each receiving different doses of CAF, and evaluated the dose delivery and the total cumulative dose. Patients receiving the higher doses experienced a marked statistical improvement over the observation period in both disease-free and overall survival in all subsets, and that has continued 10 years later. There was a steep dose-response curve, so we've learned that compromising dose, either initially because of other conditions or reducing dose later, can be detrimental to outcome.

Figure 3.1

CALGB-8541: Results of CAF Dose Reductions on DFS and OS

"Dose and dose intensity of administered chemotherapy are clinically important variables that can be manipulated in an attempt to improve DFS and OS in patients with operable breast cancer. This trial examined these parameters within a conventional dosage range.…

"Both the moderate-dose and high-dose arms delivered the same cumulative dose of chemotherapy with no significant difference in outcome (DFS or OS) between these arms for the study as a whole, but significantly better survival than for patients treated with a low-dose-intense arm. The data therefore suggest that dose reduction, perhaps below a threshold, leads to a relatively worse outcome with the currently available drugs for adjuvant treatment of patients with stage II breast cancer."

SOURCE: Budman DR et al. **Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B.** *J Natl Cancer Inst* 1998;90(16):1205-11. **Abstract**

Dr Budman is Associate Chief of the Don Monti Division of Medical Oncology and Division of Hematology at North Shore University Hospital and Professor of Medicine at New York University in Manhasset, New York.

Anthracycline dose-response curves

There's evidence of a dose-response in several studies comparing anthracycline doses. Craig Henderson's study published in the *Journal of Clinical Oncology* evaluated three doses of doxorubicin — 60, 75, and 90 mg/m^2 — combined with cyclophosphamide 600 mg/m^2 with or without subsequent paclitaxel. Doxorubicin doses above 60 mg/m^2 added nothing but toxicity and the dose-response curve suggests doses below 60 mg/m^2 are detrimental. In the FEC trials, epirubicin 100 mg/m^2 was better than 75 or 50 mg/m^2 and there was dose-response as well.

Capecitabine in the metastatic breast cancer setting

When I see a patient who received adjuvant anthracyclines and taxanes for metastatic disease, I generally use an oral agent such as capecitabine. We know capecitabine is efficacious in that setting and quality of life is improved. I haven't seen much hand-foot syndrome in my patients with the appropriate dosing. Depending on the patient's age and renal function, I use between 750 and 1,000 mg/m^2 twice daily for 14 out of 21 days. One concern with capecitabine is dihydropyrimidine dehydrogenase (DPD) deficiency, but that occurs in only one out of 1,000 patients.

The dosing of capecitabine is controversial. Because it has a broad therapeutic index, I believe we can utilize lower doses and maintain efficacy with little toxicity. In the capecitabine/docetaxel (XT) trial, dose reduction from 2,500 mg/m^2 total daily dose to half that dose still retained efficacy. I find the original dose utilized in the Phase I trial — 1,000 to 1,300 mg/m^2 total daily dose — particularly interesting as chronic treatment, and that has not been adequately explored. The two-week on, one-week off schedule was based on European data with small numbers of patients, which showed you could deliver more drug that way, but that doesn't necessarily mean it's better. We know in the preclinical models, capecitabine also has antiangiogenic properties, so it may be useful to look again at the dose and schedule.

Clinical trials of capecitabine for metastatic disease

Excluding 5-FU from Henderson's trial of doxorubicin/cyclophosphamide was purely empirical — no one really knows whether it adds efficacy or just toxicity. There is research underway integrating capecitabine with these regimens in the metastatic setting. We know capecitabine is an active drug. In the first-line setting for metastatic cancer, it's equivalent to CMF, and in heavily pretreated patients who failed anthracyclines and taxanes, it results in a 30 percent response rate (Figure 3.2).

Taxanes are particularly active, and Nabholtz's trial showed that AT is better than AC in the metastatic setting. Additionally, ET has been shown to be better than EC, and perhaps we can eliminate the alkylating agents. These combinations are being studied in Europe. A randomized trial is comparing docetaxel/epirubicin/capecitabine (TEX) versus docetaxel/epirubicin. In Phase II trials, this triplet was

very active and if the biochemical evidence of the upregulation of thymidine phosphorylase by capecitabine is clinically significant, one would expect the triplet to be superior in this trial.

Figure 3.2

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

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

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

Capecitabine versus paclitaxel as second-line therapy

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

CI = confidence interval

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

Clinical trials of capecitabine in the adjuvant setting

Capecitabine is an obvious choice to study in the adjuvant setting. I'm most interested in Hyman Muss' Intergroup study comparing capecitabine versus AC or CMF in women over age 65. Based on the chemistry of capecitabine, it wouldn't surprise me if it proves to be equivalent in efficacy with a superior toxicity profile. In addition, it has the advantage of being an oral regimen. US Oncology and MD Anderson each have adjuvant studies evaluating the combination of capecitabine and docetaxel, but these trials are not mature and it will be some time before we know the results.

Evaluating strategies combining biologic agents with chemotherapy

We believe it's important to study signal transduction inhibitors combined with chemotherapy. We're particularly interested in using small molecules to block EGFR function. To that end, we are planning a trial combining a dual kinase inhibitor with capecitabine. Our tissue culture experiments showed marked

synergy between these two agents. A French group has published data from a head-and-neck model showing that the tyrosine kinase inhibitors of EGFR upregulate thymidine phosphorylase, which could be the rationale behind that synergy.

Limitations in utilizing body surface area to calculate dose

We have dosed patients by "per meter squared (m^2)" since the 1960s, but this was based on the erroneous belief that utilizing body surface area (BSA) normalized dosing between people — the larger the person, the larger the dose (Figure 3.3). We know now that BSA has very little meaning; the important considerations are how the individual absorbs or metabolizes the drug, and metabolism varies tremendously.

Obese patients raise particular concern. The CALGB examined this issue across adjuvant treatments and recommended we not dose-reduce even the morbidly obese patient. I must admit most of my morbidly obese patients have comorbid conditions, such as hypertension, diabetes, etcetera, and I am reticent to administer large doses of cytotoxic drugs to such patients. So, despite the CALGB's recommendation, I cap the body surface area at 2.0 m^2.

Figure 3.3

Body Surface Area (BSA) as a Determinant of Drug Dosing

"BSA was introduced in medical oncology to safely predict a suitable starting dose in phase I clinical trials from preclinical animal toxicology data. From that starting point in phase I trials it has spread throughout the practice of oncology with little justification. The formula to calculate body surface area takes two precisely quantifiable variables, height and weight, and estimates a value for surface area. The formula used to do this has never been adequately validated. Very few of the organ functions that determine the pharmacokinetics of a drug are related to body surface area; further when organ function has been related to body surface area other measures such as lean body weight have been found superior to surface area. For the majority of drugs, the relationship between BSA and kinetics has not been studied and where the relationship between BSA and kinetics has been examined only a few drugs such as the taxanes have relationships been found."

SOURCE: Sawyer M, Ratain MJ. **Body surface area as a determinant of pharmacokinetics and drug dosing.** *Invest New Drugs* 2001;19(2):171-7. **Abstract**

Sequencing hormonal agents in the metastatic setting

One of the burning issues in breast cancer today is how best to integrate the various hormonal therapies. We now have a panoply of hormonal therapies available: antiestrogens, aromatase inhibitors, a pure antiestrogen that knocks out the estrogen receptor, and the old progestins. I suspect we'll shuffle between these agents once we have a better understanding of cell phenotypes. Then we'll be able to identify the appropriate hormonal therapy for each patient and tailor our treatment before we see actual clinical resistance.

In the metastatic setting, I generally use an aromatase inhibitor first, then an antiestrogen and then fulvestrant. Unless there's a contraindication, I begin with aromatase inhibitors because I believe there's sufficient evidence that they are better than tamoxifen for front-line therapy in metastatic disease. I see approximately a 10 percent incidence of articular complaints with aromatase inhibitors, but I've found that switching the structure, from a nonsteroidal to a steroidal aromatase inhibitor or vice versa, seems to diminish those complaints.

Fulvestrant in the metastatic setting

Fulvestrant is an active drug and it's been shown to be equivalent to anastrozole, but we don't know where to sequence it. In elderly women, there's a higher incidence of estrogen receptor-positive breast cancer, but there's no way to know if these elderly patients are reliably taking their oral hormonal agents. In this setting, fulvestrant is an ideal drug because you don't have to worry about compliance. The responses I've seen to fulvestrant have been mainly in this population and I assume that patients who respond after failing an oral hormonal agent do so because of the activity of the fulvestrant, although I can't be certain that some of it isn't a compliance issue with the oral therapy.

Fulvestrant can't be absorbed orally, so it requires injections. Five cubic centimeters has been considered the standard maximum volume that one should inject, but we don't actually know whether 250 mg is the appropriate dose. Fulvestrant trials comparing 125 to 250 mg showed the higher dose was better, but we don't know whether an even higher dose would be more efficacious. It's frustrating that we really don't know the limits of fulvestrant's dose-response curve.

The injection itself is not a problem for the motivated patient, but the visits can be a problem for patients who have to rely on others to get to their appointments, as is often the case with the elderly. The majority of patients find it supportive and reassuring to be seen on a regular basis for their treatment, however there are some patients who try to deny their disease and become more agitated by the treatment visits.

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Madarnas Y et al. **Are medical oncologists biased in their treatment of the large woman with breast cancer?** *Breast Cancer Res Treat* 2001;66(2):123-33. **Abstract**

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Edited comments by Francesco Boccardo, MD

Rationale for the use of aromatase inhibitors following adjuvant tamoxifen

The newer aromatase inhibitors are as effective as, if not better than, tamoxifen as first-line therapy for advanced disease. They do not affect the uterus or increase the risk of thrombo-embolic disease. On the other hand, aromatase inhibitors can lead to osteoporosis. As reported in the ATAC trial, the aromatase inhibitors are associated with an increased incidence of fractures.

Approximately 10 to 12 years ago we began exploring the role of adjuvant aromatase inhibitors following a course of adjuvant tamoxifen. Although adjuvant tamoxifen is very effective, it is not devoid of serious side effects. Attention to the possible mechanisms of tamoxifen resistance was also growing. One particular mechanism of resistance, an increase in aromatase activity in the breast tumors of women exposed to tamoxifen, provided strong biological support for this sequencing approach.

We believed a sequential approach could have potential advantages over a five-year course of adjuvant tamoxifen or even an adjuvant aromatase inhibitor. A sequential approach would allow women to receive a class of compounds that might help circumvent tamoxifen resistance while limiting the exposure to aromatase inhibitors and costs of treatment.

Trial evaluating three years of adjuvant tamoxifen followed by two years of adjuvant aminoglutethimide

In 1992, aminoglutethimide was the only aromatase inhibitor available, and we began a sequencing trial with it. Based on a prior adjuvant trial by Coombes, in which approximately 25 percent of women treated with aminoglutethimide plus hydrocortisone discontinued treatment due to side effects, we selected a low dose of aminoglutethimide.

In our trial, 380 postmenopausal women who had completed three years of adjuvant tamoxifen were randomly assigned to two more years of tamoxifen or 250 mg of aminoglutethimide. Most of the women had ER-positive, node-positive disease. Although no difference was found in the overall recurrence rate, a difference in the sites of recurrence was observed — more visceral recurrences were seen in the patients who continued on tamoxifen. Additionally, patients who

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switched to aminoglutethimide had a significantly longer survival. This difference was probably related to an increase in both breast cancer-unrelated and breast cancer-related deaths in the patients continuing on tamoxifen.

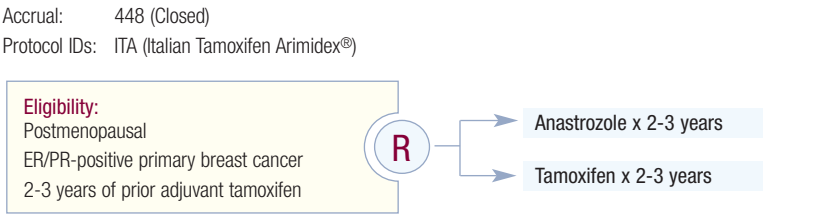
Italian Tamoxifen Arimidex® (ITA) trial

When anastrozole became available in 1998, we designed a companion trial to our aminoglutethimide study that was similar in design to allow for a pooled analysis of the data from the two trials. The new trial, known as the Italian Tamoxifen Arimidex® (ITA) trial (Figure 4.1), substituted anastrozole for aminoglutethimide and restricted enrollment to postmenopausal women with ER-positive, node-positive breast cancer.

Following treatment with two to three years of adjuvant tamoxifen, 448 women were randomly assigned to continue tamoxifen or switch to anastrozole for a total of five years of adjuvant therapy. The treatment groups were balanced with respect to median age, tumor size and grade, number of involved nodes, type of primary treatment, and prior radiation therapy or chemotherapy. The median age for both groups was 63 years. The median duration of tamoxifen therapy prior to randomization was 28 months in each group.

Figure 4.1

ITA Study: Anastrozole versus Tamoxifen Following Adjuvant Tamoxifen



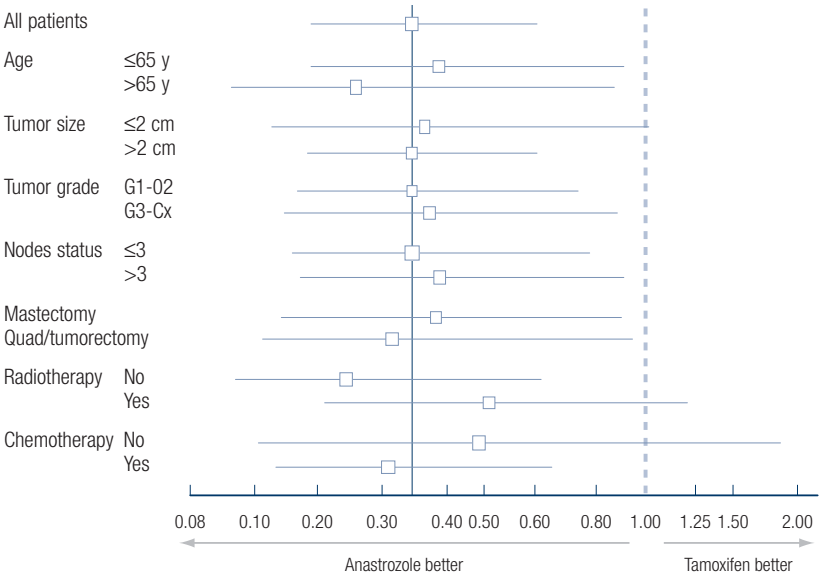
SOURCE: Boccardo F et al. Presentation, San Antonio Breast Cancer Symposium, 2003.

After a median follow-up of three years, 17 recurrences occurred in the women who switched to anastrozole and 45 recurrences occurred in the women who continued on tamoxifen. The women who continued on tamoxifen had more second primary tumors (including five endometrial cancers), more distant metastases and more locoregional recurrences (including ipsilateral breast, loco-regional node recurrences, or both). According to the Kaplan-Meier curves, the women who switched to anastrozole had a significantly longer event-free, progression-free and local relapse-free survival. They also had a longer, although not significant (p = 0.06), distant metastases-free survival. Overall survival (p = 0.1) was also longer for the women who switched to anastrozole, but there were few deaths because the data are immature.

The treatment discontinuation rates for both groups were similar (8.4 percent for tamoxifen and eight percent for anastrozole). Women who continued on tamoxifen exhibited significantly more gynecologic changes, many of which were serious and required hospitalization. More severe treatment-related adverse events were reported in the women who continued on tamoxifen (Figure 4.2).

Figure 4.2

ITA Trial: Hazard of Progression by Subgroup



SOURCE: Boccardo F et al. Presentation, San Antonio Breast Cancer Symposium, 2003.

Implications of the recent adjuvant aromatase inhibitor trials

Given its relatively small size and immature data, we should avoid overinterpreting the results from the ITA trial. However, these data together with previous data support an advantage for switching adjuvant therapy. The data on switching adjuvant therapy are consistent with the data from the ATAC and MA17 trials. In the MA17 trial comparing letrozole to placebo in women who had received five years of adjuvant tamoxifen, placebo may have potentially represented active therapy since it is postulated that tamoxifen may become a stimulatory growth factor. Hence, it has been hypothesized that some of the women who discontinued adjuvant tamoxifen after five years might have had a withdrawal response.

We don't truly know which of our patients will benefit from an adjuvant aromatase inhibitor. Only a small proportion of women treated with anastrozole in our trial or the ATAC trial or treated with supplementary letrozole in MA17 actually benefited. I would probably be a bit conservative in applying these trial data, since mortality is the primary endpoint for adjuvant therapy. We can select women who are not candidates for tamoxifen who would benefit from an aromatase inhibitor. For women with progressive thickening of the endometrium or tamoxifen intolerance it might be prudent to consider switching to an aromatase inhibitor.

Nonprotocol role of adjuvant aromatase inhibitors following a two- to five-year course of adjuvant tamoxifen

In some specific subsets of women, it is appropriate to switch from tamoxifen to an aromatase inhibitor after two or five years of tamoxifen. There is no reason to continue tamoxifen in women who may be at risk for problems with tamoxifen, because we now have alternatives. The evidence is not yet compelling to state that an aromatase inhibitor should be substituted for tamoxifen, and I am not in a position to make a recommendation that will affect so many thousands of women.

At the moment, if patients are tolerating tamoxifen well, have undergone hysterectomy and are not at risk for thromboembolic events, I'm not likely to recommend switching to an aromatase inhibitor.

In the future, I expect most, if not all, women will receive adjuvant therapy with aromatase inhibitors, and many of them will be treated empirically for the risk of osteoporosis.

Select publications

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

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

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

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

Coombes R et al. **Adjuvant aminoglutethimide therapy for postmenopausal patients with primary breast cancer.** *Cancer Res* 1987;47:2496-9. **Abstract**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1):3;**Abstract 3**.

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

PowerPoint® Atlas:
Sequencing Adjuvant Endocrine Therapies

Editor's Note: The PowerPoint® files of the following slides are located on CD 1 and can also be downloaded at **BreastCancerUpdate.com**.

Slide 1: Italian Tamoxifen Arimidex® (ITA) trial schema

Slide 2: GROCTA-4B trial schema

Slide 3: GROCTA-4B trial overview

Slide 4: GROCTA-4B: Metastatic events and breast cancer deaths

Slide 5: GROCTA-4B: Survival after relapse

Slide 6: ITA trial: Breast cancer events

Slide 7: ITA trial: Serious adverse events

Slide 8: CAN-NCIC-MA17 trial schema

Slide 9: MA17: Disease-free survival and recurrences

Slide 10: MA17: Kaplan-Meier DFS curves

Slide 11: MA17: Overall survival

Slide 12: MA17: Safety profile

Slide 13: CRC-TU-TEAM trial schema: Tamoxifen versus exemestane after 2-3 years of adjuvant tamoxifen

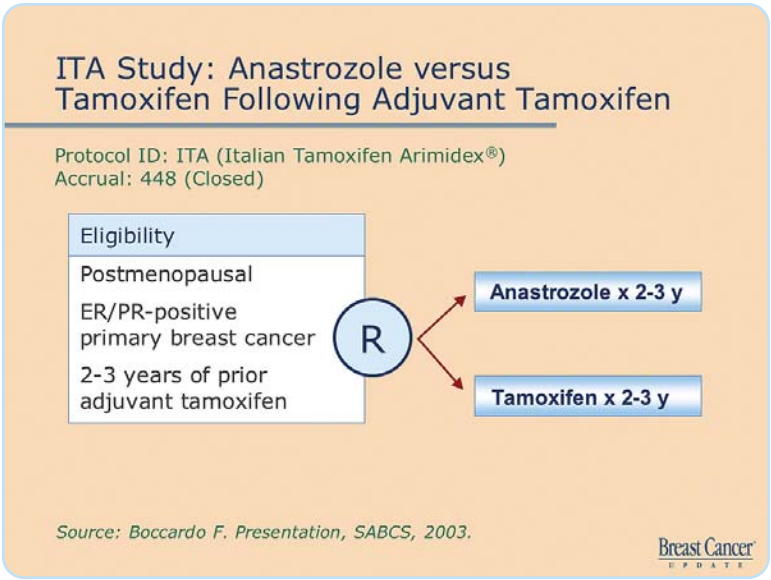
Slide 14: CRC-TU-TEAM: Efficacy endpoints

Slide 15: CRC-TU-TEAM: Comparison of adverse events

Slide 16: Adjuvant trials of sequencing aromatase inhibitors

Slide 17: Summary of adjuvant aromatase inhibitor trials

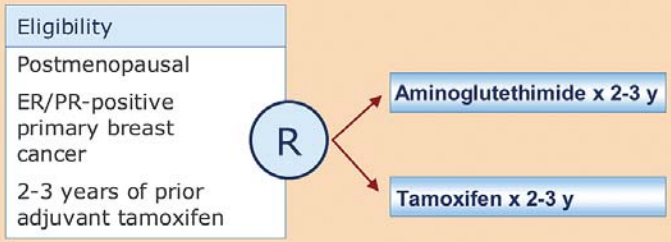
Slide 1



Slide 2

GROCTA-4B Study: Aminoglutethimide versus Tamoxifen after Adjuvant Tamoxifen

Protocol ID: GROCTA-4B
Accrual: 380 (Closed)



Source: Boccardo F et al. J Clin Oncol 2001;19:4209-15.

Breast Cancer UPDATE

Slide 3

GROCTA-4B

- Failed to recruit enough patients
- Significant aminoglutethimide toxicity: 14% stopped therapy versus 4% for tamoxifen
- Non-breast cancer deaths
  - Tamoxifen: 10 (8 cardiovascular)
  - Aminoglutethimide: 2
- Switched to ITA with anastrozole

Source: Boccardo F et al. J Clin Oncol 2001;19:4209-15.

Breast Cancer UPDATE

Slide 4

GROCTA-4B: Metastatic Events and Breast Cancer Deaths

Metastatic events	Total	Visceral	Bone/ST
Tamoxifen	42	16	26
Aminoglutethimide	42	6	36

Breast cancer deaths	
Tamoxifen	19
Aminoglutethimide	10

ST = soft tissue

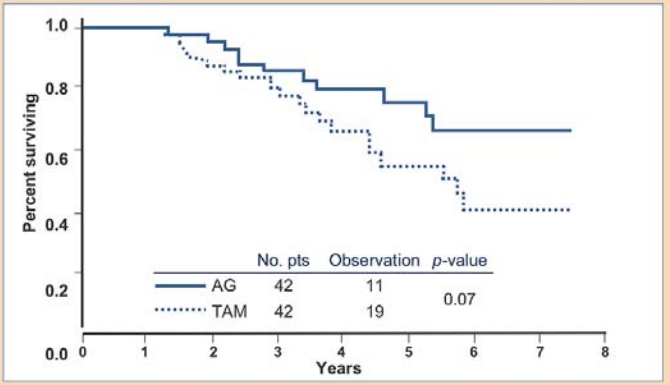
"Switching patients to aminoglutethimide led to a reduced risk of dying of breast cancer."

Source: Boccardo F et al. J Clin Oncol 2001;19:4209-15.

Breast Cancer UPDATE

Slide 5

GROCTA-4B: Survival after Relapse



Adapted from: Boccardo F et al. J Clin Oncol 2001;19:4209-15.

Breast Cancer UPDATE

Slide 6

ITA Trial: Breast Cancer Events

Median follow-up: 24 months
Accrual: 426

Breast events	
Continue tamoxifen	26 (19 recurrences)
Switch to anastrozole	10 (8 recurrences)

Hazard rates for women switched to anastrozole

Relapse: 0.36 (0.17 - 0.75, $p = 0.006$)
Death: 0.18 (0.02 - 1.57, $p = 0.07$)

Source: Boccardo F et al. Breast Cancer Res Treat 2003;Abstract 3.

Breast Cancer UPDATE

Slide 7

ITA Trial: Serious Adverse Events

Median follow-up: 24 months
Accrual: 426

Serious adverse events	
Continue tamoxifen	29
Switch to anastrozole	14

Source: Boccardo F et al. Breast Cancer Res Treat 2003;Abstract 3.

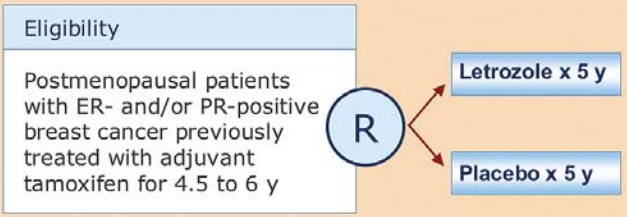
Breast Cancer UPDATE

Slide 8

Letrozole versus Placebo in Women Completing at Least Five Years of Adjuvant Tamoxifen

Protocol ID: CAN-NCIC-MA17

Accrual: 5,187 (Closed)



Source: Goss P et al. N Engl J Med 2003;349(19):1793-802.

Breast Cancer UPDATE

Slide 9

MA17 Results: Disease-Free Survival and Recurrences

	Letrozole (n=2,575)	Placebo (n=2,582)	*p*-value
4-y DFS rate	93%	87%	$p < 0.001$
Events	75 (2.9%)	132 (5.1%)	$p < 0.00008$

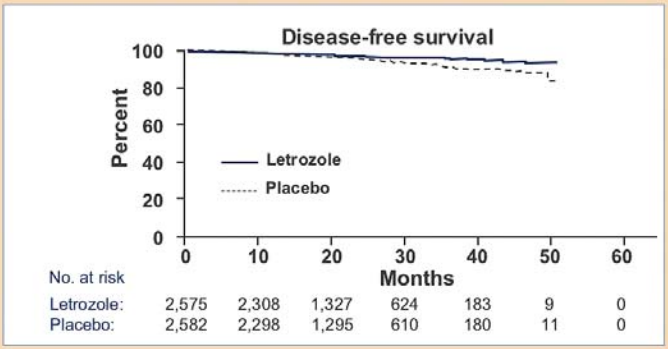
Median duration of follow-up was 2.4 years

Source: Goss P et al. N Engl J Med 2003;349(19):1793-802.

Breast Cancer UPDATE

Slide 10

MA17 Results: Disease-Free Survival



Adapted from: Goss P et al. N Engl J Med 2003;349(19):1793-802.

Breast Cancer UPDATE

Slide 11

MA17 Results: Overall Survival

	Letrozole (n=2,575)	Placebo (n=2,582)	Hazard ratio (95% CI)	*p*-value
4-y OS rate	96%	94%	0.76 (0.48 - 1.21)	0.25
Deaths	31	42		

Median duration of follow-up was 2.4 years

Source: Goss P et al. N Engl J Med 2003;349(19):1793-802.

Breast Cancer UPDATE

Slide 12

MA17: Safety Profile

	% of Patients		
	Letrozole (n=2,154)	Placebo (n=2,145)	*p*-value
Hot flashes	47	41	<0.001
Arthralgias	21	17	<0.001
Myalgias	12	10	0.02
Edema	17	16	0.17
Hypercholesterolemia	12	12	0.67
Cardiovascular events	4	4	0.40
Fractures	4	3	0.24
Osteoporosis	6	5	0.07
Vaginal bleeding	4	6	0.01

The number of patients discontinuing treatment due to side effects was not significantly different in the letrozole and placebo arms (4.5% vs 3.6%, respectively; $p = 0.11$).

Source: Goss P et al. N Engl J Med 2003;349(19):1793-802.

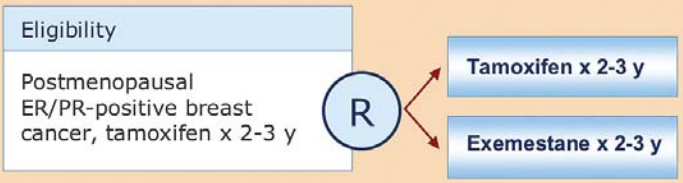
Breast Cancer UPDATE

Slide 13

Phase III Randomized Study of Adjuvant Exemestane versus Tamoxifen

Protocol IDs: CRC-TU-TEAM, EU-20149

Accrual: 4,742 (Closed)



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

Breast Cancer UPDATE

Slide 14

Hazard Ratios in the Exemestane Group as Compared with the Tamoxifen Group

End Point	Unadjusted Hazard Ratio (95% CI)	*p*-value
Disease-free survival	0.68 (0.56-0.82)	<.001
ER-positive	0.64 (0.52-0.79)	
ER+, progesterone-receptor-positive	0.66 (0.51-0.87)	
ER+, progesterone-receptor-negative	0.58 (0.38-0.90)	
Breast-cancer-free survival	0.63 (0.51-0.77)	<.001
Time to contralateral breast cancer	0.44 (0.20-0.98)	0.04
Overall survival	0.88 (0.67-1.16)	0.37

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

Breast Cancer UPDATE

Slide 15

Comparison of Significantly Different Adverse Events between Exemestane and Tamoxifen

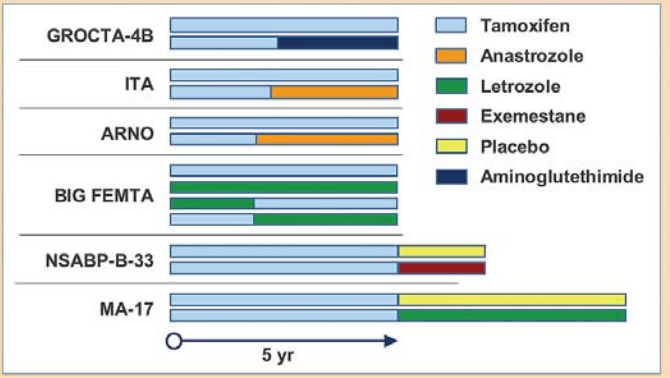
Type of Event	Exemestane Group	Tamoxifen Group	*p*-value
	Any Grade	Any Grade	
Visual disturbances	7.4%	5.7%	0.04
Osteoporosis	7.4%	5.7%	0.05
Gynecologic symptoms	5.8%	9.0%	<0.001
Arthralgia	5.4%	3.6%	0.01
Diarrhea	4.3%	2.3%	<0.001
Vaginal bleeding	4.0%	5.5%	0.05
Cramps	2.8%	4.4%	<0.001
Thromboembolic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

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

Breast Cancer UPDATE

Slide 16

Adjuvant Trials of Aromatase Inhibitors: Substitute or in Sequence with Tamoxifen



Breast Cancer UPDATE

Slide 17

Aromatase Inhibitors: Adjuvant and Switching Trials

- Adjuvant: ATAC (advantage to anastrozole)
- Switch from tamoxifen at…
  - 2-3 years (advantage to aminoglutethimide, anastrozole, exemestane)
  - 5 years (advantage to letrozole)

Does switching from tamoxifen to an aromatase inhibitor provide an advantage or is it simply substituting optimal therapy, which would have been better given up front?

Breast Cancer UPDATE

Post-test: *Breast Cancer Update*, Issue 3, 2004

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Potential strategies to increase the dose of fulvestrant include a loading dose sequence and the administration of one five-milliliter injection in each buttock.**
   a. True
   b. False

2. **SWOG-S0226 will compare which of the following:**
   a. Fulvestrant
   b. Anastrozole
   c. Fulvestrant plus anastrozole
   d. All of the above
   e. Both a and c

3. **The SoFEA study will enroll patients with breast cancer that:**
   a. Have not previously been treated
   b. Have failed a prior aromatase inhibitor
   c. Have failed prior fulvestrant
   d. All of the above
   e. None of the above

4. **A Phase II trial of gefitinib in patients with tamoxifen-resistant or ER-negative breast cancer demonstrated**
   a. An 11 percent clinical benefit rate in the patients with ER-negative disease
   b. A 66 percent clinical benefit rate in patients with tamoxifen-resistant breast cancer
   c. Both a and b
   d. Neither a nor b

5. **The use of tumor markers to monitor patients with breast cancer and to indicate when a change in therapy is needed has been shown in pilot trials to affect outcomes.**
   a. True
   b. False

6. **In the national survey of oncology practices evaluating the delivery of adjuvant chemotherapy dose intensity, 50 to 60 percent of patients received less than 85 percent of the standard reference dose intensity.**
   a. True
   b. False

7. **In the national survey of oncology practices evaluating the delivery of adjuvant chemotherapy dose intensity, approximately what percentage of patients received growth factor support?**
   a. 10 percent
   b. 25 percent
   c. 50 percent
   d. >70 percent

8. **Bonadonna's 1995 report of delivered CMF dose intensity revealed that patients who received less than 65 percent of the standard dose had a disease-free and overall survival no different than those who received no chemotherapy.**
   a. True
   b. False

9. **In CALGB-8541, comparing three dose levels of CAF, significantly poorer survival rates were seen in the group who received:**
   a. High-dose therapy
   b. Moderate-dose therapy
   c. Low-dose therapy
   d. No significant difference was seen between any of the dose levels

10. **In the Italian Tamoxifen Arimidex® (ITA) trial, women who switched to anastrozole demonstrated:**
    a. Significantly longer event-free, progression-free and local relapse-free survival
    b. Trend for distant metastases-free survival
    c. Trend for improved overall survival, albeit with immature data
    d. a, b and c

Post-test Answer Key: 1a, 2d, 3b, 4c, 5a, 6a, 7b, 8a, 9c, 10d

Evaluation Form: *Breast Cancer Update*, Issue 3, 2004

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding*	4 = *Good*	3 = *Satisfactory*	2 = *Fair*	1 = *Poor*	NA= *not applicable to this issue of BCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of BCU address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. . . . . 5 4 3 2 1 NA
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 NA
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 NA
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 NA
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens. . . . . 5 4 3 2 1 NA
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 NA
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer. . . . . 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
John F R Robertson, MD, FRCS	5 4 3 2 1	5 4 3 2 1
Gary H Lyman, MD, MPH, FRCP	5 4 3 2 1	5 4 3 2 1
Daniel R Budman, MD, FACP	5 4 3 2 1	5 4 3 2 1
Francesco Boccardo, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1

Related to my practice needs 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: *Breast Cancer Update*, Issue 3, 2004

Please Print Clearly

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Research To Practice designates this educational activity for a maximum of 3.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

I certify my actual time spent to complete this educational activity to be ___ hour(s).

Signature: _____

Will the information presented cause you to make any changes in your practice?

___Yes ___No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity.

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What other topics would you like to see addressed in future educational programs?

_____

_____

What other faculty would you like to hear interviewed in future educational programs?

_____

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Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

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