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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 4 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Howell, Gradishar, Gnant and Perez on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**. This monograph also contains a "Journal Club" feature, which highlights several important recent publications. Corresponding PowerPoint slides are included on the CD.

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UPCOMING EDUCATIONAL EVENTS

Best of ASCO — San Francisco
June 17-18, 2005
San Francisco, California
Event website: **www.asco.org/meetings**

Best of ASCO — Dallas
June 25-26, 2005
Dallas, Texas
Event website: **www.asco.org/meetings**

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

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

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

Join us for a live, interactive continuing medical education program.

Controversies in Systemic Therapy of Breast Cancer
June 25, 2005, The Waldorf Astoria, New York, New York

This program will focus on key management options for women with early and metastatic breast cancer and recent relevant research results from the 2005 ASCO meeting.

For more information, log onto **www.BreastCancerUpdate.com/CMEmeetings** or email us at Meetings@ResearchToPractice.net. To register, call (800) 233-6153.

Editor's Note

No regrets

Case history:

- **December 2004**

Mrs B is a 57-year-old woman who was diagnosed with ER-positive invasive breast cancer in April 2001. She had one positive sentinel lymph node and received AC → T chemotherapy, after which her oncologist prescribed tamoxifen. The patient and the doctor discussed the recently presented ATAC data; however, the oncologist recommended that they "stick with the tried and true endocrine therapy."

Mrs B has now been receiving tamoxifen for two and a half years. Her bone density is normal, and she has no complaints other than modest weight gain and vasomotor symptoms that she attributes to tamoxifen. Since the original diagnosis, at least five major randomized trials have demonstrated that patients treated with aromatase inhibitors experienced fewer relapses compared to patients receiving tamoxifen either in the up-front adjuvant setting or after two to three or five or more years of tamoxifen.

During a routine follow-up visit, the oncologist mentions these studies but recommends continuing tamoxifen. The patient agrees.

- **October 2005**

Mrs B is seen for an unscheduled visit because of the gradual and progressive onset of lower back pain. A diagnostic workup reveals bone and pulmonary lesions compatible with metastases, and needle biopsy of the lung confirms recurrence. An aromatase inhibitor is initiated.

Our CME group recently published a first ever "Patterns of Care" case-based survey of national breast cancer clinical research leaders. The fascinating results from this project were then compared to a previous identical survey of community-based oncologists.

One of the most important findings from this comparison is the suggestion that the case scenario described above is happening every day in this country, mainly in community practice as opposed to academic centers (1.1).

1.1 Patterns of Care Survey: Sequencing Aromatase Inhibitors after Tamoxifen

- A 65-year-old woman in average health on tamoxifen x 2 years as described below
- Original tumor: 1.2 cm, ER-positive, HER2-negative, Grade II IDC
- Three positive nodes
- Patient is tolerating tamoxifen as described below

How would you manage this patient's therapy?

	Without severe side effects from tamoxifen		20-pound weight gain		Moderate hot flashes refractory to nonhormonal therapy	
Continue tamoxifen	7%	45%	7%	17%	7%	16%
Stop tamoxifen and switch to exemestane	70%	32%	70%	32%	59%	36%
Stop tamoxifen and switch to anastrozole	15%	12%	25%	35%	24%	36%
Stop tamoxifen and switch to letrozole	8%	11%	8%	16%	10%	12%

Breast Cancer Specialists (n=31) General Oncologists (n=150)

SOURCE: *Breast Cancer Update Patterns of Care* 2005;2(1):18.

The debate over the role of aromatase inhibitors versus tamoxifen in the adjuvant setting continues, and counter-arguments can be made on each side. For every patient who develops a fracture on an aromatase inhibitor, other patients experience a DVT, stroke or endometrial cancer on tamoxifen; however, for most people with breast cancer, the overwhelming concern is decreasing the likelihood of disease recurrence. At this point, aromatase inhibitors clearly do it better.

One might "cover oneself" ethically and perhaps legally by sharing with patients what we know about the risks and benefits of various options for long-term adjuvant endocrine therapy, but patients also want a recommendation. It is remarkable that postmenopausal patients visiting breast cancer specialists today are much more likely to be encouraged to switch to an aromatase inhibitor during their first five years of tamoxifen.

Gabe Hortobagyi has the most direct approach to this issue: He simply switches postmenopausal women to an aromatase inhibitor regardless of how long they have been on tamoxifen. Plain and simple, the elegance of this strategy is attractive, but currently it would have to be labeled "C" for controversial.

In this edition of our series, Tony Howell and Michael Gnant, the PI and co-PI of two critical Austrian trials of endocrine therapy, update us on the rapidly evolving clinical trial results with the aromatase inhibitors in the adjuvant setting.

Tony eloquently reviews not only the 68-month update from ATAC but also the first results of the BIG 1-98 trial with data on letrozole versus tamoxifen at 30 months. While the efficacy findings of these two trials look similar at early time points, Tony notes the unexpected finding of increased deaths from myocardial infarction in patients treated with letrozole in the BIG study. He goes on to speculate about whether continued follow-up of trials of all three major aromatase inhibitors will show differences in their safety profiles, particularly related to cardiovascular disease.

At this point, community-based and research oncologists are generally starting postmenopausal patients with ER-positive tumors on an aromatase inhibitor — usually anastrozole. One of the major reasons oncologists have a greater comfort level with this treatment strategy is their increasing confidence with regard to the issue of bone loss. In great part, this can be attributed to Dr Gnant's work evaluating zoledronate in premenopausal patients made postmenopausal with an LHRH agonist and then treated with either tamoxifen or anastrozole.

I interviewed Dr Gnant at the 2002 San Antonio Breast Cancer Symposium when he presented the first data set from his trial demonstrating that zoledronate totally abrogated bone loss in both patient populations. This encouraging finding was unchanged with two more years of follow-up in his most recent presentation at the 2004 San Antonio meeting and is good news, as are the ATAC observations that there is no increase in the rate of hip fractures, and that the overall fracture rate is decreasing after patients stop anastrozole at five years. Nonetheless, the bone issue must continue to be closely monitored, and Dr Gnant puts a plug in for good old-fashioned outdoor exercise as a means to improve bone density. He gently chides American women who "don't go out in the winter because it's too cold, and don't go out in the summer because it's too hot." I guess they don't have TiVo® in Austria.

Dr Gnant also discusses findings from another important endocrine trial, specifically the Austrian/German study that randomly assigned patients at two to three years to either continue tamoxifen or switch to anastrozole. As with the other large switching trial — the IES study with exemestane — these data documented a major reduction in relapse rate in patients who switched to anastrozole, and most of the events avoided were distant recurrences. These findings directly relate to the patient presented at the beginning of this commentary, and one can say with reasonable confidence that there is at least a one-in-three chance that this woman would have remained recurrence free if she had switched to exemestane or anastrozole.

The same can be said about letrozole with regard to the patient who completes five years of tamoxifen. Peter Ravdin's Adjuvant! model* now provides estimates of risk of relapse at various time points after diagnosis and how these might be modified by the use of an aromatase inhibitor. This information should be offered to all postmenopausal women on adjuvant tamoxifen.

* **www.adjuvantonline.com**

The decision to "switch or not switch" will probably only be on the table for the next few years, as the last remaining patients from the "pre-acceptance of ATAC" era pass through oncology offices. Nonetheless, tens of thousands of people with breast cancer are currently receiving therapy that appears to have a suboptimal risk-to-benefit ratio, particularly related to breast cancer control. All of our adjuvant systemic interventions improve the odds for patient populations globally, but for an individual person, we never know the exact impact of a specific therapy. When relapse does occur, both patient and physician look back and hope that prior decisions about adjuvant therapy offered the best chance to remain recurrence free.

In that regard, one of the common explanations patients and oncologists provide when justifying their decision to begin adjuvant chemotherapy for small node-negative tumors is the need to feel that they are doing everything possible to prevent disease recurrence. This does a great deal to prevent painful feelings of regret if relapse occurs, and one might assume that this same thought would and should apply to a significantly less toxic intervention like endocrine therapy.

Someone (ASCO Tech Assessment #4?) needs to step up to the plate and make it clear that at this point, five years of adjuvant tamoxifen is suboptimal adjuvant therapy for many or most postmenopausal patients with ER-positive invasive breast cancer.

—Neil Love, MD
NLove@ResearchToPractice.net

Select publications

BIG 1-98 Collaborative Group. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** **www.ibcsg.org**. **Abstract**

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**

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

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

Jakesz R, 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.** San Antonio Breast Cancer Symposium 2004;**Abstract 2**.

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**

Anthony Howell, MD

EDITED COMMENTS

ATAC trial: 68-month follow-up

Disease-free survival and overall survival

We now have the 68-month data from the ATAC trial, and we see continued improvement in disease-free survival in patients receiving anastrozole versus tamoxifen — a 3.3 percent absolute difference and a 17 percent improvement in the hazard ratio for relapse in hormone receptor-positive patients (Howell 2005).

Anastrozole improves the recurrence rate and the time to distant recurrence; we also saw a nonsignificant improvement in time to breast cancer death. However, no difference in overall survival has yet been demonstrated between patients receiving anastrozole versus tamoxifen.

While we hoped to see a difference in mortality at this point, a mortality improvement was not observed with tamoxifen in NSABP-B-14 until after approximately seven years of follow-up. We're at six years with ATAC, so it may be a year or two before any mortality improvement is demonstrated, but we do expect it to occur because we see a distant disease-free survival advantage with anastrozole.

Two-year recurrence rate and contralateral breast cancer

A peak in recurrences occurs at two years for patients on tamoxifen, and it's similar to the peak that we see in patients who receive no treatment. We see this peak in all patients on tamoxifen but especially in patients who have node-positive disease. This two-year peak was blunted by anastrozole.

This is obviously important because if patients start with tamoxifen, some will relapse on tamoxifen who would not have relapsed on anastrozole, and we've lost those patients.

In addition, we see increased toxicity with tamoxifen over those first two and a half years, so from both the efficacy and toxicity standpoints, it is probably better to begin adjuvant hormonal therapy with an aromatase inhibitor.

Contralateral breast cancer rate and prevention

In the ATAC trial, contralateral breast cancer was reduced by 50 percent with anastrozole (2.1), which is similar to the data from other aromatase inhibitor

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trials. That's a 50 percent reduction compared to tamoxifen, but it's a 75 percent reduction compared to no treatment.

The ATAC data prompted investigators to launch the IBIS-2 prevention trial in which patients at increased risk are randomly assigned to anastrozole versus placebo. We also have an IBIS-2 trial for patients with DCIS in which the randomization is the same as in the NSABP DCIS trial — tamoxifen versus anastrozole. In our DCIS trial, we are comparing anastrozole to tamoxifen because that is the standard; however, we are using a placebo in the high-risk trial because we don't believe tamoxifen is the standard for patients who are at increased risk for breast cancer but do not have DCIS.

2.1 Reduction in Incidence of Contralateral Breast Cancer with Anastrozole versus Tamoxifen: 68-Month Update from the ATAC Trial

	Reduction	95% CI	*p*-value
All patients (n=94)	42%	12-62	0.01
Hormone receptor-positive patients	53%	25-71	0.001

CI = confidence interval

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

ATAC toxicity data

At the 2004 San Antonio meeting, we presented updated toxicity data including new data on hysterectomy rates (2.2). The rate on tamoxifen was 5.1 percent, whereas on anastrozole it was only 1.3 percent (Howell 2004). The rate of endometrial cancer is 0.8 percent on tamoxifen and 0.2 percent on anastrozole, so clearly endometrial cancer doesn't account for all of the increase seen in the hysterectomy rate. This suggests that some women are undergoing unnecessary hysterectomies. I believe this issue pushes the economics in favor of anastrozole despite the increased cost of this agent.

The other story is the joint symptoms we see with aromatase inhibitors. In the data reported, tamoxifen had approximately a 29 percent joint symptom rate and with anastrozole the rate was approximately 36 percent. Matt Ellis' group presented an interesting abstract at San Antonio indicating that women with these symptoms may have lowered vitamin D levels and that giving them vitamin D improved some of the joint symptoms (Taylor 2004). The data are very early, and they are conducting more studies, but if we could solve this joint problem with vitamin D, it would be extraordinary.

We know from the ATAC trial that more serious adverse events are associated with tamoxifen than with anastrozole, and that despite the joint symptoms, patients tend to stay on anastrozole more than they stay on tamoxifen, which is an important efficacy issue.

2.2 ATAC Trial 68-Month Analysis: Adverse Events*

	Anastrozole (%)	Tamoxifen (%)	Odds ratio (anastrozole vs tamoxifen)	*p*-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Hysterectomy	1.3	5.1	—	<0.0001
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/arthralgia	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001

AE = adverse events; SAE = serious adverse events

* Adverse events on treatment or within 14 days of discontinuation
† Fractures occurring before recurrence (includes patients no longer on treatment)

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

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**.

Bone density

In the 68-month follow-up of the ATAC trial, the fracture rates were 7.7 percent with tamoxifen versus 11 percent with anastrozole (Howell 2005). We saw no increase in hip fractures with anastrozole, which is important, but the fracture rate with anastrozole is still a concern. Another issue is fracture rate over time, and I presented the data out to six years.

With tamoxifen, the annual fracture rate is approximately 1.5 to two percent, whereas with anastrozole it's approximately 2.5 percent. What surprised me was that at year five-six in the trial, the fracture rate was lower in the anastrozole group than in the tamoxifen group, although not significantly lower. It seems that as soon as anastrozole is stopped, the fracture rate goes down.

The trial had a bone subprotocol in which we evaluated lumbar spine and trochanter bone mineral density over time. In the first year an approximately 2.5 percent drop in bone mineral density occurred on anastrozole, and at two years it was just over a four percent drop.

This is similar to the IES data with exemestane and the MA17 data with letrozole. The impact on bone mineral density is a class effect of aromatase inhibitors and is not limited to anastrozole. We need to learn how to manage this (Coleman 2004; Perez 2004).

In San Antonio, Michael Gnant presented the extraordinary Austrian data on using zoledronic acid to prevent bone mineral loss in premenopausal patients (Gnant 2004). Patients were randomly assigned to receive goserelin plus tamoxifen versus goserelin plus anastrozole; then, in a subrandomization, patients received zoledronic acid or not. They found that the loss of bone mineral density on anastrozole over three years in this study was completely abrogated by administering zoledronic acid.

Deep vein thrombosis, stroke and cardiovascular events

In the ATAC trial, 4.5 percent of women on tamoxifen experienced deep vein thrombosis, whereas approximately 2.8 percent on anastrozole developed this side effect. That's similar to the other studies and similar to the rate seen in women on hormone replacement therapy. We also continue to see a reduction in ischemic cerebrovascular events on anastrozole versus tamoxifen — two percent versus 2.8 percent, respectively.

The important data in my mind are the new and slightly worrisome findings on cardiac events in the aromatase inhibitor trials. In ATAC, the rate of cardiac events was 4.1 percent on anastrozole and 3.4 percent on tamoxifen. The increase on anastrozole was not statistically significant — the *p*-value was 0.12.

The IBCSG-1-98 data presented at the St Gallen's meeting reported on increases in Grades III to V cardiac events with letrozole, which were statistically significant. The rates were 3.6 percent in patients on letrozole compared to 2.5 percent in patients on tamoxifen, with 26 versus 13 myocardial deaths, respectively (BIG 1-98 Collaborative Group 2004).

Coombes, reporting on the IES trial in San Antonio, reported a statistically significant increase — 20 myocardial infarctions on exemestane and eight on tamoxifen (Coombes 2004). This issue needs to be monitored carefully.

IBCSG-1-98: Letrozole versus tamoxifen up front or sequentially

The IBCSG-1-98 trial has approximately 4,000 patients in each of four arms. Patients in the first arm receive tamoxifen for five years. In the second arm, patients begin with tamoxifen and then switch to letrozole. In the third arm, patients begin on letrozole and switch to tamoxifen, while patients in the fourth arm receive letrozole for five years.

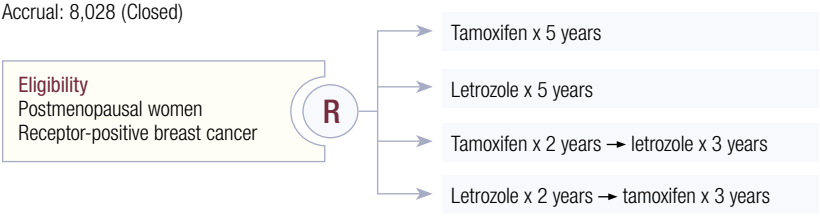
The IBCSG-1-98 efficacy data at 30 months look almost identical to the ATAC data at 33 months, favoring the aromatase inhibitor over tamoxifen (BIG 1-98 Collaborative Group 2004; [2.3]). The disease-free survival is a 21 percent reduction in the IBCSG-1-98 versus a 22 percent reduction in the ATAC trial. Time to recurrence was reduced 18 percent in IBCSG-1-98 and 17 percent in ATAC. The

distant disease-free survival, which is possibly a surrogate for breast cancer survival, is also similar to ATAC.

2.3 Phase III Study Comparing Letrozole versus Tamoxifen as Adjuvant Endocrine Therapy

Protocol IDs: IBCSG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, NCT00004205, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98

Accrual: 8,028 (Closed)



SOURCES: NCI Physician Data Query, April 2005; BIG 1-98 Collaborative Group. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** **www.ibcsg.org**. **Abstract**

Selection of an aromatase inhibitor for adjuvant therapy

We have two studies evaluating an aromatase inhibitor up front — ATAC with anastrozole and IBCSG-1-98 with letrozole; however, we have more data on anastrozole with more than five years of follow-up. There doesn't appear to be any difference in efficacy of these two agents, so thus far, I use anastrozole based on the toxicity profiles and longer follow-up.

I use exemestane after two to three years of tamoxifen based on the IES data (Coombes 2004). However, if you compare the IES exemestane data to the data from the combined ARNO 95/ABCSG-8 trials, in which the patients were switched to anastrozole, the agents appear to be similar in terms of efficacy (Jakesz 2004).

The hazard ratio for relapse-free survival was 0.73 in the IES study and 0.60 in the ARNO study, so I believe these two agents are equivalent in this situation. We now have data to support the use of either anastrozole or exemestane after two or three years of tamoxifen. After five years of tamoxifen, we have only the MA17 trial data, so I use letrozole in this setting (Goss 2003).

Adjuvant aromatase inhibitors in premenopausal patients with ER-positive breast cancer

Three important randomized trials are enrolling premenopausal women with hormone-receptive disease — SOFT, TEXT and PERCHE. The ABCSG-AU12 trial randomly assigned approximately 2,000 patients to goserelin plus tamoxifen

versus goserelin plus anastrozole, with a second randomization to zoledronic acid or not. That study will report in one or two years and should tell us whether tamoxifen or an aromatase inhibitor is superior when combined with goserelin in premenopausal women. We expect that goserelin with anastrozole will be better, which is why so many patients are already being treated off protocol.

Aromatase inhibitors are ineffective in premenopausal women without ovarian suppression. We need to be careful when patients experience chemotherapy-induced amenorrhea. Some women will begin menstruating again, and estradiol levels can recover without menses. If you measure the estradiol level and it's postmenopausal, it can go up again the next week and the aromatase inhibitor becomes ineffective. We know estrogen levels fluctuate in these women and we need to be absolutely certain the ovaries are suppressed, by using goserelin, for example, or even going so far as ovarian ablation.

Select publications

BIG 1-98 Collaborative Group 2005. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study. www.ibcsg.org. Abstract**

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

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

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

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**

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Perez EA et al. **Effect of letrozole versus placebo on bone mineral density in women completing 5 years (yrs) of adjuvant tamoxifen: NCIC CTG MA.17b.** San Antonio Breast Cancer Symposium 2004;**Abstract 404**.

Taylor M et al. **Incidence of 25-OH vitamin D deficiency in patients with a history of breast cancer who have musculoskeletal symptomatology.** San Antonio Breast Cancer Symposium 2004;**Abstract 3072**.

Phase II trial of capecitabine/paclitaxel as first-line therapy for metastatic disease

The rationale behind our study (Gradishar 2004) was to determine whether we could see a similar benefit to that observed in Joyce O'Shaughnessy's docetaxel/capecitabine randomized trial (O'Shaughnessy 2002).

There were differences in the two trials. Our study was largely in the first line, whereas O'Shaughnessy's trial had a mix of patients receiving first-, second- and third-line therapy.

The other distinction was the dose of the capecitabine. We started at 825 mg/m^2 twice a day for 14 days out of 21 days as opposed to the FDA-approved dose (1,250 mg/m^2) utilized in the other trial. We found the lower dose was better tolerated, which reflects the experience of most physicians using capecitabine as a single agent or in combination.

Dose reduction is usually necessary when starting at the FDA-approved dose. In practice, most physicians utilize one g/m^2. So when combining with paclitaxel, the decision was made proactively that we would use a lower starting dose.

There was a very good response rate of approximately 50 percent (3.1), which is similar to O'Shaughnessy's results in patients treated first line. If one is making the decision to combine capecitabine with a taxane, you could choose either docetaxel or paclitaxel and expect a robust response rate. It's a reasonable combination if one is wedded to the idea of using a combination in a particular patient.

Joanne Blum evaluated another regimen of capecitabine with paclitaxel (Blum 2004) and demonstrated results similar to ours (3.2). Multiple studies have evaluated capecitabine plus a taxane. All of the studies are imperfect because none of them address the fundamental issue of whether one might accomplish the same objective with sequential, rather than combination, therapy. Studies are ongoing to address that issue.

Dr Gradishar is the Director of Breast Medical Oncology and Associate Professor of Medicine at the Robert H Lurie Comprehensive Cancer Center at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

3.1 Gradishar Multicenter Phase II Study of Capecitabine Plus Paclitaxel as First-Line Therapy (N=47)

Efficacy endpoints	No. of responders	Response rate
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 mo	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)

Grade III/IV adverse events	No. of patients	Percent
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m^2 twice daily on days 1-14 every three weeks
Paclitaxel = 175 mg/m^2 on day 1 every three weeks

SOURCE: 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**

3.2 Blum Phase II Trial of Capecitabine and Weekly Paclitaxel in Taxane-Naïve Patients with Metastatic Breast Cancer: Efficacy and Toxicity

Response*	Percent	Grade III/IV adverse events (>5%)	No. of patients Grade III/IV	Percent Grade III/IV
Complete response	0	Hand-foot syndrome	10/0	18.2
Partial response	50	Neutropenia	3/4	12.7
Stable disease	30	Nausea	3/0	5.5
Clinical benefit	65	Leukopenia	1/2	5.5
* N = 54 evaluable patients		Diarrhea	3/0	5.5

SOURCE: Blum JL et al. **A Phase II trial of combination therapy with capecitabine and weekly paclitaxel for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** Poster. San Antonio Breast Cancer Symposium 2004;**Abstract 5053**.

Pivotal trial results of nanoparticle albumin-bound (*nab*) paclitaxel (Abraxane™)

The pivotal trial of patients with metastatic breast cancer compared paclitaxel 175 mg/m^2 to paclitaxel 260 mg/m^2 every three weeks. Patients receiving *nab* paclitaxel had a higher response rate — 30 percent versus 19 percent — and higher time to disease progression. Those findings were true in patients treated during first- and second-line therapy whether they had visceral disease or not (O'Shaughnesssy 2004). The results were also supported by an independent radiology review, which confirmed the findings throughout.

Nab paclitaxel also appears to be associated with far less severe myelosuppression and there is no need to administer steroids. One may have thought there would be no neuropathy with *nab* paclitaxel; however, it occurred in approximately 10 percent of patients. We're also using a dose of paclitaxel in the nanoparticle formulation that's 50 percent higher than standard paclitaxel — from 175 mg/m^2 to 260 mg/m^2.

Another interesting observation, corroborated in the pivotal trial and in the weekly trial that Joanne Blum reported (Blum 2003), is that the behavior of the neuropathy appears to be slightly different than that seen with standard paclitaxel. Although we don't have sufficient data to be absolutely definitive, there is a suggestion that with *nab* paclitaxel the neuropathy is much shorter lived — on the order of 10 days to three weeks — and it tends to diminish to a point where you can re-treat the patients. That's something that warrants further evaluation.

Physicians often ask how *nab* paclitaxel in this trial compares to docetaxel in a similar patient population. The first caveat is that we lack direct comparison data; however, if you evaluate the recently reported trials — including the comparison of paclitaxel to docetaxel in the Taxotere-311 study — the response rate with *nab* paclitaxel is strikingly similar to that of docetaxel at 100 mg/m^2, with a similar time to disease progression. Prior trials of docetaxel had response rates similar to that of *nab* paclitaxel, so with all the limitations of comparing across trials, there's at least a suggestion that the antitumor effect of *nab* paclitaxel is similar to docetaxel.

Optimizing adjuvant endocrine therapy

The ATAC trial adds to the existing body of evidence suggesting that the aromatase inhibitors incrementally improve outcome in patients who are postmenopausal with hormone-sensitive breast cancer. The results reported by Tony Howell at the 2004 San Antonio meeting suggest continued improvement in disease-free survival for patients receiving anastrozole compared to patients receiving tamoxifen, which simply confirms previous reports (Howell 2005).

Although we haven't seen a survival benefit, we may still see one down the line, but this was a favorable risk group of patients. It reaffirms the idea that anastrozole would be a reasonable choice for newly diagnosed postmenopausal

women with ER-positive disease. Another observation, true of all the other aromatase inhibitor trials, is that some degree of bone loss occurs.

We need to address that issue in the three aromatase inhibitors, but the degree of bone loss seems to be modest, and we have ways of addressing it in order to retain the positive aspects of the aromatase inhibitors. The trial data presented by Gnant demonstrated that the bone loss from goserelin and anastrozole could be eradicated by administering zoledronic acid twice per year, allowing us to think about optimizing adjuvant hormonal therapy without bone problems (Gnant 2004).

The ARNO study of anastrozole after two or three years of tamoxifen essentially replicates the IES trial with exemestane (Jakesz 2004). This trial evaluated whether five years of tamoxifen is optimal or whether an even greater benefit could be achieved by switching to anastrozole after two to three years of tamoxifen. This trial mirrors the report in the *New England Journal of Medicine* with exemestane, demonstrating an improved disease-free survival in patients who switched to exemestane (Coombes 2004).

I sit on the NCCN guidelines committee. If you evaluate the next rendition of the guidelines you'll find we have not dismissed the use of tamoxifen but rather moved the use of aromatase inhibitors up front. Within the NCCN guidelines, we're trying to select the aromatase inhibitor to be used based on the design of the study. For first-line therapy, we would use anastrozole. If a patient has been on tamoxifen for a period of time, exemestane is now a legitimate choice, and after five years of tamoxifen, letrozole is an option. We view all of these agents as active and well tolerated.

Evaluation of Fulvestrant versus Exemestane Trial (EFECT)

If you evaluate most of the available data with endocrine agents in the metastatic setting — tamoxifen, steroidal or nonsteroidal aromatase inhibitors or fulvestrant — the question that comes up is whether one sequence enhances patient outcome more than another. This becomes somewhat important, because if you could demonstrate that one sequence enhances the time to disease progression, it may be built on over time so that overall outcome is improved.

In theory, simply having an improvement in recurrence or progression of metastatic disease impacts quality of life. Patients now typically receive a nonsteroidal aromatase inhibitor — anastrozole or letrozole as the first treatment. The question became: If patients progress on one of those agents, what would be the next best therapy? Should it be the steroidal aromatase inhibitor exemestane or should it be fulvestrant?

Indirect data evaluating the sequence of a nonsteroidal aromatase inhibitor to fulvestrant suggest that 25 to 30 percent of patients may receive some benefit with that approach. The question being asked by EFECT is whether patients who've received a nonsteroidal aromatase inhibitor (3.3) should receive fulvestrant or exemestane.

We are randomly assigning patients to evaluate the response rate and the duration of the time until disease progression. At present, EFECT is accruing both in Europe and in North America and is on target to finish in the next year or so.

An important issue is whether fulvestrant 250 milligrams is optimal, even though that's the approved dose. Some of the data, including preclinical data generated by Kent Osborne and others, suggest that the dose is really on the low end of the curve where you might expect the optimal response rate. Although we may be able to increase the dose, giving 250 milligrams in each buttock, doing that too frequently becomes prohibitive, and patients may not tolerate it.

Some strategies have evaluated quickly increasing serum levels of fulvestrant and those strategies have included administering loading doses of 500 milligrams and then, within two weeks, administering another 250 milligrams and then proceeding to the monthly schedule.

Those strategies are based on mathematical modeling that have shown an ability to achieve steady-state levels much quicker and, consequently, achieve a biologically relevant dose of drug circulating in a given patient much faster (3.4). The EFECT trial has that strategy built into it with a 500-milligram loading dose.

3.3 Ongoing Clinical Trials of Hormonal Therapy in Postmenopausal Women with Metastatic Disease

Study	Trial design	Fulvestrant dosing/scheduling	Targeted accrual
SAKK	Phase II trial of monthly fulvestrant in postmenopausal women after progression on tamoxifen and a nonsteroidal aromatase inhibitor	250 mg monthly	93
EFECT	Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women after progression on a nonsteroidal aromatase inhibitor	500 mg day 0; 250 mg days 14, 28 and then monthly	660
SoFEA	Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER/PR-positive breast cancer who progressed on anastrozole or letrozole	250 mg monthly	750
SWOG S0226	Phase III randomized study of anastrozole with or without fulvestrant as first-line therapy in postmenopausal women with ER/PR-positive metastatic breast cancer	250 mg monthly	690
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole alone in postmenopausal women with ER/PR-positive metastatic breast cancer or premenopausal women on goserelin	500 mg day 0; 250 mg days 14, 28 and then monthly	558
ECOG 4101	Phase II trial of fulvestrant + gefitinib vs anastrozole + gefitinib in postmenopausal women with ER/PR-positive recurrent or metastatic breast cancer	250 mg monthly	148

SOURCES: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®).** Poster. Lynn Sage Breast Cancer Symposium 2003; NCI Physician Data Query, April 2005.

3.4 Earlier Achievement of Steady-State Plasma Concentrations with a Loading Dose Regimen with Fulvestrant

"When given by monthly 250 mg im injection, in the manner currently shown to produce treatment responses, fulvestrant plasma concentration profiles reach steady-state after 3-6 doses. However, the use of a loading-dose regimen may allow steady-state levels of fulvestrant to be achieved more rapidly. Such an approach may not impact on the long-term efficacy of the drug, but may allow early responses to be identified. It is possible to model the effects of the addition of a loading regimen on the attainment of steady-state fulvestrant levels. Here, an initial dose of 500 mg fulvestrant is given on day 0, followed by 250 mg fulvestrant on day 14. This is followed 14 days later by the standard fulvestrant 250 mg monthly dose. The model demonstrates that steady-state is achieved between days 28-56. The use of a fulvestrant loading dose regimen will be investigated in several of the new fulvestrant clinical trials… ."

SOURCE: Robertson JFR et al. **Endocrine treatment options for advanced breast cancer — The role of fulvestrant.** *Eur J Cancer* 2005;41(3):346-56. **Abstract**

Select publications

Blum JL et al. **A Phase II trial of combination therapy with capecitabine and weekly paclitaxel for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** Poster. San Antonio Breast Cancer Symposium 2004;**Abstract 5053**.

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** *Proc ASCO* 2003;**Abstract 64**.

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**

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

Gradishar WJ 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**

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

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

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.** San Antonio Breast Cancer Symposium 2004;**Abstract 1070**.

Michael Gnant, MD

EDITED COMMENTS

Background to the study of aromatase inhibitors in premenopausal women

We are moving toward treating every patient with an aromatase inhibitor. While these drugs are more effective than tamoxifen and better tolerated in many ways, they have one clear-cut limitation — their effect on bone. They exert the positive effect of keeping the cancer away by reducing estrogen, but this is not good for bone density or bone quality.

We were particularly interested in younger patients because they are physiologically used to higher levels of estrogen from their functioning ovaries. We undertook ABCSG-12 to first establish the severity of that treatment-induced bone loss and, second, whether it can be prevented or treated (Gnant 2004).

We found out that a significant loss occurs — on average close to 15 percent — in these premenopausal women treated with endocrine therapy. We also discovered that it could be prevented with zoledronic acid given twice a year, which we believe is an elegant and easy way to eliminate the problem.

ABCSG-12: Study design

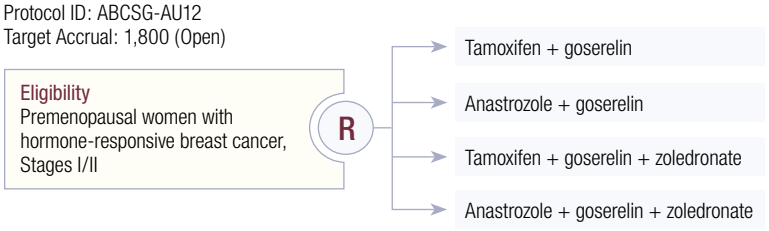
The ABCSG-12 study is a four-arm trial for premenopausal, hormone receptor-positive breast cancer patients (Gnant 2004; [4.1]). Patients in this trial are treated with endocrine treatment alone. They can receive preoperative chemotherapy to facilitate breast conservation, but postoperative chemotherapy is not administered because we have previously established that these patients — particularly the good-prognosis subgroup — can be treated without adjuvant chemotherapy.

All patients receive goserelin and are randomly assigned to receive tamoxifen versus anastrozole or the two treatments plus zoledronic acid. The treatment is for three years. This trial aims to establish the value of aromatase inhibitors for premenopausal patients because the results we have so far are derived from postmenopausal patients. We will recruit 1,800 patients and currently we have accrued close to 1,400.

Dr Gnant is a Professor of Experimental Surgical Oncology at the Medical University of Vienna in Vienna, Austria.

We currently have three-year results from the bone substudy, which closed 18 months ago with 401 patients. These patients received repeated DEXA measurements of their bone density in both their lumbar spine and trochanter.

4.1 Phase III Study Comparing an LHRH Agonist with Tamoxifen or Anastrozole with or without Zoledronate



SOURCE: Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal women receiving adjuvant goserelin and tamoxifen or goserelin and anastrozole for hormone-responsive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

Results of the bone subprotocol: Bone loss with tamoxifen

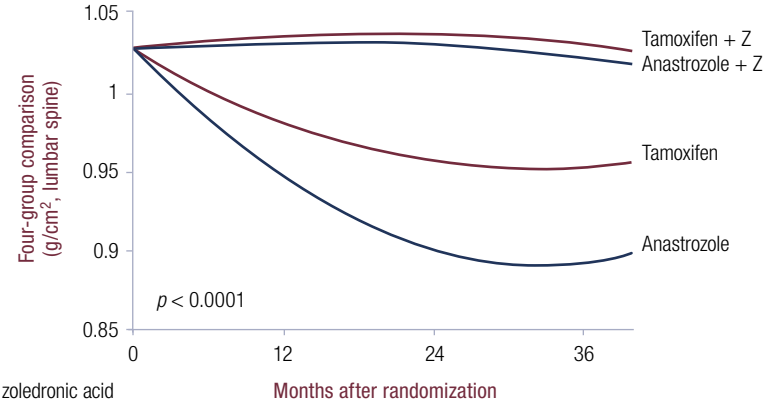
Our presentation two years ago was criticized because it was considered very early, despite the fact that this was the initial plan. Then the Data Monitoring and Steering committees decided the trial would have to be enlarged in order to prove that what we saw then was scientifically sound. Now, the results are beyond any doubt because we have much more mature data in the sense that most patients have their three-year measurements in (Gnant 2004). There will also be a five-year measurement.

One of the things that we see is some bone loss, even in the women on tamoxifen and goserelin. In postmenopausal women, we know that tamoxifen acts by basically protecting the bone with its estrogenic agonistic effects. In the premenopausal woman, however, tamoxifen is not able to balance the effects of ovarian suppression, so we see 11 percent bone loss with goserelin and tamoxifen (4.2).

Several ongoing prospective studies are monitoring bone density in postmenopausal women receiving an aromatase inhibitor — such as the Zometa-Femara® Adjuvant Synergy Trial (Z-FAST/ZO-FAST). The six-month results from the Z-FAST trial show a three percent difference between an up-front prevention type approach with zoledronic acid versus waiting for bone loss in order to treat it (Brufsky 2004).

But bone loss is associated with age, and I believe it also makes a difference whether you start out with a vivid and functioning estrogen metabolism versus a 75-year-old lady in whom estrogen levels are, by nature, very low.

4.2 ABCSG-12: Zoledronic Acid Effectively Counteracts Cancer Treatment-Induced Bone Loss in Premenopausal Women Receiving Adjuvant Goserelin with Tamoxifen or Anastrozole



SOURCE: Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal women receiving adjuvant goserelin and tamoxifen or goserelin and anastrozole for hormone-responsive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

Approach to bone in postmenopausal women on aromatase inhibitors

We have implemented a general recommendation for postmenopausal women in our country to have annual measurements of bone mineral density. So far, this has not been done on a systematic basis. Once diagnosed, bone loss should be treated.

Treatment-induced bone loss should be treated the same way natural osteoporosis is treated. My suspicion is that oncologists have a tendency to overlook the problem. If nothing else, we can contribute to awareness: We should not underestimate the problem and should treat it accordingly.

In terms of deciding when to initiate therapy and what therapy to use, we follow the recommendations of the ASCO Bisphosphonate Panel (Hillner 2003) and the American Osteoporosis Society, which suggest that treatment with calcium/vitamin D should be used for women with osteopenia — T scores between -1 and -2.5. We initiate bisphosphonates in women with osteoporosis where the T score goes down below -2.5.

Switching from tamoxifen to anastrozole after two years

Raimund Jakesz from our group presented a combined analysis of an Austrian and a German trial, which encompassed 3,200 patients overall (Jakesz 2004). This was a comparison of switching from tamoxifen to anastrozole after two

years compared to keeping patients on tamoxifen for five years in the adjuvant, postmenopausal, receptor-positive setting.

This is a clean study in which 100 percent of patients are receptor-positive. A 40 percent reduction in risk of relapse occurred in patients who switched compared to patients maintained on tamoxifen. This meets our stopping boundaries and we are currently discussing how to deal with that.

Of course, we have to inform the patients, and we will either close the trial or at least amend it in some way. In terms of side effects and toxicity, we have observed that basically all the aromatase inhibitor trials have seen a benefit to aromatase inhibitors in terms of gynecological side effects, but again, with more fractures as compared to the tamoxifen group.

One specific point that is different from the other trials is that in our trial, switching is most effective in terms of preventing distant metastases. This is interesting, because although we do not have a good explanation, it suggests there might be a later survival benefit if we keep the trial alive and keep following the patients. It's very exciting.

The effects observed are comparable in magnitude to those seen in the IES trial of switching to exemestane. You have to be quite cautious making indirect comparisons between trials, but I would suggest that the data are in the same direction. I was personally hoping that exemestane would be a little different in terms of bone, because of its steroidal structure, but this does not appear to be the case.

Select publications

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

Chlebowski RT. **Bone health in women with early-stage breast cancer.** *Clin Breast Cancer* 2005;5(Suppl 2):35-40. **Abstract**

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

Harvey HA. **Optimizing bisphosphonate therapy in patients with breast cancer on endocrine therapy.** *Semin Oncol* 2004;31(6 Suppl 12):23-30. **Abstract**

Hillner BE et al. **American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer.** *J Clin Oncol* 2003;21(21):4042-57. **Abstract**

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

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

Editor's Note:

Shortly after the interview with Dr Perez, the NCI issued a press release regarding the combined analysis of NCCTG-N9831 and NSABP-B-31, which evaluated AC followed by paclitaxel with or without trastuzumab in the adjuvant setting (see page 25, 5.1).

Overview of the adjuvant trials of trastuzumab

There are four very large trastuzumab adjuvant trials, which are complementary and reflect worldwide collaboration. The NSABP originally had overall survival as the primary endpoint. Then, based on new data, they changed the schedule of paclitaxel to be similar to what we did in the Intergroup study in 9831, in that they allowed weekly paclitaxel. They also modified their primary endpoint to be disease-free survival, which is consistent with our study. These two studies were built on what we had learned from CALGB-9344 and what we had learned in terms of tolerability from our own metastatic studies and even ECOG-E1199.

N9831 includes patients with node-positive or high-risk, node-negative, HER2-positive breast cancer. The patients are randomly assigned to either: (1) chemotherapy alone, which consists of AC once every three weeks for four cycles, followed by weekly paclitaxel for 12 doses; (2) the same chemotherapy, followed by a year of weekly trastuzumab; or (3) the same chemotherapy with the introduction of trastuzumab when the patients start receiving weekly paclitaxel (ie, 12 doses of trastuzumab in combination with weekly paclitaxel and 40 additional weeks of trastuzumab).

The BCIRG-006 and HERA trials drew from other experiences. BCIRG used AC followed by docetaxel once every three weeks as the standard chemotherapy arm. Then they added sequential trastuzumab. In the third arm, they looked at a nonanthracycline-containing regimen, which uses docetaxel/carboplatin once every three weeks with trastuzumab. HERA was completely different in that it only looked at the sequential introduction of trastuzumab after chemotherapy.

Dr Perez is a Professor of Medicine at the Mayo Medical School, Director of the Cancer Clinical Study Unit and Director of the Breast Cancer Program in the Division of Hematology and Oncology at the Mayo Clinic in Jacksonville, Florida.

The patients completed the chemotherapy and were then randomized to no trastuzumab, trastuzumab for one year or trastuzumab for two years. In HERA, trastuzumab is administered once every three weeks. They have a detailed description of which chemotherapies are potentially to be included, but the list is very long. Essentially, it's almost anything that physicians feel comfortable recommending to their patients.

Initial reporting of the adjuvant trials of trastuzumab

We have been working with the NSABP, the National Cancer Institute and the FDA for more than a year in order to obtain approval for a formal joint analysis of the NCCTG and NSABP trials of adjuvant trastuzumab for disease-free survival and overall survival. We recently obtained formal FDA approval. The next step will be to look at the first interim evaluation of the data.

There are enough events between the two trials to perform that analysis, but the question remains whether the magnitude of the difference between trastuzumab versus no trastuzumab is large enough to meet the statistical boundaries outlined for the release of the data. Although N9831 will complete accrual in a couple of months, we still need some time for all of the patients to receive trastuzumab, so we need to be very careful. We don't want to be too premature in releasing data. At the same time, if the differences are large enough to cross statistical boundaries, then we would need to go to our respective Data Monitoring Committees and have discussions related to timing of release of this information.

The data could be available soon if the differences are huge. This is very exciting because there has been a lot of work and time invested in the correct conduct of these clinical trials with appropriate monitoring, and patients have been very compliant. The BCIRG study was closed to patient accrual almost a year ago and the HERA study completed accrual a few months ago. HERA enrolled more than 4,700 patients, and I believe the timing of data release may occur at approximately the same time for all of the trials because the combined analysis of N9831 with the NSABP study includes more than 5,000 patients.

Cardiac safety of adjuvant trastuzumab

When we designed N9831, it was a coordinated effort between many groups because we wanted to have consistent cardiac testing and definitions of what we considered to be clinically acceptable. More than a four percent difference in clinical cardiac events between the trastuzumab-containing and the nontrastuzumab-containing arms would have been considered unacceptable. Although our clinical trial demonstrated that clinical cardiac events are observed in patients receiving adjuvant trastuzumab, I'm pleased to say that the difference is less than four percent compared to the control arm (Perez 2005b). The numbers are actually a bit lower than the numbers in NSABP-B-31 (Geyer 2003) but statistically quite similar.

At this point, we have not seen any difference in cardiac events between the two trastuzumab-containing arms. Not every patient has a reversal of their

cardiac events, but most patients definitely improve not only in terms the clinical symptomatology but also measurable left ventricular ejection fraction.

5.1 National Cancer Institute News Release, April 25, 2005 (excerpt)

http://www.nci.nih.gov/newscenter/pressreleases/HerceptinCombination2005

Trastuzumab Combined with Chemotherapy Improves Disease-Free Survival for Patients with Early-Stage Breast Cancer

"Results from two large randomized clinical trials for patients with HER-2 positive invasive breast cancer show that those patients with early-stage breast cancer who received Herceptin® (trastuzumab) in combination with chemotherapy had a significant decrease in risk for breast cancer recurrence compared with patients who received the same chemotherapy without trastuzumab...

"The Data Monitoring Committees overseeing the combined analysis of these trials (known as NSABP-B-31 and NCCTG-N9831) recommended that the results of a recent combined interim analysis be made public because the studies had met their primary endpoints of increasing disease-free survival...

"The improvement in overall survival also was statistically significant for women receiving a combination of chemotherapy and trastuzumab...

"Patients in the clinical trials who received trastuzumab in combination with standard combination chemotherapy had a 52 percent decrease in disease recurrence compared to patients treated with chemotherapy alone. This difference is highly statistically significant. 'This is a major advance for many thousands of women with breast cancer,' said NCI Director Andrew C von Eschenbach, MD. 'These results are one more example that we are at a major turning point in the use of targeted therapies to eliminate suffering and death from cancer,' he added.

"'These findings confirm that we now have a very potent weapon against the recurrence of cancer cells that overexpress HER-2,' said Edith A Perez, MD, who chaired the NCCTG trial and is a medical oncologist at the Mayo Clinic in Jacksonville, FL.

"Edward Romond, MD, study chair for the NSABP and professor of oncology at the University of Kentucky, in Lexington, KY, noted, 'For women with this type of aggressive breast cancer, the addition of trastuzumab to chemotherapy appears to virtually reverse prognosis from unfavorable to good.'

"Information from over 3,300 patients enrolled in these studies was used for analysis. Patients with operable breast cancer whose tumors over-expressed HER-2 were enrolled in these studies between February 2000 and April 2005. Patients were randomized to receive chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel, or doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab.

"Chemotherapy of the type given in these studies has a risk of congestive heart failure (weakening of the heart muscle) of less than 1 percent. In these studies, the likelihood of congestive heart failure in women receiving the combination of chemotherapy and trastuzumab was increased by 3 percent to 4 percent."

Phase III randomized trial comparing nanoparticle albumin-bound (*nab)* paclitaxel (Abraxane) to paclitaxel

Efficacy

Investigators enrolled patients who were eligible to receive first-, second-, third- or even fourth-line chemotherapy for metastatic breast cancer. The data are mature, were presented at the 2003 San Antonio Breast Cancer Symposium and will soon be published. This trial demonstrated improvements in the response rate and time to progression for patients treated with *nab* paclitaxel compared to patients treated with paclitaxel, when both drugs were administered once every three weeks (O'Shaughnessy 2003; [5.2]).

We recently obtained the survival data from this study, which we presented at the 2005 Miami Breast Cancer Conference. In the overall group of patients, a 10-week improvement in median survival was found for the patients assigned to *nab* paclitaxel compared to patients treated with paclitaxel, but that number did not reach statistical significance.

However, when subset analyses were performed, patients treated with *nab* paclitaxel as second-, third- or fourth-line therapy still had a 10-week improvement in median survival compared to patients treated with paclitaxel, and the number reached statistical significance (Perez 2005a; [5.2]).

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

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

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

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

Toxicities

Despite premedications, some allergic reactions were seen in the patients treated with paclitaxel. We have seen this not only with paclitaxel but also with docetaxel. In spite of almost a doubling of the paclitaxel dose with *nab* paclitaxel (260 mg/m^2 versus 175 mg/m^2 both administered once every three weeks), a significantly lower incidence of myelosuppression was observed with *nab* paclitaxel than paclitaxel (O'Shaughnessy 2003; [5.2]).

More cases of neuropathy were seen in the patients treated with *nab* paclitaxel than in patients treated with paclitaxel; however, the numbers were small in both arms of the trial. The relative rates of Grade III sensory neuropathy were 10 percent for patients treated with *nab* paclitaxel and two percent for patients treated with paclitaxel (O'Shaughnessy 2003; [5.2]).

Because we're administering more paclitaxel with the albumin-bound formulation, it's not completely unexpected that we would see more neuropathy. The investigators evaluated the evolution of the neuropathy in the small group of patients. With treatment interruption, the Grade III neuropathy associated with *nab* paclitaxel resolved to Grade I or II after a median of 22 days (O'Shaughnessy 2003).

Select publications

Baselga J et al. **Future options with trastuzumab for primary systemic and adjuvant therapy.** *Semin Oncol* 2004;31(5 Suppl 10):51-7. **Abstract**

Bell R et al. **Maximizing clinical benefit with trastuzumab.** *Semin Oncol* 2004;31(5 Suppl 10):35-44. **Abstract**

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

Emens LA, Davidson NE. **Trastuzumab in breast cancer.** *Oncology (Huntingt)* 2004;18(9):1117-28. **Abstract**

Geyer, CE Jr et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus trastuzumab in patients (pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** San Antonio Breast Cancer Symposium 2003;**Abstract 23**.

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

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

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

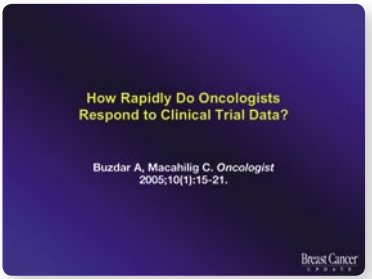
Perez EA et al. **Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial.** *J Clin Oncol* 2004;22(18):3700-4. **Abstract**

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;**Abstract 556**.

PowerPoint Journal Club

This PowerPoint Journal reviews recently published clinical research articles and presentations. In this issue, we review a study by Aman Buzdar, MD and Cynthia Macahilig demonstrating the influence of clinical trial results from the ATAC trial over 28 months on the use of tamoxifen and anastrozole in the treatment of postmenopausal women with hormone receptor-positive early breast cancer; a report by Kathy Miller, MD et al on a Phase III trial comparing capecitabine with or without bevacizumab in patients with previously treated metastatic disease; and papers by Mehrdad Nadji, MD and colleagues evaluating IHC assays for estrogen and progesterone receptors in 5,993 cases of invasive mammary carcinomas.

These PowerPoint Journal Club slides are provided in different formats in this monograph and on the enclosed enhanced CD. The slide presentation on the CD was designed for optimal viewing on a large screen in a dark room (below, right) and represents top-line data and information from the figures in this book. The PowerPoint file and PDF file of this monograph can be accessed at **www.BreastCancerUpdate.com**.



6.1

How Rapidly Do Oncologists Respond to Clinical Trial Data?

Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21.

SLIDE 6.1 Results from large clinical trials should have an impact on clinical practice. Relatively few studies, though, have assessed the influence of clinical trial results on the practice of oncology.

6.2

Response to Clinical Trial Data: Objectives

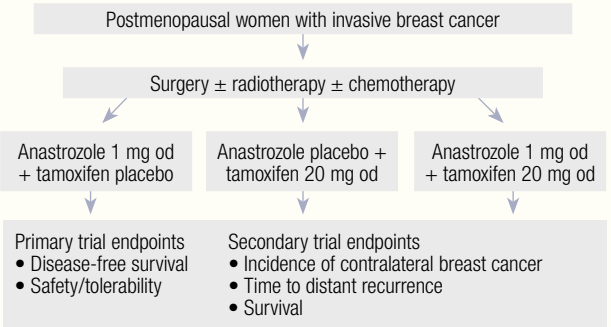
- Determine the impact of the presentation and publication of the results from the Arimidex®, Tamoxifen, Alone or in Combination (ATAC) trial on medical oncologists' prescribing patterns for adjuvant hormonal therapy in the United States.

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.2 In this paper, Buzdar and Macahilig attempt to determine the impact of the presentation and publication of the results from the ATAC trial on medical oncologists' prescribing patterns for adjuvant hormonal therapy in the United States.

6.3

ATAC Trial Design



SOURCE: With permission from Buzdar A. Presentation. SABCS 2002;**Abstract 13**.

SLIDE 6.3 ATAC compared anastrozole, tamoxifen, or the combination as adjuvant therapy in postmenopausal women (n=9,366) with operable breast cancer. The primary endpoints for the trial were disease-free survival and safety/tolerability.

6.4

ATAC Trial Results in Patients with Hormone Receptor-Positive Disease

Years of follow-up	Absolute differences in recurrence rates between anastrozole and tamoxifen
Three years	1.7%
Four years	2.4%
Five years	2.8%

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

SLIDE 6.4 After a median follow-up of 68 months, there were significant improvements in disease-free survival and time to recurrence with anastrozole compared to tamoxifen. With hormone-receptor positive disease, the absolute difference in recurrence rates increased with each year of follow-up.

6.5

Response to Clinical Trial Data: Participants

- 150 medical oncologists per study period:
  - Board certified
  - Practicing for two to 30 years
  - Spend ≥50 percent of their time in office or private practice
  - Treated ≥10 patients with breast cancer in the past 30 days
  - Wrote ≥100 prescriptions in the past six months for hormonal therapy for breast cancer

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.5 For each study period, 150 US oncologists were recruited. Participants were board certified, spent at least 50 percent of their time in office or private practice, treated at least 10 breast cancer patients in the past 30 days and wrote at least 100 prescriptions for hormone therapy in the past six months.

6.6

Response to Clinical Trial Data: Stratification

Medical oncologists were stratified according to the number of prescriptions written for hormonal therapy in the six months preceding the interview:

- Group 1 (n=75): 100 to 571 prescriptions
- Group 2 (n=45): 572 to 870 prescriptions
- Group 3 (n=30): >870 prescriptions

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.6 The medical oncologists were stratified by the number of prescriptions they wrote for hormonal therapy for breast cancer in the previous six months. Group 1 wrote 100 to 571 prescriptions. Group 2 wrote 572 to 870 prescriptions, and Group 3 wrote more than 870 prescriptions.

6.7

Response to Clinical Trial Data: Data Collection

- Structured, computer-assisted telephone interviews were 45 to 60 minutes
- Eight study periods were used:
  - July 2001
  - March 2002
  - July 2002
  - November 2002
  - February 2003
  - June 2003
  - August 2003
  - November 2003

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.7 The data were collected via structured, computer-assisted telephone interviews that lasted 45 to 60 minutes. Eight different study periods were used: July 2001, March 2002, July 2002, November 2002, February 2003, June 2003, August 2003 and November 2003.

6.8

Response to Clinical Trial Data: Predefined Questions

1. Thinking of the last five postmenopausal patients with ER-positive, early- or adjuvant-stage breast cancer whom you have treated in the past three months, what products, alone or in combination with other treatment modalities (such as hormonal, chemotherapy, radiation, surgical, etc), did you use as first therapy?
2. Please indicate the therapy you prescribed for your last five postmenopausal patients with early- or adjuvant-stage breast cancer.
3. If you used hormonal therapy, please specify the brand or product. Let's start with patient 1... (Please use the number code[s] for each product used alone or in combination.) The total must equal five patients.

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.8 Predefined questions were utilized in the telephone interviews. The medical oncologists were asked about their initial hormonal therapy choices for the last five postmenopausal patients with ER-positive, early breast cancer.

6.9

Response to Clinical Trial Data: Medical Oncologists' Demographics

Male	81% - 83%
Geographic region	
Northeast	26% - 33%
North Central	19% - 25%
South	26% - 33%
West	17% - 23%
Mean number of patients with breast cancer treated in the past six months	
Group 1	112 - 150
Group 2	142 - 176
Group 3	192 - 284
Patients with early breast cancer who are postmenopausal	59% - 61%

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.9 The majority of participants were males who were consistently distributed across the four US geographic regions. Each medical oncologist had treated a mean of 112 to 284 patients with breast cancer in the last six months. They all indicated that about 60 percent of their patients with early breast cancer were postmenopausal.

6.10

Response to Clinical Trial Data: Trends in Use of Adjuvant Systemic Therapy

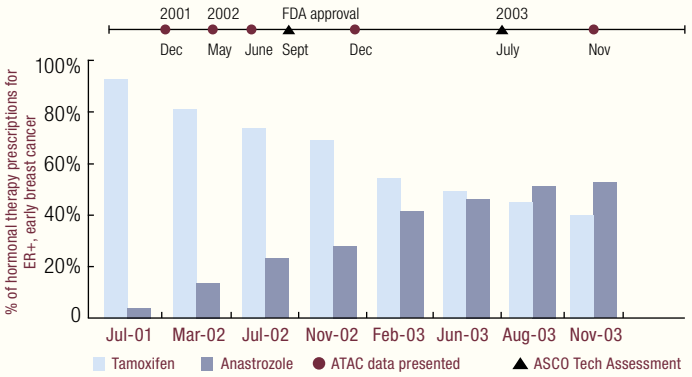
- From July 2001 to March 2002:
  – Use of adjuvant hormonal therapy increased from 81% to 91% ($p < 0.05$)
- From March 2002 to July 2002:
  – Another significant ($p < 0.05$) increase in the use of adjuvant hormonal therapy
- From July 2002 to November 2002:
  – Another significant ($p < 0.05$) increase in the use of adjuvant hormonal therapy
- From November 2002 to November 2003:
  – Use of adjuvant hormonal therapy remained stable at 98%

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.10 The reported use of adjuvant hormonal therapy for postmenopausal women with ER-positive early breast cancer increased from 81 percent in July 2001 to 98 percent in November 2003. During the same time, the use of adjuvant chemotherapy remained relatively stable, ranging from 36 to 50 percent.

6.11

Impact of ATAC Results on the Use of Anastrozole and Tamoxifen



SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.11 After the initial ATAC trial results were presented in December 2001, the reported use of anastrozole increased from two percent (July 2001) to 14 percent (March 2002) of adjuvant hormonal therapies. By November 2003, anastrozole accounted for 53 percent of the hormonal therapy choices.

6.12

Response to Clinical Trial Data: Conclusions

"The use of tamoxifen as an adjuvant therapy in postmenopausal ER-positive EBC [early breast cancer] patients has declined, while the use of anastrozole has increased significantly and now accounts for over 50% of hormonal therapy prescriptions.

"The observations in this paper suggest that clinical practice in oncology can change rapidly following the publication of robust, large-scale trial data that document clinically relevant improvements in efficacy and safety."

SOURCE: Buzdar A, Macahilig C. *Oncologist* 2005;10(1):15-21. **Abstract**

SLIDE 6.12 The reports of the positive ATAC trial results appear to have significantly influenced adjuvant hormonal therapy selection as reported by medical oncologists in the United States. Future trials should evaluate the influence of clinical trial results on prescribing patterns.

Select publications

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone, or in Combination) adjuvant breast cancer trial in post-menopausal (PM) women.** San Antonio Breast Cancer Symposium 2001;8. No abstract available

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

Baum M 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**

Buzdar A, on behalf of the ATAC Trialists' Group. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** San Antonio Breast Cancer Symposium 2002;**Abstract 13**.

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

Winer EP et al. **American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**

7.1

Randomized Phase III Trial of Capecitabine Compared to Bevacizumab Plus Capecitabine in Patients with Previously Treated Metastatic Breast Cancer

Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS.
J Clin Oncol 2005;23(4):792-9.

SLIDE 7.1 In a Phase II trial of bevacizumab in patients previously treated for metastatic breast cancer (MBC), the rates for objective response and stable disease at 22 weeks were 9.3 and 17 percent, respectively. Those benefits were the basis for a Phase III randomized trial comparing capecitabine with or without bevacizumab.

7.2

Eligibility Criteria

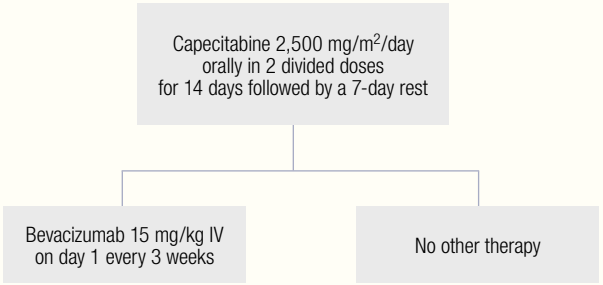
- Metastatic breast cancer (MBC)
- Prior therapy with an anthracycline and a taxane
- 1 or 2 prior chemotherapy regimens for MBC or relapse <12 months after adjuvant anthracycline and taxane therapy
- Patients with HER2-positive disease must have progressed following trastuzumab
- Bidimensionally measurable disease
- ECOG PS = 0 or 1
- Adequate renal, hepatic and hematologic function

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.2 The eligibility criteria included MBC, prior anthracycline and taxane, one or two prior chemotherapy regimens for MBC or relapse <12 months after adjuvant anthracycline and taxane, progression after trastuzumab for HER2-positive disease, ECOG PS = 0 or 1 and adequate renal, hepatic and hematologic function.

7.3

Treatment Plan



SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.3 All patients received capecitabine 2,500 mg/m^2/day orally in two divided doses for 14 days followed by a seven-day rest. Patients randomly assigned to the combination arm received bevacizumab 15 mg/kg intravenously on day one of each three-week cycle. Therapy continued for a maximum of 35 cycles.

7.4

Clinical Endpoints

- Primary
  - Progression-free survival determined by IRF*
  - Safety
- Secondary
  - Progression-free survival determined by investigator
  - Objective response rate determined by investigator and IRF*
  - Duration of response determined by investigator and IRF*
  - Quality of life
  - Survival

*Independent review facility

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.4 The primary endpoints of the trial were progression-free survival (PFS) and safety. Secondary endpoints included: PFS, objective response rate, duration of response, quality of life and survival.

7.5

Patient Characteristics

	Bevacizumab + capecitabine (n=232)	Capecitabine (n=230)
Mean age	51 years	52 years
ER-positive	41.8%	51.7%
PR-positive	32.3%	41.7%
HER2-positive (IHC 3+ or FISH+)	26.3%	20.4%
Median duration of metastatic disease	1.0 years	1.3 years
Visceral disease	77.6%	80.0%
Three or more sites of disease	49.1%	50.4%

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.5 A total of 462 patients were enrolled on the trial. Two hundred thirty patients were randomly assigned to capecitabine alone and 232 to capecitabine plus bevacizumab. The patients' baseline demographic and tumor characteristics were balanced between the groups.

7.6

Efficacy

	Bevacizumab + capecitabine (n=232)	Capecitabine (n=230)	*p*-value
Objective response rate			
Investigator	30.2%	19.1%	0.006
IRF	19.8%	9.1%	0.001
Median PFS			
IRF	4.86 months	4.17 months	0.857
Median duration of response			
IRF	5.0 months	7.6 months	—
Median overall survival	15.1 months	14.5 months	—

IRF = independent review facility; PFS = progression-free survival

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.6 The addition of bevacizumab to capecitabine resulted in significantly improved objective response rate. However, PFS, response duration, overall survival or time to deterioration of quality of life were not altered. The IRF and investigators disagreed on disease progression in 105 patients.

7.7

Incidence of Grade III Toxicities Commonly Associated with Capecitabine

	Bevacizumab + capecitabine (n=229)	Capecitabine (n=215)
Diarrhea	11.8%	10.7%
Stomatitis	1.7%	0
Hand-foot syndrome	27.5%	24.2%

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.7 Bevacizumab did not alter the frequency or severity of the Grade III toxicities associated with capecitabine.

7.8

Dose Intensity and Dosage Reductions for Capecitabine

	Bevacizumab + capecitabine (n=229)	Capecitabine (n=215)
Mean delivered dose intensity	75%	80%
Patients requiring dosage reductions	79%	65%

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.8 The mean delivered dose intensity for capecitabine was similar for the patients in both randomization arms. Dosage reductions for capecitabine were required for 65 percent of those receiving capecitabine alone versus 79 percent of those receiving the combination.

7.9

Incidence of Grade III Toxicities Commonly Associated with Bevacizumab

	Bevacizumab + capecitabine (n=229)	Capecitabine (n=215)
Hypertension	17.9%	0.5%
Proteinuria	0.9%	0
Bleeding	0.4%	0.5%
Thrombotic event	3.9%	2.3%
Pulmonary embolism	0	0

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.9 Grade III hypertension and proteinuria occurred more frequently in patients receiving bevacizumab. Grade III bleeding was rare and not different between groups, but patients receiving capecitabine alone had fewer episodes of Grade I or II epistaxis.

7.10

Conclusions

"The addition of bevacizumab to capecitabine clearly increased response rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen. Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups."

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

SLIDE 7.10 In women with previously treated MBC, the addition of bevacizumab to capecitabine increases the response rate but not PFS or response duration. Patients with less advanced disease may obtain additional benefits from bevacizumab.

7.11

Ongoing Studies Incorporating Capecitabine and Bevacizumab as First-Line Therapy

Study	Phase	Design
NCCTG XEL 450 *Primary investigator: E Perez*	II	Capecitabine (825 mg/m^2 BID) + docetaxel (75 mg/m^2) +bevacizumab
Roche ML18527 *Primary investigators: G Sledge, E Winer, B Gradishar*	II	Capecitabine (1,000 mg/m^2 BID) + bevacizumab until progression followed by weekly paclitaxel + bevacizumab or vinorelbine + bevacizumab

SOURCE: Roche Laboratories Inc.

SLIDE 7.11 Currently, two Phase II trials are incorporating capecitabine and bevacizumab into first-line chemotherapeutic regimens for metastatic disease.

Select publications

Cobleigh MA et al. **A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):117-24. **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**.

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003;**Abstract 825**.

Hilan KJ et al. **The role of VEGF expression in response to bevacizumab plus capecitabine in metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 766**.

Ignoffo RJ. **Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor.** *Am J Health Syst Pharm* 2004;61(21 Suppl 5):21-6. **Abstract**

Miller KD. **E2100: A phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer.** *Clin Breast Cancer* 2003;3(6):421-2. No abstract available

Miller KD. **Recent translational research: Antiangiogenic therapy for breast cancer — Where do we stand?** *Breast Cancer Res* 2004;6(3):128-32. **Abstract**

Overmoyer B et al. **Phase II trial of neoadjuvant docetaxel with or without bevacizumab in patients with locally advanced breast cancer.** *Proc ASCO* 2004;**Abstract 727**.

Rugo HS. **Bevacizumab in the treatment of breast cancer: Rationale and current data.** *Oncologist* 2004;9(Suppl 1):43-9. **Abstract**

8.1

Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered: Experience with 5,993 Breast Cancers

Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR.
Am J Clin Pathol 2005;123(1):21-7.

SLIDE 8.1 In breast cancer, a positive estrogen receptor (ER) status has correlated with disease-free survival and improved response with hormone therapy. Immunohistochemical (IHC) analysis of ER status may be more discriminatory for predicting overall and disease-free survival in routine assessments of hormone receptor status.

8.2

Methods: Study Sample

- 5,993 consecutive cases of breast cancer
  - 5,497 were tissue samples evaluated for ER and PR; 496 were fine needle aspiration cytology specimens evaluated for ER only
- For the majority of cases, the tissue fixative was 10% phosphate-buffered formalin

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.2 Initial observations from the daily IHC analysis of steroid receptors in the laboratory led Nadji et al to re-evaluate semiquantitation of the steroid receptor reaction. They conducted a study of the immunohistochemical staining for ER and PR in 5,993 consecutive breast cancer cases during a six-year period.

8.3

Methods: Antibodies and Control Utilized

Antibodies:

- ER detection:
  - Monoclonal antibody 1D5 (reacts with the A/B region of the N terminal domain of ERα)
- PR detection*
  - Anti-PR antibody 636

  * PR detection was not performed on the cytology specimens.

Controls:

- Positive internal samples: Tumor blocks with normal or nonneoplastic mammary epithelium
- Positive external samples: Cases of invasive mammary carcinoma
- Negative antibody sample: Nonimmune mouse IgG

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.3 Mouse IgG monoclonal antibody (1D5) that reacts with the A/B region of the N terminal domain of ERα was used to detect ER. Monoclonal anti-PR antibody 636 was used to detect PR. Positive and negative controls were also used.

8.4

Methods: Evaluation of Staining Results

- Presence of positive reaction
- Cellular localization (nuclear or cytoplasmic)
- Pattern of staining (focal or diffuse)
- Intensity of reaction in individual tumor cells (strong or weak)

Any positive reaction for ER and PR, irrespective of percentage of reactive cells, was considered positive (ie, no arbitrary percentage cutoff point was used).

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.4 The stained slides were evaluated for the presence of positive reaction, cellular localization, staining pattern (focal or diffuse) and intensity of reaction in individual tumor cells (strong or weak). Any positive reaction for ER and PR, irrespective of percentage of reactive cells, was considered positive.

8.5

Results: ER and PR Status in 5,497 Cases

Receptor status	Percent
ER-positive	75
PR-positive	55
ER-positive and PR-positive	55
ER-positive and PR-negative	20
ER-negative and PR-negative	25
ER-negative and PR-positive	0

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.5 Of the tissue specimens, 75 percent were ER-positive, 55 percent were PR-positive, 55 percent were ER-positive/PR-positive, 20 percent were ER-positive/PR-negative and 25 percent were ER-negative/PR-negative. All of the PR-positive specimens were also ER-positive; no specimens were ER-negative and PR-positive.

8.6

Results: Relationship between Histologic Subtype and ER and PR Status

Type of carcinoma	Number of specimens	ER-positive (%)	PR-positive (%)
Infiltrating ductal*	4,396	74	53
Tubular	237	100	95
Colloid	184	100	72
Papillary	44	100	80
Apocrine	40	0	0
Medullary	96	0	0
Metaplastic	120	0	0
Infiltrating lobular	380	100	77

* Not otherwise specified

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.6 Among unspecified infiltrating ductal carcinoma specimens, 74 percent were ER-positive and 53 percent were PR-positive. All pure tubular, colloid, papillary and infiltrating lobular carcinomas and none of the apocrine, medullary or metaplastic carcinomas were ER-positive. PR positivity was less predictable.

8.7

Results: Relationship between Nuclear Grade and ER Status in Cases of Infiltrating Ductal Carcinoma

Nuclear grade	Number of specimens	ER-positive
Grade I	1,151	100%
Grade II	3,298	75%
Grade III	443	2%
Total	4,892	74%

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.7 Among 4,892 cases of infiltrating ductal carcinoma (no special type), all nuclear Grade I tumors were ER-positive. In contrast, 75 percent of the nuclear Grade II tumors and only two percent of the nuclear Grade III tumors were ER-positive.

8.8

Results: Pattern of ER and PR Staining

Pattern	ER-positive (n=4,100)	PR-positive (n=3,016)
Diffuse	92%	79%
Focal	8%	21%

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.8 In most cases, positive staining for ER was diffuse. The majority of the focal pattern observed in eight percent of ER-positive cases was due to inadequate fixation or focal tumor necrosis. Inadequate fixation did not account for the focal pattern of PR staining, which was observed in 21 percent of PR-positive cases.

8.9

Conclusions

"Our study demonstrates that quantifying ER immunoreactivity is not necessary and, hence, has no practical value. A simple report of the ER result as positive or negative provides the most useful information for the treating clinician."

SOURCE: Nadji M et al. *Am J Clin Pathol* 2005;123(1):21-7. **Abstract**

SLIDE 8.9 ER positivity and negativity are predictable in certain histologic types and nuclear grades of breast cancer. With the ID5 monoclonal antibody and antigen retrieval, IHC staining for breast cancer is an all-or-none occurrence, which is clinically relevant in predicting survival. Quantitation of results is unnecessary.

Select publications

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):10-9. **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 ER et al. **Solving the dilemma of the immunohistochemical and other methods used for scoring estrogen receptor and progesterone receptor in patients with invasive breast carcinoma.** *Cancer* 2005;103(1):164-73. **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**

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**

Post-test:

Breast Cancer Update — Issue 4, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The 68-month data from the ATAC trial demonstrate that patients who received anastrozole experienced significant:
   a. Improved disease-free survival
   b. Improved overall survival
   c. a and b
   d. None of the above

2. The 68-month data from the ATAC trial showed significantly higher hysterectomy rates in patients receiving:
   a. Anastrozole
   b. Tamoxifen

3. The IBCSG-1-98 efficacy data at 30 months look similar to the ATAC data at 33 months, favoring the aromatase inhibitor over tamoxifen.
   a. True
   b. False

4. Aromatase inhibitors are ineffective in premenopausal women without ovarian suppression.
   a. True
   b. False

5. In Dr Gradishar's Phase II study of capecitabine plus paclitaxel as first-line therapy, the dose of capecitabine (14 days on, seven days off) utilized was:
   a. 825 mg/m^2 bid
   b. 1,000 mg/m^2 bid
   c. 1,250 mg/m^2 bid

6. In Dr Gradishar's Phase II study of capecitabine plus paclitaxel as first-line therapy, the overall response rate was approximately:
   a. 25 percent
   b. 35 percent
   c. 50 percent

7. The EFECT trial evaluates fulvestrant versus exemestane after progression on a nonsteroidal aromatase inhibitor.
   a. True
   b. False

8. ABCSG trial 12 was a two-arm study comparing goserelin plus either anastrozole or tamoxifen in premenopausal patients with ER/PR-positive disease.
   a. True
   b. False

9. In the combined analysis from Austrian and German trials, patients switching to anastrozole after two years of tamoxifen experienced a 40 percent reduction in risk of relapse compared to patients receiving five years of adjuvant tamoxifen.
   a. True
   b. False

10. *Nab* paclitaxel is a novel formulation of paclitaxel that can be administered:
    a. Over 30 minutes
    b. Without premedications to prevent hypersensitivity reactions
    c. At higher doses than the original formulation of paclitaxel
    d. Both a and b
    e. All of the above

11. In a Phase III randomized trial, women with metastatic breast cancer who were treated with *nab* paclitaxel had _____ compared to those treated with paclitaxel.
    a. A better response rate
    b. A longer time to progression
    c. Less myelosuppression
    d. More neuropathy
    e. All of the above

12. Phase II trials of weekly *nab* paclitaxel have demonstrated efficacy in women with metastatic breast cancer who were previously treated with paclitaxel or docetaxel.
    a. True
    b. False

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

Evaluation Form:

Breast Cancer Update — Issue 4, 2005

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy. . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse and, when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Anthony Howell, MD	5 4 3 2 1	5 4 3 2 1
William J Gradishar, MD	5 4 3 2 1	5 4 3 2 1
Michael Gnant, MD	5 4 3 2 1	5 4 3 2 1
Edith A Perez, 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:

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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?

.....

Additional comments about this activity:

.....

Degree:

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

FOLLOW-UP

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

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

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

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

Breast Cancer™ UPDATE

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Breast Cancer™

U P D A T E

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