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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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GRAND ROUNDS SLIDE PRESENTATION

Neoadjuvant Systemic Therapy

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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 this data into a management strategy 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 1 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Baum, Blum and Mackey on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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UPCOMING EDUCATIONAL EVENTS

2005 American Society of Clinical Oncology Prostate Cancer Symposium: February 17-19, 2005
Hyatt Grand Cypress
One Grand Cypress Blvd
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002665-00_18-0034689,00.asp

Miami Breast Cancer Conference: February 23-26, 2005
Loews South Beach
1601 Collins Avenue
Miami Beach, Florida
Event website:
www.cancerconf.com/index.html

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

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

Oncology Nursing Society 30th Annual Congress: April 28-May 1, 2005
Orlando, Florida
Event website: www.ons.org/nursingEd/Conferences/congress.shtml

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

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

2005 San Antonio Breast Cancer Symposium: December 2005
San Antonio, Texas
Event website:
www.sabcs.org/Index.asp

Editor's Note

Two amazing decades with tamoxifen

The rational decision at the moment is to consider tamoxifen still the gold standard. You have to recognize that there will be periods of uncertainty in the evolution of medicine and science. As it relates to the question of adjuvant anastrozole, we're just going to have to live through this period of uncertainty.

— Michael Baum, MD, ChM, San Antonio, December 10, 2001
(Shortly after presenting the initial data from ATAC trial)

In the *Lancet* paper, which is being published this week simultaneously with Tony Howell's presentation here in San Antonio, we now stick our necks out and say that anastrozole is the preferred initial treatment for postmenopausal women with hormone receptor-positive tumors.

— Michael Baum, MD, ChM, San Antonio, December 9, 2004

In 1983, I was a neophyte videographer in search of a compelling topic for my first CME extravaganza. As I scoured my mind for interesting ideas, I came across one that seemed to hold promise. Several years earlier, Chuck Vogel — a junior faculty member at the University of Miami — recruited me from my fellowship to join the breast cancer division of the Sylvester Comprehensive Cancer Center. Chuck always was and continues to be an "avid hormonalist," and during my time working with him, he taught me to think about "hormones, hormones, hormones" whenever considering therapy for metastatic disease. With this background and perspective firmly in place, the unspectacular video, "Hormonal Therapy for the 1980s," was born.

My initial aspirations for the video were quite high and with the help of the university's "sophisticated" AV staff we managed to create a Pac-Man-like animation of an estrogen molecule scurrying into the cytoplasm where a magical union occurred with the relatively recently identified estrogen receptor. Tamoxifen was also illustrated as a competitive Pac-Man blocking this activity. For the video, I interviewed five women currently receiving hormone therapies, which included tamoxifen, megestrol acetate, Halotestin®, high-dose DES and an unpleasant but very effective agent called aminoglutethimide — a first-generation aromatase inhibitor.

At that point, tamoxifen was considered a kinder, gentler palliative therapy that the research-leader community believed would never have the curative potential

of chemotherapy; however, one of the first clinical research leaders interviewed when I launched this audio series strongly contested that concept.

Michael Baum had conducted an adjuvant trial of tamoxifen in the United Kingdom, and in spite of the fact that patients with ER-negative and unknown tumors were included, the study demonstrated a disease-free and overall survival benefit for women receiving two years of therapy compared to control. Observers from the United States pretty much ignored Mike's results, assuming some type of methodologic inferiority with European research. After all, how could a pill with a cytostatic mechanism of action change the natural history of the disease, particularly when so many other smaller trials had not shown an overall survival benefit?

This irritated the hell out of Mike, who realized that the other tamoxifen trials were underpowered to detect a survival difference. With that in mind, Mike, Craig Henderson, Richard Peto and others decided to put together an international meta-analysis of all trials of adjuvant systemic therapy, including tamoxifen. The hope was that there would be an adequate number of events (deaths) to evaluate the effect of these agents on survival. The initial results were presented at a closed meeting of investigators at Heathrow Airport a few months before the 1985 NIH Consensus Conference. Sure enough, with an adequate number of observed events, tamoxifen demonstrated a significant survival benefit in postmenopausal women with node-positive tumors. In an instant, adjuvant hormonal therapy had arrived.

The next overview documented benefit for patients with node-negative tumors, and later on, for premenopausal patients. Along the way, investigators noted an increased incidence of endometrial cancer, which severely sullied the previously untainted reputation of this fascinating agent. The state of California even declared tamoxifen a carcinogen. As tens of thousands of women were treated, the drug constantly battled an association with intolerable vasomotor symptoms and weight gain despite placebo-controlled data contrary to the latter.

In 1998, NSABP-P-1 — the Tamoxifen Prevention Trial — was unblinded and in a historic, nationally broadcast press conference, Bernie Fisher and colleagues fractured another oncologic paradigm. Surprisingly, physicians and patients seemed to ignore these findings. To this day, tamoxifen is uncommonly utilized for chemoprevention, except in women with known primary tumors.

During one of our "Meet The Professors" sessions at the recent San Antonio Breast Cancer Symposium, Richard Peto (now "Sir Richard") discussed the dramatic decline in breast cancer mortality (about a third) in the United Kingdom and the United States over the last decade. When I asked Peto what he personally believed led to this encouraging trend, he responded with two words, "adjuvant tamoxifen."

You can make a pretty good argument that this little pill has prevented more suffering from cancer than perhaps any other systemic agent in the history of oncologic therapy, and translational scientists like Craig Jordan and Kent Osborne have made important connections between clinical and laboratory

observations that are leading to new treatment strategies. It also seems that the role of tamoxifen as first-line adjuvant endocrine therapy — at least for postmenopausal women — has been passed on to a new class of agents with important advantages in efficacy and tolerability.

The informal motto of our CME company is, "If it were easy, someone else would have already done it." Being a pioneer is always a great challenge, and in oncology, tamoxifen boldly went where no agent had gone before, launching an era of molecular targeted therapy. Until that moment in 1985 when Peto ascended to the podium in Bethesda, no one could conceptualize that an essentially nontoxic oral agent could make such a difference in the biology of this often nasty and relentless disease. But it did, and anastrozole, letrozole, exemestane, fulvestrant and trastuzumab are now part of daily patient care in breast cancer, and other agents like bevacizumab and lapatinib stand in the wings.

One of the reasons I enjoy chatting with Mike Baum so much is that he is a true renaissance oncologist. Like Corey Langer in lung cancer, Mike seeks to express his experiences and perceptions in art, and he shared with me two recent award-winning oil paintings that capture the pain and healing of this challenging illness (see below). I believe Mike's renderings are an apt representation of what happens in life to these patients and their families, and that the smiling and peaceful countenance so many women find a couple of years after the diagnosis of breast cancer is often the direct result of targeted agents like tamoxifen and the aromatase inhibitors. These agents quietly and usually innocuously prevent the disease from re-expressing itself, and allow patients to live healthier and longer lives.

— Neil Love, MD
NLove@ResearchToPractice.net

By Michael Baum, MD, ChM

"The Bad News Consultation"

"Two Years Later"

Michael Baum, MD, ChM

EDITED COMMENTS

ATAC trial update

The ATAC trial has reached an important point in its evolution, with a median follow-up of 68 months (1.1) (ATAC Trialists' 2005). Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy was completed.

This is important for two reasons: it makes me comfortable about the efficacy and the hypothetical "carry-over effect" we've been hearing about for tamoxifen, and it makes me comfortable with the toxicities and tolerability of anastrozole. I believe this is probably the most important of the three ATAC analyses, and it allows me, as a practicing clinician, to change practice. I speak not only as a practicing clinician but also as the past principal investigator of the trial.

The simplest interpretation of the results is that anastrozole prevents one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival. The absolute number for difference in recurrence-free survival in the patients with receptor-positive disease at six years is close to four percent. It is important to remember that this trial included a group of patients with a relatively good prognosis.

In terms of relative risk reductions, we have no reason to suppose that the relative risk reductions will be different in any subgroup, and if that one in four relative risk reduction is across the board, then in a subgroup of patients with, for example, a 40 percent chance of relapse at six years, the absolute reduction is about 10 percent, not four percent, as was seen in the ATAC trial.

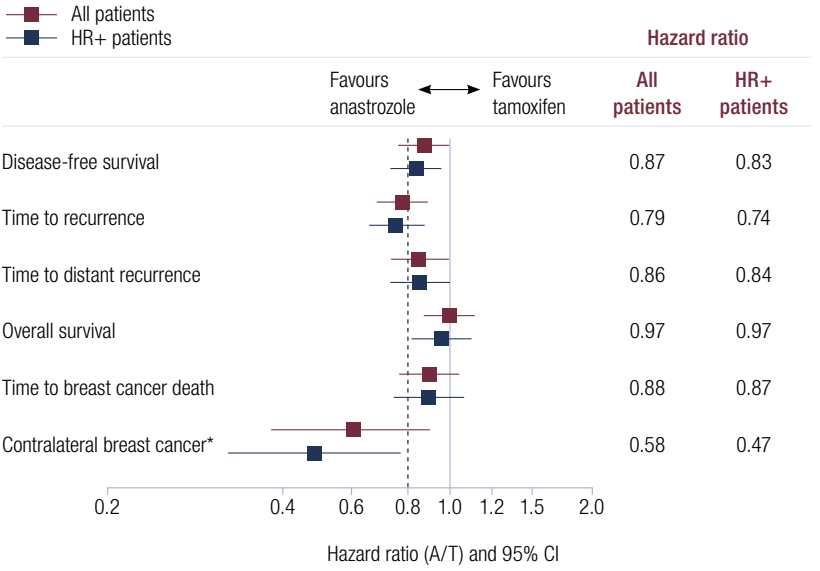
Survival as an endpoint in adjuvant therapy trials

This analysis was triggered by the number of distant recurrences and deaths from all causes. With regard to distant recurrences, our power calculations were correct; the trial was sufficiently powered to detect a significant difference. For overall survival, our power calculations were wrong, because this was a group of elderly women with a good prognosis, and the overall survival analysis is diluted by deaths from other causes before breast cancer recurrence.

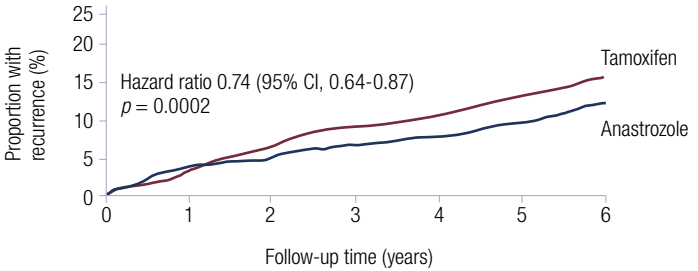
Dr Baum is Emeritus Professor of Surgery and Visiting Professor of Medical Humanities at University College, London, United Kingdom.

1.1 ATAC Trial 68-Month Analysis

Efficacy endpoints for all patients and those with hormone receptor-positive (HR+) tumors



Time-to-recurrence in patients with hormone receptor-positive tumors



Numbers at risk:

Anastrozole	2,618	2,540	2,448	2,355	2,268	2,014	830
Tamoxifen	2,598	2,516	2,398	2,304	2,189	1,932	774
Absolute difference	—	—	—	1.7%	2.4%	2.8%	3.7%

A = anastrozole; T = tamoxifen; HR+ = hormone receptor positive
* Odds ratio calculated instead of hazard ratio

SOURCE: With permission from ATAC Trialists' Group. *Lancet* 2005;365(9453):60-62. **Abstract**

I believe we can predict breast cancer survival with a fair degree of precision. I can't see any reason why we would not eventually see a significant difference in breast cancer deaths. This trend is already present and is close to significance.

Whether that will translate into overall survival is uncertain. I'm not concerned about toxic side effects contributing to other causes of death — we know enough about anastrozole not to be worried about that — but I am concerned that the effect of preventing breast cancer deaths might be diluted by competing morbidities.

I've always been a purist, arguing that the only two real outcome measures in medicine are length of life and quality of life. I am on record as saying that all other outcome measures are surrogates, but we have to avoid waiting too long for the length-of-life outcome and to accept that surrogate measures translate into length of life with a fair degree of precision.

Quality of life and toxicity data in the ATAC trial

The use of anastrozole instead of tamoxifen does not impair quality of life. We can also say, with confidence, that the gynecological symptoms linked to tamoxifen have now translated into a fourfold increase in hysterectomy rates compared with anastrozole.

That is a dramatic observation, which we nearly missed. I was persistent about tracking down all the hysterectomies in women who had their wombs at the time of randomization. We came up with an extraordinary figure — I believe it's the most extreme relative risk I've encountered in clinical trials.

The absolute numbers were 1.3 percent versus 5.1 percent (Howell 2004) for anastrozole and tamoxifen, respectively. This has a profound economic impact. I also don't know how many hysteroscopies are being performed for every hysterectomy or how much the workup costs to decide whether a woman should have a hysterectomy, but these are big cost issues.

The update doesn't give us any new information with regard to other prespecified adverse events, and no other adverse event is emerging with a frequency of more than one percent.

The fracture rate incidence is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines are beginning to come together (Howell 2004). As patients stop taking anastrozole, the fracture rate returns to that of the patients randomized to tamoxifen. Furthermore, so far no difference has occurred in fractures of the neck or femur, which are of particular concern.

I think the issue of bone is easy to manage. We should be alert to it, monitor bone mineral density, perhaps exclude patients who have established osteoporosis, and then be ready to intervene with a bisphosphonate when the patient becomes osteopenic.

The polyarthralgia with anastrozole remains a problem. We don't understand it, and it occasionally leads to withdrawal of treatment; however, the bottom line is

that a significant difference exists favoring anastrozole for patients withdrawing from treatment because of side effects. If you evaluate the totality of side effects, anastrozole does better. If you consider the issue of the gynecological symptoms leading to hysterectomy, I believe the new drug — anastrozole — has the better tolerability profile.

Hazards for breast cancer recurrence with tamoxifen versus anastrozole

We are familiar with Kaplan-Meier curves, which are useful for the statistical analysis but don't truly reflect what's going on as the hazard ratios do. The best recorded data from patients treated by local therapy alone, before systemic therapy, is from Milan. A high and narrow peak for relapse occurs at two years, which then comes down again. A second, much-flatter peak for relapse occurs at about five years.

I've been working with Romano Demicheli, Michael Retsky and Bill Hrushesky on modeling and developing hypothetical explanations for this, and our review article will soon be published in the *European Journal of Cancer*.

Little doubt exists that the initial peak is provoked by the act of surgery. Surgery switches on a suite of genes for healing. The same suite of genes necessary for wound healing is necessary for provoking the growth of cancer, so what's good for healing is also good for cancer.

In the hazard rate analysis plot from the ATAC trial, we're seeing two peaks with tamoxifen. Using semiquantitative comparison with the Milan data, the first peak is lower with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial — not only to help make therapeutic decisions, but also to give a fascinating biological insight.

I believe the strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak (1.2). If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile you've lost those patients who will relapse and ultimately die in those first two years.

ER-positive, PR-negative subset in the ATAC trial

This is a nonprotocol evaluation of the data, but it's very powerful. Professor Mitch Dowsett previously presented these data (Dowsett 2003), and now we have an update (1.3). The findings are even more striking than they were before.

Four phenotypes exist in the hormone receptor groups: double negative, double positive, and one or the other positive. The double negatives show no advantage with anastrozole compared to tamoxifen. Each of the other three phenotypes indicate an advantage with anastrozole, but the hazard rate favoring anastrozole in the estrogen receptor-positive, progesterone receptor-negative subset is 0.4 — almost a 60 percent relative risk reduction.

One would be skeptical about that as a data-derived observation, but a good mechanistic explanation exists. That particular phenotype tends to be Grade III, and tends to overexpress HER2. Earlier observations suggest that patients in whom HER2 overexpresses do favorably on aromatase inhibitors compared to tamoxifen, so I think it's probably true, although it needs to be explored prospectively in another trial.

1.2 Conclusions from the ATAC Trialists' Group

"The present data suggest that it is not appropriate to wait 5 years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1–3), and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, lend support to the approach of offering the most effective and well tolerated therapy at the earliest opportunity. 5 years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer."

SOURCE: ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. **Abstract**

1.3 ATAC: Retrospective Analysis of Time to Recurrence for ER/PR Subgroups

Patient group	HR-positive	ER/PR-positive	ER-positive/PR-negative
Hazard ratio	0.79	0.84	0.43

HR-positive = ER-positive/PR-positive, ER-positive/PR-negative, ER-negative/PR-positive

SOURCE: Howell A. Presentation. San Antonio Breast Cancer Symposium, 2004.

Switching 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 whether the patient has been on tamoxifen for one year or four years. You can wait forever for refinements, 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 trial (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 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.

1.4 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**

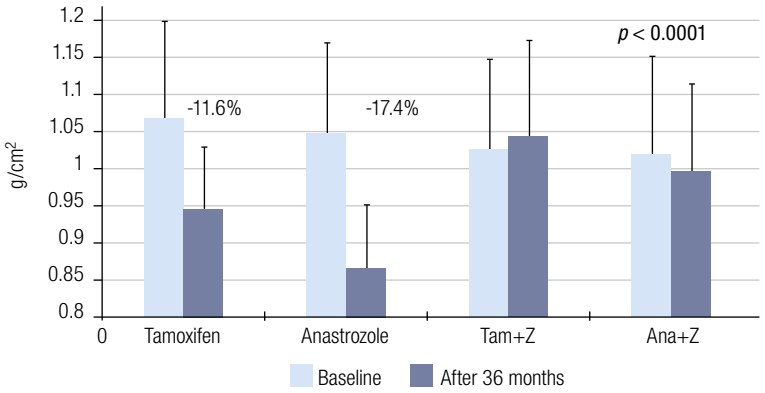
Bisphosphonates in premenopausal women on tamoxifen or anastrozole

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.

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. I find that reassuring. It is evidence that zoledronic acid, a bisphosphonate, can reverse this loss of bone mineral density. The other

thing that was somewhat of a surprise was that even the women who received tamoxifen and goserelin were losing bone.

1.5 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**.

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(9453):60-2. **Abstract**

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

Coombes RC et al; Intergroup Exemestane Study. **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**

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;83(Suppl 1):7;**Abstract 4**.

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

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, on behalf of the ATAC Trialists' Group. **"Arimidex," Tamoxifen Alone or in Combination (ATAC) trial: Completed treatment analysis.** Presentation. San Antonio Breast Cancer Symposium, 2004;**Abstract 1**.

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

Clinical trials with capecitabine

In the mid 1990s, we studied capecitabine in patients with metastatic disease who had previously received taxane therapy, and we conducted the pivotal Phase II trial that led to the FDA approval of capecitabine. In the pivotal trial, most of the 162 patients had previously received anthracycline therapy, and more than 60 percent benefited from capecitabine. The response rate was 20 percent and an additional 40 percent of patients experienced stable disease. The tolerability of this oral agent was impressive with no alopecia or myelosuppression.

We also participated in the Phase III metastatic trial comparing docetaxel with or without capecitabine, and survival was approximately three months longer in patients who received the combination (O'Shaughnessy 2002). This important trial led to the current US Oncology trial of capecitabine in the adjuvant setting, studying AC followed by docetaxel with or without capecitabine for patients with node-positive or high-risk, node-negative disease.

In our ongoing US Oncology adjuvant trial, we had to reduce the capecitabine dose after approximately the first 90 patients, but I've put many patients on this trial and the regimen is well tolerated.

US Oncology trial of capecitabine/paclitaxel in metastatic disease

We are currently investigating capecitabine 1,650 mg/m^2 total daily dose for 14 days with paclitaxel 80 mg/m^2 on days one and eight of a three-week cycle in patients with metastatic breast cancer. The regimen has been extremely well tolerated and the side effects have been those we expected from paclitaxel — alopecia, fluid retention, Grade I neuropathy, skin and nail changes — but capecitabine doesn't seem to add much to the toxicity and the clinical benefit is extraordinary. We have had some patients on this trial for one to two years.

In the taxane-naïve subset, we found this regimen to be exceedingly effective and well tolerated (2.1). We've seen long, durable responses with capecitabine/paclitaxel, and it is more tolerable than capecitabine/docetaxel. Capecitabine has also been combined with vinorelbine, which is another well-tolerated regimen.

Dr Blum is Director of the Hereditary Cancer Risk Program and Research Site Leader at Baylor-Charles A Sammons Cancer Center in Dallas, Texas.

2.1 Results from a Phase II Trial of Capecitabine and Weekly Paclitaxel in 44 Women with Taxane-Naïve Metastatic Breast Cancer

Efficacy	No. of patients (%)
Partial response	23/44 (52.3%)
Stable disease	13/44 (29.5%)
Disease progression	8/44 (18.2%)
Median duration of response	3.4 months
Grade IV treatment-related adverse events	
Leukopenia	2/44 (4.5%)
Pulmonary embolism	1/44 (2.3%)
Febrile neutropenia	1/44 (2.3%)
Grade III treatment-related adverse events occurring in more than one patient	
Hand-foot syndrome	8/44 (18.2%)
Neutropenia	3/44 (6.8%)
Diarrhea	3/44 (6.8%)
Nausea	3/44 (6.8%)
Asthenia	2/44 (4.5%)
Pain	2/44 (4.5%)
Vomiting	2/44 (4.5%)

SOURCE: Blum JL et al. **A Phase II trial of combination therapy with capecitabine (C) and weekly paclitaxel (P) for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** *Breast Cancer Res Treat* 2004;88(Suppl 1);**Abstract 5053**.

Chemotherapy for metastatic disease

I decide whether a patient should receive combination chemotherapy or sequential single agents based on the burden and pace of the disease. So, for example, women with quite a bit of visceral involvement — particularly liver involvement — may need combination therapy.

For the patient with much more indolent disease, particularly the patient with a long disease-free interval who may have had sequential hormonal therapy and is now hormone therapy refractory, I use sequential single agents. Many of my patients receive capecitabine as the first chemotherapy in this situation, because it's orally administered, does not cause alopecia and is extremely well tolerated. It is similar to taking a hormone pill.

I also use capecitabine in combination with trastuzumab in patients with HER2-positive tumors, and I've had patients on that combination for years with bone, lung, and lymph node involvement. These patients keep their hair. They come in every three weeks and the palliation from this can last for years and is extraordinary.

For patients with ER-positive, HER2-positive disease, I often utilize trastuzumab combined with endocrine therapy — for example, an aromatase inhibitor — with excellent benefit.

Clinical trials of nanoparticle paclitaxel

Nanoparticle paclitaxel is an albumin-formulated, cremophor-free, paclitaxel preparation that enters cells via a specific albumin receptor — the gp60 receptor — which leads to high intracellular concentrations of paclitaxel. In animal models of breast, lung, prostate and ovarian cancer, this agent demonstrated marked suppression of tumor growth compared to paclitaxel or the control animals.

We conducted a Phase II study with nanoparticle paclitaxel at 100 mg/m^2 weekly times three, followed by a week off therapy, in 106 patients with taxane-refractory, metastatic breast cancer (Blum 2004). The response rate was 15 percent and another 15 percent experienced stable disease, so the overall clinical benefit was 30 percent. Almost all of the patients received the full dose, and the side-effect profile was extremely favorable with only one and four percent of patients experiencing Grade IV neutropenia and sensory neuropathy, respectively. This regimen proved to be active in this taxane-refractory group of patients and was extremely well tolerated. These results are favorable compared to prior studies of weekly paclitaxel at 80 mg/m^2.

Nanoparticle paclitaxel compared to other taxanes

I believe nanoparticle paclitaxel is more active than paclitaxel based on the randomized trials. In cross-study comparisons of nanoparticle paclitaxel versus docetaxel, each given every three weeks, the response rates were similar — in the 30 percent range.

However, docetaxel in the metastatic setting, whether given weekly or every three weeks, is toxic because of side effects like asthenia, fluid retention and neutropenia, and it's difficult to administer for long periods of time. One can give docetaxel in the adjuvant setting, where treatment is short-term, but I believe nanoparticle paclitaxel is better tolerated.

If nanoparticle paclitaxel were available today, I would probably use it in lieu of other taxanes in the metastatic setting. I don't use single-agent docetaxel in this setting, but I would certainly use nanoparticle paclitaxel in lieu of weekly paclitaxel. I would like to see more data on combinations with this agent to learn more about the toxicity profiles before using it in a combination off protocol.

Avoiding premedication with nanoparticle paclitaxel

In the Phase I, II and III clinical trials, nanoparticle paclitaxel was administered over 30 minutes without premedication — such as dexamethasone or antihistamines — and it did not require G-CSF support. It is an extraordinary advantage to be able to avoid dexamethasone.

Patients dislike weekly dexamethasone — it gets them jazzed up, causes insomnia and weight gain, has significant immunologic effects and may contribute to osteopenia and osteoporosis. In addition, a hypersensitivity reaction is a frightening experience for a patient. These reactions can be catastrophic and, if severe,

may preclude further taxanes. I believe we underestimate the negative impact of dexamethasone on patients and should avoid using it.

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(9453):60-2. **Abstract**

Blum JL et al. **A Phase II trial of combination therapy with capecitabine (C) and weekly paclitaxel (P) for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** *Breast Cancer Res Treat* 2004;88(Suppl 1);**Abstract 5053**.

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** Presentation. ASCO, 2004;**Abstract 543**.

Blum JL et al. **Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer.** *J Clin Oncol* 1999;17(2):485-93. **Abstract**

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7. **Abstract**

Ibrahim NK et al. **Nanoparticle paclitaxel (ABI-007) in metastatic breast cancer (MBC): Efficacy and evidence of dose-dependent activity in two multicenter phase II studies.** *Proc ASCO* 2002;**Abstract 209**.

Ibrahim NK et al. **Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel.** *Clin Cancer Res* 2002;8(5):1038-44. **Abstract**

Lee SH et al. **Capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer.** *Med Oncol* 2004;21(3):223-31. **Abstract**

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

Mackey JR et al. **Final results of a phase II clinical trial of weekly docetaxel in combination with capecitabine in anthracycline-pretreated metastatic breast cancer.** *Clin Breast Cancer* 2004;5(4):287-92. **Abstract**

Miles D et al. **Survival benefit with capecitabine/docetaxel versus docetaxel alone: Analysis of therapy in a randomized phase III trial.** *Clin Breast Cancer* 2004;5(4):273-8. **Abstract**

Nyman DW et al. **A phase I trial of ABI-007, nanoparticle paclitaxel, administered to patients with advanced nonhematologic malignancies.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 2027**.

O'Shaughnessy J et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs Taxol in MBC: A phase III trial.** *Breast Cancer Res Treat* 2003;82(Suppl 1):3;**Abstract 44**.

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 JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer.** *Breast Cancer Res Treat* 2004;88(Suppl 1);**Abstract 1070**.

Perez EA et al. **Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer.** *J Clin Oncol* 2001;19(22):4216-23. **Abstract**

Scheithauer W, Blum J. **Coming to grips with hand-foot syndrome. Insights from clinical trials evaluating capecitabine.** *Oncology (Huntingt)* 2004;18(9):1161-8, 1173. **Abstract**

Seidman AD et al. **Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer.** *J Clin Oncol* 1998;16(10):3353-6. **Abstract**

John R Mackey, MD

EDITED COMMENTS

BCIRG-001: Phase III randomized trial comparing adjuvant TAC to FAC

Study design

In our first study, BCIRG-001, 1,500 women from 21 countries were randomly assigned to six cycles of adjuvant TAC (docetaxel, doxorubicin and cyclophosphamide) or FAC (5-FU, doxorubicin and cyclophosphamide) (3.1). The women enrolled in the trial had node-positive disease.

Overall results

We now have mature results with five years of follow-up. The trial demonstrated that adjuvant TAC significantly improved disease-free survival by 28 percent in relative terms ($p = 0.001$). Overall survival was also strikingly improved; the trial demonstrated a 30 percent relative reduction in mortality with adjuvant TAC, which was an absolute six percent improvement in overall survival (3.1).

Benefit according to number of positive axillary lymph nodes

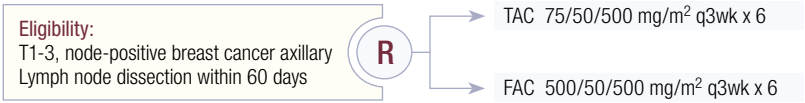
For the final analysis at 590 events, the trial was powered to determine whether a correlation exists between the number of positive axillary lymph nodes and the benefit associated with adjuvant TAC. Investigators evaluated the data to determine whether a significant difference exists in the ratio of the hazard ratios for patients with four or more involved axillary nodes and patients with one to three involved axillary nodes.

The analysis to date shows no correlation. The numbers indicate an independent, significant improvement with TAC in the patients with one to three positive nodes. In the patients with four or more positive nodes, the numbers are favoring TAC with fewer recurrences, but a statistically significant *p*-value is not reported. According to the protocol, we must compare the hazard ratios for those two groups even though no difference exists between the two (3.1); hence, we are in agreement with the FDA that adjuvant TAC is of benefit to women with node-positive breast cancer, regardless of the number of positive axillary lymph nodes.

Dr Mackey is a Medical Oncologist at Cross Cancer Institute, Alberta, Canada, Associate Professor of Medical and Experimental Oncology at the University of Alberta, Chair of the Northern Alberta Breast Cancer Program and Canadian Leader of the Breast Cancer International Research Group.

3.1 Adjuvant TAC versus FAC: Disease-Free Survival and Overall Survival after a Median Follow-Up of 55 Months (n=1,491)

Protocol ID: BCIRG-001(Closed)
Accrual: 1,491



	Hazard ratio TAC/FAC	*p*-value
Disease-free survival		
Adjusted for nodal status	0.72	0.0010
1-3 nodes (n=923)	0.61	0.0009
≥4 nodes (n=568)	0.83*	0.1700
Hormone receptor-positive	0.72	0.0076
Hormone receptor-negative	0.69	0.0297
Overall survival		
Adjusted for nodal status	0.70	0.0080

CI = confidence interval * Ratio of hazard ratios = 1.34; $p = 0.1457$

SOURCE: Mackey J. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 43**.

Safety

This would be a perfect story if an increase in side effects did not occur. In fact, TAC was associated with a high rate of febrile neutropenia. Approximately 25 percent of the women receiving TAC experienced an episode of febrile neutropenia, which was not unexpected because primary prophylaxis with G-CSF was not allowed (Martin 2003). We now know that if we were to do the study again and administer TAC with G-CSF, we would see a febrile neutropenia rate, on a per-patient basis, of about three to six percent (Martin 2004).

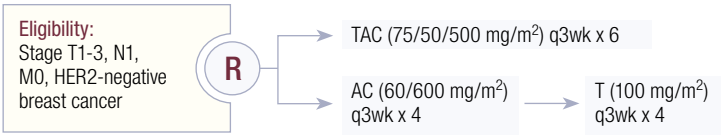
BCIRG-005: Phase III randomized trial comparing adjuvant TAC to AC followed by docetaxel

It is questioned whether chemotherapy drugs need to be combined in the adjuvant setting to obtain a maximal effect. Across the spectrum of cancer types, sequential monotherapy is not usually a curative approach. Because paclitaxel could not be safely combined with anthracyclines, sequential therapy became, in some sense, the standard of care; however, a pharmacokinetic interaction does not occur with docetaxel and doxorubicin.

BCIRG-005 is comparing the combination of TAC to AC followed by docetaxel. This study has completed its accrual of over 3,000 patients and we are waiting for mature data to determine whether six cycles of adjuvant TAC is different, in terms of efficacy, from four cycles of AC followed by four cycles of docetaxel.

3.2 Phase III Trial Comparing the Sequential Approach to the Combination Approach of Taxanes and Anthracyclines

Protocol IDs: BCIRG-005, GMA TAX301
Accrual: 3,301 (Closed; interim analysis planned first quarter 2006)



"The sequence of AC followed by a taxane is gaining acceptance as an important treatment in adjuvant breast cancer. Comparing this AC → T regimen, which requires 8 cycles, to 6 cycles of TAC (already compared to the standard regimen FAC as adjuvant therapy in BCIRG 001) will answer an important general/theoretical question and an important question for patients. The theoretical question is whether it is better to use drugs in combination or sequence. This is important for patients because it would reduce the amount of time on therapy to give the drugs in combination. An important feature of this study is that 6 cycles of the combination are given; other studies of this nature are giving 4 cycles. This difference may be crucial to provide a fair assessment of the relative merit of combination and sequential approaches."

T = docetaxel

SOURCE: www.BCIRG.org

BCIRG-006: Phase III randomized adjuvant trastuzumab trial

I believe the most exciting adjuvant trial we've done in a long time is BCIRG-006, in which patients with HER2-positive tumors on all of the arms received docetaxel. Patients were randomly assigned to receive: AC followed by docetaxel; AC followed by docetaxel in combination with trastuzumab; or docetaxel, carboplatin and trastuzumab for six cycles with trastuzumab continued for one year.

The trial required the centralized FISH analysis of all of the tumor blocks prior to randomization. All of the 3,200 patients with HER2-positive disease have undergone randomization and treatment. Now we're in the follow-up phase and are anticipating disease-free survival data by the first quarter of 2006.

BCIRG-006 has an Independent Data Monitoring Committee and an Independent Cardiac Safety Monitoring Committee, which have been meeting regularly to keep a close eye on the cardiac safety data. We're quite gratified to say that they're comfortable with what has been happening in the study; they have not requested any amendments to the protocol or any release of data.

I am currently blinded to the cardiac events but, in evaluating the available trial data in aggregate, we are not seeing a substantial cardiac signal. Also, the Independent Cardiac Data Monitoring Committee, which can evaluate the data on a per-arm basis, is not indicating any concern.

Initial selection of adjuvant hormonal therapy in postmenopausal women

At least two thirds of the postmenopausal women we're seeing have hormone receptor-positive disease. I am on the ATAC Steering Committee and our 47-month data (Baum 2003) and the recently published 68-month data (ATAC Trialists' 2004) suggest safety and disease-free survival efficacy with anastrozole. The early signals indicate that anastrozole is probably a better drug; however, its potential long-term side effects have to be kept in mind.

When we lay these data on the table, about two thirds of these women choose anastrozole, but one third stay with our old standby, tamoxifen.

Role of aromatase inhibitors in postmenopausal women following two to three years of adjuvant tamoxifen

About 50 percent of my patients are switching to an aromatase inhibitor following two to three years of adjuvant tamoxifen. Even though the disease-free survival data is clean and compelling, women are not switching as frequently as I would have guessed.

Role of aromatase inhibitors in postmenopausal women after five years of adjuvant tamoxifen

Data from the Canadian MA17 trial suggest that after five years of tamoxifen, women receiving extended adjuvant therapy with letrozole do better than women receiving no further therapy (Goss 2003). I'm concerned because that study was closed prematurely.

I'm also disappointed that with 2.5 years of follow-up, we're not going to have any more meaningful survival data because the trial was unblinded and women were crossed over. I'm a real believer in the importance of overall survival advantages to make definitive treatment recommendations. To date, we have no convincing overall survival data from any of the adjuvant aromatase inhibitor trials.

Although we might switch a woman to letrozole today, we're not going to have data in the near future to tell us how long we should continue that treatment, nor are we going to have data about the overall survival benefit. Even though it appears to be a safe and effective intervention, I have doubts about the long-term effects, particularly on bone. In addition, I'm disappointed that we don't have the survival signal or the possibility of obtaining a survival signal from that study.

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(9453):60-2. **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**

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

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

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.** *J Clin Oncol* 2004;22(14 Suppl);**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**

Crown J et al. **Docetaxel and paclitaxel in the treatment of breast cancer: A review of clinical experience.** *Oncologist* 2004;9(Suppl 2):24-32. **Abstract**

Fallowfield L et al. **Intergroup exemestane study: Results of the quality of life sub-protocol.** *Breast Cancer Res Treat* 2004;**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**

Heys SD et al. **Docetaxel as adjuvant and neoadjuvant treatment for patients with breast cancer.** *Expert Opin Pharmacother* 2004;5(10):2147-57. **Abstract**

Hillner BE. **Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer.** *Cancer* 2004;101(6):1311-22. **Abstract**

Howell, on behalf of the ATAC Trialists' Group A. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** *Breast Cancer Res Treat* 2004;88(Suppl 1);**Abstract 1**.

Mackey J. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 43**.

Martin M et al. **Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 620**.

Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 43**.

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**

Pegram MD et al. **Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer.** *J Natl Cancer Inst* 2004;96(10):759-69. **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**

Vogel CL et al. **The role of growth factor support following neutropenic events in early stage breast cancer (BC) patients treated with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC): A sub-analysis of BCIRG 001.** *Proc ASCO* 2004;**Abstract 677**.

4.1

Advances in Neoadjuvant Systemic Therapy

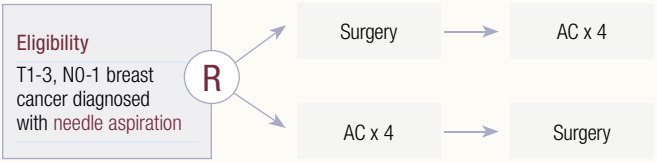
- Chemotherapy
- Endocrine therapy
- Biologic therapy

SLIDE 4.1 All three major systemic treatment strategies for breast cancer have been evaluated in the neoadjuvant setting. This slide set focuses on a number of key clinical trials evaluating neoadjuvant chemotherapy, endocrine treatment and biologic therapy.

4.2

Phase III Trial of Preoperative versus Standard Postoperative AC

Protocol ID: NSABP-B-18
Accrual: 1,523 (Closed)



Objectives:

- Assess relationship between tumor response and outcome
- Assess if preoperative AC provides better DFS and OS
- Assess rate of conservative surgery

SOURCE: Fisher B et al. *J Clin Oncol* 1998;16(8):2672-85. **Abstract**

SLIDE 4.2 NSABP-B-18 was a classic randomized trial that enrolled over 1,500 women who had operable breast cancer between 1988 and 1993. Women were randomly assigned to either surgery followed by AC or AC followed by surgery.

4.3

NSABP-B-18: Results

Clinical response in patients receiving up-front chemotherapy followed by surgery (N=693)

Response rate:	80%
Complete response	36%
Partial response	44%
Nonresponse:	20%
Stable disease	17%
Progression	3%

Significant predictors of response:
- Small tumor size
- Clinically positive nodes

SOURCE: Fisher B et al. *J Clin Oncol* 1998;16(8):2672-85. **Abstract**

SLIDE 4.3 In women receiving preoperative chemotherapy, the in-breast response rate was 80 percent. Progression during chemotherapy was three percent.

4.4

NSABP B-18: Results

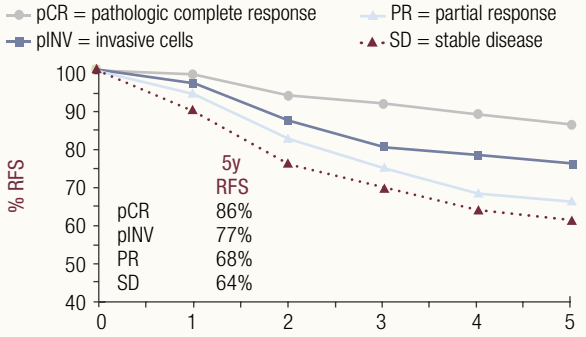
	Preop chemotherapy	Postop chemotherapy
Lumpectomy rate	67%	60%
Positive nodes	41%	57%
Local recurrence after lumpectomy	10.7%	7.6%
Disease-free survival		
5 years[1]	67%	67%
9 years[2]	55%	53%
Overall survival		
5 years[1]	80%	81%
9 years[2]	69%	70%

SOURCES: [1] Fisher B et al. *J Clin Oncol* 1998;16(8):2672-85. **Abstract**
[2] Wolmark N et al. *J Natl Cancer Inst Monogr* 2001;30:96-102. **Abstract**

SLIDE 4.4 The lumpectomy rate was significantly higher in women who received preoperative therapy (67 percent) compared to those who had initial surgery (60 percent). No difference in disease-free or overall survival was evident for patients receiving preoperative versus postoperative chemotherapy.

4.5

NSABP B-18: Pathologic Complete Response → Improved Outcome



SOURCE: With permission from Fisher B et al. *J Clin Oncol* 1998;16(8):2672-85. **Abstract**

SLIDE 4.5 A striking correlation was noted between response in the breast and relapse-free survival. Women who had a pathologic complete response (pCR) were three times less likely to have a recurrence than women who had stable disease.

4.6

The Milan Experience in Two Nonrandomized Trials of Primary Chemotherapy

- 536 patients with tumors ≥2.5 cm
- Combinations of CMF ± anthracyclines for 3-4 cycles
- Findings:
  - 85% were able to undergo conservative surgery
  - Pathologic response
    - 3% pathologic complete response
    - 2% noninvasive disease only
    - 13% microscopic foci of tumor
  - Significant variable in multivariate Cox model for RFS:
    - Degree of pathologic remission ($p = 0.03$)
    - Nodal status at surgery ($p < 0.001$)

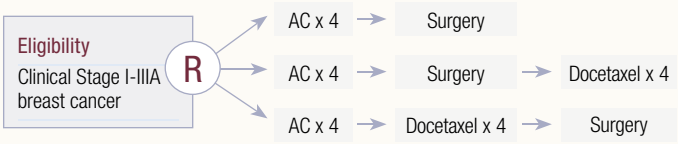
SOURCE: Bonadonna G et al. *J Clin Oncol* 1998;16(1):93-100. **Abstract**

SLIDE 4.6 The experience from Milan with preoperative chemotherapy includes two sequential nonrandomized trials with over 500 patients. In patients who had tumors 2.5 centimeters or larger and were treated with preoperative therapy, 85 percent were able to undergo conservative surgery.

4.7

Phase III Trial Evaluating the Addition of a Taxane to Preoperative AC

Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)



Clinical study questions:

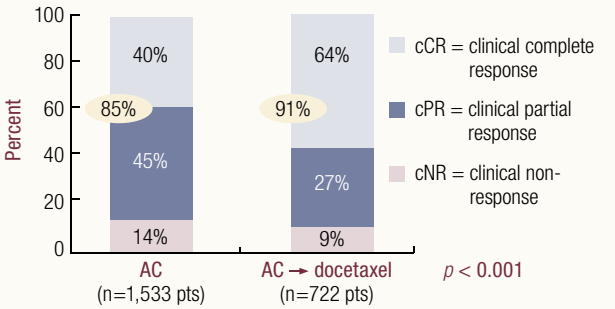
- Does the addition of docetaxel to AC improve DFS and OS, and does long-term outcome correlate with in-breast response?
- Can sequential AC followed by docetaxel further improve rate of conservative surgery compared to AC alone?
- Can response to preoperative AC be used to predict benefits of additional therapy?

SOURCE: Bear H et al. *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

SLIDE 4.7 NSABP-B-27 closed in December 2000 after enrolling 2,411 patients. There were three randomized arms: AC alone followed by surgery; AC followed by surgery followed by four cycles of docetaxel; and AC followed by docetaxel followed by surgery.

4.8

NSABP-B-27 Initial Results: Clinical Response

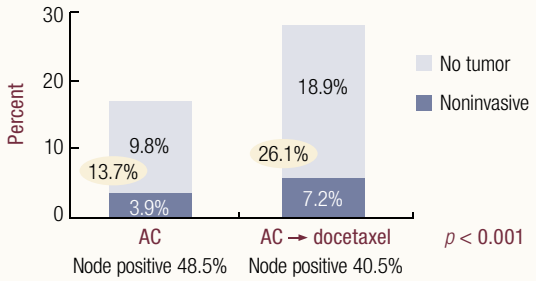


SOURCE: Bear H et al. *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

SLIDE 4.8 The data were first presented in San Antonio in 2001 and were subsequently published in 2003 in the *Journal of Clinical Oncology*. A statistically significant (85 percent versus 91 percent) difference occurred in the overall response rate in the breast.

4.9

NSABP-B-27 Initial Results: Pathologic Response (pCR) in Breast



No difference in rate of breast conservation: 61% vs 63%

SOURCE: Bear H et al. *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

SLIDE 4.9 Pathologic complete response rate was nearly doubled. No difference was observed in the breast conservation rate.

4.10

NSABP-B-27: 68-Month Update of Study Endpoints (Hazard Ratios Compared to AC)

	AC → T → Surg (n=803)	AC → Surg → T (n=799)
Overall survival	0.94 ($p = 0.57$)	1.07 ($p = 0.53$)
Disease-free survival with cPR after AC	0.86 ($p = 0.10$) 0.68 ($p = 0.003$)	0.91 ($p = 0.27$) 0.90 ($p = 0.40$)
Relapse-free survival	0.81 ($p = 0.03$)	0.91 ($p = 0.32$)

No significant difference in overall or disease-free survival by treatment but improved response-free survival compared to AC

T = docetaxel; cPR = clinical partial response

SOURCE: Bear H. Presentation. San Antonio Breast Cancer Symposium, 2004; **Abstract 26**.

SLIDE 4.10 NSABP-B-27 reported 68-month follow-up at San Antonio in 2004. The addition of docetaxel did not result in a statistically significant improvement in overall or disease-free survival but did result in improved relapse-free survival.

4.11

NSABP-B-27: 68-Month Update: Hazard Ratios of pCR versus non-pCR

	Hazard ratio	*p*-value
Overall survival	0.33	<0.0001
Disease-free survival	0.45	<0.0001

Pathologic complete response in the breast associated with improved OS and DFS in all treatment groups

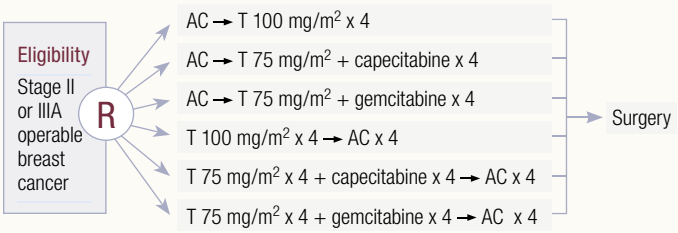
SOURCE: Bear H. Presentation. San Antonio Breast Cancer Symposium, 2004; **Abstract 26**.

SLIDE 4.11 Achievement of pCR was associated with a highly significant improvement in overall and disease-free survival, regardless of which treatment regimen patients received.

4.12

Preoperative Capecitabine or Gemcitabine Plus Docetaxel in Sequence with AC

Protocol IDs: NSABP-B-40, CTSU
Accrual: 1,200 (pending) in 2.5 years



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

SOURCE: NSABP Protocol Summary, November 2004.

SLIDE 4.12 NSABP-B-40 will replace trial B-27 and is expected to open in early 2005. The target accrual is approximately 1,200 patients. Patients will be randomly assigned to one of six chemotherapy regimens evaluating preoperative capecitabine or gemcitabine plus docetaxel in sequence with AC.

4.13

NSABP-B-40 Endpoints

Primary endpoint

- Determine if capecitabine or gemcitabine plus docetaxel in sequence with AC will increase pCR relative to docetaxel alone in sequence with AC

Secondary endpoint

- Compare clinical and pCR rates among regimens using molecular and genetic markers from needle biopsies collected in RNAlater® before therapy and between chemo regimens to identify molecular predictors of pCR to each regimen

SOURCE: NSABP Protocol Summary, November 2004.

SLIDE 4.13 The primary objective of B-40 is to determine whether docetaxel-based combinations in sequence with AC will increase the pCR rate compared to docetaxel alone in sequence with AC. The NSABP will also attempt to identify genetic and molecular markers predictive of pCR to each chemotherapy regimen.

4.14

Pathologic Complete Response Rates by Tumor ER Status: Preoperative Trials from MD Anderson Cancer Center

		pCR	
Chemotherapy	No. of pts	ER-negative	ER-positive
FAC x 3	532	14.5%	1.2%
FAC x 4	78	27.6%	6.1%
Paclitaxel x 4	81	7.1%	5.7%
Paclitaxel q3wk → FAC x 4	127	30.9%	5.6%
Paclitaxel qwk → FAC x 4	128	54.5%	14.3%
(A + docetaxel) x 4	72	15.9%	7.1%
Total	**1,018**	**20.6%**	**5.0%**

SOURCE: Buzdar AU et al. San Antonio Breast Cancer Symposium, 2003;**Abstract 302**.

SLIDE 4.14 Aman Buzdar and colleagues evaluated a series of preoperative chemotherapy trials conducted at MD Anderson to correlate pCR with hormone receptor status. A 20 percent pCR rate occurred in women with ER-negative disease compared to five percent in women with ER-positive disease.

4.15

IBCSG Pilot: Predictive Markers of pCR

- 399 patients with $T_{2\text{-}4}$, $N_{0\text{-}2}$ who received up to 6 cycles of anthracycline or anthacycline + taxane
- Significant univariate predictors
  - — Absent ER
  - — High Ki-67
  - — Grade III tumor
  - — Receipt of infusional therapy
- Significant multivariate predictors
  - — Absent ER and PR OR 4.22 $p < 0.0001$
  - — Grade III tumor OR 3.36 $p = 0.001$

SOURCE: Colleoni M et al. *Clin Cancer Res* 2004;10(19):6622-8. **Abstract**

SLIDE 4.15 The International Breast Cancer Study Group enrolled 399 patients in a pilot trial evaluating factors predictive of pCR. The absence of estrogen and progesterone receptor status and high tumor grade were related to pCR.

4.16

Advances in Neoadjuvant Systemic Therapy

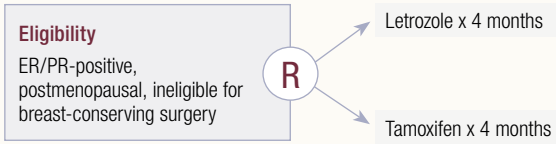
- Chemotherapy
- Endocrine therapy
- Biologic therapy

SLIDE 4.16 Another neoadjuvant strategy is endocrine treatment, both in premenopausal and postmenopausal patients.

4.17

Double-Blind Randomized Study of Neoadjuvant Letrozole vs Tamoxifen

Protocol ID: Multinational Novartis Pharmaceuticals
Accrual: 337 (Closed)



SOURCE: Ellis M et al. *J Clin Oncol* 2001;19(8):3808-16. **Abstract**

SLIDE 4.17 In one major study, 337 postmenopausal patients with primary breast cancer who were ineligible for breast-conserving surgery were randomly assigned to four months of letrozole or tamoxifen prior to re-evaluation for surgery.

4.18

Letrozole vs Tamoxifen: Results for Patients with ER/PR-Positive Tumors

	Letrozole	Tamoxifen	*p*-value
Confirmed (ER/PR-positive)	124 (100%)	126 (100%)	
Overall tumor response (CR + PR)			
Clinical	74 (60%)	52 (41%)	0.004
Ultrasound	48 (39%)	37 (29%)	0.118
Mammography	47 (38%)	25 (20%)	0.002
Breast-conserving surgery	60 (48%)	45 (36%)	0.036
Clinical disease progression	10 (8%)	15 (12%)	0.303

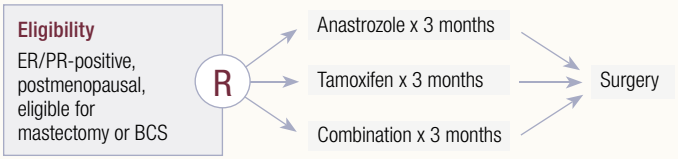
SOURCE: Ellis M et al. *J Clin Oncol* 2001;19(8):3808-16. **Abstract**

SLIDE 4.18 Patients treated with letrozole experienced greater tumor response than patients treated with tamoxifen. Conversion from ineligibility to breast-conserving surgery was more frequent in the letrozole arm (48 percent) than in the tamoxifen arm (36 percent).

4.19

Phase III Trial of Neoadjuvant Anastrozole vs Tamoxifen vs the Combination

Protocol ID: IMPACT
Accrual: 330 (Closed)

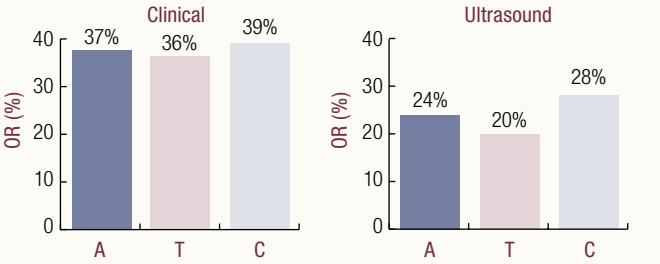


SOURCE: Smith I. Presentation. SABCS, 2003;**Abstract 1**.

SLIDE 4.19 The IMPACT study presented by Ian Smith and Mitchell Dowsett in San Antonio in 2003 randomly assigned 330 patients to preoperative anastrozole, tamoxifen or the combination. Only 56 percent of patients were judged to require mastectomy prior to therapy.

4.20

IMPACT: Objective Response (OR) in the Overall Population (330 Intent-to-Treat)



A vs T: OR 1.05 (0.61, 1.81) $p = 0.87$
C vs T: OR 1.15 (0.67, 2.00) $p = 0.61$

A vs T: OR 1.23 (0.65, 2.32) $p = 0.53$
C vs T: OR 1.48 (0.79, 2.79) $p = 0.22$

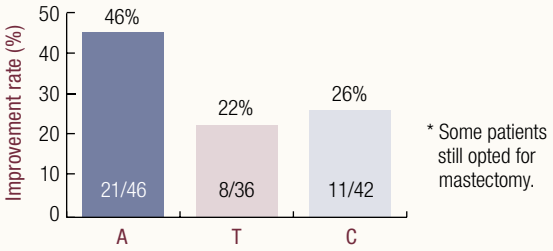
SOURCE: Smith I. Presentation. SABCS, 2003;**Abstract 1**.

SLIDE 4.20 Clinical response rates were similar across the three arms. Note that all patients in the letrozole study were ineligible for breast-conserving surgery, whereas only 56 percent of patients in IMPACT required mastectomy at baseline. The smaller tumor size in IMPACT may have made clinical assessment more difficult.

4.21

IMPACT: Improvement in Feasible BCS Surgery (%)

(Change from mastectomy to BCS* by surgeons' assessment)



A vs T: OR 2.94 (1.11, 7.81) $p = 0.03$*
C vs T: OR 1.24 (0.44, 3.53) $p = 0.68$

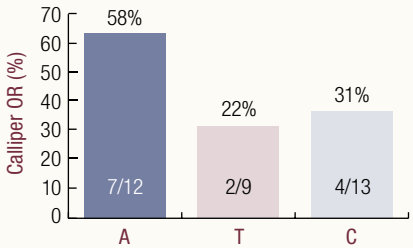
SOURCE: Smith I. Presentation. SABCS, 2003;**Abstract 1**.

SLIDE 4.21 Of the patients initially judged to need a mastectomy, anastrozole resulted in a doubling of the eligibility for conservative surgery. Forty-six percent of those patients were able to undergo less than a mastectomy versus 22 and 26 percent of patients in the tamoxifen alone and combination arms, respectively.

4.22

Clinical Response (%) in HER2-Positive Tumors

(34 out of 239 patients treated per protocol)



A vs T: OR 4.90 (0.70, 34.30) $p = 0.09$
C vs T: OR 1.56 (0.22, 11.09) $p = 0.66$

SOURCE: Smith I. Presentation. SABCS, 2003;**Abstract 1**.

SLIDE 4.22 A relatively small percentage of patients had HER2-positive disease — 34 out of 239 patients. A trend was observed toward improved response rates with anastrozole (58 percent) compared to tamoxifen (22 percent).

4.23

Advances in Neoadjuvant Systemic Therapy

- Chemotherapy
- Endocrine therapy
- Biologic therapy

SLIDE 4.23 Another systemic strategy being tested in the neoadjuvant setting is biologic therapy. To this point, the major available data has come from trials of neoadjuvant trastuzumab in patients with HER2-positive tumors.

4.24

Preoperative Trastuzumab and Paclitaxel: Dana-Farber Trial in Stage II/III Disease

LVEF testing	Treatment plan	
Baseline	Paclitaxel q21d x 4 trastuzumab qwk x 12	
After 12 weeks trastuzumab and paclitaxel	↓	Assess clinical response
	Definitive breast surgery	
	↓	Assess pathological response
After 2 cycles AC After 4 cycles AC	AC q21d x 4	Between 42 and 63 days from last trastuzumab dose

SOURCE: Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53. **Abstract**

SLIDE 4.24 Dana-Farber conducted a series of studies evaluating trastuzumab in combination with chemotherapy. Harold Burstein and colleagues reported a study of preoperative trastuzumab and paclitaxel in the *Journal of Clinical Oncology* in 2003.

4.25

Tumor Response: Preoperative Trastuzumab and Paclitaxel

	No.	PD	SD/NA*	cPR	cCR	pCR
Total	40	1 3%	9 23%	18 45%	12 30%	7 18%
IHC 3+	32	1 3%	4 13%	16 50%	11 34%	6 19%
IHC 2+	8	0	5 63%	2 25%	1 13%	1 13%

* One patient was off study due to a paclitaxel hypersensitivity reaction and was not assessable.

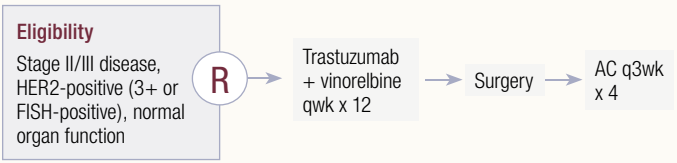
SOURCE: Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53. **Abstract**

SLIDE 4.25 The overall pCR rate in this trial was 19 percent in patients whose tumors were IHC 3+ and 13 percent in patients with IHC 2+ scoring.

4.26

Phase II Study of Preoperative Vinorelbine and Trastuzumab

Protocol ID: Dana-Farber Cancer Institute
Accrual: 40 (Closed)



Note: Higher-risk patients subsequently received postoperative trastuzumab/paclitaxel; all patients received a total of 52 weeks of trastuzumab.

SOURCE: Harris LH et al. *Proc ASCO* 2003;**Abstract 86**.

SLIDE 4.26 Lindsey Harris at Dana-Farber conducted a Phase II study evaluating trastuzumab and vinorelbine based on data with that combination in the metastatic setting. Approximately 60 percent of patients had Stage III disease.

4.27

Preoperative Vinorelbine and Trastuzumab: Response in Breast and Lymph Nodes

Response	No. of patients	Response rate (%)
cCR	16	38
cPR	21	50
cCR + PR	37	88
cSD	4	10
cPD	1	2
pCR*	8	19

* Absence of invasive disease in breast

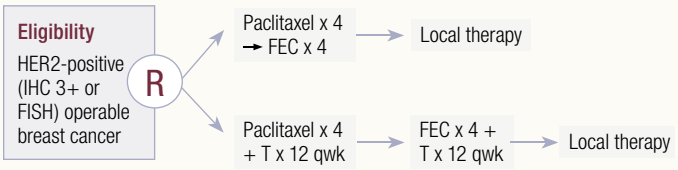
SOURCE: Winer E. Presentation. Key Biscayne, FL. November 6, 2004.

SLIDE 4.27 These data were initially presented at ASCO in 2003. The results are strikingly similar to their prior study of preoperative trastuzumab and paclitaxel. Overall response rate was 88 percent with pCR rate of 19 percent.

4.28

MD Anderson Preoperative Trial: Chemotherapy with or without Trastuzumab in HER2-Positive Patients

Accrual: 42 of 168 planned (Closed by IDMC)



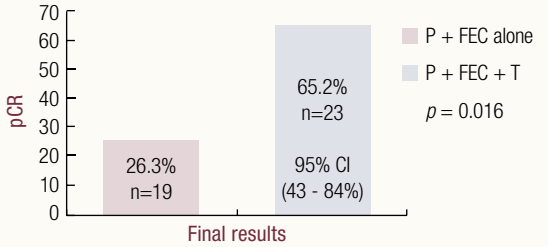
T = trastuzumab

SOURCE: Buzdar AU. *Proc ASCO* 2004;**Abstract 520**.

SLIDE 4.28 Aman Buzdar at ASCO 2004 presented findings from a trial in patients with HER2-positive operable breast cancer. The study compared four cycles of paclitaxel followed by four cycles of FEC compared to this same regimen with concurrent trastuzumab. Target accrual was 168 patients, but accrual to the trial was stopped by the MD Anderson Data Safety Monitoring Board.

4.29

Pathologic Complete Response Rates



No cases of CHF; ≥10% drop EF in 5 and 7 patients respectively

SOURCE: Buzdar AU. *Proc ASCO* 2004;**Abstract 520**.

SLIDE 4.29 Patients who received concurrent preoperative chemotherapy and trastuzumab had a significantly higher pCR rate (65 percent) than patients who received chemotherapy alone (25 percent). The regimen appeared to be tolerable in spite of the administration of concurrent trastuzumab and epirubicin. No incidents of congestive heart failure were observed.

4.30

What Explains the Very High Path CR Rate in This Study?

- Chance (unlikely)
- Favorable patient population
  - All other preoperative trials with trastuzumab have included some patients with LABC
- More prolonged therapy with trastuzumab (24 weeks) than in other trials
- Use of anthracycline as part of regimen
- Concurrent anthracycline and trastuzumab

SOURCE: Winer E. Presentation. Key Biscayne, FL, November 6, 2004.

SLIDE 4.30 It's possible but unlikely that chance alone contributed to the high pathologic CR rate in this study. The trial did not include patients with Stage III disease. Prolonged administration of trastuzumab — 24 weeks of therapy — may also have played an important role. Finally, the concurrent use of an anthracycline and trastuzumab may have led to the high pathologic CR rate.

Select publications

Bear HD et al. **A randomized trial comparing preoperative (preop) doxorubicin/cyclophosphamide (AC) to preop AC followed by preop docetaxel (T) and to preop AC followed by postoperative (postop) T in patients (pts) with operable carcinoma of the breast: Results of NSABP B-27.** Presentation. San Antonio Breast Cancer Symposium, 2004;**Abstract 26**.

Bear HD et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

Bonadonna G et al. **Primary chemotherapy in operable breast cancer: Eight-year experience at the Milan Cancer Institute.** *J Clin Oncol* 1998;16(1):93-100. **Abstract**

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing Stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53. **Abstract**

Buzdar AU et al. **Pathological complete response to chemotherapy is related to hormone receptor status.** *Breast Cancer Res Treat* 2003;82(51);**Abstract 302**.

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**.

Colleoni M et al. **Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: A study of preoperative treatment.** *Clin Cancer Res* 2004;10(19):6622-8. **Abstract**

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16. **Abstract**

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

Harris L et al. **Preoperative trastuzumab and vinorelbine (HN) is a highly active, well-tolerated regimen for HER2 3+/FISH+ Stage II/III breast cancer.** *Proc ASCO* 2003;**Abstract 86**.

Smith I et al. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 1**.

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

Post-test:

Breast Cancer Update — Issue 1, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The most recent analysis of the ATAC trial data had a follow-up of:
   a. 36 months
   b. 47 months
   c. 68 months

2. In the most recent analysis of ATAC, the relative reduction in recurrence for anastrozole compared to tamoxifen was about _____.
   a. Five percent
   b. 10 percent
   c. 25 percent
   d. 40 percent

3. The percent of women who underwent hysterectomies in the ATAC trial was _____ and _____ for anastrozole and tamoxifen, respectively.
   a. 1.3, 5.1
   b. 0.4, 2.4
   c. Unknown

4. In the ATAC trial, the relative reduction in recurrence for anastrozole compared to tamoxifen in patients with the ER-positive, PR-negative phenotype was approximately 60 percent.
   a. True
   b. False

5. The adjuvant trial evaluating capecitabine/docetaxel required a dose adjustment for one of the drugs. Which one of the following statements is true?
   a. The dose of capecitabine was increased
   b. The dose of capecitabine was decreased
   c. The dose of docetaxel was increased
   d. The dose of docetaxel was decreased
   e. None of the above

6. The Phase I trials of nanoparticle paclitaxel have evaluated which schedule(s) of administration?
   a. Weekly
   b. Every three-week
   c. Daily
   d. Both a and b
   e. Both a and c

7. Nanoparticle paclitaxel has been compared to _____ in a randomized Phase III trial.
   a. Paclitaxel
   b. Docetaxel
   c. Both a and b
   d. None of the above

8. BCIRG-001 demonstrated that adjuvant _____ improved disease-free and overall survival compared to FAC.
   a. TAC
   b. AC followed by docetaxel
   c. FAC
   d. Both a and b
   e. None of the above

9. In order to determine the importance of administering chemotherapy in combination as opposed to sequentially, BCIRG-005 is designed to compare adjuvant TAC to AC followed by docetaxel.
   a. True
   b. False

10. Which regimens are being evaluated in BCIRG-006?
    a. AC followed by docetaxel
    b. AC followed by docetaxel in combination with trastuzumab
    c. Docetaxel, carboplatin and trastuzumab
    d. Both a and b
    e. a, b and c

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

Evaluation Form:

Breast Cancer Update — Issue 1, 2005

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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
Michael Baum, MD, ChM	5 4 3 2 1	5 4 3 2 1
Joanne L Blum, MD	5 4 3 2 1	5 4 3 2 1
John R Mackey, 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

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Breast Cancer Update — Issue 1, 2005

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☐ Yes ☐ No

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.....

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☐ Yes, I am 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:

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Breast Cancer™ UPDATE

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Breast Cancer™ UPDATE

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