BCU | 2005 VOL 4 | ISSUE 2

Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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POWERPOINT JOURNAL CLUB

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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 2 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Chang, Henderson, Dickler and Professor Peto on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

10th National Comprehensive Cancer Network Annual Conference
March 16-20, 2005
Westin Diplomat
3555 South Ocean Drive
Hollywood, Florida
Event website: www.nccn.org/professionals/meetings/10thannual/default.asp

29th Annual Symposium of the American Society of Breast Disease
April 14-16, 2005
Las Vegas, Nevada
Event website: www.asbd.org/pages/symposium.html

96th Annual Meeting of the American Association for Cancer Research
April 16-20, 2005
Anaheim, California
Event website:
www.aacr.org/2005AM/2005AM.asp

41st American Society of Clinical Oncology Annual Meeting
May 13-17, 2005
Orange County Convention Center
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002092,00.asp

Lynn Sage Breast Cancer Symposium
October 6-9, 2005
Chicago, Illinois
Event website: www.cancer.northwestern.edu/education/lynnsage.cfm

2005 San Antonio Breast Cancer Symposium
December 8-11, 2005
San Antonio, Texas
Event website: www.sabcs.org/index.asp

Editor's Note

Stop complaining and solve the problem

After 30 years of studying cancer biology and knowing all the different pathways and growth factor signaling, we're at a very exciting point where we may actually use combination targeted therapies that will be different for different patients. We have to move away from giving the same treatment to everybody. It's all a mindset. We have to give the right agent to a small subset of patients.

Also, clinical trialists have to accept the idea of assessing the activity of these agents in patients with earlier stage disease — perhaps Stage IIIB, or first-line metastatic — as soon as we have demonstrated safety in clinical trials. If you use targeted agents in heavily pretreated patients with metastatic disease, the activity will be very low.

This is the development process for targeted therapies. It's a new era and it takes time because people are still stuck doing large metastatic studies looking for a signal, and then slowly moving forward. That takes a long time for women, if you think about it.

— Jenny C Chang, MD

We have a tendency to divide all trial outcomes into either positive or negative when, in fact, most of what we generate is noninformative.

— I Craig Henderson, MD

Every now and again I get cranky about the glacier-like pace of cancer research. Recently, I was whining about this to a well-known "translational scientist," and his somewhat defensive response focused on the measly two to three percent of patients participating in clinical trials and the great need to increase trial accrual. Sure, blame it on the patients!

Clinical research can be viewed as a market-driven business, and the supply-and-demand concept should have the same validity as in selling fried chicken. I would wager that better financial compensation to physicians and maybe even to patients would solve a lot of the problem lickety split.

I guess it's too much to ask for something simple like a fee increase, so we will need to continue relying on the unselfishness and altruism of patients (and their physicians) who are willing to participate in clinical research.

If I had cancer (God forbid, as they say), participation in a clinical trial would be inviting for at least two reasons:

1. It would provide additional assurance that my therapy would be within the standards of excellence. I don't fully trust anyone anymore, including myself, and the more eyes on my chart the better.

2. Maybe we will learn something useful that might benefit me and my fellow patients.

With regard to motivation #2, it would be a lot more exciting to be part of a Jenny Chang-like neoadjuvant trial in which my tumor would be carefully studied and correlated with my clinical course, than to enter another 3,000-patient adjuvant extravaganza in which I might avoid the key event that results in a statistically significant *p*-value. (Although that would be fine also.)

I also like the idea of being enrolled in a Phase II trial of a novel molecularly targeted agent or combination like the bevacizumab-erlotinib study described by Maura Dickler in this issue of *Breast Cancer Update*. Neither of those agents is likely to make me ill, and who knows what might happen?

Surprises can and do occur in Phase I and II studies, and Craig Henderson speaks about this phenomenon when he recounts the pivotal Phase II trial of trastuzumab in the early 1990s. "The most important and exciting study I've done in my career," says Craig, who describes the work-related euphoria he felt when administering this highly targeted, relatively nontoxic, scientifically compelling therapy and seeing tumors shrink.

Craig describes an impressive response to trastuzumab in a woman with massive ascites and liver metastases, and he notes that you don't have to be a rocket scientist to know that this type of observation — even if only in a handful of patients — is a signal we can't ignore.

Drs Chang and Dickler give me hope that other new advances are around the corner...or at least in the neighborhood.

In the neoadjuvant trial of women with HER2-positive tumors that Dr Chang first reported at the 2003 San Antonio Breast Cancer Symposium, 25 percent of patients experienced a partial tumor response after just three weekly doses of trastuzumab. "It was stunning," she said. Most of the patients were indigent women presenting with locally advanced breast cancer.

Given that the patients in Dr Chang's study had such large tumors, a 50 percent decrease in measurable diameter in *any* tumor in three weeks is remarkable for a nontoxic molecularly targeted therapy. It is ironic that these patients, suffering from poverty — both personally and oncologically — have been part of the vanguard of a new area of clinical research.

It is also sobering to consider that the basic trial concept of sequential biopsies while administering trastuzumab had not previously been implemented, although tens of thousands of patients have now received this landmark agent. Dr Chang argues persuasively that in the future, promising targeted therapies

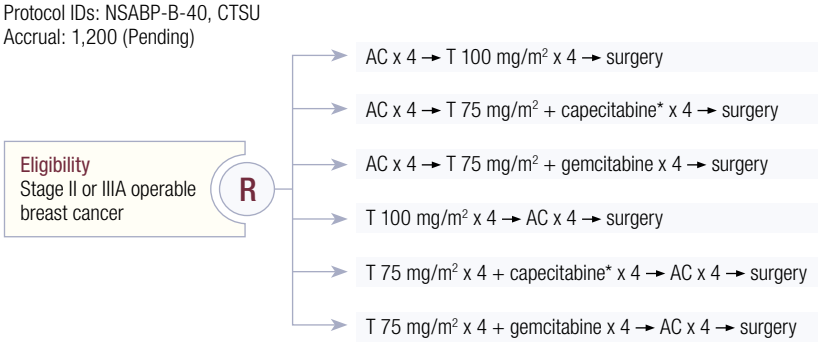
must be tested much sooner in the neoadjuvant setting, and this strategy makes sense.

So let's do it! NSABP-B-40 — a neoadjuvant trial with major emphasis on tissue correlation — is about to be launched (1.1). Every surgeon and oncologist in this country can enter patients through the CTSU (**www.CTSU.org**). Let's commit to enroll patients with newfound zeal. Maybe we should decrease the frequency of television ads for erectile dysfunction medications by 10 percent and invest those dollars in promoting B-40. Call it a societal tax. Whatever, let's just get the study done now.

I tried to convince Richard Peto on this program that the concept of clinical research that results in modest advances in frequent tumors with high mortality rates is getting boring. He, however, rightfully points to the projected halving of breast cancer mortality from 1990 to 2010 as supporting the stepwise approach to progress. Okay, I can't argue with that, so let's do much more of both mega-randomized Phase III trials and clever, strategic, tissue-correlated Phase I and II studies...and let's do that a lot sooner than later.

— Neil Love, MD
NLove@ResearchToPractice.net

1.1 NSABP-B-40 Trial Schema: Preoperative Capecitabine or Gemcitabine plus Docetaxel in Sequence with AC



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

SOURCE: NSABP Protocol Summary, November 2004.

Neoadjuvant trastuzumab trial

We looked at the activity and efficacy of neoadjuvant single-agent trastuzumab in treatment-naïve women with HER2-overexpressing, locally advanced breast cancer. We administered three weeks of single-agent trastuzumab and measured the tumor size before and after treatment.

The endpoints assessed in the study were twofold: (1) efficacy and (2) the mechanism of action of trastuzumab. For the second endpoint, we looked at several pathways — proliferation, growth factor and apoptosis pathways (Chang 2003a).

We enrolled 40 patients, and after only three weeks of trastuzumab, 25 percent of the patients had a partial response (50 percent reduction). The others had stabilization of disease, and none progressed. At that point, we used four cycles of docetaxel and continued weekly trastuzumab.

All of the patients underwent surgery, and the pathologic CR rate was high — about 35 percent. The combination of docetaxel and trastuzumab appears to be synergistic and yields high pathologic CR rates, which is very encouraging.

Until this study was done, cell-line and in vitro models suggested that trastuzumab was predominantly active through a decrease in proliferation. However, if it were only proliferation, you would not see such a massive reduction in tumor size. We found that the primary mechanism of action for trastuzumab is by inducing apoptosis (Chang 2003a; [2.1]).

This has important implications. Number one — trastuzumab is unlikely to be antagonistic with chemotherapy, because they both affect apoptosis, so they would more likely be synergistic.

Secondly, we might think that in studies of patients with metastatic disease — like with chemotherapy, which we use for a defined period of time — we could think about administering trastuzumab for a period of time, stopping, evaluating how the patients do then reintroducing trastuzumab in the future.

Dr Chang is an Associate Professor at the Breast Center at Baylor College of Medicine in Houston, Texas.

2.1 Induction of Apoptosis with Neoadjuvant Trastuzumab

"Contrary to in vitro data, human breast cancer specimens obtained from this prospective in vivo study demonstrate for the first time that trastuzumab induces apoptosis but does not affect cell cycle kinetics in the primary breast cancers of women receiving neoadjuvant treatment. This data suggests that trastuzumab would not likely antagonize the effects of chemotherapy by reducing the proliferation rate, which might be of concern with other growth factor inhibitors. In addition, since trastuzumab results in tumor cell death, shorter treatment durations rather than indefinite long-term treatment should be investigated."

SOURCE: Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab.** San Antonio Breast Cancer Symposium 2003;Abstract 24.

Neoadjuvant trial of trastuzumab in combination with paclitaxel and FEC

I think Dr Buzdar's data with neoadjuvant trastuzumab in combination with paclitaxel and FEC are extremely provocative, because they demonstrate a very high pathologic complete response rate (Buzdar 2004; [2.2]). It was a small study whose results need to be confirmed by a larger study with very careful cardiac monitoring, because they administered trastuzumab together with an anthracycline, even though it was epirubicin.

I have some reservations in terms of Dr Buzdar's cardiac monitoring data. There were no documented cases of cardiac failure, but in other studies, trastuzumab was given for a long time before the cardiac toxicity was realized. Other combinations may be as effective, like the combination of a taxane, carboplatin and trastuzumab. A taxane, trastuzumab and vinorelbine combination is synergistic also. Several regimens may circumvent the problem of cardiac toxicity associated with trastuzumab.

Pan-HER2 inhibition

I'm very interested in the concept of a pan-HER2 inhibitor. Work by Kent Osborne with a mouse xenograft indicates that complete blockade of the HER2 pathway is necessary to elicit a cure. When MCF-7/HER2 + human breast cancer cell xenografts were implanted in mice, they found that with the combination of trastuzumab, gefitinib and pertuzumab — which results in pan-HER2 blockade — tumors actually regressed completely and never came back when the combination was stopped (Arpino 2004; [2.3]). I think we're moving into an era in which you are going to have an escape mechanism unless you block the HER family completely. If you have an escape mechanism, that could actually result in worsening of the disease.

Treatment of women with ER-negative, HER2-positive metastatic disease

In these patients, the decision to use trastuzumab alone or in combination with chemotherapy depends on the pace and bulk of the disease. If the disease is

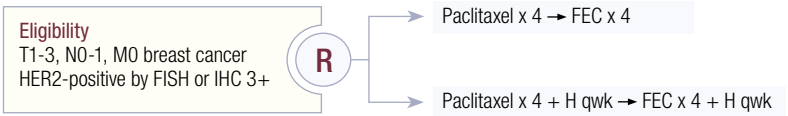
indolent and the woman has, perhaps, a skin nodule and locoregional disease, I may try single-agent trastuzumab, which buys significant quality of life. But, I do actually believe in the synergism with chemotherapy, and would add in chemotherapy shortly after.

Then comes a big question: Do you continue trastuzumab indefinitely, switching around the chemotherapies? The study that would address this has never been done. My personal bias is to continue trastuzumab. Initially, I did not do this, but I do now.

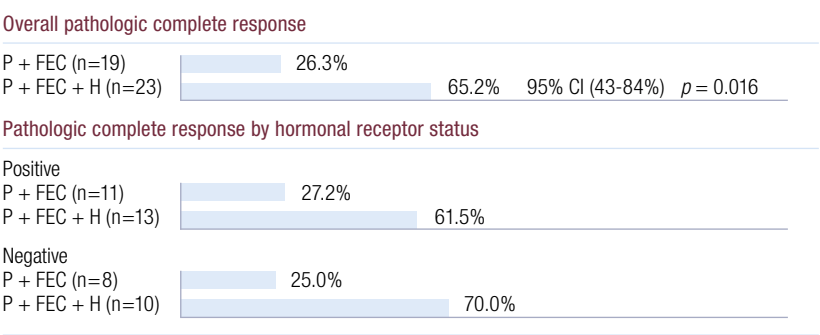
The reason is anecdotal; it's personal experience. You see responses that you have never seen in the days before trastuzumab. The duration of response is much longer with the combination of trastuzumab plus changing around the chemotherapies. Again, that is anecdotal, and it's not evidence based.

2.2 Phase III Study of Neoadjuvant Therapy with Anthracycline-Containing Chemotherapy and Paclitaxel with or without Trastuzumab in Patients with HER2-Positive Breast Cancer

Accrual: 42 (Early closure by DSMB)



Paclitaxel (P) = 225 mg/m^2 every three weeks
FEC = 500/75/500 mg/m^2
H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly



SOURCE: Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004;Abstract 520.

Neoadjuvant docetaxel trial

We recruited women with locally advanced breast cancer to define who would benefit from a neoadjuvant taxane. We obtained six core biopsies before four cycles of docetaxel 100 mg/m^2 every three weeks.

After the four cycles of taxane monotherapy, we remeasured the primary cancer and compared the clinical reduction in tumor size associated with docetaxel; the patients then underwent surgery (Chang 2003b). The response rate was 60 to 70 percent, and the pathologic complete response rate was 14 to 15 percent.

From each pretreatment core biopsy, we were able to extract about three to six micrograms of RNA. Then, we performed an elaborate t-test between the women who did and those who did not respond — a "good-guy/bad-guy" case control study design — to find differentially expressed genes. We found 92 differentially expressed genes between the responders and nonresponders (Chang 2003b).

Because of the small sample size (24 patients), we were able to do another analysis known as leave-one-out cross-validation, which takes one of the samples out, reanalyzes the data and guesses the status of the sample that was removed.

When we did that, we were 88 percent accurate in predicting who would respond to docetaxel. For the next eight patients who came in, we basically guessed whether they would respond, and we were right eight out of eight times (Chang 2003b).

On the basis of this *Lancet* paper (Chang 2003b), we have tried to establish patterns for different chemotherapy regimens. Through the Specialized Programs of Research Excellence (SPORE) mechanism, we have now almost completed a 120-patient study looking at the profiles of patients treated with docetaxel and AC. The preliminary data indicate that they are different. In the near future, we may have expression profiles that predict for response to docetaxel and AC, so we can individualize treatment for women with breast cancer.

2.3 Complete Disappearance of ER+/HER2+ Breast Cancer Cell Xenografts with the Combination of Gefitinib, Trastuzumab and Pertuzumab

Blockade of HER family signaling

Agent	Dimer pair
Gefitinib	HER1/HER2 HER1/HER3
Trastuzumab	HER2/HER2
Pertuzumab	HER1/HER2 HER2/HER3

Effect of HER family inhibitor on tamoxifen-stimulated tumor growth

Agents	Complete response
Tamoxifen + pertuzumab	5/18
Tamoxifen + pertuzumab + trastuzumab	12/18
Tamoxifen + pertuzumab + trastuzumab + gefitinib	18/20

SOURCE: Arpino G et al. Presentation. San Antonio Breast Cancer Symposium, 2004;**Abstract 23**.

Neoadjuvant docetaxel trial: Specific markers predicting for response

Beta-tubulin was overexpressed in tumors resistant to docetaxel. Beta-tubulin has been well documented to be involved in the mechanism of taxane resistance. On the other hand, tumors that were rapidly proliferating were more likely to be responsive to docetaxel (Chang 2003b).

Heat shock protein 27 (HSP27) overexpression is documented in doxorubicin resistance. Yet, HSP27-overexpressing cell lines remain sensitive to docetaxel. We found HSP27 was overexpressed in patients with tumors that were sensitive to docetaxel (Chang 2003b). This indicates that the patterns of gene expression for responders to docetaxel and AC — the two most commonly used regimens — are likely to be different. Therefore, we will have a tool to individualize treatments.

Select publications

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

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

Blackwell KL et al. **A phase II, open-label, multicenter study of GW572016 in patients with trastuzumab refractory metastatic breast cancer.** *Proc ASCO* 2004;**Abstract 3006**.

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

Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab.** San Antonio Breast Cancer Symposium, 2003a;**Abstract 24**.

Chang JC et al. **Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer.** *Lancet* 2003b;362(9381):362-9. **Abstract**

Gelmon KA et al. **Use of trastuzumab beyond disease progression: Observations from a retrospective review of case histories**. *Clin Breast Cancer* 2004;5(1):52-8. **Abstract**

Kostler WJ et al. **Single-agent trastuzumab versus trastuzumab plus cytotoxic chemotherapy in metastatic breast cancer: A single-institution experience.** *Anticancer Drugs* 2005;16(2):185-190. **Abstract**

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

Pegram MD et al. **Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer.** *J Natl Cancer Inst* 2004;96(10):739-49. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

I Craig Henderson, MD

EDITED COMMENTS

The role of adjuvant aromatase inhibitors in postmenopausal women

Based on data from various adjuvant endocrine therapy trials, I believe it is unreasonable to withhold aromatase inhibitors from postmenopausal women with hormone receptor-positive disease. ATAC is still the definitive adjuvant trial in terms of comparing tamoxifen to an aromatase inhibitor, and the data are very compelling (ATAC Trialists' Group 2005; Howell 2004). An aromatase inhibitor is now my drug of choice and that changed in just the past years.

Having said that, I'm not certain that the last "shoe has dropped." We have not yet seen a survival benefit with aromatase inhibitors, and it's possible that the late effects may be different than the early effects. I'm not prepared to completely abandon the SERMs in adjuvant therapy.

It is also quite plausible that optimal endocrine therapy will vary from patient to patient, and there may be a subset that benefits more from tamoxifen while another benefits more from withdrawal of estrogen, which is what we accomplish with aromatase inhibitors.

In addition, we now have selective estrogen receptor downregulators (SERDs) like fulvestrant on the horizon. While we don't have data yet in the adjuvant setting, I imagine it won't be long before we begin to see data with these agents.

As for switching patients from tamoxifen to an aromatase inhibitor, I discuss this with every postmenopausal patient on tamoxifen. My tendency, which is based on my intuition rather than data, is to advise patients on tamoxifen to complete two or three years and then switch. We don't know the optimal time to switch, and we don't know the optimal duration of various endocrine therapies. While we know that five years of tamoxifen is as good or better than 10 years, the optimal duration of aromatase inhibitors is unknown at this time.

Anticancer effect of bisphosphonates

It is possible that when we introduce a bisphosphonate to reduce bone loss, we may be introducing an anticancer treatment as well. I find Ingo Diel's hypothesis

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very compelling. Enough circumstantial evidence exists that I believe we should seriously consider the possibility that bone mediates metastases in breast cancer and, therefore, the state of the bone will indirectly impact survival. There's no question that much of the data suggests a decrease in breast cancer mortality when one uses a bisphosphonate (Diel 1998, 2000); [3.1].

3.1 Phase III Trials of Adjuvant Clodronate (1600 mg PO qd) for Early Stage Breast Cancer

Author	Reduction in skeletal mets	Reduction in nonskeletal mets	Survival in clodronate arm
Diel I et al	Yes	Yes	Increased
Powles T et al	Yes	No	Increased
Saarto T et al	No	No	No significant difference

SOURCES:

Diel I et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Med* 1998;339(6):357-63. **Abstract**

Powles T et al. **Oral clodronate (BONEFOS®) reduces skeletal complications and mortality in breast cancer patients with bone metastases: Retrospective analysis of patients from a randomized, placebo-controlled trial.** San Antonio Breast Cancer Symposium, 2004;**Abstract 3056**.

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

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19(1):10-7. **Abstract**

Saarto T et al. **Ten-year follow-up of a randomised controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients.** *Proc ASCO* 2004;**Abstract 527**.

Surrogate endpoints to detect effects of new agents

We're moving into an era in which we're beginning to combine biologic agents with chemotherapy or other biologic agents. Investigators from UCLA presented data at the 2004 San Antonio Breast Cancer Symposium examining trastuzumab plus bevacizumab and showed responses with the combination that couldn't be achieved with trastuzumab alone (Pegram 2004). It's a small study, but it gives us a clue as to where we are headed in breast cancer treatment.

I've been trying to figure out how we can learn about drug interactions when combining agents without conducting large randomized trials. There are biological agents that have a synergistic effect when combined with conventional cytoxics or have some effect by themselves.

There are also agents with only synergistic effects and none on their own. In randomized trials with real patients, such agents may be quickly abandoned if no positive effects are seen.

Somehow we've got to keep clinicians and patients excited about new drugs and find something that signals us to take them to the next level. I believe our

best hope right now is to use surrogate endpoints such as PET scanning, which is being used by some investigators. With PET scans we can measure the effects of therapy on proliferation very early and may be able to inhibit proliferation without actually inducing apoptosis.

Amplifying weak signals detected in clinical trials

The initial Phase I trastuzumab trial was conducted by Dennis Slamon at UCLA. Then UCSF and Memorial Sloan-Kettering jointly conducted the Phase II study. When we submitted the Phase II data to the *New England Journal of Medicine*, with a response rate just over 11 percent, they said it wasn't positive enough and rejected it. These were studies conducted by well-known investigators at top institutions, but the *Journal* felt it was premature.

Personally, the trastuzumab study was probably the most important and exciting thing I've done in my career. We had a patient at UCSF with massive ascites and large liver metastases who had progressed on three different types of chemotherapy. When she received single-agent trastuzumab, she had a 50 percent response rate and no toxicities. Her ascites disappeared and her quality of life improved. We had to look beyond the 11 percent response rate, because we could see that for some patients it truly worked.

When we see such responses despite a weak signal, we need to determine how to make that signal larger. If we had not targeted the population with HER2-positive disease, it would have taken almost 30 years to complete the trastuzumab study with approximately 10,000 women, and the positive effect would have been diluted because most tumors do not overexpress HER2.

By examining the population with HER2-positive disease alone, we amplified the signal and found that trastuzumab reduces mortality by 25 percent in the worst form of the disease. The challenge now is to take these weak signals — drugs with only five percent response rates — and determine how to amplify them.

Early in my career, I was warned that whereas a false positive will get sorted out, a false negative could bury a drug forever. In cancer we can't afford to do that. Trastuzumab was a near miss and if we hadn't seen the positive effects, I don't think we'd be examining other targeted agents like gefitinib, bevacizumab or erlotinib. Gefitinib is another example where we saw only a 10 percent response rate in randomized trials, but fortunately physicians who were paying attention to clinical results kept it alive and kept the whole field of targeting EGFR alive as well.

AKT inhibitors and targeted therapy

Currently I'm excited about the development of an AKT inhibitor, perifosine (KRX-0401). Researchers at a small German company first identified this agent's antiproliferative and apoptotic effects. Sausville and his colleagues at the NCI showed that this agent inhibits AKT and since then three or four other labs have demonstrated this as well (Patel 2002). Currently it's the only drug that's in the clinic that is known to have this pronounced effect on AKT.

While we do not yet have proof of principle that the inhibition of AKT is the mechanism of action for perifosine, we know it affects MAP kinase and p21waf1/cip1 and has multiple effects in the cell. At the beginning of my career, I really believed that the way we would cure cancer was related to dose, but I no longer believe that. I'm keen on drugs that target new areas of the cancer cell that we couldn't target five, 10 or 20 years ago. This drug looks like it has that potential, and it has an antitumor effect that's well documented.

Numerous challenges exist when developing new agents, such as determining which patients to target and how to characterize them and determining the ideal doses to be used.

Select Publications

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

Diel IJ. **Antitumour effects of bisphosphonates: First evidence and possible mechanisms.** *Drugs* 2000;59(3):391-9. **Abstract**

Diel IJ et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Med* 1998;339:357-363. **Abstract**

Howell on behalf of the ATAC Trialists' Group. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** San Antonio Breast Cancer Symposium, 2004;**Abstract 1**.

Leighl NB et al. **Phase II study of perifosine in metastatic or advanced breast cancer**. San Antonio Breast Cancer Symposium 2004;**Abstract 1077**.

Patel V et al. **Perifosine, a novel alkylphospholipid, induces p21(WAF1) expression in squamous carcinoma cells through a p53-independent pathway, leading to loss in cyclin-dependent kinase activity and cell cycle arrest.** *Cancer Res* 2002;62(5):1401-9. **Abstract**

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

Pegram MD et al. **Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment**. *J Clin Oncol* 1998;16(8):2659-71. **Abstract**

Powles T et al. **Oral clodronate (BONEFOS) reduces skeletal complications and mortality in breast cancer patients with bone metastases: Retrospective analysis of patients from a randomized, placebo-controlled trial.** San Antonio Breast Cancer Symposium, 2004;**Abstract 3056**.

Powles T et al. **Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer.** *J Clin Oncol* 2002;20(15):3219-24. **Abstract**

Robertson JF. **Selective oestrogen receptor modulators/new antioestrogens: A clinical perspective**. *Cancer Treat Rev* 2004;30(8):695-706. **Abstract**

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19(1):10-7. **Abstract**

Saarto T et al. **Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients.** *Proc ASCO* 2004;**Abstract 527**.

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**

The late emergence of survival benefits in adjuvant trials of endocrine therapy

There is an overwhelming amount of data available evaluating the survival benefit from adjuvant tamoxifen. Vast numbers of women have been randomly assigned in trials between tamoxifen and no tamoxifen.

Initially, there was a definite difference in recurrence, with no definite difference in breast cancer mortality. Then there was a definite difference in recurrence and in breast cancer mortality.

In many of the breast cancer trials, the major differences in mortality become evident a decade after the treatment is initially given. There is little difference in the first few years and then a major difference emerges five, 10, or 15 years after treatment.

It could well be that this trend will hold true with the ATAC trial. There is a promising difference in early recurrence, and it might well be that over time, as with tamoxifen, that will translate into differences in breast cancer mortality and overall mortality.

Tamoxifen had almost no effect on mortality when the average follow-up in the trials was just two years. There is a definite, but small, effect on five-year mortality. However, the effect on 15-year breast cancer mortality is more than twice as great as the effect on five-year mortality.

The difference in mortality *after* the first five years is bigger than the difference in mortality during the first five years. So, what appears to be a small difference in mortality after a short-term follow-up may translate into quite a substantial difference in mortality at a 15-year follow-up.

ER status and breast cancer mortality

For women with hormone-sensitive breast cancer, the death rate from breast cancer remains high throughout the first and second decade. However, that does not hold true for ER-negative disease. In ER-negative disease, there is a very high death rate in the first five years, which declines 10 to 15 years after treatment.

Professor Sir Richard Peto is Professor of Medical Statistics and Epidemiology and co-founder and co-director of the Clinical Trial Service Unit at the University of Oxford in the United Kingdom.

Comparatively, the 15-year risk of breast cancer mortality is actually much the same for both ER-positive and ER-negative disease, although the five-year risk of death from breast cancer is much higher for ER-negative disease.

Because of the prolonged period of high mortality associated with ER-positive disease, it is important to take a 20-year perspective on treatment. The focus for therapy of breast cancer should extend beyond the first decade and into the second decade. This holds true for hormonal therapy, radiotherapy and chemotherapy.

In women under 50 years of age, chemotherapy has a very large effect on early recurrences. It has a moderate effect on five-year mortality, but it has twice the effect on 15-year mortality. In ER-positive disease, chemotherapy has the greatest effect on breast cancer mortality after the initial five years of treatment.

Declines in breast cancer mortality

During the 1990s there was a big drop in the national mortality rates from breast cancer, first in the United Kingdom and then in other countries, including the United States (4.1). This decrease in breast cancer mortality has remained steady or improved, while the incidence rate of breast cancer is slightly increasing as women have fewer children, have their first child at an older age and have more body fat after menopause.

In the 1980s there was an improvement in breast cancer treatment with widespread use of hormonal and chemotherapeutic adjuvant regimens. These improvements in treatment during the 1980s produced a reduction in breast cancer mortality during the 1990s. Further improvements in breast cancer treatment during the 1990s are going to keep breast cancer mortality rates falling during the present decade.

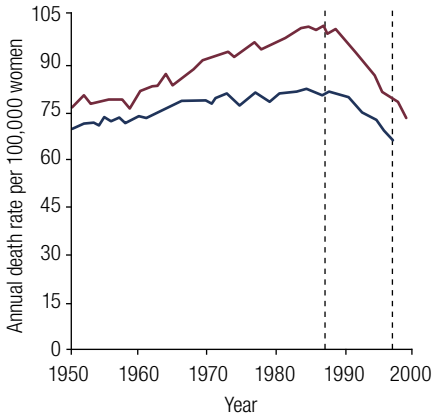
The mortality rate has already decreased by a third, and continues to fall. The change in practice in one decade produces the trends in mortality in the next decade. That is really the pattern and that's what one should expect from trial results.

We have evidence that better local control produces a small but real difference in later mortality from breast cancer. Therefore, earlier diagnosis results in a reduction in breast cancer mortality. In addition to national screening programs, there's been an increase of breast cancer awareness over the last few decades, which may have led to earlier diagnosis and downstaging.

In Britain, the national screening program began in 1991. So, the main benefits from screening are going to be seen during the present decade, as well as during the next decade.

The improvements in breast cancer control during the 1990s will translate into decreases in national death rates during the first and possibly the second decade of this century. Therefore, the decrease in breast cancer mortality during the 1990s is not chiefly due to screening; it is due to the changes in management that occurred during 1980s.

4.1 Decrease in Breast Cancer Mortality for Women Ages 50 to 69 in United Kingdom and United States



Over the 10-year period from 1987 to 1997, the annual breast cancer death rate per 100,000 women ages 50 to 69 decreased by 22% in the United Kingdom and 18% in the United States.

United Kingdom

United States

SOURCE: Peto R et al. **UK and USA breast cancer deaths down 25% in the year 2000 at ages 20 – 69 years.** Reprinted with permission from Elsevier (*The Lancet* 2000, 355, 1822). No abstract available

Meta-analysis of local therapy trials

Over the past few decades, there have been nearly 100 randomized trials of different methods of achieving local control in breast cancer: radiotherapy versus no radiotherapy or more surgery rather than less surgery or more surgery versus less surgery but adding radiotherapy. Some of these therapies do not make very much difference in local control, so it is not surprising that there is no material effect on long-term survival (Peto 2004).

When you look at treatments that involve a major difference — for example, a 30 percent local recurrence risk versus a 10 percent local recurrence risk — then you are going to get a mortality difference of around five percent — 50 percent mortality versus 45 percent mortality — at 15 years. So, there's a real effect.

The conclusion is that local control does matter. It is not an enormous effect, but it is a real effect. A difference of about 20 percent in the five-year risk of local recurrence translates to approximately a five percent difference in the probability of death from breast cancer over the next two decades.

Select Publications

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

Peto R. **Meta-analysis of local therapy.** San Antonio Breast Cancer Symposium, 2004;**Abstract P5**.

Peto R et al. **UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years.** *Lancet* 355(9217):1822, 2000 May 20. No abstract available

Phase II trial of bevacizumab plus erlotinib in patients with metastatic breast cancer (18 patients)

Efficacy

In the preliminary analysis, we saw one partial response, and that patient has now had approximately an 80 percent reduction in a chest wall mass and nodal metastases (Dickler 2004; [5.1]).

She's had a very durable response for about 15 months, which is impressive. A few other patients are nearing achievement of partial responses, but currently we just have the one partial response and many patients with stable disease.

Side effects

The side effects observed are secondary to the anti-EGFR therapy, including skin rash and diarrhea. Skin rash occurs in about three-quarters of patients and can be treated in the majority of with oral tetracycline, and the diarrhea is very controllable with Imodium®.

Typically, patients can push through these side effects and improve on their own. Bevacizumab was very well tolerated, with no infusion reactions and minimal bleeding. Hypertension occurs in 15 to 20 percent of patients, but it can be well controlled with medication.

Correlative studies

We're also looking at EGFR status, ER, PR, HER2, VEGF and VEGF receptor status. We're also sending serial blood samples to Hope Rugo at UCSF, and in collaboration with John Park, they are looking at circulating tumor cells, circulating endothelial cells and serum angiogenic factors.

The New England Journal article demonstrated that circulating tumor cells can help predict response to therapy before CAT scans (Cristofanilli 2004). We want to determine whether changes in tumor cells and endothelial cells can potentially predict response to antiangiogenic therapy.

Dr Dickler is an Assistant Attending Physician, Breast Cancer Medicine Service, at Memorial Sloan-Kettering Cancer Center in New York, New York.

5.1 Phase II Trial Combining Anti-VEGF and Anti-EGFR Therapies in Patients with Metastatic Breast Cancer

Protocol → Bevacizumab 15 mg/kg IV q3wk x 4 + erlotinib 150 mg oral qd x 56

Note: For metastatic breast cancer, 52% and 48% of patients had one or two prior chemotherapy regimens, respectively; 40% and 24% received hormonal therapy and trastuzumab, respectively.

Efficacy (n=18)		Grade III/IV drug-related toxicities	
Complete response	0%	Rash	0%
Partial response	6%	Diarrhea	4%
Stable disease at nine weeks	33%	Nausea	4%
Stable disease > six months	6%	Vomiting	4%
Median time to progression	4 months	Hypertension	8%
Duration of response	8.8 months		

SOURCE: Dickler M. Presentation. ASCO, 2004;**Abstract 2001**.

Rationale for evaluating trastuzumab in combination with bevacizumab

The UCLA group is studying this very interesting combination (Pegram 2004). Preclinical data recently published by Konecny and colleagues demonstrate that VEGF is upregulated in HER2-positive breast cancer (Konecny 2004), so there's a rationale for why we believe that VEGF may be important and may partially explain the aggressive phenotype of HER2-positive breast cancer.

Management of patients with ER-positive, HER2-positive metastatic breast cancer

Off protocol, I always start with single-agent hormonal therapy if the patient has minimal symptoms from their cancer. I never want to lose an opportunity to administer an effective therapy that will also provide good quality of life. I tend to use an aromatase inhibitor, as opposed to tamoxifen, for first-line therapy for postmenopausal women. I watch patients and re-image in about three months, and if they're progressing and I have concerns, I sometimes add trastuzumab. I have one patient who has been doing very well for approximately two years with this combined strategy.

First-line therapy for patients with ER-negative, HER2-positive disease

I look at patient's tumor bulk, sites of disease and whether or not they're symptomatic to determine approach to treatment. I've had a couple of patients who are relatively asymptomatic whom I've treated with trastuzumab monotherapy. Chuck Vogel's data demonstrated that clinical benefit rates may be almost 50 percent (Vogel 2002).

In those patients receiving monotherapy, I can administer treatment every three weeks. They can continue to work; they have no alopecia or treatment-related symptoms and good quality of life. I've learned that metastatic breast cancer is a chronic illness, and although it is life threatening and without cure, women will live for years. It's distressing to make patients who are asymptomatic experience the side effects of our treatments.

In patients who are symptomatic from their cancer, I utilize trastuzumab and taxanes. The benefits of those agents far outweigh the downside of the side effects. I tend to use weekly paclitaxel in combination with trastuzumab, then vinorelbine in combination with trastuzumab. I've also utilized the carboplatin/paclitaxel/trastuzumab triplet, and currently at my institution we are performing a pilot trial evaluating carboplatin/trastuzumab in combination with nanoparticle paclitaxel.

Solvent-free albumin-bound nanoparticle paclitaxel

Nanoparticle paclitaxel is a very interesting agent. It may be as good or better than paclitaxel, and we may have to worry less about the hypersensitivity reactions associated with paclitaxel, which is a tremendous advantage. Hypersensitivity reactions are rare, but real, and occasionally life threatening.

We can also avoid the steroid-associated toxicity, particularly when administering weekly paclitaxel to patients with metastatic disease who may receive the agent for one or even two years. Many of those women experience insulin insensitivity and diabetes, develop proximal muscle weakness and gain weight — all side effects due to the steroids.

In light of the data from Dr Blum's trial demonstrating benefit to ABI-007 in patients with taxane-refractory metastatic breast cancer (Blum 2004; O'Shaughnessy 2004), I would be comfortable substituting nanoparticle paclitaxel for paclitaxel in patients with metastatic disease if the agent was FDA approved.* In terms of utilizing it in the adjuvant setting, particularly in a dose-dense fashion, we definitely need safety data but I don't know if we need to treat thousands of patients in an adjuvant clinical trial.

*** Abraxane™ Receives FDA Approval**

Nanoparticle paclitaxel (ABI-007; Abraxane™) was granted FDA approval on January 7, 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

SOURCE: **www.fda.gov/cder**

Algorithm for selection of chemotherapy in the metastatic setting

Positive data exist for several combinations, including capecitabine/docetaxel (O'Shaughnessy 2002) and paclitaxel/gemcitabine (Albain 2004). The doxorubicin/docetaxel combination improved response rate but didn't improve overall survival, and George Sledge demonstrated that sequential therapy was as good

as combination treatment in terms of overall survival (Sledge 2003), so I tend to use sequential single agents for the vast majority of my patients.

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

For the patient who's had adjuvant AC → T, I frequently use capecitabine or vinorelbine as first-line therapy. For someone who's chemotherapy-naïve, my first choice would probably be weekly paclitaxel followed by either vinorelbine or capecitabine. I don't use early-line doxorubicin up front very often in my asymptomatic patients, because I think it causes a lot of fatigue and alopecia. Weekly paclitaxel also results in alopecia, but I prefer to use weekly paclitaxel more than doxorubicin in the metastatic setting.

Selection of adjuvant endocrine therapy

Several very large, well-designed trials have evaluated aromatase inhibitors in the adjuvant setting for postmenopausal patients. The aromatase inhibitors add benefit immediately after surgery, after two to three years of tamoxifen or as extended adjuvant therapy.

In breast cancer, the highest risk of recurrence is typically within the first two to three years after surgery. In women who participated in the ATAC trial, you can see a difference in the disease-free survival curves well before the two and a half year mark (Baum 2003; Howell 2004, 2005).

Not only do you lose patients to an early breast cancer recurrence in the first two to three years, but you also lose some women to adverse events on the tamoxifen arm. The IES study (Coombes 2004) and MA17 (Goss 2003) really do not take those facts into consideration, because those women have already dropped out prior to randomization.

I typically offer anastrozole to the majority of postmenopausal patients with receptor-positive tumors after surgery and chemotherapy. When women come in after two to three years of tamoxifen, I discuss switching to an aromatase inhibitor. When women come in at the end of five years of tamoxifen, I discuss the letrozole data.

MD Anderson trial of neoadjuvant chemotherapy with or without trastuzumab

The results reported at ASCO (Buzdar 2004) were very exciting but further study is required. Approximately 40 patients were randomized on that study, and I believe the long-term toxicity data, particularly with regard to the myocardium, will be important.

Although neoadjuvant trastuzumab increased pathologic response rate — which is a promising sign that it will add to efficacy — it remains uncertain whether it will result in improved survival. I'm not using neoadjuvant trastuzumab in my patients. I would "never say never" because, for example, women with inflammatory breast cancer have a very high risk of developing distant metastatic disease. In general, at Sloan-Kettering we do not use adjuvant trastuzumab in a nonprotocol setting.

Select Publications

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;**Abstract 510**.

Blum JL et al. **Long term disease control in taxane-refractory metastatic breast cancer treated with nab paclitaxel.** *Proc ASCO* 2004;**Abstract 543**.

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

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

Dickler M et al. **Phase II trial of erlotinib (OSI-774), an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, and bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF), in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2004;**Abstract 2001**.

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

Howell A et al. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** San Antonio Breast Cancer Symposium, 2004;**Abstract 1**.

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

Konecny GE et al. **Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients.** *Clin Cancer Res* 2004;10(5):1706-16. **Abstract**

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

O'Shaughnessy J 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**.

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

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

Michael Baum, MD, ChM

EDITED COMMENTS

Portions of the following were misprinted in the previous issue of BCU and are reprinted here for your convenience.

Switching postmenopausal patients from adjuvant tamoxifen to aromatase inhibitors

I am now absolutely confident that women who've been on tamoxifen for two or three years should switch to an aromatase inhibitor. We have excellent data for both exemestane and anastrozole from three trials. Boccardo's small ITA trial with anastrozole was the first to report (Boccardo 2003), followed by the large IES study (Coombes 2004) with exemestane and the joint Austrian-German study of anastrozole presented in San Antonio (Jakesz 2004). Overwhelming evidence indicates that a switch to an aromatase inhibitor is beneficial.

I recommend the switch regardless of how long the patient has been on tamoxifen. You can wait forever for refinements in clinical trials, but no one is ever going to do a trial of a switch at one year or a switch at four years. We just have to stretch the available evidence and be sensible about it, and I think it would be reasonable to switch.

The MA17 trial is a well-conducted study (Goss 2003) in women who have already received five years of tamoxifen. It shows proof of principle that you can influence the natural history of breast cancer after five years of tamoxifen. I've gone on record that I'm bitterly disappointed that they closed the trial (6.1) and then allowed the placebo group to switch to letrozole, because they are treating the placebo group with experimental therapy — five years on tamoxifen, an average of two and a half years placebo, and then letrozole. That is an unproven treatment and I don't think we'll ever really learn the long-term benefit and toxicity.

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

Bisphosphonates in premenopausal women on tamoxifen or anastrozole

The Austrian study presented in San Antonio analyzed the capacity of zoledronic acid to prevent bone loss (Gnant 2004). The patients are all premenopausal women receiving an LHRH agonist. They are then randomly assigned to anastrozole or tamoxifen, followed by a second randomization to zoledronic acid or not.

Dr Baum is Emeritus Professor of Surgery and Visiting Professor of Medical Humanities at University College in London, United Kingdom.

In the main-effect analysis, zoledronic acid protects against osteopenia and osteoporosis. In the four-arm analysis, the bone mineral density in the goserelin plus anastrozole arm is the lowest, but the curve for goserelin plus anastrozole plus zoledronic acid runs parallel with the curve for goserelin plus tamoxifen plus zoledronic acid (6.2). I find that reassuring. It is evidence that zoledronic acid, a bisphosphonate, can reverse this loss of bone mineral density. The other result that was somewhat of a surprise was that even the women who received tamoxifen and goserelin were losing bone.

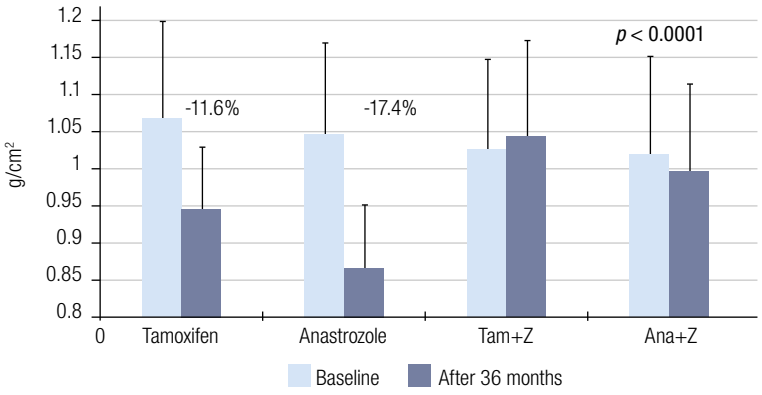
6.1 Premature Closure of Intergroup Trial MA17

"The trial was stopped prematurely because of a significant improvement in disease-free survival favoring the letrozole group. Those on placebo were then offered letrozole. In my opinion this is a pity, for although it is of scientific interest to note that the natural history of the disease can be perturbed after 5 years of tamoxifen, this study will never be able to address the issue of clinical utility in overall survival or provide a proper harm-benefit analysis.

"... In my opinion, the early stopping of MA-17 because of ill-judged stopping rules is a breach of contract with the client and therefore unethical. The implications of this are magnified by the negative influence that the decision has had on other trials. I am concerned by the decision of the NSABP to abort their B-33 protocol, which was evaluating exemestane, on the basis of preliminary results of the MA-17 trial. There is an imminent threat to the future of aromatase inhibitor trials and management decisions of countless women for generations to come on the basis of only 29 life-threatening events in one trial (vide infra)."

SOURCE: Baum M. *Cancer Control* 2004;11(4):217-21. **Abstract**

6.2 Changes in Bone Mineral Density of the Lumbar Spine (L1-L4) Caused by Anastrozole or Tamoxifen in Combination with Goserelin (± Zoledronic Acid) in ABCSG-12



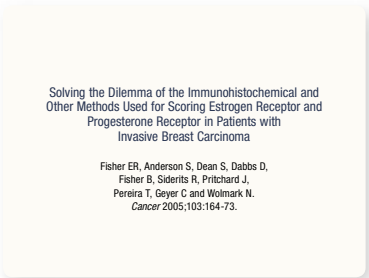
Tam = tamoxifen; Z = zoledronic acid; Ana = anastrozole

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

PowerPoint Journal Club

The PowerPoint Journal Club will review important, recently published articles and meeting presentations. In the current issue, we a review a paper by Edwin Fisher and colleagues evaluating scoring methods for estrogen and progesterone receptors and an article by Soonmyung Paik and colleagues about the Onco*type* DX™ multigene assay. We also review data presented by Raimund Jakesz at the 2004 San Antonio Breast Cancer Symposium regarding ABCSG trial 8 and ARNO trial 95 of switching postmenopausal women to anastrozole after two years of adjuvant tamoxifen.

PowerPoint presentations are provided in two different formats: in print and on CD (see the thumbnails below). The CD versions of the PowerPoint presentations were designed for optimal viewing on a large screen in a dark room (below, right). This design can be difficult to read in print, and consequently the print versions have been designed to facilitate ease of reading.



7.1

Solving the Dilemma of the Immunohistochemical and Other Methods Used for Scoring Estrogen Receptor and Progesterone Receptor in Patients with Invasive Breast Carcinoma

Fisher ER, Anderson S, Dean S, Dabbs D,
Fisher B, Siderits R, Pritchard J,
Pereira T, Geyer C and Wolmark N.
Cancer 2005;103:164-73.

SLIDE 7.1 The ligand-binding, dextran-coated charcoal (DCC) technique, which quantitatively estimates estrogen receptors (ER) and progesterone receptors (PR), has been used to derive most of the data about prognosis and tumor response after tamoxifen. For numerous reasons, immunohistochemistry (IHC) has largely replaced DCC for the detection and quantification of ER and PR.

7.2

Objectives

In patients enrolled in NSABP-B-09, correlate immunohistochemistry (IHC) and ligand-binding, dextran-coated charcoal (DCC) estimates for ER and PR with:

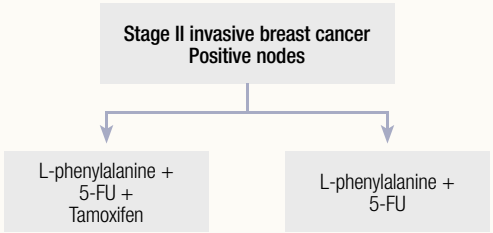
- Overall survival
- Disease-free survival
- Recurrence-free survival

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.2 A number of methods are used for scoring IHC results as either positive or negative. In this article, Fisher et al attempt to resolve issues about the lack of consensus of an optimal IHC method. The objective of this study was to correlate different IHC and DCC estimates for ER and PR with overall, disease-free and recurrence-free survival in patients enrolled in NSABP-B-09.

7.3

NSABP-B-09 Trial Schema



SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.3 NSABP-B-09 randomly assigned 1,891 women with node-positive, Stage II breast cancer to two years of adjuvant L-phenylalanine/5-FU with or without tamoxifen. ER status was assessed by DCC, and values of >10 fmol/mg were considered positive. This analysis included 402 patients with adequate pathologic material in both arms of the study.

7.4

Methods

Five methods were used to score ER and PR by IHC:

1. **Any-or-none method**
2. **Intensity of stain scored subjectively (0-3)**
3. **Proportion of stained nuclei present scored subjectively (0-3)**
4. **Product of results from method 2 and 3 (0-9)**
5. **Sum of results from method 2 and 3 (0-6)**

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.4 Five IHC scoring methods were used on this test set: any-or-none (any proportion of any positive degree of intensity considered positive), intensity of stain, proportion of stained nuclei present, product of second and third methods and sum of second and third methods.

7.5

Statistical Significance of Methods' Abilities to Predict Disease-Free Survival at Five and Ten Years: Univariate Analysis

	Five-year disease-free survival		Ten-year disease-free survival	
Method	ER	PR	ER	PR
DCC	NS	0.0009	NS	0.0015
IHC 1	0.0053	NS	NS	NS
IHC 2	0.0010	NS	NS	NS
IHC 3	NS	NS	NS	NS
IHC 4	0.0034	NS	NS	NS
IHC 5	0.0027	NS	NS	NS

NS = no split (ie, cut-off) for positive and negative receptor status identified

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.5 ER-positivity measured only by IHC methods utilizing any-or-none and intensity of staining related significantly to a favorable five-year disease-free survival (DFS). PR-positivity measured only by DCC was significantly related to five-year and 10-year DFS.

7.6

Statistical Significance of Methods' Abilities to Predict Recurrence-Free Survival at Five and Ten Years: Univariate Analysis

	Five-year recurrence-free survival		Ten-year recurrence-free survival	
Method	ER	PR	ER	PR
DCC	NS	0.0056	NS	NS
IHC 1	0.0014	NS	NS	NS
IHC 2	0.0005	NS	NS	NS
IHC 3	0.0030	NS	NS	NS
IHC 4	0.0010	NS	NS	NS
IHC 5	0.0024	NS	NS	NS

NS = no split (ie, cut-off) for positive and negative receptor status identified

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.6 ER-positivity measured by any IHC methods related significantly to a favorable five-year recurrence-free survival (RFS). ER-positivity was not significantly related to a favorable 10-year RFS. PR-positivity measured only by DCC was significantly related to five-year RFS and was not significantly related to 10-year RFS.

7.7

Statistical Significance of ER Assay Methods: Overall Survival at Five and Ten Years: Univariate Analysis

	Five-year overall survival		Ten-year overall survival	
Method	ER	PR	ER	PR
DCC	0.0001	0.0045	0.0032	0.0044
IHC 1	<0.0001	0.0020	0.0008	NS
IHC 2	<0.0001	0.0004	0.0019	0.0017
IHC 3	<0.0001	NS	0.0029	NS
IHC 4	<0.0001	0.0051	0.0022	NS
IHC 5	0.004	0.0036	0.0153	NS

NS = no split (ie, cut-off) for positive and negative receptor status identified

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.7 ER-positivity measured by DCC and five IHC methods related significantly to a favorable five- and 10-year overall survival (OS). For 10-year OS, PR-positivity measured only by DCC and the IHC method utilizing intensity of staining was significantly related to OS.

7.8

Results

- High interobserver agreement for IHC
- Good concordance between DCC and IHC
- Univariate analysis
  - ER-positive scores by all methods related to a favorable overall survival at five and 10 years
- Multivariate analysis
  - ER-positive scores by all methods related to a favorable overall survival at five and 10 years in patients with an unfavorable lymph-node status

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.8 Interobserver agreement for IHC estimates and concordance between DCC and the IHC methods were good. On univariate analysis, ER-positivity related to favorable five- and 10-year overall survival. On multivariate analysis, ER-positivity related to favorable five- and 10-year overall survival in patients with an unfavorable lymph-node status.

7.9

Conclusions

"... the IHC methods, at least for determining ER status in lymph node-positive patients, appear to satisfy all of the requirements for representing a surrogate for the DCC method. The simplicity of the dichotomous any-or-none algorithm appears to be an appropriate selection for practical use and avoids the delusion of precision implied by the more complex techniques for receptor assessment. Its use also should result in more patients receiving antiestrogen therapy."

SOURCE: Fisher et al. *Cancer* 2005;103:164-73. **Abstract**

SLIDE 7.9 Fisher et al conclude that the any-or-none IHC method for assessing ER status seems to be a good test to use in clinical practice.

Select publications

Alberts SR et al. **Comparison of estrogen receptor determinations by a biochemical ligand-binding assay and immunohistochemical staining with monoclonal antibody ER1D5 in females with lymph node positive breast carcinoma entered on two prospective clinical trials.** *Cancer* 1996;78(4):764-72. **Abstract**

Allred DC et al. **Prognostic and predictive factors in breast cancer by immunohistochemical analysis.** *Mod Pathol* 1998;11(2):155-68. **Abstract**

Bardou VJ et al. **Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases.** *J Clin Oncol* 2003;21(10):1973-9. **Abstract**

Chebil G et al. **Comparison of immunohistochemical and biochemical assay of steroid receptors in primary breast cancer — clinical associations and reasons for discrepancies.** *Acta Oncol* 2003;42(7):719-25. **Abstract**

Diaz LK et al. **Interobserver agreement for estrogen receptor immunohistochemical analysis in breast cancer: A comparison of manual and computer-assisted scoring methods.** *Ann Diagn Pathol* 2004;8(1):23-7. **Abstract**

Diaz LK, Sneige N. **Estrogen receptor analysis for breast cancer: Current issues and keys to increasing testing accuracy.** *Adv Anat Pathol* 2005;12(1):10-19. **Abstract**

Elledge RM et al. **Estrogen receptor (ER) and progesterone receptor (PgR), by ligand-binding assay compared with ER, PgR and pS2, by immuno-histochemistry in predicting response to tamoxifen in metastatic breast cancer: A Southwest Oncology Group Study.** *Int J Cancer* 2000;89(2):111-7. **Abstract**

Fisher B. **Treatment of primary breast cancer with L-PAM/5-FU and tamoxifen: An interim report.** *Breast Cancer Res Treat* 1983;3(Suppl):7-17. **Abstract**

Fisher B et al. **Adjuvant chemotherapy with and without tamoxifen in the treatment of primary breast cancer: 5-year results from the National Surgical Adjuvant Breast and Bowel Project Trial.** *J Clin Oncol* 1986;4(4):459-71. **Abstract**

Fisher B et al. **Influence of tumor estrogen and progesterone receptor levels on the response to tamoxifen and chemotherapy in primary breast cancer.** *J Clin Oncol* 1983;1(4):227-41. **Abstract**

Fisher B et al. **Relation of estrogen and/or progesterone receptor content of breast cancer to patient outcome following adjuvant chemotherapy.** *Breast Cancer Res Treat* 1983;3(4):355-64. **Abstract**

Fisher B et al. **Treatment of primary breast cancer with chemotherapy and tamoxifen.** *N Engl J Med* 1981;305(1):1-6. **Abstract**

Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81. **Abstract**

Mohsin SK et al. **Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: A validation study.** *Mod Pathol* 2004;17(12):1545-54. **Abstract**

Takei H et al. **Predictive value of estrogen receptor status as assessed by ligand-binding assay in patients with early-stage breast cancer treated with breast conserving surgery and radiation therapy.** *Oncol Rep* 2002;9(2):375-8. **Abstract**

Wells CA et al; European Working Group for Breast Screening Pathology. **Consistency of staining and reporting of oestrogen receptor immunocytochemistry within the European Union — an inter-laboratory study.** *Virchows Arch* 2004;445(2):119-28. **Abstract**

Yoshida N et al. **Prediction of prognosis of estrogen receptor-positive breast cancer with combination of selected estrogen-regulated genes.** *Cancer Sci* 2004;95(6):496-502. **Abstract**

8.1

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J and Wolmark N. *N Engl J Med* 2004;351:2817-26.

SLIDE 8.1 The distant recurrence rate in women with ER-positive, node-negative breast cancer has not been well defined.

8.2

Primary Objectives

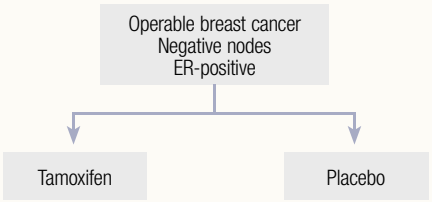
- Validate the ability of a 21-gene RT-PCR assay and recurrence-score algorithm to quantify the likelihood of distant recurrence in patients participating in NSABP-B-14 with node-negative, ER-positive breast cancer treated with adjuvant tamoxifen
- Determine if a statistically significant relationship exists between the recurrence score and the risk of distant recurrence

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.2 Paik et al evaluated a 21-gene reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay. The objective was to determine if the recurrence-score (RS) algorithm predicted the distant recurrence rate in patients who participated in NSABP-B-14 receiving tamoxifen

8.3

NSABP-B-14 Trial Schema



SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.3 NSABP-B-14 enrolled 2,892 women with operable, ER-positive, node-negative, primary breast cancer who were randomly assigned to adjuvant therapy with tamoxifen or placebo. An additional 1,235 women were enrolled and received adjuvant tamoxifen. This analysis included paraffin blocks from 668 of the 2,617 women treated with adjuvant tamoxifen.

8.4

Development of the Onco*type* DX™ Recurrence Score Assay: Genes Utilized

16 cancer and five reference genes from three studies

Proliferation Ki67 STK15 Survivin CCNB1 (cyclin B1) MYBL2	**HER2** GRB7 HER2	**Estrogen** ER PGR BCL2 SCUBE2
	GSTM1	
	CD68	**Reference** ACTB (β-actin) GAPDH RPLPO GUS TFRC
Invasion MMP11 (stromelysin 3) CTSL2 (cathepsin L2)	BAG1	

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.4 These 21 genes — selected from three preliminary studies with 447 patients and 250 candidate genes — were used to determine the recurrence score.

8.5

Development of the Oncotype DX Recurrence Score Assay: Formula

Recurrence score = +0.47 x GRB7 group score
-0.34 x ER group score
+1.04 x Proliferation group score
+0.10 x Invasion group score
+0.05 x CD68
-0.08 x GSTM1
-0.07 x BAG1

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

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.5 The algorithm in this slide determined the recurrence score. The range of recurrence scores (RS) was 0 to 100. Patients were classified into the following categories: low risk (RS<18), intermediate risk (18≤RS<31) and high risk (RS≥31).

8.6

Results

Kaplan-Meier estimates of the 10-year distant recurrence rate according to a 21-gene recurrence score in women participating in NSABP-B-14 (n=668) with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen

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

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

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.6 The Oncotype DX assay was used to measure gene expression for 668 patients enrolled on NSABP-B-14. Fifty-one percent, 22 percent and 27 percent of the patients were categorized as low, intermediate and high risk, respectively. Kaplan-Meier estimates for 10-year distant recurrence rates were significantly lower for the low-risk than the high-risk group.

8.7

Results

Overall survival according to 21-gene recurrence score in women participating in NSABP-B-14 (n=668) with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen

Risk group (RS)	Number of patients	Number of events (%)
Low (<18)	338	70 (21%)*
Intermediate (18-30)	149	48 (32%)*
High (≥31)	181	71 (39%)*

* $p < 0.001$

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.7 The RS was also significantly correlated with overall survival ($p < 0.001$). The data presented in this table are found in the appendix to the article by Paik et al.

8.8

Conclusions

"Using a prospectively defined gene-expression assay and an algorithm for calculating recurrence scores, we were able to quantify the likelihood of distant recurrence in patients with node-negative, estrogen-receptor-positive breast cancer who had been treated with tamoxifen. The difference in the risk of distant recurrence between patients with low recurrence scores and those with high recurrence scores was large and statistically significant."

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. **Abstract**

SLIDE 8.8 The calculated RS predicted the likelihood of distant recurrence and overall survival in patients with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen. At the 2005 San Antonio Breast Cancer Symposium, Paik et al presented data demonstrating the RS is also able to predict the benefit with adjuvant chemotherapy in this patient subset.

Select publications

Cobleigh M et al. **Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: High throughput RT-PCR assay of paraffin-embedded tumor tissues.** *Proc ASCO* 2003;**Abstract 3416**.

Cronin M et al. **Measurement of gene expression in archival paraffin-embedded tissues: Development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay.** *Am J Pathol* 2004;164(1):35-42. **Abstract**

Esteban J et al. **Tumor gene expression and prognosis in breast cancer: Multi-gene RT-PCR assay of paraffin-embedded tissue.** *Proc ASCO* 2003;**Abstract 3416**.

Fisher B et al. **A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors.** *N Engl J Med* 1989;320(8):479-84. **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**

Fisher B et al. **Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer.** *J Natl Cancer Inst* 1997;89(22):1673-82. **Abstract**

Fisher B et al. **Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: Updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials.** *J Natl Cancer Inst* 2004;96(24):1823-31. **Abstract**

Fisher B et al. **Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: Long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials.** *Lancet* 2004;364(9437):858-68. **Abstract**

Habel LA et al. **A large case-control study of gene expression and breast cancer death in the Northern California Kaiser Permanente population.** *Breast Cancer Res Treat* 2004;88(1 Suppl 1):118; **Abstract 3019**.

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

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

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

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

Van de Vijver MJ et al. **A gene-expression signature as a predictor of survival in breast cancer.** *N Engl J Med* 2002;347(25):1999-2009. **Abstract**

Van 't Veer LJ et al. **Gene expression profiling predicts clinical outcome of breast cancer.** *Nature* 2002;415(6871):530-6. **Abstract**

9.1

Benefits of Switching Postmenopausal Women with Hormone-Sensitive Early Breast Cancer to Anastrozole After 2 Years Adjuvant Tamoxifen: Combined Results from 3,224 Women Enrolled in the ABCSG Trial 8 and the ARNO 95 Trial

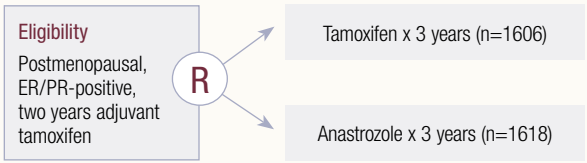
Raimund Jakesz, MD, on behalf of the Austrian Breast & Colorectal Cancer Study Group (ABCSG) and the German Adjuvant Breast Cancer Group (GABG)
2004 San Antonio Breast Cancer Symposium

SLIDE 9.1 The results from ABCSG 8 and ARNO 95 were combined for the efficacy analysis of switching from adjuvant tamoxifen to anastrozole after two years of tamoxifen in postmenopausal women with hormone-sensitive breast cancer. Results were presented at the 2004 San Antonio Breast Cancer Symposium by R Jakesz, MD.

9.2

ABCSG 8/ARNO 95: Anastrozole after Two Years Adjuvant Tamoxifen

ABCSG 8 accrual: 2,262 (closed)
ARNO 95 accrual: 962 (closed)



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

SLIDE 9.2 Both trials were initiated in 1996. In 2003, the decision was made to perform a combined analysis. The similarity in design of the two trials allowed for the combination of trial results for efficacy assessment. The majority of patients had Grade I or II tumors with favorable nodal status.

9.3

ABCSG 8/ARNO 95: Study Endpoints

- Primary Endpoint
  - Event-free survival (EFS)*
- Secondary Endpoint
  - Distant recurrence-free survival (RFS)
  - Tolerability

* Event = locoregional recurrence, distant metastases or contralateral breast cancer

SLIDE 9.3 The primary endpoint of the study was event-free survival, and secondary endpoints included distant recurrence-free survival and tolerability. Both ABCSG 8 and ARNO 95 trials were similar in design and study endpoints to other trials of switching from tamoxifen to an aromatase inhibitor.

9.4

ABCSG 8/ARNO 95 Combined Analysis Event-Free Survival (EFS): 28 Months, Median Follow-Up

	Events n=177	Three years EFS	Hazard ratio A/T (95%CI)	*p*-value
Anastrozole (n=1,618)	67	95.8%	0.60*	0.0009
Tamoxifen (n=1,606)	110	92.7%		

A = anastrozole; T = tamoxifen
Events = locoregional recurrences, distant metastases, contralateral breast cancer
* Hazard ratio of <1.0 indicates greater benefit in favor of anastrozole

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

SLIDE 9.4 At a median follow-up of 28 months, there was a 40% reduction in events — which included recurrences, second breast cancers and death — in the anastrozole arm which was highly significant. A subgroup analysis of EFS showed the benefit of anastrozole occurred irrespective of age or nodal status, with greater benefit conferred on ER-positive/PR-negative tumors.

9.5

ABCSG 8/ARNO 95 Combined Analysis
Localization of Events

	Total (n=3,224)	Tamoxifen (n=1,606)	Anastrozole (n=1,618)
Events	177	110	67
Locoregional	44	24	20
Contralateral BC	28	16	12
Distant recurrences	121	75	46

Events occurring simultaneously are included twice.

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

SLIDE 9.5 Most of the differences in events related to distant recurrence, which occurred in 75 women on tamoxifen and 46 on anastrozole.

9.6

ABCSG 8/ARNO 95 Combined Analysis
Variables Affecting EFS

	Hazard ratio* (95% CI)	*p*-value
Treatment (anastrozole/tamoxifen)	0.59 (0.43-0.81)	0.0009
Nodal status (positive or negative)	2.03 (1.64-2.52)	<0.0001
Grading (G3/G1,2,x)	1.93 (1.21-3.09)	0.0058

* Hazard ratio of <1.0 indicates greater benefit in favor of anastrozole

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

SLIDE 9.6 The benefit of switching from tamoxifen to anastrozole was independent of other prognostic factors such as nodal status and tumor grade. The anastrozole/tamoxifen hazard ratio (HR) for treatment was 0.59 with a highly significant *p* value of 0.0009, even though the differences due to nodal status (HR=2.03) and grade (HR=1.93) were also highly significant.

9.7

ABCSG 8/ARNO 95 Combined Analysis
Distant Recurrence-Free Survival (DRFS)

	DRFS	
	Hazard ratio* (95% CI)	*p*-value
Anastrozole vs tamoxifen	0.61 (0.42-0.87)	0.0067

*Hazard ratio of <1.0 indicates greater benefit in favor of anastrozole

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

SLIDE 9.7 There was a highly significant improvement in the distant recurrence-free survival in the anastrozole arm, with a hazard ratio of 0.61 at $p = 0.0067$ level of significance.

9.8

ABCSG 8/ARNO 95 Combined Analysis
Overall Survival (OS)

	Number	Deaths	Three years OS (%)	Hazard ratio A/T* (95%CI)	*p*-value
Anastrozole	1618	45	97.1%	0.76 (0.52-1.12)	0.16
Tamoxifen	1606	59	96.4%		

A = anastrozole; T = tamoxifen
*Hazard ratio of <1.0 indicates greater benefit in favor of anastrozole

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

SLIDE 9.8 No difference in overall survival was observed, with only 104 deaths at the time of this analysis. However, these results are consistent with those from the ATAC trial of adjuvant anastrozole, tamoxifen or the combination (68 months of follow-up) and the IES trial of switching to exemestane after adjuvant tamoxifen (37.4 months of follow-up).

9.9

ABCSG 8/ARNO 95 Combined Analysis Summary

- Switching from tamoxifen to anastrozole resulted in significant improvements in event-free survival and distant recurrence-free survival
- Benefits from switching to anastrozole were independent of baseline prognostic factors
- Both treatments were well tolerated
  - Low incidence of prespecified side effects in both groups
  - More fractures with anastrozole (2.4%) compared to tamoxifen (1.2%)

SLIDE 9.9 The outcome from three other switching trials were previously reported in 2003 and 2004. These include the ITA, IES and the NCIC-MA17 trials. All these trials reported significant improvement in disease-free survival. The results from this combined analysis provide further evidence of the benefits of switching from tamoxifen to an aromatase inhibitor.

Select publications

Aapro MS. **Long-term implications of bone loss in breast cancer.** *Breast* 2004;13(Suppl 1):29-37. **Abstract**

Baum M. **Current status of aromatase inhibitors in the management of breast cancer and critique of the NCIC MA-17 Trial.** *Cancer Control* 2004;11(4):217-21. **Abstract**

Boccardo F. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1):6;**Abstract 3**.

Boccardo F. **Switching trial of adjuvant tamoxifen with an aromatase inhibitor in postmenopausal patients with breast cancer.** *Clin Breast Cancer* 2004;5(Suppl 1):13-7. **Abstract**

Choueiri TK et al. **Role of aromatase inhibitors in the treatment of breast cancer.** *Clin Ther* 2004; 26(8):1199-214. **Abstract**

Chung CT, Carlson RW. **Adjuvant aromatase inhibitors following tamoxifen for early-stage breast cancer in postmenopausal women: What do we really know?** *Clin Breast Cancer* 2004;5(Suppl 1):18-23. **Abstract**

Coleman R, on behalf of the ATAC Trialists' Group. **Association between prior chemotherapy and the adverse event (AE) profile of adjuvant anastrozole (A) or tamoxifen (T): A retrospective analysis from the ATAC trial.** *Journal of Clinical Oncology* 2004;22(14S);**Abstract 767**.

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

Coombes 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 analyses.** *Breast Cancer Res Treat* 2004;88(Suppl 1):7;**Abstract 3**.

Distler W, on behalf of the ATAC Trialists' Group. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Journal of Clinical Oncology* 2004;22(14S);**Abstract 770**.

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

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(Suppl 1):7;**Abstract 4**.

Fallowfield L et al. **Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial.** *J Clin Oncol* 2004;22(21):4261-71. **Abstract**

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

Grana G. **Shifting paradigms in hormonal therapy for breast cancer.** *Cancer Biol Ther* 2004;3(9):797-805. **Abstract**

Harwood KV. **Advances in endocrine therapy for breast cancer: Considering efficacy, safety, and quality of life.** *Clin J Oncol Nurs* 2004;8(6):629-37. **Abstract**

Howell A, on behalf of the 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**

Howell A, Dowsett M. **Endocrinology and hormone therapy in breast cancer: aromatase inhibitors versus antioestrogens.** *Breast Cancer Res.* 2004;6(6):269-74. **Abstract**

Jakesz R, on behalf of the ABCSG. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** *Breast Cancer Res Treat* 2004;88(Suppl 1):7;**Abstract 2**.

Janicke F. **Are all aromatase inhibitors the same? A review of the current evidence.** *Breast* 2004; 13(Suppl 1):10-8. **Abstract**

Jones KL, Buzdar AU. **A review of adjuvant hormonal therapy in breast cancer.** *Endocr Relat Cancer* 2004 Sep;11(3):391-406. **Abstract**

Locker GY, on behalf of the ATAC Trialists' Group. **Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in postmenopausal women with early breast cancer from a US healthcare system perspective: The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial.** *Breast Cancer Res Treat* 2004;88(Suppl 1):105; **Abstract 2085**.

Mackey JR, Joy AA. **Skeletal health in postmenopausal survivors of early breast cancer.** *Int J Cancer* 2005; [Epub ahead of print]. **Abstract**

Tobias JS. **Recent advances in endocrine therapy for postmenopausal women with early breast cancer: Implications for treatment and prevention.** *Ann Oncol* 2004;15(12):1738-47. **Abstract**

Post-test:

Breast Cancer Update — Issue 2, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In a neoadjuvant docetaxel trial published by Chang et al in *The Lancet*, differential patterns of expression of 92 genes were found to correlate with response.
   a. True
   b. False

2. Overexpression of which of the following is related to taxane resistance:
   a. Beta-tubulin
   b. HSP27
   c. Both a and b
   d. None of the above

3. A neoadjuvant trastuzumab trial presented by Chang at the 2003 San Antonio Breast Cancer Symposium demonstrated that trastuzumab, in vivo, induces apoptosis.
   a. True
   b. False

4. A neoadjuvant trial of trastuzumab plus chemotherapy, reported by Buzdar at ASCO 2004, utilized which of the following anthracyclines:
   a. Doxorubicin
   b. Epirubicin
   d. Mitoxantrone
   e. Liposomal doxorubicin

5. The 68-month analysis of the ATAC trial demonstrates continued reduction in recurrence rates with anastrozole compared to tamoxifen.
   a. True
   b. False

6. Diel's trial of adjuvant clodronate shows which of the following in patients who received bisphosphonate therapy:
   a. Decreased skeletal metastases
   b. Decreased nonskeletal metastases
   c. Increased survival
   d. All of the above

7. The UCLA trial examining trastuzumab plus bevacizumab, presented at the 2004 San Antonio Breast Cancer Symposium, showed encouraging response rates with the combination.
   a. True
   b. False

8. At ASCO 2004, Dickler reported preliminary results of a Phase II trial evaluating bevacizumab in combination with _____.
   a. Trastuzumab
   b. Capecitabine
   c. Erlotinib
   d. Gefitinib

9. Konecny and colleagues recently published data demonstrating that VEGF is upregulated in HER2-positive breast cancer, which may partially explain the aggressive phenotype of HER2-positive breast cancer.
   a. True
   b. False

10. A trial by Vogel demonstrated that trastuzumab monotherapy resulted in clinical benefit in approximately _____ percent of women with HER2-positive metastatic breast cancer.
    a. 25
    b. 35
    c. 50

11. Nanoparticle paclitaxel (Abraxane™) was granted FDA approval in January 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
    a. True
    b. False

12. The ATLAS and ATTOM trials randomize patients after five years of adjuvant tamoxifen to:
    a. Letrozole versus observation
    b. Tamoxifen versus observation
    c. Anastrozole versus observation
    d. Exemestane versus observation

13. Over the 10-year period from 1987 to 1997, the annual breast cancer mortality rate in the United States:
    a. Increased
    b. Remained steady
    c. Decreased

Post-test Answer Key: 1a, 2a, 3a, 4b, 5a, 6d, 7a, 8c, 9a, 10c, 11a, 12b, 13c

Evaluation Form:

Breast Cancer Update — Issue 2, 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 is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	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
Jenny C Chang, MD	5 4 3 2 1	5 4 3 2 1
I Craig Henderson, MD	5 4 3 2 1	5 4 3 2 1
Professor Sir Richard Peto	5 4 3 2 1	5 4 3 2 1
Maura N Dickler, 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 2, 2005

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

ME No.: ..... Last 4 Digits of SSN (required): .....

Street Address: ..... Box/Suite: .....

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

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

Signature: ..... Date: .....

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?

.....

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 would be willing to participate in a follow-up survey.

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

Additional comments about this activity:

.....

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.

Breast Cancer™ UPDATE

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This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Roche Laboratories Inc.

Breast Cancer™

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Last review date: March 2005
Release date: March 2005
Expiration date: March 2006
Estimated time to complete: 3.25 hours