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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, 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 absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 5 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Tripathy, Dixon and Davidson on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

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.

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. **www.BreastCancerUpdate.com** includes 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 **blue underlined text**. This monograph also contains a "Journal Club" feature, which highlights several important recent publications, and corresponding PowerPoint slides are included on the CD.

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Dr Tripathy – **Grants/Research Support:** Genentech BioOncology, GlaxoSmithKline, Roche Laboratories Inc; **Consultant:** EMD Pharmaceuticals Inc, Genentech BioOncology, Roche Laboratories Inc. **Dr Dixon** – **Grants/Research Support:** AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals, Pfizer Inc. **Dr Davidson** – **Consultant and Honorarium:** AstraZeneca Pharmaceuticals LP; **Speakers Bureau:** Eli Lilly and Company.

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UPCOMING EDUCATIONAL EVENTS

2005 ASCO/AACR Workshop — Methods in Clinical Cancer Research
July 30-August 5, 2005
Vail, Colorado
Event website: **www.vailworkshop.org**

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org/annual_meeting**

European Cancer Conference
October 30-November 3, 2005
Paris, France
Event website: **www.fecs.be**

Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow
November 2-5, 2005
New York, New York
Event website: **www.mssm.edu/tcf/symposiumxxii**

Oncology World Congress
November 16-19, 2005
New York, New York
Event website: **www.oncologycongress.com**

28th Annual San Antonio Breast Cancer Symposium
December 8-11, 2005
San Antonio, Texas
Event website: **www.sabcs.org/Index.asp**

Miami Breast Cancer Conference
February 22-25, 2006
Miami Beach, Florida
Event website: **www.cancerconf.com**

Fifth European Breast Cancer Conference
March 21-25, 2006
Nice, France
Event website: **www.fecs.be**

The patients whose photographs appear in the Editor's Note gave their permission to appear in this monograph.

Editor's Note

Gallery of honor

On a recent muggy Miami morning, I motored up I-95 to visit the breast cancer practice of medical oncologist Sandra Franco, my former colleague at the University of Miami Sylvester Cancer Center. Our CME group recently received a grant from the National Cancer Institute through the Small Business Innovative Research mechanism to produce and evaluate a pilot DVD to assist in patient education regarding clinical trials. As part of this effort, Sandra had arranged for us to videotape interviews with four of her patients who are participating in current NSABP randomized studies. This visit was highly enlightening.

The DVD is focused specifically on NSABP-B-35, which randomly assigns postmenopausal women with ER-positive DCIS to either tamoxifen or anastrozole. Like many other NSABP trials in breast and colon cancer, this study addresses a simple but important clinical question and is likely to provide a clear answer. In the United Kingdom, the IBIS-II trial has an identical randomization (1.1).

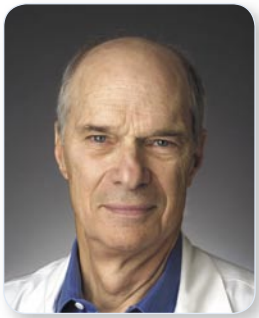
The constantly mushrooming database on the use of adjuvant aromatase inhibitors would seemingly make the results of B-35 easy to predict. (Women on anastrozole will experience fewer recurrences, second primary breast cancers, endometrial cancers, hysterectomies and strokes, but more arthralgias and potentially more fractures, depending on how meticulously docs follow bone densities and intervene when necessary.) However, the age of evidence-based oncology means that many physicians and patients want definitive Phase III data before moving AIs from invasive to noninvasive disease, and B-35 will likely deliver the goods, albeit a few years from now.

1.1 Active Clinical Trials Comparing Tamoxifen to Anastrozole in Postmenopausal Women with DCIS

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

SOURCE: NCI Physician Data Query, June 2005.

On the DVD, Richard Margolese, the principal investigator of B-35, reviews the background and rationale for the study and what he tells his patients about the potential risks and benefits of participation. Sandra Franco and her oncology research nurse Cynthia Frankel also appear on the program and provide their perspectives on the trial based on their experiences in a community practice setting. The four patients we interviewed describe their reactions to the diagnosis of breast cancer and why they chose to participate in a research study.



Richard Margolese, MD

Sandra Franco, MD

Cynthia Frankel, RN

Ms L, a participant in NSABP-B-35

Ms F, a participant in NSABP-B-38

Ms R, a participant in NSABP-B-38

A few weeks later I thought of these patients while sitting with the multitudes at ASCO in Orlando on May 16, staring wide-eyed as Kathy Miller, Eric Winer, Edward Romond, Edith Perez, Martine Piccart-Gebhart and George Sledge described and discussed the very impressive benefits of treatment with bevacizumab/paclitaxel in the first-line metastatic setting (ECOG-E2100) and the astonishing (as per George) benefits of trastuzumab with chemotherapy in the adjuvant setting (NSABP-B-31, NCCTG-N9831 and HERA).

Ms M, a participant in NSABP-B-31

The only one of these presenters who has not appeared on this series is Edward Romond, who sat down with me immediately after the ASCO session to review the historic data he presented on the combined NSABP-

NCCTG adjuvant trastuzumab analysis. It turns out that Ed is a faithful listener of *Breast Cancer Update* as he winds through the roads of Kentucky.

The most memorable moment from Dr Romond's interview was his recounting of a patient who entered the trial several years ago. This mother of an 11-year-old son had 25 positive axillary nodes and wished to enter NSABP-B-31 but was concerned that her automobile would not be able to make the weekly four-hour round-trip sojourn to Lexington to receive therapy. Both Ed and the patient anguished about the potential lost opportunity to advance oncologic science and possibly reduce the patient's high risk of recurrence.

Dr Romond asked the young woman if someone in her family might drive her back and forth to the clinic, and this prompted the patient to contact her father in Texas, who immediately purchased a car to allow his daughter to enter the study. The patient was randomly assigned to the chemo-trastuzumab arm of B-31 and tolerated therapy without difficulty. Three years later, she remains free of recurrence, and based on the data Ed presented at Orlando, it seems quite likely that this may be a direct outcome of the administration of trastuzumab.

Ed's compelling interview will be on the next issue of our series along with a very memorable chat with George Sledge, who moderated the historic ASCO session and delivered the penultimate presentation — a discussion of the clinical and research implications of the data on adjuvant trastuzumab. I've had the honor of interviewing George a number of times over the years, and when I shot him an email a few days before ASCO requesting that he again meet with me, I figured he would be too busy being probed by the *Today Show* and other hungry media mouths to have enough time for the usual 75 minutes we allocate for interviews.

Sure enough, George's schedule was totally booked, but taking a very deep breath, I modestly suggested that we meet at 6:00 AM on May 17, the day after the ASCO "education" session. His short but acquiescent email reply made my day: "Cruel and unusual punishment…but OK."

When we sat down to chat, it seemed like the dawn of a new day in many ways. I mentioned to George that the conversation reminded me a bit of an interview in December 2001 with Mike Baum, just moments after his first presentation of the ATAC trial data. It is interesting to imagine that if tamoxifen and other hormonal therapies never existed, and the ATAC trial were the first formal randomized test of endocrine therapy versus control (like the trastuzumab trials), the magnitude of benefit would have been very similar to what was observed with trastuzumab.

During the May 16 ASCO "education session," every trial result presenter utilized a closing slide acknowledging all who contributed. Topping each list was a "thank you" to patient participants.

Damn right. Patients understand better than anyone the cruel impact of this disease, and it gives them some comfort to be part of the problem's solution.

Sandra's four patients typify the heterogeneity of people who place their bodies on the front lines of this war.

The first patient I met is a frail septuagenarian from Chicago whose decision last summer to retire to the tropical paradise of South Florida seemed questionable when she and her husband were greeted by four consecutive hurricanes and an abnormal mammogram, which led to a diagnosis of DCIS.

"We've been married 52 years," she said with a proud smile, "but with all the chaos, I thought our marriage was going to end. But it turned out that our relationship was enhanced a great deal. My husband was with me through everything, and when I didn't feel well during radiation therapy and didn't want to take the pills for the study, he said, 'You have to take those pills! Come what may, you have to take those pills.' So he's been right at my side, and we actually have become much closer."

This spunky lady chose to enter B-35 because "there is just not enough that people can do to stop the scourge of breast cancer. I want to protect my kids and my grandchildren, and I'm very, very adamant about that." This view is echoed by the other three patients on the DVD.

Two of the women are in their early fifties and participate in NSABP-B-38, comparing adjuvant therapy with TAC versus dose-dense AC → T versus dose-dense AC → T/gemcitabine. Both women had recently completed dose-dense AC → T/gem and looked fairly well, which bodes favorably for the tolerance of the experimental arm of this important study.

These patients became tearful when asked why they chose to enter the trial, and it was clear that the basis for this decision was doctor-patient trust. They described an instant sense of warmth and comfort during their first meeting with Dr Franco, and it is clear that research participation is an important source of empowerment for these patients and their physician.

The fourth patient is a miracle. Several months ago, this 45-year-old woman was shocked to discover that despite a lifetime of meticulous health consciousness, she had been diagnosed with HER2-positive breast cancer with 11 positive lymph nodes. Fully aware of the approximately four percent risk of cardiac toxicity with adjuvant trastuzumab, she chose to enter NSABP-B-31 and was randomly assigned to receive AC → T/trastuzumab.

Several days before the interview, during this woman's third cycle of AC, Cynthia Frankel phoned and asked the patient if she had seen or read the news during the past couple of days. The patient had been busy with her family and job and had not yet learned what Cynthia was about to tell her: B-31 had been closed due to an unexpectedly dramatic beneficial effect observed in the trastuzumab-containing arm.

This kind and sincere mother of two is now continuing treatment knowing that trastuzumab will further reduce her risk of relapse by about 50 percent. (Peter Ravdin must be chained to his computer right now trying to pound out new numbers for Adjuvant! based on this revolutionary data set.)

My job is to be a skeptic and to ask research leaders probing, prosecuting attorney-like questions, and while I complain a great deal about the lack of progress in our field, May 16 was a mighty good day, and while we owe a lot to people like Richard Margolese, Bernie Fisher and Norm Wolmark, these leaders will be the first to tell you that it's the docs and nurses in the trenches, like Sandra Franco and Cynthia Frankel, and patients like their four courageous trial participants, who may eliminate this cruel disease in the near future.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

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

Baum M, on behalf of the ATAC Trialists' Group. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) women.** San Antonio Breast Cancer Symposium 2001;8. No abstract available

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

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13. **Abstract**

Frisby KA et al. **Clinical trial accrual patterns and barriers among newly diagnosed adult patients at a community cancer center: A prospective study.** *Proc ASCO* 2005;**Abstract 6017**.

Guarino MJ et al. **Barriers exist to patient participation in clinical trials.** *Proc ASCO* 2005;**Abstract 6015**.

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. *Proc ASCO* 2005a. No abstract available

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

Perez EA et al. **NCCTG N9831: May 2005 update.** Presentation. ASCO 2005. No abstract available

Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. No abstract available

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer — Combined analysis of NSABP-B31/NCCTG-N9831.** Presentation. ASCO 2005. No abstract available

Umutyan P et al. **Overcoming barriers to accrual: An assessment of 1,187 cancer patients' (Pts) and caregivers' awareness of and willingness to participate in cancer clinical trials (CCTs).** *Proc ASCO* 2005;**Abstract 6016**.

Vogel CL, Franco SX. **Clinical experience with trastuzumab (herceptin).** *Breast J* 2003;9(6): 452-62. **Abstract**

Vogel VG et al. **National surgical adjuvant breast and bowel project update: Prevention trials and endocrine therapy of ductal carcinoma in situ.** *Clin Cancer Res* 2003;9(1 Pt 2):495-501. **Abstract**

Editor's note:

This interview was conducted shortly before the release of findings of NSABP-B-31, NCCTG-9701 and the HERA trial, all evaluating trastuzumab in the adjuvant setting.

Biologic rationale for continuing trastuzumab after disease progression

The rationale is purely speculative. We know trastuzumab and chemotherapy work synergistically in the laboratory. In the clinic, they are at least additive. One of the questions is whether that synergy might exist with another chemotherapeutic agent, maybe through another mechanism.

When a patient's disease becomes resistant to trastuzumab plus a taxane, there may still be some synergy between trastuzumab and another chemotherapeutic agent. This is one of the main biologic reasons to consider continuing trastuzumab, which is different from the usual paradigm in cancer treatment in which we don't ever treat patients with any drug that has been associated with clinical resistance.

Second-line response data from trastuzumab pivotal trial

I published a follow-up report (Tripathy 2004) of the crossover portion from the pivotal trastuzumab study (2.1). In the pivotal trial, patients with metastatic disease were randomly assigned to chemotherapy alone or chemotherapy plus trastuzumab, and they were allowed to cross over to trastuzumab upon progression. Even the patients who were receiving chemotherapy plus trastuzumab could cross over to trastuzumab with another chemotherapy. A few patients received trastuzumab in combination with hormonal therapy (Slamon 2001).

It's important to recognize that this was an expanded-access trial. It did not require scans at regular times, and it didn't have the rigorous follow-up of a regular clinical trial. We looked at the data retrospectively and had a very conservative estimate of the response rate. If patients did not have data from a scan or from physical exams, we would not classify them as responders (Tripathy 2004).

Dr Tripathy is a Professor of Internal Medicine and Director of the Komen UT Southwestern Breast Cancer Research Program at the University of Texas Southwestern Medical Center in Dallas, Texas.

In the group of patients who were initially treated with trastuzumab plus chemotherapy, we found that 11 percent had an objective response when they received trastuzumab beyond progression. In the group of patients who initially received chemotherapy alone and crossed over to trastuzumab with or without chemotherapy, the response rate was 14 percent (Tripathy 2004), which is similar to the results reported by Cobleigh in patients who had been previously treated with chemotherapy (Cobleigh 1999).

This expanded-access trial demonstrated that there is some activity with the continuation of trastuzumab, and we didn't see any safety issues (Tripathy 2004). But the trial doesn't tell us about the independent contribution of trastuzumab in this situation. This will only be answered with trials that randomly assign patients who are progressing on trastuzumab to chemotherapy alone or chemotherapy plus trastuzumab.

2.1 Continuation of Trastuzumab Beyond Disease Progression

"The trial provided additional and encouraging safety data on patients treated with trastuzumab. The limited efficacy results suggest that patients who received trastuzumab before disease progression, particularly those who had a previous response to trastuzumab therapy in the initial trial, may respond to a second trastuzumab-containing regimen. However, the extent of the independent therapeutic contribution of trastuzumab in this setting and the optimal duration of treatment could not be ascertained from this extension trial. These questions await controlled studies designed to test this approach to treating progressive metastatic breast cancer."

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

Nonprotocol approach to patients whose disease progresses on a trastuzumab-containing regimen

Right now, in the absence of data, we have to use our best knowledge and extensions of the clinical and laboratory data to guide our patients. I personally believe there may be a role for continuing trastuzumab with another chemotherapeutic agent. My patients also usually feel strongly about it, and we often elect to go that route. I don't use this approach with all of my patients, and I certainly explain to them that we don't know the answer.

In this situation, trastuzumab appears to be safe. The rate of cardiotoxicity on the extension trial was very low in the patients who were already on trastuzumab and hadn't developed cardiac problems (Tripathy 2004). I generally continue trastuzumab, but not indefinitely. Once a patient goes through two or three combinations, I think it's probably prudent to stop trastuzumab and try either single-agent or combination chemotherapy.

MD Anderson Phase III randomized neoadjuvant trial of an anthracycline-based regimen with or without trastuzumab

Many of us would have guessed that the pathologic complete response (pCR) rate would be high. However, we were all surprised when we saw the magnitude of difference for the neoadjuvant trastuzumab regimen, which had a pCR rate in the 60 percent range (Buzdar 2005; [2.2]). We had never seen pCR rates so high. Obviously, this needs to be validated in a larger study, and one is planned.

A potential explanation for such a high pCR rate is that the patients received longer duration chemotherapy (paclitaxel and FEC) instead of just four cycles. Another reason might be that synergy exists between the anthracyclines and trastuzumab, which has not been previously tested because of the concerns of cardiotoxicity. They did report some subclinical reductions in ejection fractions in the patients on the trastuzumab arm, but not much in the way of clinical cardiotoxicity (Buzdar 2005).

2.2 Phase III Randomized Neoadjuvant Trial of an Anthracycline-Based Regimen with or without Trastuzumab: Pathologic Complete Response Rates

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

P = paclitaxel; FEC = 5-fluorouracil, epirubicin and cyclophosphamide

SOURCE: Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

Role of adjuvant aromatase inhibitors

I believe a clear, consistent story is emerging without a lot of conflicts and conundrums — adjuvant aromatase inhibitors are better than tamoxifen. Whether the aromatase inhibitors are used at the time of initial diagnosis, after two to three years or five years of tamoxifen, there is a favorable impact on local, distant and even contralateral breast cancer recurrences.

The unresolved questions are: Should you use a little tamoxifen, maybe two years, and then cross over? Should you just use an aromatase inhibitor right off the bat and maybe even think of continuing beyond five years? The trial that will provide the most information in this regard is the BIG FEMTA/BIG 1-98 trial, which is comparing: (1) five years of letrozole, (2) five years of tamoxifen, (3) two years of letrozole followed by three years of tamoxifen and (4) two years of tamoxifen followed by three years of letrozole.

The results from the noncrossover arms have already been reported at the 2005 St Gallen Conference (Thürlimann 2005; Kudachadkar 2005). At 26 months of

follow-up, there is the expected benefit, very similar to what was seen in the ATAC trial. The length of follow-up for the BIG FEMTA trial is nowhere near the length of follow-up in the ATAC trial, but the hazard ratios seem to be in the same neighborhood. We obviously need more follow-up time. The data on the crossover arms, which are of greatest interest, have not been reported.

Management of postmenopausal women who have completed five years of an adjuvant aromatase inhibitor

At this point, I discontinue the adjuvant aromatase inhibitor after the completion of five years of therapy. This is an area where you would discuss things with the patient. It reminds me of the situation I used to have with tamoxifen 10 years ago. I used to leave patients on adjuvant tamoxifen longer. They would be uncomfortable coming off, and we didn't have any data at that point. Since that time, we have had data from at least one study, NSABP-B-14, in which rerandomization to a total of 10 years of adjuvant tamoxifen showed an actual increase in relapse compared to five years of adjuvant tamoxifen (Fisher 2001).

We have to be very careful with this. Obviously, bone mineral density is one issue. It looks as though, from both the Austrian study (Gnant 2004) and the Zometa-Femara Adjuvant Synergy Trial (Z-FAST; [Brufsky 2004]), that early intervention with a bisphosphonate can essentially abrogate the loss in bone mineral density. However, there are other symptoms of total estrogen deprivation that we may not know about yet (eg, effects on the vascular or CNS system). I believe exposing a patient to more than five years of an adjuvant aromatase inhibitor at this point involves uncharted waters in terms of risks.

Management of postmenopausal women in the midst of receiving five years of adjuvant tamoxifen

With the data I have now, my recommendation is to switch those patients to an aromatase inhibitor. I won't call them and have them rush to the clinic, but when I see them next, I will review the data and switch over at whatever point in the course of therapy they are, whether it's at one, two, three or four years. It's hard for me to say, "Let's just leave you on tamoxifen for another two years," because in the crossover studies, the effect on recurrences seems to occur soon after changing therapy. I believe at any point, a woman is better off with aromatase inhibitors. The big question is: Is there any way to recapture some of the benefit with tamoxifen on the back end?

Management of postmenopausal women who have completed five years of adjuvant tamoxifen

In this situation, my opinion might be different from what you've heard before. Patients who are off of tamoxifen still have a risk of recurrence, and one can extrapolate the benefits of an aromatase inhibitor to right after the patient discontinues tamoxifen or sometime later. I think we need to estimate the patient's residual risk. We know that at five years there's still a considerable risk, especially

among patients at high risk. Once you go out to 10 and 15 years, then the risks all start to converge, but they're still around 0.5 to one percent per year.

Over a five- to 10-year period, that risk could add up to seven to 10 percent. If you can reduce the risk by one third, then it might be worth it. I actually believe it's reasonable to consider aromatase inhibitors in any patient with hormone receptor-positive breast cancer who is within a 10- or even 15-year period. It may sound like a big departure from what others are saying, but based on the clinical and biological data, I believe it's a reasonable thing to do. The caveat, again, is that we have to monitor for side effects.

Role of fulvestrant

The trials of fulvestrant conducted to date do not provide a clear indication as to where we should be using this drug. The up-front study comparing tamoxifen to fulvestrant was essentially equivalent. As second-line therapy, fulvestrant seemed to perform equally as well as anastrozole (Robertson 2003; [2.3]).

At this point in time, the sequencing and timing for fulvestrant are unclear. I think it's reasonable to use the drug — maybe not up front, but as second- or third-line therapy. This is where you might look at the patient's preferences in terms of an intramuscular or an oral drug.

2.3 Combined Analysis of Two Phase III Multicenter Trials Comparing Fulvestrant to Anastrozole as Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer

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

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

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

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

A recent study of 261 women with metastatic breast cancer demonstrated that about one third preferred a monthly intramuscular injection (Paley 2005). I would have guessed that 10 percent or less of the women would prefer an intramuscular injection. I've always assumed that oral drugs were preferable, if they were equally effective. Therefore, I was surprised to see that many patients preferred an intramuscular injection. I need to query my patients more when I start looking at these options.

Chemotherapy selection in patients with metastatic disease

When we have many chemotherapy drugs that, as single agents, provide response rates that overlap with each other, it shouldn't be looked at as a conundrum, but rather as an opportunity to individualize therapy based on the side-effect profiles. I'm starting to use drugs with less toxicity first, because we generally see the longest duration of response with the drug we use first.

We might as well have that long period of time be the one with the least toxicity. Utilizing an agent that does not result in hair loss should be considered, if that's important to the patient. Or, in the patient with pre-existing neuropathy from diabetes or prior chemotherapy, avoidance of an agent with neurotoxicity is important.

For me, the single most important factor is what treatment the patient has previously received. If a patient has progressed on an adjuvant taxane, I'm more likely to use a nontaxane drug. Although, granted, you can see responses to docetaxel and nanoparticle albumin-bound (*nab*) paclitaxel upon progression with the original paclitaxel formulation.

Nab paclitaxel

The availability of *nab* paclitaxel is a welcome advance in drug delivery. Combining paclitaxel tightly with a nanoparticle allows it to dissolve without the use of Cremophor®, which is one of the compounds in the original paclitaxel formulation that causes acute allergic reactions and necessitates the use of steroids. Evidence also exists from laboratory models that you may have better tumor penetration with *nab* paclitaxel.

What is happening in humans is hard to know, but in a head-to-head study, the clinical endpoints of response rate and time to progression were actually improved with *nab* paclitaxel compared to the original paclitaxel formulation. It was a difficult comparison because the doses weren't the same.

It may be that *nab* paclitaxel was more tolerable, and patients were able to receive a higher dose; therefore, they had a better response. When we look at most of the toxicities, however, there were fewer with *nab* paclitaxel. The exception was peripheral neuropathy, for which *nab* paclitaxel had a higher incidence (O'Shaughnessy 2003; [2.4]). This may have been related to the overall dose of paclitaxel.

2.4 Phase III Randomized Trial Comparing *Nab* Paclitaxel to Paclitaxel as First-, Second-, Third- or Fourth-Line Therapy in Women with Metastatic Breast Cancer

	Nab paclitaxel (n = 229)	Paclitaxel (n = 225)	*p*-value
Complete response + partial response[1]			
Investigator assessment			
Overall	33%	19%	<0.001
First-line therapy	42%	27%	0.029
Independent radiology review			
Overall	21%	10%	0.002
First-line therapy	29%	14%	0.011
Median time to tumor progression[1]	21.9 weeks	16.1 weeks	0.029
Median survival[2]			
Overall	65 weeks	55.3 weeks	0.322
≥Second-line therapy	56.4 weeks	46.7	0.020
Neutropenia (Grade IV)[1]	9%	22%	<0.001
Sensory neuropathy (Grade III)[1]	10%	2%	<0.001
Hypersensitivity (Grade III)	0	1%	0.150

SOURCES: [1] O'Shaughnessy J et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs Taxol in MBC: A Phase III trial.** Presentation. San Antonio Breast Cancer Symposium 2003;**Abstract 44**.

[2] Perez E. Presentation. Miami Breast Cancer Conference 2005. No abstract available

Choice of taxanes in the metastatic setting

A weekly regimen of the original paclitaxel formulation would have been my choice in the past. Now that we have data with *nab* paclitaxel, I think that's a reasonable option also. From the data, *nab* paclitaxel may be preferable.

It outperformed the original paclitaxel formulation when administered every three weeks (O'Shaughnessy 2003). A weekly regimen also seems to outperform an every three-week regimen of the original paclitaxel formulation (Seidman 2004), and I'm left wondering which is the best drug to use.

For patients who prefer an every three-week schedule, I believe *nab* paclitaxel is the way to go. Otherwise, it's a toss-up between every three-week *nab* paclitaxel and a weekly regimen of the original paclitaxel formulation. I don't believe there's a way to compare the two. CALGB is planning to conduct a head-to-head trial comparing weekly regimens of *nab* paclitaxel and the original paclitaxel formulation.

First-line therapy for patients with metastatic disease who received adjuvant AC and a taxane

I look at these patients as being anthracycline and taxane refractory, but if a long period has passed (ie, two or more years) since the adjuvant therapy, you

could certainly retry a taxane. *Nab* paclitaxel or a weekly regimen of the original paclitaxel formulation would be attractive choices. However, I'm generally treating these patients as anthracycline and taxane refractory, and I'm using capecitabine. Not only is capecitabine FDA approved for that indication, it seems to have among the higher response rates in the anthracycline- and taxane-refractory group of patients.

Alternatives to capecitabine would include vinorelbine and gemcitabine. I believe combinations of these drugs are also something to consider. We're so geared toward thinking of single agents, but combinations do have a role, particularly for more symptomatic patients. It's hard to know which combination wins out. Data exist on combinations of vinorelbine/capecitabine, gemcitabine/vinorelbine and gemcitabine/capecitabine.

Select publications

Brufsky A et al. **Zoledronic acid (ZA) for prevention of cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (Let): Preliminary results of the Z-FAST trial.** San Antonio Breast Cancer Symposium 2004;**Abstract 1114**.

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

Cobleigh MA et al. **Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease.** *J Clin Oncol* 1999;17(9):2639-48. **Abstract**

Come SE, Borges VF. **Role of fulvestrant in sequential hormonal therapy for advanced, hormone receptor-positive breast cancer in postmenopausal women.** *Clin Breast Cancer* 2005;6(Suppl 1):15-22. **Abstract**

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13. **Abstract**

Dodwell D, Vergote I. **A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer.** *Cancer Treat Rev* 2005;[Epub ahead of print]. **Abstract**

Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-90. **Abstract**

Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment-induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen: Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

Gradishar WJ. **Clinical value of fulvestrant in breast cancer.** *Clin Breast Cancer* 2005;6(Suppl 1):4. No abstract available

Gradishar WJ, Sahmoud T. **Current and future perspectives on fulvestrant.** *Clin Breast Cancer* 2005;6(Suppl 1):23-9. **Abstract**

Howell A, Buzdar A. **Are aromatase inhibitors superior to antiestrogens?** *J Steroid Biochem Mol Biol* 2005;93(2-5):237-47. **Abstract**

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

Jones SE, Pippen J. **Effectiveness and tolerability of fulvestrant in postmenopausal women with hormone receptor-positive breast cancer.** *Clin Breast Cancer* 2005;6(Suppl 1):9-14. **Abstract**

Kudachadkar R, O'Regan RM. **Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer.** *CA Cancer J Clin* 2005;55(3):145-63. **Abstract**

Leonard R et al. **Optimizing the management of HER2-negative metastatic breast cancer with capecitabine (Xeloda).** *Semin Oncol* 2004;31(5 Suppl 10):21-8. **Abstract**

Marty M et al. **Anthracyclines vs taxanes plus trastuzumab in HER2-positive metastatic breast cancer (MBC): A cross trial comparison of pivotal studies.** *Proc ASCO* 2005;**Abstract 743**.

Marty M et al. **Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered as First-Line Treatment: Results of a Randomized Phase II Trial by the M77001 Study Group.** *J Clin Oncol* 2005;[Epub ahead of print]. **Abstract**

Montemurro F et al. **Continuation of trastuzumab beyond disease progression.** *J Clin Oncol* 2005;23(12):2866-8. No abstract available

Montemurro F et al. **Outcome of patients with HER2+ advanced breast cancer (ABC) progressing during trastuzumab (T)-based treatment.** *Proc ASCO* 2005;**Abstract 593**.

O'Shaughnessy J et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs Taxol in MBC: A phase III trial.** Presentation. San Antonio Breast Cancer Symposium 2003;**Abstract 44**.

Paley M et al. **Preferences for oral and parenteral antitumor therapy: A survey of 260 patients with metastatic breast cancer.** *Proc ASCO* 2005;**Abstract 619**.

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

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

Schaller G et al. **Efficacy and safety of trastuzumab plus capecitabine in a German multicentre phase II study of pre-treated metastatic breast cancer.** *Proc ASCO* 2005;**Abstract 717**.

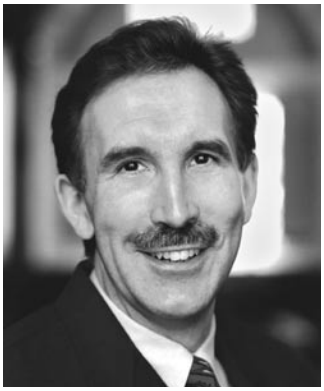
Seidman A et al. **CALGB 9840: Phase III study of weekly paclitaxel via a 1-hour infusion versus standard 3-hour infusion every third week on the treatment of metastasic breast cancer with trastuzumab for HER2 positive metastatic breast cancer and randomized for trastuzumab in HER2 normal metastatic breast cancer.** *Proc ASCO* 2004;**Abstract 512**.

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **Abstract**

Thürlimann B. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind phase III study.** *Breast* 2005;14(Suppl 1):3;S4.

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

Response to neoadjuvant systemic therapy



The number of patients receiving neoadjuvant endocrine therapy has increased significantly, and many oncologists who've tried this approach and found that it worked have adopted this strategy. I believe more physicians should be utilizing this because it's effective at downstaging some large tumors, making inoperable tumors operable.

When we're selective and treat only patients with ER-rich tumors, meaning Allred scores 6, 7 and 8, the number of patients who progress or actually fail to respond is very small. We treated approximately 250 such patients with neoadjuvant endocrine therapy, and only three or four of the patients had disease progression.

We have also learned that we can treat patients longer than three or four months with neoadjuvant therapy and see continued response. We've treated patients for up to a year and found that the number of patients with a complete response continues to rise the longer we treat them. If the tumor is shrinking but still not small enough for breast-conserving surgery at three or four months, continuing therapy will give added benefit, and eventually, most of these tumors will become small enough for breast conservation.

Neoadjuvant endocrine therapy versus chemotherapy

At ASCO in 2004, Semiglazov presented data from a small neoadjuvant study in which approximately 120 older postmenopausal women with ER-positive breast cancer were randomly assigned to receive doxorubicin/paclitaxel or an aromatase inhibitor — either anastrozole or exemestane (Semiglazov 2004). The response rates were in the 80 percent range and statistically similar whether the patients received endocrine therapy or chemotherapy (3.1).

Interestingly, the study revealed that the rate of breast-conserving surgery was higher in women who had received endocrine therapy. It was a small number, so it didn't quite reach statistical significance, but the *p*-value was 0.054. I believe the reason for this is related to the way the tumor responds to neoadjuvant therapy. At ASCO 2005, we presented data showing that we're significantly more

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likely to be successful performing breast-conserving surgery after neoadjuvant endocrine therapy than chemotherapy. One reason for this is that approximately 20 to 30 percent of patients who respond well to neoadjuvant chemotherapy are left with multiple islands of tumor scattered throughout an area of the breast that corresponds to the size of the original tumor, whereas the pattern following neoadjuvant endocrine therapy is that the tumor shrinks and implodes.

3.1 Neoadjuvant Trial of Endocrine Therapy versus Chemotherapy in Postmenopausal Women with ER-Positive Breast Cancer: Efficacy Data

Efficacy parameter	Chemotherapy*	Anastrozole	Exemestane	*p*-value
Clinical objective response	76%	75.6%	81.5%	NR
Mammography objective response	61.9%	62.1%	71%	NR
Pathologic complete response	7.4%	3.3%	6.8%	NR
Breast conservation	23.9%	33.3%	34%	0.054
Local recurrence rate	3.2%	3.3%	3.4%	>0.5

* Chemotherapy = doxorubicin + paclitaxel; NR = not reported

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

Tolerability of neoadjuvant systemic therapy

One interesting aspect of the Semiglazov series was the side-effect profiles (3.2). In the patients randomly assigned to chemotherapy, many experienced neutropenia, some developed febrile neutropenia, a large percentage lost their hair and a significant number experienced neuropathy. On the other hand, the toxicities from endocrine therapy consisted of hot flashes and muscular aches and pains. Our impression is that elderly patients tolerate endocrine therapy much better than chemotherapy.

This study did not reveal any toxicity differences between anastrozole and exemestane. We're conducting a number of randomized studies comparing anastrozole, letrozole and exemestane, and it's fairly clear that the side-effect profiles are different. With letrozole, the biggest side effect is fatigue; with anastrozole, we see more muscular aches and pains and some nausea. With exemestane, patients experience more diarrhea.

Neoadjuvant systemic therapy to reduce spread of cancer secondary to surgery

We presented a study at San Antonio in which over 200 patients were randomly assigned to receive either anastrozole or letrozole for 14 days prior to surgery (Murray 2004). We were examining biological factors in the tumor and found

that proliferation was reduced between 80 and 84 percent in absolute terms within those 14 days.

We saw that within a few days of starting an aromatase inhibitor, we can switch off proliferation, so our strategy now in postmenopausal patients with invasive, ER-positive breast cancer is to begin an aromatase inhibitor straight away. If one is concerned that surgery spreads cancer, then it's my view that if cancer cells are dying as a result of this approach, they are much less likely to take hold and metastasize.

A study reported to the Association of Surgeons in the United Kingdom examined patients who'd been given preoperative tamoxifen and found that they did better in terms of recurrence than patients who were started on routine adjuvant tamoxifen after surgery. It wasn't a large study, nor was it randomized, but it's anecdotal evidence, and scientifically it makes sense.

Treating patients with aromatase inhibitors doesn't increase their risk of deep vein thrombosis or pulmonary embolus, so they can be given safely before surgery. It also allows patients to choose when to have an operation. Since they are on treatment, they can go on holiday with no rush to undergo surgery. Also, when the patient leaves the office, they already have a treatment, and you can tell them that by tomorrow their tumor will have started to shrink. Patients like that approach, and psychologically, we have found it to be a tremendous benefit.

3.2 Neoadjuvant Trial of Endocrine Therapy versus Chemotherapy in Postmenopausal Women with ER-Positive Breast Cancer: Toxicity Data

Category (Grade)	Neoadjuvant chemotherapy*	Neoadjuvant endocrine therapy
Alopecia	79%	0%
Neutropenia (II-IV)	43.1%	0%
Neuropathy CTC (II-III)	32%	0%
Fatigue (II)	8.1%	15.2%
Cardiotoxicity (LVEF <50%)	7%	0%
Stomatitis (III)	6.5%	0%
Febrile neutropenia	5%	0%
Hot flashes (II)	1.6%	23.3%
Arthralgia (I-II)	1.6%	6.7%
Myalgia	1.6%	5%
Vaginal bleeding	0%	6.7%

* Chemotherapy = doxorubicin + paclitaxel

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

Efficacy data from ATAC and BIG FEMTA/BIG 1-98

The data from the ATAC and BIG 1-98 trials are difficult to compare for a number of reasons (ATAC Trialists' Group 2005; Thürlimann 2005a, b; [3.3]). The percentage of patients with positive nodes was 34 percent in the ATAC trial versus 41.3 percent in the IBCSG-1-98 trial. The percentage of patients who received chemotherapy was 21.3 percent in ATAC versus 25.3 percent in IBCSG-1-98. I believe that might be important because the overview suggested patients benefit more from hormonal therapy given alone than when combined with chemotherapy.

Secondly, the BIG 1-98 data are a short-term analysis — follow-up is only 25.8 months, whereas for the ATAC trial the follow-up is five years — and some concerns exist as to how the BIG 1-98 data are being analyzed. The trial has four arms, and patients who switched therapy after two years were included in the analysis, but only up until the time when they were switched. That's a bit unusual, because one would expect some of the benefit from the first two years of tamoxifen and letrozole to continue.

BIG 1-98 did show quite clearly that it is more beneficial to use an aromatase inhibitor than tamoxifen when treating patients early, and it suggests that at least some patients — possibly a large percentage of patients — should receive aromatase inhibitors up front. If we don't give patients aromatase inhibitors initially, then a large number will recur in the first two years. This was seen in the ATAC trial also.

3.3 BIG 1-98 (N = 8,010) and ATAC (N = 9,366) Efficacy Data

Endpoint	BIG 1-98[1] hazard ratio (25.8 months)	ATAC[2] hazard ratio (68.0 months)
Disease-free survival	0.81	0.87
Time to recurrence	0.72	0.79
Time to distant recurrence	0.73	0.86
Time to breast cancer death	NR	0.88
Overall survival	0.86*	0.97*

* Not significant; NR = not reported

SOURCES: [1] Thürlimann B for the BIG 1-98 Collaborative Group. **Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. First results of IBCSG 18-98/BIG 1-98.** Presentation. St Gallen Breast Cancer Conference 2005. *Breast* 2005a;14(Suppl 1):3;S4.

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

Cardiac toxicity and safety data from the ATAC and BIG 1-98 trials

BIG 1-98 revealed a high incidence of hypercholesterolemia with letrozole, and the number of cardiac deaths was doubled in the patients receiving letrozole (Thürlimann 2005a, b). The numbers were small — 26 deaths on letrozole and 13 on tamoxifen — and it's important to remember that despite the cardiac deaths, more patients were alive on letrozole than on tamoxifen, so it was beneficial in terms of overall breast cancer mortality. We saw similar findings of excessive cardiac events with exemestane.

Later this year, the ATAC data on adverse events in terms of heart effects and the number of patients reported to develop hypercholesterolemia will be presented. My understanding is that no major adverse effects are being seen with anastrozole. I've always believed letrozole is more potent, and we may not want the most potent drug in the adjuvant setting, because the most potent drug may have more adverse events. The letrozole data concerns me a bit. Clearly, we need longer-term data before we start using letrozole up front for five years.

The data that have been released from ATAC in terms of cardiac deaths do not suggest excessive deaths with anastrozole, and the overall hazard ratio for breast cancer deaths in ATAC is favorable, but the overall mortality is 0.97 (ATAC Trialists' Group 2005).

Another interesting aspect of the BIG 1-98 and ATAC findings was that the annual fracture rates were identical. We are currently conducting an open-label study examining letrozole, exemestane and anastrozole and their effects on lipids, clotting and bone. The results will be quite important. However, based on the current data, I believe most postmenopausal patients with ER-positive breast cancer should receive anastrozole front line for adjuvant therapy.

Endocrine switching trials in the adjuvant setting

The combined analysis of the Austrian (ABCSG Trial 8) and the German (ARNO 95) trials, in which patients were switched to anastrozole after two years of adjuvant tamoxifen, is difficult to compare to the Intergroup Exemestane Study (IES), in which patients were switched to exemestane (Jakesz 2004, Coombes 2004).

In the IES, 44.2 percent of women had node-positive disease and 32.7 percent received chemotherapy, whereas in the combined analysis, 25.9 percent of patients had positive nodes, none of them received chemotherapy and the majority of patients had Grade I or II disease. Perhaps, then, it shouldn't be surprising that a marked benefit was seen with anastrozole, with a hazard rate for breast cancer events of 0.60 and a mortality hazard ratio of 0.76, almost reaching statistical significance. However, in the United States, I believe many of these patients would have received chemotherapy and, therefore, we would have seen slightly less benefit from switching therapies.

I believe postmenopausal patients with ER-positive tumors who have been on tamoxifen for a couple of years will generally benefit from switching to either anastrozole or exemestane. Based on the data, I believe both are effective.

As for toxicities, in the IES data we did see more myocardial infarcts with exemestane than with tamoxifen, which corresponds to what we have seen with letrozole. Tamoxifen is protective against myocardial infarcts, so we might just be seeing the tamoxifen preventative effect. As for the IES bone subprotocol, they didn't find exemestane to be any better than the other aromatase inhibitors in terms of protecting bone (Coleman 2004).

Trials of fulvestrant in premenopausal women

In premenopausal women, we're doing some interesting work with fulvestrant. Part of the problem with fulvestrant is that the doses used in postmenopausal women did not show a benefit in premenopausal women. In our study, which we will probably present in San Antonio later this year, we're comparing preoperative tamoxifen to preoperative fulvestrant at a dose of 750 mg, which is three times the dose currently used in postmenopausal women. From our preliminary data, it is clear that fulvestrant is having some effect on these tumors. The hope is we might have another agent that is useful in premenopausal women.

Select publications

Coleman RE et al. **Intergroup Exemestane Study: 1-year results of the bone sub-protocol.** San Antonio Breast Cancer Symposium 2004;**Abstract 401**.

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

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

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

Murray J et al. **Letrozole and anastrozole: A pre-operative study of their effects on ER-positive breast cancers in postmenopausal women.** San Antonio Breast Cancer Symposium 2004;**Abstract 406**.

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

Thürlimann B et al. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** *Breast* 2005a;14(Suppl 1):3;S4.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. ASCO 2005b;**Abstract 511**.

Regulation of estrogen receptor expression

I'm very interested in hormone-responsive breast cancer and struck by the fact that clinically, approximately 25 percent of breast cancers lack the estrogen receptor. We have been thinking about why that is and are exploring mechanisms for regulation of the estrogen receptor.

One of the mechanisms that we're interested in is the concept that epigenetic silencing mechanisms might lead to loss of estrogen receptor expression. These changes modify expression of a gene and are potentially reversible, unlike mutations, which are permanent, and we are thinking about whether we can take advantage of this therapeutically.

In addition, a lot of genes are epigenetically silenced in cancer in general, not just breast cancer, and these changes are felt to be a hallmark for cancer. We can detect these changes molecularly on small specimens, and so the possibility exists that they might be useful as risk assessment or screening tools.

It's believed that most normal mammary epithelial cells actually have very little estrogen receptor expression. The Baylor group has suggested that some pre-malignant lesions, such as atypical hyperplasias, are rich in estrogen receptor expression, and we know that many ductal carcinoma in situ lesions, because we measure it now, are estrogen receptor-positive. However, we don't know how this progression takes place and whether it represents two kinds of invasive breast cancer that deviate early or whether one logically progresses into the other.

Histone deacetylase inhibitors to modify gene expression

In breast cancer, the estrogen receptor is generally intact. The problem in estrogen receptor-negative breast cancer is that the tumor doesn't transcribe the RNA, so it doesn't make the protein. We were very interested in these epigenetic modifications — histone modifications or DNA methylation — as a way of silencing estrogen receptor gene expression, and using PCR-based techniques, it appears this happens in many cancers.

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It's interesting that this exists and that in the laboratory we can reverse it. We can use histone deacetylase inhibitors — like suberoylanilide hydroxamic acid (SAHA) and a number of compounds that are being tested in Phase I and Phase II trials — and we can also use the DNA methyltransferase inhibitor azacitidine, which has just been FDA approved for myelodysplastic syndromes. We have a lot of preclinical cell culture data, so now we're moving on to animal models.

We are conducting our first clinical trial with preoperative SAHA in healthy women with primary breast cancer. A core biopsy will be taken initially for research purposes, and then patients will take three days of SAHA, which is an oral agent. At the time of the definitive surgery, post-treatment tissue will be examined for the usual endpoints — change in Ki67, change in histones — because we expect it will modify the histone acetylation. It's largely an exploratory trial, the question being: What gene expression patterns and profiles and proteome patterns are modified by this histone deacetylase inhibitor? We have never done this before, and I hope to see changes in the estrogen receptor occur, because I believe the estrogen receptor is just one of many genes that are epigenetically modified (4.1). We are not going to restrict this trial to estrogen receptor-negative patients. We hope we'll have some and that will be one of several candidate genes we'll be evaluating.

While I am interested in the estrogen receptor, others have noted that retinoic acid receptor beta is also epigenetically silenced in many breast cancers. If in the lab we can change that — turn it back on — then we can treat with retinoids, and there's been a lot of interest in using various retinoids for treatment of malignancies, including breast cancer.

One hypothesis is that the cancer turned these genes off for a reason; it needed to inactivate them in order to move along its carcinogenic progression — a tumor suppressor gene, for example — so it is hoped that re-expressing these will result in tumor inhibitory or suppressor effects.

4.1 Effect of HDAC Inhibitors on Estrogen Receptor mRNA and Protein

"5-aza-2'-deoxycytidine (AZA), and the histone deacetylase (HDAC) inhibitor, Trichostatin A (TSA), resulted in expression of functional ER mRNA and protein. Therefore, we sought to characterize the effects of a recently described HDAC inhibitor, Scriptaid, on cell growth and ER expression and function in ER negative human breast cancer cell lines. Scriptaid treatment of three ER negative cell lines, MDA-MB-231, MDA-MB-435 and Hs578t, resulted in significant growth inhibition and increased acetylation of H3 and H4 histone tails. Quantitative Real Time PCR showed 2000-20,000-fold increase of ER mRNA transcript in all three cell lines after 48 h of Scriptaid treatment. Further, dose dependent re-expression of an estrogen responsive gene, the progesterone receptor (PR), indicated that induced ER is functional."

SOURCE: Keen JC et al. **A novel histone deacetylase inhibitor, scriptaid, enhances expression of functional estrogen receptor alpha (ER) in ER negative human breast cancer cells in combination with 5-aza 2'-deoxycytidine.** *Breast Cancer Res Treat* 2003;81(3):177-86. **Abstract**

Neoadjuvant trials targeting breast cancer prevention

In our preoperative trials, we are taking advantage of the concept of the contralateral breast as a prevention test model. We have a trial in which postmenopausal women who are not going to receive adjuvant chemotherapy receive neoadjuvant anastrozole. All the patients have initial core biopsies of the contralateral breast, which is presumably an at-risk but healthy breast, and the biopsies are repeated six months after they begin anastrozole.

A variety of correlative studies will be performed, including evaluation of lipids and breast density. We hope to see a decrease in breast density and determine the impact on lipids with anastrozole. We will use those tissues for exploratory studies, looking for a gene that might be modulated by anastrozole in the breast tissue itself. Then, perhaps, we can establish suitable endpoints that could be used to shorten future chemoprevention trials.

We are about to start a parallel trial evaluating a statin. The interest in whether statins can reduce breast cancer risk basically comes from observations made in the cholesterol-lowering trials, where in some cases it appeared women who took these agents had a lower breast cancer risk. For that particular trial, we're going to target women who have ER-negative breast cancer, because it would be too complicated to conduct in the context of ongoing hormone therapy.

Cardiovascular effects of aromatase inhibitors

Cardiovascular events are a potential issue with the aromatase inhibitors. However, we're also less certain now about what impact estrogen itself has on the heart. We used to believe it was good for the heart and taking it away was bad, but then the data from the Women's Health Initiative (WHI) indicated estrogen is probably not good for the heart (Rossouw 2002; [4.2]). As a result of the WHI, we might think estrogen withdrawal would be better for the heart, but considering the aromatase inhibitor trial data, that may not be the case. It's a complex issue.

4.2 WHI: Effects of Estrogen Plus Progestin on Coronary Heart Disease (CHD)

"The WHI finding that estrogen plus progestin does not confer benefit for preventing CHD among women with a uterus concurs with HERS findings among women with clinically apparent CHD, with the Estrogen Replacement for Atherosclerosis trial, in which estrogen plus progestin did not inhibit progression, and with a trial in women with unstable angina that did not observe a reduction in ischemic events." [Citations omitted]

SOURCE: Rossouw JE et al. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Avoiding taxane-associated adverse events with *nab* paclitaxel

Nab paclitaxel is an interesting drug. I've been thinking about it recently for a young patient with metastatic breast cancer who had a very difficult reaction to docetaxel a few years ago. She received a number of hormone therapies, and now she's hormone resistant; she has also received a number of chemotherapies, including vinorelbine and capecitabine.

When she was in a trial that involved an anthracycline and docetaxel, she had an acute hypotensive reaction. We tried it again, and she had the same reaction, so we stopped the docetaxel and continued the anthracycline. We haven't tried a taxane since. Now *nab* paclitaxel is being considered in the hope that she could get the benefits of a taxane without the adverse reaction.

The toxicity profile of *nab* paclitaxel appears to be better than the other taxanes, and premedication is not needed, which is a big plus. The other advantage is that the administration time is shorter. The problem with the Phase III trial was that it compared an every three-week schedule for *nab* paclitaxel and paclitaxel, whereas I usually give paclitaxel on a weekly schedule (O'Shaughnessy 2003).

Phase II studies of weekly *nab* paclitaxel have been reported (O'Shaughnessy 2004), but we don't know how weekly paclitaxel and *nab* paclitaxel compare head to head. *Nab* paclitaxel is an intriguing drug, and it's good to have an alternative that simplifies administration and minimizes toxicity.

Sequence of single chemotherapy agents in metastatic disease and the role of capecitabine

My philosophy in treating older versus younger women with chemotherapy is basically the same, but sometimes the choices of the patients are different. Many times in metastatic disease, we use all of the available therapies, so what we're really deciding on is the order — what to start with. Many patients make that decision based on their personal values.

I find many of my older patients are attracted to capecitabine because it is an oral agent (4.3). Some of my younger patients think of intravenous therapy as more aggressive, and they prefer that strategy. But this perception is based on gut reaction rather than being reality based.

I am a big fan of capecitabine. Maybe it comes from being a "hormonal therapy person" who prefers pills to begin with, because I use capecitabine a lot for salvage chemotherapy in women who've already had an anthracycline and taxane for metastatic disease.

In oncology, we tend to remember our successes, but I have seen several very impressive responses with capecitabine in dire circumstances. I have had women on capecitabine for a considerable period of time with relatively good quality of life.

4.3 Evaluation of Capecitabine Dose in Elderly Women (Median Age = 73) with Advanced Breast Cancer

"This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens. In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m^2 twice daily merits consideration as 'standard' for women aged 70 years and older who are candidates to cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function."

SOURCE: Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005;23(10):2155-61. **Abstract**

Select publications

Anderson GL et al; Women's Health Initiative Steering Committee. **Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial.** *JAMA* 2004;291(14):1701-12. **Abstract**

Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005;23(10):2155-61. **Abstract**

Gralow JR. **Optimizing the treatment of metastatic breast cancer.** *Breast Cancer Res Treat* 2005;89(Suppl 1):9-15. **Abstract**

Hess D et al. **Capecitabine and vinorelbine in elderly patients (> or =65 years) with metastatic breast cancer: A phase I trial (SAKK 25/99).** *Ann Oncol* 2004;15(12):1760-5. **Abstract**

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

Keen JC et al. **A novel histone deacetylase inhibitor, scriptaid, enhances expression of functional estrogen receptor alpha (ER) in ER negative human breast cancer cells in combination with 5-aza 2'-deoxycytidine.** *Breast Cancer Res Treat* 2003;81(3):177-86. **Abstract**

O'Shaughnessy J et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in MBC: A phase III trial.** San Antonio Breast Cancer Symposium 2003;**Abstract 44**.

O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 1070**.

Rossouw JE et al. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Thürlimann B et al. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** *Breast* 2005a;14(Suppl 1):3;S4.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. ASCO 2005b;**Abstract 511**.

Zamora P et al. **Capecitabine (X) as single agent in elderly patients (p) with metastatic breast cancer (MBC).** *Proc ASCO* 2005;**Abstract 843**.

PowerPoint Journal Club

This PowerPoint Journal reviews recently published clinical research articles and presentations. In this issue, we review an article by Davide Mauri et al on a meta-analysis of neoadjuvant versus adjuvant systemic therapy and a report by Ivo Olivotto et al on a population-based validation of the Adjuvant! program for early breast cancer.

PowerPoint Journal Club slides are provided in two formats, in this monograph and on the enhanced CD. The slide presentation on the CD is designed for optimal viewing on a large screen in a dark room (below, right) and represents top-line data and information from the figures in this book. This format of PowerPoint can be difficult to read in print, and consequently, the version below has been designed to facilitate ease of reading and comprehension.

Neoadjuvant versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis

Mauri D, Pavlidis N, Ioannidis J.

J Natl Cancer Inst 2005;97(3):188-94.

5.1

Neoadjuvant versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis

Mauri D, Pavlidis N, Ioannidis J.

J Natl Cancer Inst 2005;97(3):188-94.

SLIDE 5.1 Interest in preoperative systemic therapy has increased because of its association with local tumor regression and reduction in the extent of local surgery required. This meta-analysis assesses potential advantages of neoadjuvant versus adjuvant systemic therapy in breast cancer treatment.

5.2

Methods

- Database search for randomized studies with same regimens as neoadjuvant and adjuvant therapy
  - MEDLINE and EMBASE
  - Cochrane Central Register of Controlled Trials
- Manual search for published randomized trials from 1995-2003
- Screen reference lists for additional publications
- Contact investigators for clarification and additional data

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.2 Mauri and colleagues identified suitable randomized studies for the meta-analysis by searching several web-based databases and oncology journals for publications of trials. The studies compared neoadjuvant with adjuvant therapy regardless of additional surgery or radiation treatment.

5.3

Trials Eligible for Meta-Analysis (N = 3,946)

Study	Regimens	Enrollment interval (yr)
Avril/Mauriac et al	Epirubicin, vincristine, methotrexate; mitomycin, thiotepa, vindesine	1985-89
Danforth et al	Fluorouracil, leucovorin, doxorubicin, cyclophosphamide and G-CSF	1990-95
Gazet et al	Goserelin, formestane, mitoxantrone, mitomycin, methotrexate	1990-93
Makris et al	Mitoxantrone, mitomycin, methotrexate/tamoxifen	1990-95
NSABP-B-18	Doxorubicin, cyclophosphamide	1988-93
Scholl et al	Fluorouracil, doxorubicin, cyclophosphamide	1983-86
Scholl/Broet et al	Fluorouracil, doxorubicin, cyclophosphamide	1986-90
Semiglazov et al	Thiotepa, methotrexate, fluorouracil	1985-90
van der Hage et al	Fluorouracil, epirubicin, cyclophosphamide	1991-99

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.3 Nine trials were included, with outcomes of 1,933 and 1,928 patients randomly assigned to neoadjuvant and adjuvant study arms, respectively. Cancer stage, tumor size and nodal status varied across studies. Pre- and postmenopausal patients were included in all but one trial with only premenopausal patients.

5.4

Study Outcomes

- Primary Outcomes
  - — Overall survival
  - — Disease progression
  - — Locoregional disease recurrence
  - — Distant disease recurrence
- Secondary Outcomes
  - — Local clinical response (neoadjuvant arm)
  - — Pathologic response (neoadjuvant arm)
  - — Surgical approach (lumpectomy, quadrantectomy, mastectomy, radiotherapy without surgery or none)

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.4 The analysis included the primary outcomes of death from any cause, disease progression, locoregional disease recurrence and metastases. Secondary outcomes included local clinical response, pathologic response in the neoadjuvant arm and the surgical approach in each study arm.

5.5

Statistics

- Estimates of risk ratio (RR) for outcomes
- Assessment of between-study RR variance
- Combination of data across studies using fixed and random effects analysis
- Evaluation of impact of study size on summary effect results

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.5 The meta-analysis was conducted using risk ratio (RR) estimates. An assessment of the variance across studies was made to determine heterogeneity between RRs, and data were combined using fixed and random effects methods. Trial size effects on results were also examined.

5.6

Primary Outcomes

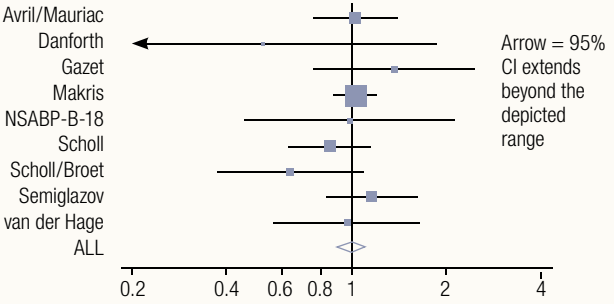
Primary outcomes of neoadjuvant versus adjuvant therapy	Summary risk ratio % (95% CI), random effects analysis	*p*-value
Death	1.0 (0.90-1.12)	—
Disease progression	0.99 (0.88-1.11)	—
Distant recurrences	0.94 (0.83-1.06)	—
Locoregional recurrences	1.22 (1.03-1.44)	0.018

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.6 Primary outcomes between the two study arms were the same except for a 22 percent significant increase in relative risk of locoregional recurrences associated with neoadjuvant treatment.

5.7

Neoadjuvant versus Adjuvant Risk Ratio of Death (95% CI)

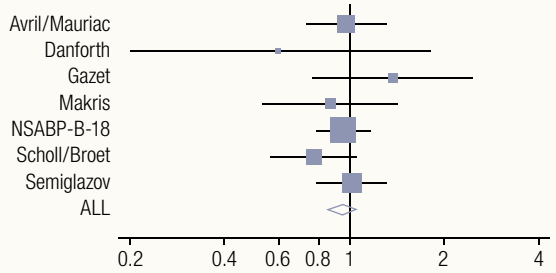


SOURCE: Mauri D et al. **Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis.** *J Natl Cancer Inst* 2005;97(3):188-94, by permission of Oxford University Press. **Abstract**

SLIDE 5.7 There was no difference in death rates between the neoadjuvant and adjuvant treatment arms. The summary risk ratio was 1.0 with a 95 percent confidence interval of 0.90 to 1.12.

5.8

Neoadjuvant versus Adjuvant Risk Ratio of Distant Recurrence (95% CI)

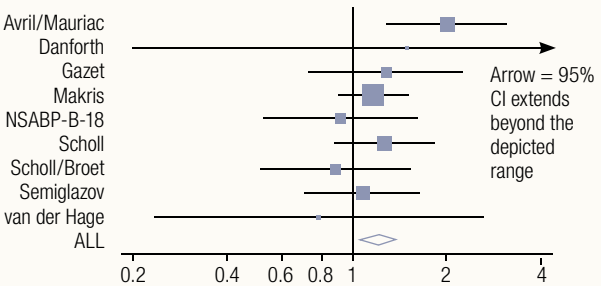


SOURCE: Mauri D et al. **Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis.** *J Natl Cancer Inst* 2005;97(3):188-94, by permission of Oxford University Press. **Abstract**

SLIDE 5.8 As with the data on mortality, no difference in distant recurrence rates between neoadjuvant and adjuvant treatment arms was observed across trials. The summary risk ratio was 0.94 with a 95 percent confidence interval of 0.83 to 1.06.

5.9

Neoadjuvant versus Adjuvant Risk Ratio of Locoregional Recurrence (95% CI)



SOURCE: Mauri D et al. **Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis.** *J Natl Cancer Inst* 2005;97(3):188-94, by permission of Oxford University Press. **Abstract**

SLIDE 5.9 Locoregional recurrence was the only primary outcome associated with a statistically significant difference in rates between treatment arms across studies. The summary risk ratio was 1.22 ($p = 0.015$), indicating a 22 percent *increased* relative risk for locoregional recurrence with neoadjuvant treatment.

5.10

Secondary Outcomes

Significantly large variability in rates for secondary outcome measures across studies precluded summary estimates:

- Complete clinical response
- Pathologic response
- Conservative local treatment

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.10 Summary estimates were not made for any of the secondary outcome measures because of a high degree of variance in rates across studies.

5.11

Local Treatment

- Neoadjuvant study arms
  - More conservative local therapy
  - Radiotherapy without surgery more frequently administered
  - Increased risk of locoregional recurrence, especially for radiotherapy without surgery

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.11 Neoadjuvant arms had higher rates of conservative local therapy. Radiotherapy without surgery was administered more frequently in neoadjuvant arms. Increased risk of loco-regional recurrence was associated with neoadjuvant treatment, especially when radiotherapy was administered without surgery.

5.12

Impact of Study Size and Periods on Summary Effect

- No difference due to trial size in results for:
  - Death ($p = 0.46$)
  - Distant disease recurrence ($p = 0.45$)
  - Locoregional recurrence ($p = 0.84$)
- Results unaffected by study period
- Summary estimates unchanged with data accumulation

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.12 Study size did not affect outcome results for survival, distant disease or locoregional recurrence, although disease progression appeared to be more favorably associated with neoadjuvant treatment in smaller studies. Results also did not change with the addition of data over time.

5.13

Conclusions

- No difference between neoadjuvant and adjuvant therapies
  - Overall survival
  - Disease progression
  - Distant disease recurrence
- Risk of locoregional recurrence greater with neoadjuvant therapy
  - Radiotherapy without surgery

SOURCE: Mauri D et al. *J Natl Cancer Inst* 2005;97(3):188-94. **Abstract**

SLIDE 5.13 These results cannot be extrapolated to agents of greater potency or different modes of action that have not been evaluated in trials comparing neoadjuvant to adjuvant therapy.

Select publications

Avril A et al. **Results of 10 years of a randomized trial of neoadjuvant chemotherapy in breast cancers larger than 3 cm.** *Chirurgie* 1998;123(3):247-56. **Abstract**

Broet P et al. **Short and long-term effects on survival in breast cancer patients treated by primary chemotherapy: An updated analysis of a randomized trial.** *Breast Cancer Res Treat* 1999;58(2):151-6. **Abstract**

Danforth DN Jr et al. **Preoperative FLAC/granulocyte-colony-stimulating factor chemotherapy for Stage II breast cancer: A prospective randomized trial.** *Ann Surg Oncol* 2003;10(6):635-44. **Abstract**

Fisher B et al. **Effect of preoperative chemotherapy on the outcome of women with operable breast cancer.** *J Clin Oncol* 1998;16(8):2672-85. **Abstract**

Fisher B et al. **Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation.** *N Engl J Med* 2002;347(8):567-75. **Abstract**

Fisher B et al. **Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.** *N Engl J Med* 2002;347(16):1233-41. **Abstract**

Gazet JC et al. **Estrogen-receptor-directed neoadjuvant therapy for breast cancer: Results of a randomised trial using formestane and methotrexate, mitozantrone and mitomycin C (MMM) chemotherapy.** *Ann Oncol* 2001;12(5):685-91. **Abstract**

Jakesz R, for ABCSG. **Comparison of pre- vs postoperative chemotherapy in breast cancer patients: Four-year results of Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 7.** *Proc Am Soc Clin Oncol* 2001;20:125;**Abstract 125**.

Makris A et al. **A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer.** *Ann Oncol* 1998;9(11):1179-84. **Abstract**

Mauriac L et al. **Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: A unicentre randomized trial with a 124-month median follow-up.** *Ann Oncol* 1999;10(1):47-52. **Abstract**

Ragaz J. **Emerging modalities for adjuvant therapy of breast cancer: Neoadjuvant chemotherapy.** *NCI Monogr* 1986;1:145-52. **Abstract**

Ragaz J et al. **Neoadjuvant-preoperative-chemotherapy for breast cancer — Preliminary report of the Vancouver trial.** *Prog Clin Biol Res* 1985;201:77-87. No abstract available

Scholl SM et al. **Neoadjuvant chemotherapy in operable breast cancer.** *Eur J Cancer* 1991;27(12):1668-71. **Abstract**

Scholl SM et al. **Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: Preliminary results of a randomised trial.** *Eur J Cancer* 1994 S6;30A(5):645-52. **Abstract**

Semiglazov VF et al. **Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer.** *Ann Oncol* 1994;5(7):591-5. **Abstract**

Wolmark N et al. **Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18.** *J Natl Cancer Inst Monogr* 2001;30:96-102. **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(22):4224-37. **Abstract**

6.1

Population-Based Validation of the
Prognostic Model Adjuvant! for Early Breast Cancer

Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ,
Norris BD, Davis GJ, Chia SK, Gelmon KA.

J Clin Oncol 2005;23(12):2716-25.

SLIDE 6.1 Adjuvant! is a tool developed to objectively predict the absolute benefit of adjuvant systemic therapy for early breast cancer. This report assesses the validity of Adjuvant! based on a comparison of predicted estimates with observed outcomes for a population of women with Stage I or II breast cancer.

6.2

Adjuvant!

- Based on SEER registry 10-year observed overall survival
- Estimates 10-year risk for breast cancer outcomes:
  - Breast cancer-specific survival (BCSS)
  - Event-free survival (EFS)
  - Efficacy of adjuvant tamoxifen and chemotherapy
  - Efficacy of combined chemotherapy/endocrine therapy

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.2 Adjuvant! estimates 10-year risks for breast cancer outcomes of BCSS, EFS and efficacy of adjuvant tamoxifen, chemotherapy and combined chemotherapy/endocrine therapy. It is based on Surveillance, Epidemiology and End Results (SEER) registry data of breast cancer diagnoses between 1988 and 1992.

6.3

Methods

- Data from Breast Cancer Outcomes Unit (BCOU) database of British Columbia Cancer Agency (BCCA)
  - Patients diagnosed 1989-1993 with invasive, pathologic Stage I or II breast cancer
  - Prospectively recorded: Demographic, pathologic, staging, initial treatment, outcomes
  - Adjuvant chemotherapy: AC x 4, CMF or other
- Study endpoints: 10-year OS, BCSS and EFS

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.3 Seventy-five percent of patients from British Columbia with newly diagnosed breast cancer were referred to the BCCA between 1989 and 1993. From their database, data were gathered for patients' demographic, pathologic, staging, initial treatment and outcome information for this comparison study.

6.4

Methods (cont)

- 10-year OS, BCSS and EFS for each patient determined with Adjuvant! v 5.0
- T-test comparison: Predicted versus observed outcomes
- Adjuvant! relevant if predicted and observed outcomes within 2%
- Application of Adjuvant! Prognostic Factor Impact Calculator (PFIC) to patient subgroups to adjust for lymphatic/vascular invasion (LVI)

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.4 Predicted outcomes for OS, BCSS and EFS were determined with Adjuvant!. Results were compared with observed values. LVI presence was an important prognostic factor in the BCOU data but was not automatic in the Adjuvant! algorithm. Its inclusion required the PFIC feature.

6.5

Results

- 4,083 patients were eligible for evaluation
- Entire study cohort
  - Predicted and observed OS, BCSS and EFS within 1% ($p > 0.05$)
- Patient subgroups
  - Predicted OS and BCSS well matched to observed ($p > 0.05$)
  - Adjuvant! overestimated low EFS ($p < 0.05$)
  - Adjuvant! underestimated high EFS ($p < 0.05$)

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.5 Overall predicted and observed outcomes were within one percent for OS, BCSS and EFS. With patient subgroups, the predicted and observed OS and BCSS were not different. However, Adjuvant! overestimated low EFS and underestimated high EFS.

6.6

Results (cont)

- Patient subgroups
  - Most predicted and observed outcomes within 2%
  - Deviations
- >2% significant difference for BCSS in women ≥76 years
- Adjuvant! predicted more favorable outcome:
  - 20- to 35-year-old women
  - Lymphatic/vascular invasion
  - Combined endocrine and chemotherapy

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.6 Adjuvant! also overestimated BCSS, OS and EFS in women younger than age 35 years or with lymphatic or vascular invasion or with combined endocrine and chemotherapy.

6.7

Observed versus Predicted Results

	Overall survival	Breast cancer-specific survival	Event-free survival
Adjuvant! predicted outcome	71.7%	83.2%	71.0%
Observed outcome	72%	82.5%	70.1%
Predicted minus observed	-0.3%	0.7%	0.9%

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.7 For the entire study cohort, the average predicted and observed outcomes for 10-year OS, BCSS and EFS were within one percent and were not significantly different ($p > 0.05$).

6.8

Adjustments to Adjuvant!

- Lymphatic or metastatic invasion
  - LVI presence associated with 1.5-fold increase in risk
  - BCCA guidelines indicate adjuvant systemic therapy with LVI
  - Predicted and observed results not different after PFIC adjustment for LVI
- Adjuvant! suggests PFIC adjustment for patients ≤36 years old
- Prognostic factors of LVI, young age or HER2 overexpression are not automatic in Adjuvant! algorithm, but may be incorporated with the PFIC feature

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.8 BCCA required treatment for patients with LVI, so they were included in the subgroup of patients receiving adjuvant systemic therapy. Use of Adjuvant!'s PFIC to adjust for this increased risk factor resulted in insignificant differences between outcomes. Similar adjustments are recommended for young age.

6.9

Conclusions

- Adjuvant! online valid for average patient in absence of systemic therapy
- Adjuvant! not automatically adjusted for special histologic subtypes
- Adjustment of Adjuvant! with PFIC recommended for patients age ≤35 years; HER2 status; LVI presence
- Adjuvant! needs validation for modern treatment regimens
- Adjuvant! is not a replacement for good clinical judgment

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

SLIDE 6.9 Adjuvant! performed reliably. To derive reliable predictions of prognosis without adjuvant systemic therapy and absolute benefits of adjuvant systemic therapy, patients younger than 35 years or with additional adverse prognostic factors require risk adjustments using the PFIC feature.

6.10

Adjuvant! Version 7.0

- Baseline prognostic estimates include patients <35 years old and ER positivity
- Extensive update of information about hormonal and chemotherapy options
- Update of guidelines for use

SOURCE: **www.adjuvantonline.com**

SLIDE 6.10 Since the acceptance of Olivotto's article for publication, the Adjuvant! program has been updated. Version 7.0 has added the prognostic factors of young patients <35 years and ER positivity to the baseline prognostic estimates. Updated information about hormonal and chemotherapy options was also added.

Select publications

Aebi S et al. **Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer?** *Lancet* 2000;355(9218):1869-74. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Polychemotherapy for early breast cancer: An overview of the randomized trials.** *Lancet* 1998;352(9132):930-42. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomized trials.** *Lancet* 1998;351(9114):1451-67. **Abstract**

Gasparini G et al. **Tumor microvessel density, p53 expression, tumor size and peritumoral lymphatic vessel invasion are relevant prognostic markers in node-negative breast carcinoma.** *J Clin Oncol* 1994;12(3):454-66. **Abstract**

Levine M. **Clinical practice guidelines for the care and treatment of breast cancer: Adjuvant systemic therapy for node-negative breast cancer (summary of the 2001 update).** *CMAJ* 2001;164(2):213. No abstract available

Loprinzi CL, Thome SD. **Understanding the utility of adjuvant systemic therapy for primary breast cancer.** *J Clin Oncol* 2001;19(4):972-9. **Abstract**

Lundin J et al. **A web-based system for individualized survival estimation in breast cancer.** *BMJ* 2003;326(7379):29. No abstract available

Nixon AJ et al. **Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer.** *J Clin Oncol* 1994;12(5):888-94. **Abstract**

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Post-test:

Breast Cancer Update — Issue 5, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In an expanded-access trial, patients who had progressed on a trastuzumab and chemotherapy regimen experienced an objective response rate of 11 percent when they received trastuzumab with or without chemotherapy beyond progression.
   a. True
   b. False

2. In a recent Phase III randomized trial, patients receiving neoadjuvant trastuzumab and an anthracycline-containing regimen had a pathologic complete response rate of approximately 65 percent.
   a. True
   b. False

3. Which of the following regimens are being evaluated in the BIG 1-98 trial?
   a. Five years of letrozole
   b. Five years of tamoxifen
   c. Two years of letrozole followed by three years of tamoxifen
   d. Two years of tamoxifen followed by three years of letrozole
   e. All of the above

4. In Phase III randomized trials, fulvestrant demonstrated at least comparable efficacy as first- or second-line therapy to which of the following?
   a. Tamoxifen
   b. Anastrozole
   c. Both

5. When compared to the original paclitaxel formulation, *nab* paclitaxel had a better response rate and time to progression given every three weeks.
   a. True
   b. False

6. In the combined analysis of ABCSG-8/ARNO 95, switching to anastrozole after two years of tamoxifen resulted in a 40 percent reduction of breast cancer events (HR = 0.60) compared to five years of adjuvant tamoxifen.
   a. True
   b. False

7. In a study of women with metastatic breast cancer, approximately what percentage said they would prefer an intramuscular injection to an oral medication, if they were both considered equally effective?
   a. 10 percent
   b. 30 percent
   c. 70 percent
   d. 100 percent

8. In the Semiglazov study, comparing neoadjuvant chemotherapy versus endocrine therapy, the response rates were:
   a. Significantly higher in patients receiving chemotherapy
   b. Significantly higher in patients receiving endocrine therapy
   c. Statistically similar between the two groups

9. Semiglazov demonstrated that neoadjuvant chemotherapy resulted in similar rates of toxicity to neoadjuvant endocrine therapy.
   a. True
   b. False

10. The hazard ratio for disease-free survival was comparable in the ATAC trial, with 68 months of follow-up, and BIG 1-98, with 25.8 months of follow-up.
    a. True
    b. False

11. In BIG 1-98, cardiac deaths occurred twice as frequently in patients receiving tamoxifen compared to those receiving letrozole.
    a. True
    b. False

12. The bone subprotocol of the IES trial (switching to exemestane after two years of tamoxifen versus five years of tamoxifen) demonstrated that exemestane protected bone to a similar degree as tamoxifen.
    a. True
    b. False

Post-test answer key: 1a, 2a, 3e, 4c, 5a, 6a, 7b, 8c, 9b, 10a, 11b, 12b

Evaluation Form:

Breast Cancer Update — Issue 5, 2005

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 will be 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	N/A = 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 and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- 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 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy. . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Debu Tripathy, MD	5 4 3 2 1	5 4 3 2 1
J Michael Dixon, MD	5 4 3 2 1	5 4 3 2 1
Nancy E Davidson, 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 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

Evaluation Form:

Breast Cancer Update — Issue 5, 2005

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

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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:

.....

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?

.....

Additional comments about this activity:

.....

Degree:

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

FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

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