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# Breast Cancer™ UPDATE

## Conversations with Oncology Research Leaders
### Bridging the Gap between Research and Patient Care

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### HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** 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 **red underlined text**.

# *Breast Cancer Update:*
## A CME Audio Series and Activity

### STATEMENT OF NEED/TARGET AUDIENCE

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

### GLOBAL LEARNING OBJECTIVES

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

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

### PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 6 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Hayes, Livingston and Dowsett on the integration of emerging clinical research data into the management of breast cancer.

### ACCREDITATION STATEMENT

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**Daniel F Hayes, MD**

Consultant and Honorarium: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Dako Diagnostics AG, Genomic Health Inc, Immunicon Corporation, Novartis Pharmaceuticals, Roche Laboratories Inc, Wyeth

Grants/Research Support: Amgen Inc, Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Immunicon Corporation, Novartis Pharmaceuticals

**Robert B Livingston, MD**

Grants/Research Support: Amgen Inc, Bristol-Myers Squibb Company, Roche Laboratories Inc

**Mitchell Dowsett, PhD**

Grants/Research Support and Honorarium: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals, Roche Laboratories Inc

Consultant: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Novartis Pharmaceuticals, Roche Laboratories Inc

### Pharmaceutical agents discussed in this program

| GENERIC | TRADE | MANUFACTURER |
|---|---|---|
| anastrozole | Arimidex® | AstraZeneca Pharmaceuticals LP |
| capecitabine | Xeloda® | Roche Laboratories Inc |
| cyclophosphamide | Cytoxan®<br>Neosar® | Bristol-Myers Squibb Company<br>Pfizer Inc |
| docetaxel | Taxotere® | Aventis Pharmaceuticals Inc |
| doxorubicin | Adriamycin®<br>Rubex® | Pfizer Inc<br>Bristol-Myers Squibb Company |
| erythromycin lactobionate | Various | Various |
| exemestane | Aromasin® | Pfizer Inc |
| filgrastim | Neupogen® | Amgen Inc |
| fluorouracil (5-FU) | Various | Various |
| fulvestrant | Faslodex® | AstraZeneca Pharmaceuticals LP |
| gefitinib | Iressa® | AstraZeneca Pharmaceuticals LP |
| letrozole | Femara® | Novartis Pharmaceuticals |
| methotrexate | Various | Various |
| paclitaxel | Taxol® | Bristol-Myers Squibb Company |
| pegfilgrastim | Neulasta® | Amgen Inc |
| prochlorperazine maleate | Compazine® | GlaxoSmithKline |
| tamoxifen citrate | Nolvadex® | AstraZeneca Pharmaceuticals LP |
| trastuzumab | Herceptin® | Genentech BioOncology |
| vinorelbine | Navelbine® | GlaxoSmithKline |
| vorozole | * | Janssen Pharmaceutica Products LP |

*Not FDA approved

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# Editor's Note

## Doc, what would you do if you were in my shoes?

I recently chatted with a 64-year-old urologist whose life unraveled two years ago when a routine PSA screening led to the diagnosis of high-grade localized prostate cancer. While one might argue what defines "standard of care" in this situation, the most likely approach would be a combination of radiation therapy and two or more years of an LHRH agonist.

The treatment this physician/patient chose was quite nonstandard — radical prostatectomy, radiation therapy, combination chemotherapy and long-term maximal androgen blockade with an LHRH agonist and an antiandrogen.

"I wanted to do everything possible to attack the tumor," he told me. One can hardly argue with his intent, and fortunately this man is currently free of cancer with an undetectable PSA. However, it is interesting to speculate whether this was an evidence-based decision that was acceptable for this patient's physician to prescribe — or for our healthcare system to support. Many analogous therapeutic questions in the adjuvant breast cancer setting leave medical oncologists in a quandary.

**Should adjuvant chemotherapy be used in women with smaller, node-negative tumors?**

This is an agonizing and very common decision. Many of us have referenced a classic 1987 Australian survey of 104 women who had previously received chemotherapy.[1] More than half of the patients in that survey indicated that they would be treated with chemotherapy again for as little as a one percent improvement in five-year survival — the same benefit that is often projected for women with node-negative tumors. Some observers have noted that this sample population is biased because the surveyed patients had already chosen to receive adjuvant chemotherapy.

Peter Ravdin's ADJUVANT! online computer model (www.adjuvantonline.com/) has been very helpful in this situation by providing an estimate of the actual benefit derived from systemic therapy. As discussed in this issue by Dr Dan Hayes, a new and important source of assistance may be on the horizon in the form of more sophisticated tumor prognostic factors such as the Onco*type*™ DX assay.

**Should dose-dense adjuvant chemotherapy be utilized?**

I have been surprised by the relatively slow integration of this clinical strategy since Mark Citron's presentation of the CALGB-9741 trial results in December 2002. While the benefits from a dose-dense strategy require further definition, the downside currently appears to be mainly economic.

Are patients being accurately informed about the implications of these data when they are counseled about treatment options? For breast cancer patients with mindsets like the aforementioned urologist, a non-dose-dense regimen of AC→T might be unacceptable.

**Is adjuvant capecitabine an acceptable alternative for women not enrolled in a clinical trial?**

This valuable form of targeted chemotherapy is particularly attractive because of its oral formulation. An ongoing randomized adjuvant trial (CALGB-49907) will compare capecitabine to AC or CMF in women over the age of 65.

Does the utilization of adjuvant capecitabine as one of the treatment arms provide support to oncologists wishing to use it for patients not enrolled in a clinical trial? Most breast cancer clinical research leaders do not currently support that approach.

A related and vexing problem may be encountered in the patient with an ER-negative, HER2-negative tumor who has received neoadjuvant chemotherapy with a taxane and an anthracycline. Should chemotherapy be administered when such a patient has extensive residual tumor in the mastectomy specimen or multiple residual axillary lymph nodes on axillary dissection? Many clinicians utilize "pseudo-adjuvant" capecitabine in this situation, but reliable clinical research data do not yet support this strategy.

**Which type of adjuvant endocrine therapy is optimal?**

Controversy over the treatment of the postmenopausal woman is fading quickly as clinical research data accumulates on the superiority of aromatase inhibitors over tamoxifen. Therapy for premenopausal women — on the other hand — is far more controversial.

Not only is the role of ovarian ablation or suppression unclear, but many clinicians combine this intervention with tamoxifen or an aromatase inhibitor — a still unproven strategy that is currently being tested in several important clinical trials.

Should adjuvant trastuzumab be utilized in women with ER-negative, HER2-positive disease and multiple positive axillary lymph nodes? While research leaders uniformly discourage this practice, a small but significant fraction of community-based oncologists selectively utilize this strategy.

One of the most provocative questions our group has posed at CME meetings is, "What therapy would you wish to receive if you were diagnosed with

breast cancer and had an ER-negative, HER2-positive tumor with 12 positive axillary nodes?" It's easy to say, "We have no evidence for the trastuzumab," but like my urologist friend, a very high-risk tumor can make us throw out the rulebook.

Patients love to ask oncologists what they would do if they were in the "same shoes," and many physicians refuse to answer to avoid misleading patients into believing an "optimal" alternative truly exists.

To add another perspective to these debates, last year our CME group conducted three "Breast Cancer Patient Perspectives Town Meetings" in which we provided survivors with electronic keypads and asked them to vote on a number of clinical scenarios and cases.

A print report of this project was included in a prior issue of our series, and we have also presented these findings at ASCO[2] and in San Antonio.[3] In response to the many requests we've received from oncologists, we have included a PowerPoint slide atlas with graphics of some of these data in this issue of *Breast Cancer Update*.

Like similar patient surveys, considerable heterogeneity was observed in the breast cancer survivors' perceptions of the difficult trade-offs associated with adjuvant systemic therapy. Many were almost completely focused on reducing the risk of cancer recurrence, while others were much more intent on reducing treatment-related side effects and toxicities.

Physicians counseling patients who are facing these difficult-to-answer questions must be sensitized to the fact that a "one size fits all" approach denies patients the important opportunity to participate in making decisions with lifelong implications.

**— Neil Love, MD**
**NLove@ResearchToPractice.net**

[1]Simes RJ, Coates AS. **Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed?** *J Natl Cancer Inst Monogr* 2001;(30):146-52. **Abstract**

[2]Love NH et al. **Influence of prior therapy on breast cancer survivors' preferences for adjuvant systemic therapy in hypothetical scenarios.** *Proc ASOC* 2004; **Abstract 591**.

[3]Love NH et al. **Heterogeneity in breast cancer survivors perceptions of adjuvant systemic therapy options after verbal counseling from a physician panel in a town meeting.** *Breast Cancer Res Treat* 2003;82(1, Suppl);**Abstract 142**.

## Genetic profiling to predict prognosis

Currently, 75 percent of our patients have node-negative tumors of which nearly 80 percent are ER-positive. At best, adjuvant chemotherapy improves survival in this group by two or three percent over a 10-year period. Should we treat 100 patients in order to improve the survival of three? If you're one of the three, the answer is yes. It would be much more efficient if we could identify and treat only the patients in whom the disease is likely to recur.

The NSABP has partnered with Genomic Health Inc to develop a multiplex RT-PCR system that can analyze up to 300 genes at a time. In three preliminary studies, they were able to narrow it down to approximately 20 genes that appeared to be prognostic in patients with node-negative, ER-positive tumors who received tamoxifen. It was then tested prospectively in the tamoxifen arm of NSABP-B-14, and three categories of patients were successfully identified. They were able to profile 99 percent of the 600 or 700 specimens they analyzed, which indicates this is a very robust assay that works even on archived tissues.

At 10 years, 51 percent of the patients had a favorable prognostic profile, 22 percent had an intermediate profile and the remaining 27 percent had a poor profile, with recurrence rates of seven percent, 14 percent and 30 percent, respectively. I struggle with whether or not to recommend chemotherapy to these patients, but if this data is accurate I can tell at least half of them that their prognosis is so good that chemotherapy is not indicated.

We don't know whether the assay used in B-14 would have the same effect in women with node-negative, ER-positive disease who received adjuvant anastrozole because it hasn't been tested, but their prognosis is at least as good as those who received tamoxifen, so I cannot imagine it would not be applicable. Although I don't know this for certain, I believe it's likely this assay will be applied to tissues collected in the ATAC study.

I co-chair the American Society of Clinical Oncology Tumor Marker Guidelines Panel, which has established a very conservative group of recommendations

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because most of the tumor marker studies have been conducted without any forethought as to how patients were treated, how the samples were selected or how they're processed. On the contrary, the assay generated by NSABP, in collaboration with Genomic Health, was studied the way I believe a tumor marker should be.

## Prospective Intergroup study stratifying patients by risk based on tumor genetic profile

The Intergroup is designing a prospective study that will use the Genomic Health assay to prospectively stratify patients with node-negative, ER-positive disease into three prognostic groups: good, intermediate and poor. All patients will receive tamoxifen, patients with a poor profile will also receive chemotherapy, and patients in the intermediate group will be randomly assigned to chemotherapy or no chemotherapy.

George Sledge is designing this trial, which will be led by ECOG and probably will include every cooperative group in North America. The trial design is not yet finalized, but if it proceeds as described, it will probably be the last prospective trial of chemotherapy versus no chemotherapy in the adjuvant setting.

Randomization of the patients in the intermediate group will determine whether this assay can identify predictive factors for this group and which patients are most likely to benefit from the chemotherapy.

## Predicting pathologic response to chemotherapy based on genetic profiling in the neoadjuvant setting

At ASCO 2003, Lajos Pusztai and his colleagues reported on a preliminary study suggesting they could identify patients most likely to have a complete pathologic response to combination chemotherapy based on gene expression profiling (1.1).

Similarly, two or three other studies, including work conducted at Georgetown, suggest that not only can general resistance to all chemotherapies be predicted, but resistance to single agents in neoadjuvant therapy — such as a taxane versus doxorubicin — can also be predicted.

This research is very much in its infancy, and Dr Pusztai will chair a SWOG neoadjuvant trial with fine-needle aspiration before treatment to confirm his preliminary findings.

While Dr Pusztai's study evaluated combination chemotherapy, we know that cyclophosphamide, doxorubicin and 5-FU work in very different ways. Logic tells us we'll probably find that some genes are associated with resistance to all chemotherapy and other genes are specific for individual drugs.

For a long time we have fantasized about being able to individualize therapy based on a patient's genes, but I believe we're beginning to develop the tools and the technology to do just that.

**1.1** Accuracy of a Gene Expression Profile in Predicting Complete Pathologic Response (pCR) to Neoadjuvant Weekly Paclitaxel (T) followed by Sequential Chemotherapy (FAC) (N=21)

| Parameter | Result |
|---|---|
| Overall accuracy | 81% |
| Positive predictive value for pCR | 75% |
| Overall specificity | 93% |
| Sensitivity | 50% |

"Patients predicted to have pCR to T/FAC preoperative chemotherapy had a 75% chance of experiencing pCR compared to 25-30% that is expected in unselected patients. This finding may help physicians to select individual patients who are most likely to benefit from T/FAC adjuvant chemotherapy."

SOURCE: Pusztai L et al. **Emerging science: Prospective validation of gene expression profiling-based prediction of complete pathologic response to neoadjuvant paclitaxel/FAC chemotherapy in breast cancer.** *Proc ASCO* 2003;**Abstract 1**.

## Pharmacogenomics and pharmacogenetics

This field is about to explode. This field involves the study of genes and how they predict response to drugs. For example, we all have the same genes that metabolize drugs in our liver, but each patient has a slightly different set of alleles. Two patients may take the same drug but they probably metabolize it differently. For more than 100 years we've known that metabolism varies, but now we have the genetic tools to begin to understand it.

The NIH has funded a large consortium of experts to examine various drugs. Mark Ratain has received funding to evaluate chemotherapeutic agents. We have been examining whether we can use a patient's phenotype to determine the appropriate dose of chemotherapy.

Anne Schott conducted a study with docetaxel, which is metabolized by the same gene that metabolizes erythromycin. Patients received an injection of erythromycin, and then their phenotypes were established via a breath test to determine how quickly they metabolized the drug.

Patients were then given a dose of docetaxel based on their metabolic phenotype and their body surface area. I participated in this trial and some patients received doses a lot higher than normal and did fine, while other patients received doses much lower than normal and experienced toxicities.

SWOG and most of the major cooperative groups are planning large-scale correlative studies of pharmacogenomics. We're trying to collect and bank white cell DNA and tumor specimens to examine single nucleotide polymorphisms in various genes that may be important for metabolism to see if we can determine

who will experience toxicities and, perhaps, who will benefit from therapies. I encourage clinicians to support this important work. I believe a major breakthrough will occur in this field, and these banks will be gold mines in the future.

## Proposed SWOG trial evaluating continued trastuzumab after progression on trastuzumab and a taxane

The trial will randomly assign patients to vinorelbine or vinorelbine plus continued trastuzumab. We need to determine if continuing trastuzumab in this setting is beneficial. Theoretically, it shouldn't be unless there's synergy, which has been suggested by Dennis Slamon's work. Dr Pusztai will chair this study, which began at MD Anderson and is being adopted by the Intergroup.

This may be the last trial in the metastatic setting to randomly assign patients to trastuzumab, so it's an ideal place to look for a predictive factor. In this study, we'll examine circulating tumor cells and HER2 expression on the cells to determine whether we can predict which patients will benefit from or be resistant to trastuzumab.

This study is important because we don't know the value of continuing trastuzumab after progression. In my practice, when a patient progresses on trastuzumab, I have a mixed approach. Occasionally I continue the drug, but I'd like evidence that it's beneficial.

## Treatment of patients following progression on hormonal therapy

Patients on hormonal therapy may have tumors that have become relatively resistant to specific hormonal agents, like SERMS. Because of evidence that cross talk occurs in the EGFR family (especially between HER2 and ER), combining an agent like trastuzumab with tamoxifen may effectively overcome resistance of a previously resistant drug and produce better results. Several attempts have been made to mount randomized trials to determine if this is true, but they're difficult to conduct in the adjuvant setting because most of these patients are on tamoxifen when they relapse.

We can't randomly assign patients with progressive disease on tamoxifen to continuing tamoxifen alone versus tamoxifen plus trastuzumab, because the control arm is unethical. One trial attempted to randomly assign patients to trastuzumab with or without tamoxifen, but it was not very practical and that trial has been aborted.

In my practice, I use an aromatase inhibitor when a patient progresses on adjuvant tamoxifen, assuming the patient does not have rapidly progressing visceral disease that might prompt me to start chemotherapy immediately. I struggle with how to treat premenopausal patients, but generally suggest ovarian ablation, either surgically or with an LHRH antagonist.

When I use an LHRH antagonist, I tend to add an aromatase inhibitor because Klijn's meta-analysis suggests that combination hormonal therapy is probably superior to single agents (1.2). It's one of the few instances in which I believe combination endocrine therapy makes sense.

### 1.2 Meta-Analysis of Four Randomized Trials Comparing Combined Tamoxifen and LHRH Agonist versus LHRH Agonist Alone in Premenopausal Women with Advanced Breast Cancer

"The meta-analysis, combining the results of four randomized, comparative trials, included more than 500 patients with 355 deaths at the time of analysis. The maturity of three of the four trials (overall death rate, 70%) means that the conclusions of this meta-analysis are unlikely to alter with time. It represents the largest randomized cohort of premenopausal breast cancer patients treated with pharmacologic endocrine therapies for advanced disease. Using combined endocrine treatment to produce maximal estrogen blockade resulted in both a clinically relevant and statistically significant reduction in the risk of dying or progression/death (a 22% lower risk of dying and a 30% lower risk of progression/death) compared with the LHRH agonist-alone group. Although the treatment differences in the individual studies for progression-free survival were much more homogeneous than for the survival end point, there was no significant heterogeneity between trials."

SOURCE: Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19(2):343-53. **Abstract**

## Combination versus single-agent endocrine therapy

Many studies have evaluated combination versus single-agent endocrine therapy. In almost every case, the response rates to the combinations are higher, but in most cases, the survival rates are almost identical. The toxicities are also higher with combination therapy, so I tend to use sequential endocrine therapy. I don't know what to make of the statistic "duration of response."

The important endpoint for endocrine studies in the metastatic setting is the length of time until chemotherapy is needed, because we're trying to palliate these patients. To my knowledge, this has almost never been evaluated, although obviously, the longer the patient is in response, the longer the interval before they need chemotherapy.

## Management of premenopausal patients with ER-positive disease

Data suggest that in premenopausal patients with ER-positive metastatic disease, ovarian ablation plus an aromatase inhibitor results in a small prolongation of survival compared to ovarian ablation alone. In the adjuvant setting, no one really knows how to treat women under the age of 40 with ER-positive disease who continue to menstruate after chemotherapy. Some physicians believe they should undergo ovarian ablation and receive tamoxifen, some believe their ovaries should be ablated and they should receive aromatase inhibitors, and others believe tamoxifen alone is satisfactory.

Three randomized trials in premenopausal patients are being opened in Western Europe, North America and in the international Intergroup. Investigators will be

able to choose one or more studies to fit their bias. For example, if they believe premenopausal women should undergo ovarian ablation after chemotherapy, they can choose a study evaluating aromatase inhibitors versus tamoxifen, or if they're not sure about ovarian ablation, they can choose a study in which young women will receive tamoxifen with or without ovarian ablation. I believe we'll have an answer in the next few years.

In the metastatic setting, I tend to add an aromatase inhibitor to ovarian ablation in premenopausal patients because the complications of estrogenopenia are less concerning — unfortunately, most patients are not going to survive long enough for this to be an issue.

However, in the adjuvant setting, especially in a group of patients with a relatively good prognosis, combining these agents may cause substantial health consequences. I support these randomized trials because they compare the competing morbidity of long-term estrogen depletion to the risk of the breast cancer.

## Fulvestrant in the treatment of metastatic disease

I use fulvestrant as third-line therapy in patients whose disease has progressed on tamoxifen and an aromatase inhibitor. That's the current indication, but it wouldn't surprise me to see it moved up because data from the randomized trials clearly suggest it is as effective as aromatase inhibitors in patients who progressed after tamoxifen (1.3). The clinical question is whether the patient prefers a pill versus parenteral injection. For some patients, the injection is easier, but most patients prefer taking a pill. In my experience, the tolerability of fulvestrant is similar to that of the aromatase inhibitors.

## SWOG trial comparing combination versus single-agent hormonal therapy

SWOG is about to initiate a study in which patients will be randomly assigned to anastrozole with or without fulvestrant. We need to determine whether it's better to give these agents sequentially or in combination, and I'm hopeful we can measure the length of time until the patient needs chemotherapy.

Based on historical data and my own clinical experience, I expect sequential single-agent therapy will be just as effective as the combination and will have fewer side effects. However, I am supportive of this trial and will enroll patients willingly because if it turns out I'm wrong, then we've made a step forward.

The combination may result in better outcomes for biological reasons. By depleting estrogen levels as low as possible, and then using an estrogen receptor downregulator, we're doing more than just preventing estrogen from getting into the cells. It's like putting water in the gas tank — we not only prevent the estrogen from getting in, but we damage the engine as well.

A secondary endpoint will be response rates in patients who receive anastrozole followed by fulvestrant. Responses have been shown in retrospective analyses of trials, but this will more precisely measure how often responses occur. We're also going to perform a number of correlative science studies looking at the HER2 and

EGFR pathways and interactions to see if we can identify a group of patients who might benefit more from the combination than from sequential single agents.

**1.3** Combined Results from Two Multicenter Trials Comparing Fulvestrant to Anastrozole for the Treatment of Advanced Breast Cancer in Postmenopausal Women Who Progressed on Prior Endocrine Therapy

| Efficacy | Fulvestrant n=428 | Anastrozole n=423 |
|---|---|---|
| Objective response | 19.2% | 16.5% |
| Complete response | 4.7% | 2.6% |
| Partial response | 14.5% | 13.9% |
| Stable disease for ≥24 weeks | 24.3% | 24.3% |
| Median time to disease progression | 5.5 months | 4.1 months |
| Clinical benefit | 43.5% | 40.9% |
| **Toxicity*** | **Fulvestrant n=423** | **Anastrozole n=423** |
| Gastrointestinal disturbances** | 46.3% | 43.7% |
| Hot flashes | 21.0% | 20.6% |
| Joint disorders | 5.4% | 10.6% |
| Thromboembolic disease | 3.5% | 4.0% |

*Proportions of patients with predefined adverse events
**Gastrointestinal disturbances included anorexia, constipation, diarrhea, nausea and emesis

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

## Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is an exciting area of research. In terms of outcome, it doesn't matter whether adjuvant chemotherapy is given before or after surgery, but giving it preoperatively may offer some benefits. Obviously, neoadjuvant therapy can increase the chances of breast preservation, but it may also be useful in individualizing therapy. By using serial biopsies and genomics, we may be able to identify futile therapies and switch to another therapy earlier.

In NSABP-B-27, all patients received AC and were randomly assigned to one of three arms: surgery, surgery followed by docetaxel, or docetaxel followed by surgery. The question is whether we can identify patients whose response to AC alone is sufficient and their risk is too low to warrant further adjuvant chemotherapy. Perhaps we can identify patients who are resistant to all therapies, in which case further chemotherapy is not indicated.

In the next 10 years neoadjuvant trials will be designed to individualize therapy. Genomics and proteomics will be used to examine tumor profiles and evaluate how patients respond to therapies. The patient's pharmacogenomic profile and the presence of micrometastatic disease may be utilized to select a therapeutic regimen that is specific to her needs.

## Select Publications


Braun S et al. **Pooled analysis of prognostic impact of bone marrow micrometastasis: 10-year survival of 4199 breast cancer patients.** *Breast Cancer Res Treat* 2003;**Abstract 7**.

Buchholz TA et al. **Lack of bcl-2 and bax expression correlates with pathological complete response to doxorubicin-based neoadjuvant chemotherapy in breast cancer.** *Breast Cancer Res Treat* 2003;**Abstract 308**.

Dontu G et al. **In vitro propagation and transcriptional profiling of human mammary stem/progenitor cells.** *Genes Dev* 2003;17(10):1253-70. **Abstract**

Dontu G et al. **Stem cells in normal breast development and breast cancer.** *Cell Prolif* 2003;36(Suppl 1):59-72. **Abstract**

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

Hannemann J et al. **Changes in gene expression profiling due to primary chemotherapy in patients with locally advanced breast cancer.** *Proc ASCO* 2004;**Abstract 502**.

Jones S et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2003;**Abstract 10**.

Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19(2):343-53. **Abstract**

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10; **Abstract 16**.

Pusztai L et al. **Emerging science: Prospective validation of gene expression profiling-based prediction of complete pathologic response to neoadjuvant paclitaxel/FAC chemotherapy in breast cancer.** *Proc ASCO* 2003;**Abstract 1**.

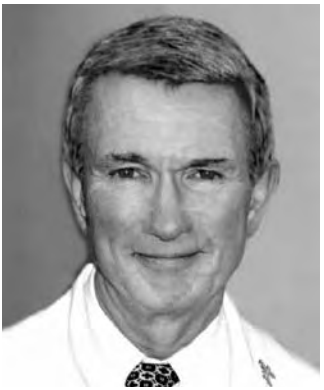
Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. **Abstract**

Schott AF et al. **Individualized chemotherapy dosing based on metabolic phenotype.** *Proc ASCO* 2001;**Abstract 306**.

Stearns V et al. **Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine.** *J Natl Cancer Inst* 2003;95(23):1758-64. **Abstract**

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

## SWOG-S0221: Dose-dense versus "dose-denser" chemotherapy



### *Rationale for SWOG-S0221*

The initial trial design of SWOG-S0221 was based on two small pilot studies that demonstrated that very dose-dense therapy for 20 to 24 weeks — with weekly doxorubicin and daily oral cyclophosphamide requiring G-CSF support — produced promising results in patients with node-positive disease. Patients with a median of four positive nodes had an 86 percent five-year disease-free survival, which compared favorably to the standard NSABP AC regimen in a similar population (2.1).

The results of CALGB-9741 were published in the *Journal of Clinical Oncology* in 2003, and that changed the landscape of clinical research in the adjuvant setting. Members of the Intergroup share a strong desire to build upon that trial, which showed the every two-week administration of AC and paclitaxel, with G-CSF support, was better than the every three-week schedule.

The logical next step would be a comparison of every two-week AC and our weekly doxorubicin and daily cyclophosphamide regimen — "dose-dense versus dose-denser." The evaluation of weekly paclitaxel was suggested by the outcome of the MD Anderson neoadjuvant study (2.2), which randomly assigned patients to every three-week versus weekly paclitaxel, with the FAC component constant in both arms. A major advantage was seen in the pathologic complete response — 28 versus 14 percent — for patients who received weekly paclitaxel.

### *SWOG-S0221 study design*

The study design was changed to preserve the design of CALGB-9741, but modified to examine the ultimate dose-densification schedule that is practical. Randomization includes four possible treatment options: every two-week AC or continuous AC, each followed by either every two-week or weekly paclitaxel.

Growth factor support is used in each arm of the trial. Pegfilgrastim — the pegylated form of G-CSF — is utilized in the every two-week arms, and patients treated with the weekly doxorubicin and daily cyclophosphamide regimen will

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receive filgrastim because we do not have experience with pegfilgrastim and concurrent chemotherapy and the FDA will not allow it.

## 2.1 Comparison of Event-Free Survival between the Dose-Dense Anthracycline-Based Regimen and the NSABP Standard and Dose-Intensified Regimens

| | (F)AC + G-CSF[1*] (n=52) | NSABP-B-22[2**] (n=2,305) | NSABP-B-25[3***] (n=2,548) |
|---|---|---|---|
| Event-free survival at 5 years | 86% | 62% | 66% |

*(F)AC + G-CSF dose-dense therapy
**NSABP standard regimen
***NSABP dose-intensified regimen

"In the first 30 patients, chemotherapy involved three drugs; doxorubicin was given on a weekly basis at 20 mg/m$^2$/wk and fluorouracil (5-FU) at 300 mg/m$^2$/wk for 24 weeks, both intravenously (IV). Cyclophosphamide was administered at 60 mg/m$^2$/d orally for 24 weeks. In the last 22 patients, 5-FU was omitted, and the dose of doxorubicin was increased to 24 mg/m$^2$/wk given for a total of 20 weeks to the same total dose (480 mg/m$^2$). Cyclophosphamide was given at 60 mg/m$^2$/d orally for 20 weeks. In all 52 patients, G-CSF was administered on each day of treatment, except that of IV chemotherapy… ."

SOURCES: [1]Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20:3637-43. **Abstract**

[2]Fisher B et al. **Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-22.** *J Clin Oncol* 1997;15(15):1858-69. **Abstract**

[3]Fisher B et al. **Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-25.** *J Clin Oncol* 1999;17(11):3374-88. **Abstract**

## 2.2 Phase III Randomized Trial of Weekly versus Every Three-Week Neoadjuvant Paclitaxel Followed by FAC: Pathological Complete Remission Rates (pCR)

| | Node-positive | | Node-negative | |
|---|---|---|---|---|
| Schedule | Weekly (n=50) | q3wk (n=51) | Weekly (n=68) | q3wk (n=67) |
| pCR | 14 (28%) | 7 (14%) | 20 (29%) | 9 (13%) |

SOURCE: Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC: Final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;**Abstract 135**.

The study is a two-by-two factorial design (2.3). We will not have enough statistical power to formally test for superiority of each of the four arms, but we have more than enough power to test for the weekly versus every two-week approaches, which was the same statistical approach taken in CALGB-9741. The study will accrue approximately 4,500 patients, which is almost twice as many as CALGB-9741.

**2.3** Phase III Trial of Continuous Schedule AC + G Versus the Every Two-Week Schedule of AC Followed by Paclitaxel Given Either Every Two Weeks or Weekly for 12 Weeks as Postoperative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

Protocol ID: SWOG-S0221
Accrual: 4,500 patients (Open)

Eligibility:
Stage I - III invasive breast cancer, node-positive or high-risk node-negative, with no prior cytotoxic chemotherapy or radiation therapy.

R

- AC q2wk + PEG-G x 6 cycles → T q2wk + PEG-G x 6
- Continuous AC + G x 15 weeks → T q2wk + PEG-G x 6
- AC q2wk + PEG-G x 6 cycles → T qwk x 12
- Continuous AC + G x 15 weeks → T qwk x 12

G = filgrastim; T = paclitaxel; PEG-G = pegfilgrastim; continuous AC = weekly doxorubicin + daily, oral cyclophosphamide

Southwest Oncology Group Study Coordinators:
George Budd, MD — Tel: 216-444-6480
Halle CF Moore, MD — Tel: 216-444-2644

SOURCE: NCI Physician Data Query, July 2004.

### *Tolerability of continuous AC plus G-CSF*

In general, continuous AC plus G-CSF is much better tolerated than intermittent AC with much less nausea and vomiting. Every time I speak with physicians who have used it for a few months, they tell me, "I can't believe it. Patients just aren't getting sick." That's not quite true. They have some nausea, but generally it's the nausea associated with a morning dose of cyclophosphamide, and usually you can take care of it by prescribing prochlorperazine. The fatigue is much less severe but more continuous.

One side effect of continuous AC plus G-CSF that is not typically seen with AC at standard doses is hand-foot syndrome. With 12 weeks of therapy, approximately 10 percent of patients will have Grade II hand-foot syndrome. I think it reflects epithelial cell damage from a proliferating compartment that has a relatively low turnover compared to the bone marrow.

Hand-foot syndrome is managed in the same manner as in a patient receiving capecitabine or continuous infusion 5-FU — discontinue the anthracycline for one week. The symptoms of hand-foot syndrome are typically much improved and you can resume at a reduced dose; we usually reduce the dose by 25 percent.

## Incorporation of pegfilgrastim into dose-dense schedules

Studies performed with standard regimens given every three weeks or every two weeks demonstrated pegfilgrastim is equivalent to filgrastim in maintaining neutrophil counts. The toxicities are comparable and generally consist of bone pain resulting from the rapid expansion of the bone marrow.

The FDA's point of view seems to be that filgrastim and pegfilgrastim are different drugs, and one should not assume pegfilgrastim can be administered concurrently with chemotherapy and maintain effective concentrations of the chemotherapy. I think this is a shortsighted view, and in the long run it's going to slow the progress of clinical research. However, I'm certainly not in a position to counter the FDA and recommend that people administer pegfilgrastim concurrently with chemotherapy.

When doxorubicin is administered on a weekly basis, the levels of the agent are therapeutically effective for three to four days, and cyclophosphamide has a half-life of 12 hours for the activated metabolites. In our pilot studies we have treated over 300 patients.

We have been giving G-CSF concurrently with concentrations of these drugs even though we avoided the administration of G-CSF on the same day as the doxorubicin. I think one of the major concerns expressed by the FDA is that because pegfilgrastim is present for about 11 days, if you have a weekly treatment program, pegfilgrastim will obviously still be present when you administer the second dose of doxorubicin.

Two theoretical concerns exist. Pegfilgrastim may stimulate bone marrow stem cells that could then be affected by a DNA-damaging agent, which would result in a greater incidence of acute leukemia. The second concern is that filgrastim and pegfilgrastim may have different toxicities.

## Leukemia secondary to dose-dense adjuvant chemotherapy

In the Ellis pilot trials evaluating (F)AC + G-CSF, one patient developed acute myeloid leukemia — and she had the characteristic translocation for an anthracycline-associated leukemia. Over 300 patients who received this regimen have now been followed for a median of four years, and only this one patient developed leukemia.

In addition, the Southwest Oncology Group did a neoadjuvant trial of over 100 patients, also chaired by Dr Ellis, in which the median follow-up is now approximately three and a half years, with no cases of acute leukemia. Conservatively, one can say that the incidence of acute leukemia observed with this regimen will not be greater than the incidence of acute leukemia one would expect with the same regimen given without growth factor support.

If you look at the MD Anderson database at 10 years follow-up, the expected frequency of acute leukemia after the administration of doxorubicin for patients who survive 10 years is about one percent. The leukemogenic risk may actually be lower with regimens that administer lower individual doses of the drug.

The NSABP experience suggests that the risk of acute leukemia may be related to peak blood levels. They conducted studies in which the dose of cyclophosphamide ranged from 600 to 1,200 to 2,400 mg/m$^2$, and those studies showed a higher incidence of leukemia in the patients receiving higher doses of cyclophosphamide.

At the time, some physicians speculated that it was related to the use of G-CSF in the higher-dose arms, but I think it was probably related to the presence of higher peak chemotherapy concentrations. We know that higher peak concentrations of alkylating agents are likely to be associated with development of leukemia.

Anthracycline-related leukemias tend to occur relatively early — between 12 and 36 months after treatment — so if you have a median follow-up of four years, you can be reasonably confident making a statement regarding the incidence of those leukemias. Leukemias related to alkylating agents are typically spread over a much longer period of time and continue to occur throughout a 10-year time period.

## Counseling patients about the risk of leukemia from adjuvant chemotherapy

I tell every patient who will receive an anthracycline, "You probably have a lifetime risk for developing acute leukemia of about one percent as a result of this treatment."

The risk of acute leukemia from alkylating agents depends on the agent utilized and the way it's administered. If you look at CMF (cyclophosphamide, methotrexate and 5-FU) with oral cyclophosphamide — analogous to our AC program — the incidence of acute leukemia is no higher in more than 20 years of follow-up than in the women who received Bonadonna CMF.

No evidence exists to indicate that daily oral cyclophosphamide given for six months or cyclophosphamide given two weeks on and two weeks off for six months is more leukemogenic than no therapy.

## Rationale for the effectiveness of dose-dense scheduling

The results of CALGB-9741 support the basic hypothesis I've had since the late 1980s, which is if you achieve a critical concentration necessary for cell kill, you're more likely to get an effective result in direct proportion to the amount of time, or area under the curve, that the tumor cells are exposed.

If you administer doxorubicin once a week, tumor cells are exposed at least 50 percent of the time. If you give doxorubicin every two weeks, they're exposed about three to four days out of every two weeks. If you give it once every three weeks, the tumor cells are exposed for three or four days every three weeks.

That may sound a little simple-minded, and the explanation is probably more complex, but I think the exposure of cells to effective concentrations of chemotherapy over a longer period of time is the key to why dose-dense therapies work better.

A second reason, which may be very important, is the antiangiogenic hypothesis. We now have good preclinical data that demonstrate that with continuous exposure, certain classes of agents — cyclophosphamide, the vincas and the taxanes — result in much better cell kill and tumor regressions than intermittent exposure. There is solid evidence in preclinical systems that an antiangiogenic effect is the primary reason for that cell kill.

## Optimizing adjuvant doxorubicin/cyclophosphamide

With weekly therapy, I think we have a pretty good handle on the effect of dose reductions, mostly from the Europeans. For doxorubicin, if you don't deliver 15 mg/m$^2$ per week, at least in the setting of advanced disease, response rate goes down, and I think response rate is a crude surrogate for cell kill.

One of the main reasons we incorporated filgrastim early on was that my colleague, Dr Ellis, and I initially did a trial in which we gave continuous AC (15 mg/m$^2$ per week of doxorubicin) without growth factor support. Only about 15 percent of patients were able to tolerate the intended dose. With growth factor support, approximately 90 percent of patients receive the intended dose.

Every three-week AC is an outmoded regimen. If AC is utilized, it should be given every two weeks with growth factor support. Again, you have to realize that my treatment approach is different from many other physicians because I use CMF more frequently than AC.

For a patient for whom I'm worried enough about risk factors to think she needs an anthracycline-based regimen, I would use the every two-week schedule of AC with growth factor support.

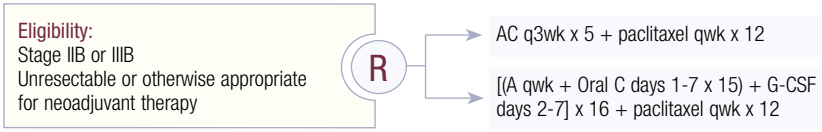
## SWOG trial S0012 of neoadjuvant therapy in locally advanced and inflammatory disease

In the Southwest Oncology Group we have a trial of neoadjuvant therapy for women with locally advanced and inflammatory disease, comparing intermittent AC versus AC plus G-CSF (2.4). That trial is accruing reasonably well. All patients receive paclitaxel, but it's a two-arm study and paclitaxel is administered weekly for 12 weeks.

I would like to see an Intergroup trial in which patients who have resectable disease but want to receive neoadjuvant therapy are randomly assigned to a dose-dense versus a less dose-dense schedule. In other words, a trial asking the same basic question that we're asking in SWOG-S0221, because with an endpoint of pathologic complete response in a two-arm design, we could potentially have an answer in a couple of years while we're still completing the adjuvant study.

### 2.4 Doxorubicin, Cyclophosphamide and Paclitaxel with or without Filgrastim in Treating Women with Inflammatory or Locally Advanced Breast Cancer

Protocol IDs: SWOG-S0012, CTSU
Accrual: 350 (Open)




G-CSF = filgrastim

Study Contact:
Georgiana Ellis, MD, Protocol Chair
Tel: 206-598-4518

*SOURCE:* NCI Physician Data Query, July 2004.

## Incorporation of capecitabine into regimens with metronomic scheduling

Capecitabine is a drug that meets the criteria for dose density. It's administered two weeks out of three, which is not continuous but it's close. If the current Intergroup trial shows an advantage for continuous versus every two-week therapy, I would favor seeing the next study evaluate the addition of capecitabine.

I think we would want to add capecitabine to a taxane, not to the AC regimen, because if you add capecitabine to AC, you're going to see the same thing we saw in the initial studies when we added 5-FU. Our original study was with FAC plus G-CSF, and hand-foot syndrome occurred in 70 percent of the patients. You could add capecitabine to AC every two weeks, or you could add it to the paclitaxel at the back end.

## Select publications


Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-43. **Abstract**

Fisher B et al. **Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-25.** *J Clin Oncol* 1999;17(11):3374-88. **Abstract**

Fisher B et al. **Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-22.** *J Clin Oncol* 1997;15(5):1858-69. **Abstract**

Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC- final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;**Abstract 135**.

Mitchell Dowsett, PhD

EDITED COMMENTS

## IMPACT neoadjuvant trial

The IMPACT trial compared anastrozole, tamoxifen and a combination of the two as neoadjuvant therapy in postmenopausal women with ER-positive tumors that were more than two centimeters. Initially, Ki67 was our primary endpoint; however, we turned the study into a larger trial with clinical endpoints. We tried to base the study on the ATAC trial and used a placebo-controlled, double-blind design — neither the patients nor the surgeons knew what the patients were receiving.

### *Clinical outcomes*

At the last San Antonio Breast Cancer Symposium, my colleague, Ian Smith, presented the clinical outcomes data from the 330 patients enrolled (3.1). In the intent-to-treat analysis for clinical response, no difference was found between anastrozole, tamoxifen and the combination. In the women requiring mastectomy at baseline, anastrozole demonstrated a significant advantage over tamoxifen in terms of rendering the women eligible for breast-conserving surgery — between 40 and 50 percent of the women in the anastrozole arm and just over 20 percent in the tamoxifen arm.

In a previous neoadjuvant trial comparing an aromatase inhibitor to tamoxifen, letrozole was used. In that particular study, all of the patients required mastectomy at baseline. We felt it was important to compare our study's results with that letrozole study.

For some biologically and clinically interesting reason, patients requiring mastectomy seem to do better with an aromatase inhibitor than with tamoxifen. It would be great to find out why the aromatase inhibitors have greater antitumor effect in these larger tumors.

My clinical colleagues remind me that clinical response is a soft endpoint and, particularly in smaller tumors, it's difficult to measure small changes between a three-centimeter and a two-centimeter tumor. Clearly, in patients requiring mastectomy, the tumors are much larger; therefore, an error in establishing and measuring response is less likely. We had hoped that the clinical response in the IMPACT trial would be a surrogate endpoint for the outcomes in the ATAC trial,

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which demonstrated that adjuvant anastrozole was better than tamoxifen or the combination at increasing relapse-free survival. In essence, however, clinical response was not a good surrogate.

**3.1** Anastrozole (A) versus Tamoxifen (T) versus the Combination (C) as Neoadjuvant Endocrine Therapy for Postmenopausal Patients with Estrogen Receptor-Positive Breast Cancer: The IMPACT Trial (N=330)

| | A | T | C |
|---|---|---|---|
| Objective clinical tumor response[1] | 37.2% | 36.1% | 39.4% |
| Patients requiring mastectomy at baseline who became eligible for breast-conserving surgery after 3 months of treatment[1] | 45.7% | 22.2% | 26.2% |
| Geometric mean reductions in Ki67 after 2 weeks of treatment[2] | 76.0% | 59.0% | 64.0% |

SOURCES: [1]Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;**Abstract 1**.

[2]Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;**Abstract 2**.

### *Biomarkers*

As a translational scientist, my attraction to neoadjuvant trials exists because pretreatment biopsy material is obtainable. In this circumstance the second specimens are particularly valuable. Indeed, we had specimens from about 156 patients who were evaluable at two weeks, and we compared them with the 230 to 240 patients with specimens taken pretreatment and at three months.

We evaluated a number of biomarkers — apoptosis, ER, PR, HER2 and EGFR. However, we focused on Ki67 — a marker of those cells that are actively cycling. We've done many of these types of studies over the years, but this is the largest. It was also the most important study because it gave us the opportunity to ask: Could the change in Ki67 actually predict the outcome of the ATAC trial?

It was a delight to be able to report that the outcome with the biomarker was comparable to the outcome of the ATAC trial. The reduction in Ki67 associated with neoadjuvant anastrozole was just below 80 percent at two weeks, and that reduction increased marginally to 82 percent at three months.

For neoadjuvant tamoxifen, the reduction in Ki67 at two weeks was about 60 percent. Both at two weeks ($p = 0.004$) and at three months ($<0.001$), the reduction in Ki67 was significantly less for tamoxifen than for anastrozole. The combination arm at two weeks and at three months performed exactly the same as the tamoxifen arm.

Some other provocative observations became evident when we evaluated the detail of the changes in Ki67. In the anastrozole arm, only three or four out of

over 50 patients did not show a numerical reduction in proliferation after two weeks. This suggests that probably over 90 percent of patients show some sort of biological response to anastrozole.

In the tamoxifen arm, eight out of 50 patients did not show a reduction in Ki67, and the overall reductions were smaller. Perhaps only half of the patients with ER-positive disease are clinically responsive, but biologically they appear much more responsive. Our overall conclusion from the IMPACT trial was that the changes in Ki67 are probably a better surrogate marker for the benefit from these drugs than clinical response.

## Results of the IMPACT trial and HER2 status

HER2 was an interesting marker to evaluate in the IMPACT trial. In the patients with disease that was both ER- and HER2-positive, we saw a 58 percent response rate with anastrozole and a 21 percent response rate with tamoxifen. Given the very small numbers of trial participants with ER- and HER2-positive disease, the difference wasn't statistically significant.

These data are comparable to the data reported by Matt Ellis, demonstrating that neoadjuvant letrozole had a markedly better response rate than tamoxifen in patients with either HER1- or HER2-positive disease. This substantiates that in the neoadjuvant setting, patients with ER- and HER2-positive disease respond better to an aromatase inhibitor than to tamoxifen.

## Planned neoadjuvant trial of anastrozole and gefitinib

In our next trial, we'll be incorporating a tyrosine kinase inhibitor with an endocrine agent, and Ki67 will be our primary endpoint. The trial has a slightly complicated but novel design. Initially, all 180 patients will receive anastrozole alone for two weeks; then they will be randomly assigned to gefitinib or placebo. The patients will be treated for three months.

This design allows for a biopsy at two weeks to determine whether the response to gefitinib will be greater in patients who are not having a substantial reduction in Ki67 with anastrozole. The hypothesis is that we will see enhanced suppression of Ki67 — particularly in patients with little or no change in Ki67 while on anastrozole alone because that is the biologically refractory group.

We believe that patients who aren't responding well to an endocrine agent are the most likely to benefit from an agent that inhibits growth factor receptors.

## Influence of endocrine therapy on the progesterone receptor

In a previous study published in the *Journal of Clinical Oncology*, we compared vorozole and tamoxifen. The aromatase inhibitor vorozole produced a very rapid and substantial fall in PR levels. Since the PR gene is exquisitely estrogen-sensitive, that's not a surprise. After two weeks of tamoxifen, we actually saw an increase in PR levels in most patients.

Even at three months, when the PR levels began to fall, they still didn't go below the baseline level. We see this as one of the clearest indications that tamoxifen has

a substantial agonist effect, at least on the PR gene. We believe that is one of the key reasons the aromatase inhibitors are more beneficial than tamoxifen.

## ATAC adjuvant trial: Subgroup analysis of patients with ER-positive, PR-negative disease

The ATAC trial enrolled 9,366 patients, and the first report demonstrated a significant benefit for the patients with hormone receptor-positive disease who were treated with anastrozole compared to tamoxifen.

The hazard ratio for disease-free survival in this group was 0.78. The 47-month analysis had a similar hazard ratio. Because the ATAC trial was designed in 1994 and initiated in 1996, it didn't require the patients to have ER- and/or PR-positive disease for enrollment.

Hence, a very small proportion of patients had ER- and PR-negative disease, and a larger cohort had ER- or PR-unknown disease. We retrospectively analyzed the histological blocks from those patients for their ER and PR status to obtain a more comprehensive view of the influence of the ER and PR status on the outcomes of the trial. We asked whether the PR status had any impact on the relative benefit associated with anastrozole and tamoxifen in patients with ER-positive disease.

In the patients with ER- and PR-positive disease, which consisted of approximately 5,700 patients, anastrozole was more beneficial than tamoxifen, with a hazard ratio of 0.82. In the patients with ER-positive and PR-negative disease, a very substantial difference was noted, with a hazard ratio of 0.48, indicating that patients treated with adjuvant anastrozole had half as many relapses as patients treated with adjuvant tamoxifen (3.2).

**3.2** Recurrence Rates in the ATAC Trial According to Estrogen and Progesterone Receptor Status

| Receptor status | N | Hazard ratio for anastrozole versus tamoxifen (95% CI)* | Anastrozole | Tamoxifen |
|---|---|---|---|---|
| ER-positive, PR-positive | 5,704 | 0.82 (0.65-1.03) | 7% | 8% |
| ER-positive, PR-negative | 1,370 | 0.48 (0.33-0.71) | 9% | 17% |
| ER-negative, PR-positive | 220 | 0.79 (0.40-1.5) | 22% | 26% |
| ER-negative, PR-negative | 699 | 1.04 (0.73-1.47) | 27% | 27% |

*Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M, on Behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;Abstract 4.

The comparison between patients with ER- and PR-positive disease to patients with ER-positive and PR-negative disease was borderline for statistical significance. Although this was a retrospective subgroup analysis, I hope that other aromatase inhibitor trials will perform the same analyses to substantiate this finding.

## Trials evaluating sequential adjuvant hormonal therapy

The MA17 trial data are exciting but controversial because the trial was stopped early. Irrespective, we have data indicating that the relapse rate in patients who had taken five years of adjuvant tamoxifen was reduced by about 50 percent with the introduction of letrozole. Because the trial was stopped early, we won't be able to determine whether a survival benefit exists as well.

Does tamoxifen over a five-year period sensitize micrometastases to the influence of the aromatase inhibitors? As a translational scientist, I wonder if we could identify the patients at highest risk for relapse. The collaborators in the MA17 trial are addressing this question.

In the MA17 trial, it would be fascinating to determine whether the patients who are at the greatest risk for relapse after five years of adjuvant tamoxifen and would benefit most from the aromatase inhibitor are, indeed, those with ER-positive and PR-negative disease. They have the potential to perform that study very soon, because 98 percent of the ER and PR data has already been collected.

The Italian trial by Boccardo, in patients treated with adjuvant tamoxifen for two years followed by adjuvant anastrozole for three years, clearly demonstrates a significant benefit for switching to the aromatase inhibitor, but I believe the data are premature. The MA17 trial enrolled thousands of patients, but the Italian trial only enrolled a few hundred patients.

## Biological rationale for the sequencing of adjuvant hormonal therapy

If the ATAC trial data from the patients with ER-positive and PR-negative disease were confirmed, it would be difficult to substantiate the use of adjuvant tamoxifen followed by adjuvant letrozole in that group of patients.

The relapse rate was too high with adjuvant tamoxifen to suggest such a sequential strategy, and it may be best to use an aromatase inhibitor early in that group of patients.

In the patients with ER- and PR-positive disease, in whom the relapse rates for tamoxifen and anastrozole were more similar, one could argue for the use of such a sequential strategy. However, I suspect even in that group of patients it is best to accept the gain associated with the aromatase inhibitors as initial adjuvant therapy, rather than allow a few patients to relapse and have to treat their metastatic disease.

## Mechanisms of resistance in estrogen-deprived breast cancer cells

We have a series of preclinical models in which we've been investigating the mechanisms of resistance to estrogen deprivation. Cells that are estrogen-deprived for a short time become quiescent, but if we keep them in that environment for about 20 weeks without any further perturbation, they begin to grow again. This is similar to the patient who's receiving an aromatase inhibitor and then becomes resistant to it.

Over the years we have considered this to be estrogen independence. Richard Santen and his colleagues have substantiated our evidence that it's due to estrogen hypersensitivity — the cells grow in response to the very small amount of residual estrogen in the cell culture medium. We have asked: What made these cells hypersensitive? Again we came back to the growth factor receptors. In these cells, we see HER2 is overexpressed, the ER is phosphorylated and active, and the PR levels are increased.

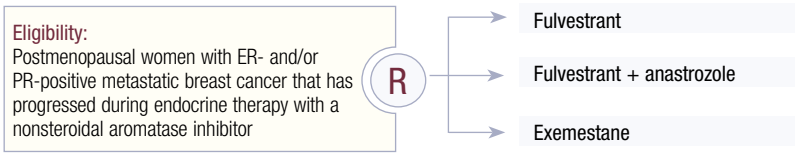
What can we do about it? We've considered utilizing fulvestrant, a pure antiestrogen. In patients with estrogen hypersensitivity, we have observed that fulvestrant is effective and tamoxifen is not. Two clinical trials — the Evaluation of Fulvestrant versus Exemestane Clinical Trial (EFECT) and the Study of Fulvestrant versus Exemestane with/without Anastrozole (SoFEA) — will determine whether we can translate that into the clinical setting.

## EFECT and SoFEA trials

EFECT is an American and European study that will randomly assign patients who have failed therapy with a nonsteroidal aromatase inhibitor to fulvestrant or exemestane. Our own study, SoFEA (3.3), is slightly different from EFECT because it is based on the observation that the addition of small amounts of estrogen to cells that have been estrogen-deprived for a long time reduces the effectiveness of fulvestrant.

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

Protocol ID: SoFEA
Accrual: 750 (Proposed)




Study Contact:
Stephen Johnston, MD, Principal Investigator
Tel: 0207 808 2748
ICR - Clinical Trials & Statistics Unit

SOURCE: National Cancer Research Network Trials Portfolio. Available at **http://controlled-trials.com/isrctn/trial/%7c/o/44195747.html** Accessed on June 18, 2004.

That scenario equates to the withdrawal of a nonsteroidal aromatase inhibitor and the addition of fulvestrant. Hence, the third arm of our trial includes a nonsteroidal aromatase inhibitor and fulvestrant. The SoFEA trial will randomly assign 750 patients who have failed therapy with a nonsteroidal aromatase inhibitor to exemestane, fulvestrant alone or fulvestrant plus anastrozole.

I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone. In that particular study, we are using a loading-dose schedule for fulvestrant — 500 mg initially, followed two weeks later with another 250 mg, and then monthly injections.

Since fulvestrant has a long half-life of about 40 days, it takes a long time to reach steady state levels. This strategy allows the fulvestrant levels to reach steady state and the drug to be effective more quickly.

## Phenotypic changes induced by tamoxifen therapy

We constructed a tissue microarray from the tumors of 39 patients who became resistant to adjuvant tamoxifen. We had pretreatment samples taken at excision and samples taken at the time of relapse on adjuvant tamoxifen.

Initially, 29 patients had ER-positive disease. At the time of relapse, five of those patients had ER-negative disease and the other 24 had ER-positive disease. Hence, different mechanisms might be operative in tamoxifen resistance.

More surprising, three patients who initially had ER-positive, HER2-negative disease had HER2-positive disease at the time of relapse. Of the 29 patients who initially had ER-positive disease, seven had a change in their phenotype.

If we had treated those seven patients based on their pretreatment specimens, we would have either treated them with endocrine therapy or denied them trastuzumab inappropriately. These patients accounted for 24 percent of the total population, so a greater focus should be placed on trying to obtain biopsy specimens from patients at the time of relapse.

I should add one cautionary remark: most patients had local relapses. We need to confirm a new primary wasn't misdiagnosed. We're currently doing molecular analyses — comparative genomic hybridization between the pretreatment and the relapse specimens — to confirm that those patients had relapses and not new tumors.

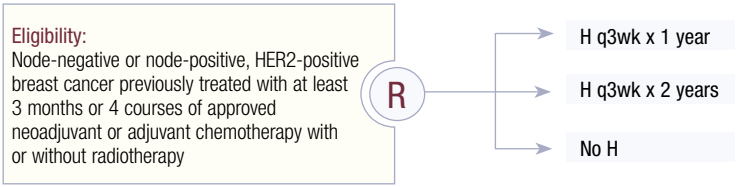
The majority of the data comparing the HER2 status in primary and metastatic disease has evaluated lymph nodes, which is not quite comparable to our data. A study from a Belgian group of 106 patients found an approximately five or six percent difference in HER2 status, which is not much different from our finding in 29 patients. If the metastases become HER2-positive, we ought to know that to consider using trastuzumab.

## HERA trial of adjuvant trastuzumab

The HERA trial (3.4) is a relatively pragmatic study. Patients initially receive an approved adjuvant chemotherapy regimen, and then they are randomly assigned to trastuzumab monotherapy for either one or two years or no trastuzumab. It's my responsibility and that of Brian Leyland-Jones, who co-chairs the Trans-HERA Committee, to collect the tumor blocks from that trial and perform biomarker analyses.

### 3.4 Phase III Randomized Study of Trastuzumab (Herceptin®) in Women with HER2-Positive Primary Breast Cancer

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 4,482 patients (Open)




H = trastuzumab

Study Contact:
Martine J Piccart-Gebhart, Chair
Tel: 32-2-5413206
Breast International Group

*SOURCE:* NCI Physician Data Query, July 2004.

## Select Publications


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

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

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

Bundred NJ et al. **Fulvestrant, an estrogen receptor downregulator, reduces cell turnover index more effectively than tamoxifen.** *Anticancer Res* 2002;22(4):2317-9. Abstract

Coleman R et al. **Association between prior chemotherapy and the adverse event (AE) profile of adjuvant anastrozole (A) or tamoxifen (T): A retrospective analysis from the ATAC trial.** *Proc ASCO* 2004;Abstract 767.

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;Abstract 770.

Dowsett M, on Behalf of the ATAC Trialists Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;Abstract 4.

Dowsett M et al. **Molecular changes in tamoxifen-relapsed breast cancer: Relationship between ER, HER2 and P38-MAP-kinase.** *Proc ASCO* 2003;Abstract 7.

Dowsett M et al. **Molecular effects of anastrozole (A) and tamoxifen (T) alone and combined (C) in the IMPACT trial of neoadjuvant treatment of primary breast cancer.** *Proc ASCO* 2004; Abstract 537.

Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;**Abstract 2**.

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

Forward DP et al. **Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer.** *Br J Cancer* 2004;90(3):590-4. **Abstract**

Gancberg D et al. **Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites.** *Ann Oncol* 2002;13(7):1036-43. **Abstract**

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

Harper-Wynne CL et al. **Comparison of the systemic and intratumoral effects of tamoxifen and the aromatase inhibitor vorozole in postmenopausal patients with primary breast cancer.** *J Clin Oncol* 2002;20(4):1026-35. **Abstract**

Johnston S. **Fulvestrant and the sequential endocrine cascade for advanced breast cancer.** *Br J Cancer* 2004;90(Suppl 1):15-8. **Abstract**

Jones SE et al. **A retrospective analysis of the proportion of patients responding for > 1 year in two phase III studies of fulvestrant vs. anastrozole.** *Proc ASCO* 2004;**Abstract 737**.

Reddy JC et al. **Patient benefit from trastuzumab plus a taxane regardless of estrogen receptor (ER) status or prior adjuvant therapy for HER2+ metastatic breast cancer (MBC).** *Proc ASCO* 2004;**Abstract 674**.

Robertson J et al. **Oestrogen receptor expression in human breast cancer during long-term fulvestrant treatment.** *Proc ASCO* 2004;**Abstract 536**.

Robertson JF et al. **Pharmacokinetics of a single dose of fulvestrant prolonged-release intramuscular injection in postmenopausal women awaiting surgery for primary breast cancer.** *Clin Ther* 2003;25(5):1440-52. **Abstract**

Santen RJ et al. **Adaptive hypersensitivity to estrogen: Mechanism for sequential responses to hormonal therapy in breast cancer.** *Clin Cancer Res* 2004;10(1 Pt 2):337S-45S. **Abstract**

Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;**Abstract 1**.

Smith IE et al. **Assessment of lipids and bone-derived resorption products during neoadjuvant therapy with anastrozole (A), v tamoxifen (T), v combination (C) in the IMPACT trial.** *Proc ASCO* 2004;**Abstract 675**.

Vergote I, Robertson JF. **Fulvestrant is an effective and well-tolerated endocrine therapy for postmenopausal women with advanced breast cancer: Results from clinical trials.** *Br J Cancer* 2004;90(Suppl 1):11-4. **Abstract**

# PowerPoint Atlas: Patient Perspectives Project*

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

**Slide 1:** Patient perspectives project overview

**Slide 2:** Patient demographics

**Slide 3:** Scenario 1: Influence of prior therapy on choices

**Slide 4:** Scenario 2: Influence of prior therapy on choices

**Slide 5:** Scenario 3: Influence of prior therapy on choices

**Slide 6:** Prior chemo influence on perception of toxicity

**Slide 7:** Influence of side effects on choice of chemotherapy

**Slide 8:** Benefits required to receive chemotherapy

**Slide 9:** Prior hormonal therapy influence on perception of toxicity

**Slide 10:** Side effects of adjuvant hormonal therapy

**Slide 11:** Recall of receiving prognostic information

**Slide 12:** Effect of emotional distress on understanding treatment

**Slide 13:** Effect of informational complexity on understanding

*Love NH et al. **Heterogeneity in breast cancer survivors perceptions of adjuvant systemic therapy options after verbal counseling from a physician panel in a town meeting.** *Breast Cancer Res Treat* 2003;82(1, Suppl);**Abstract 142**.

Love NH et al. **Influence of prior therapy on breast cancer survivors' preferences for adjuvant systemic therapy in hypothetical scenarios.** *Proc ASCO* 2004, **Abstract 591**.

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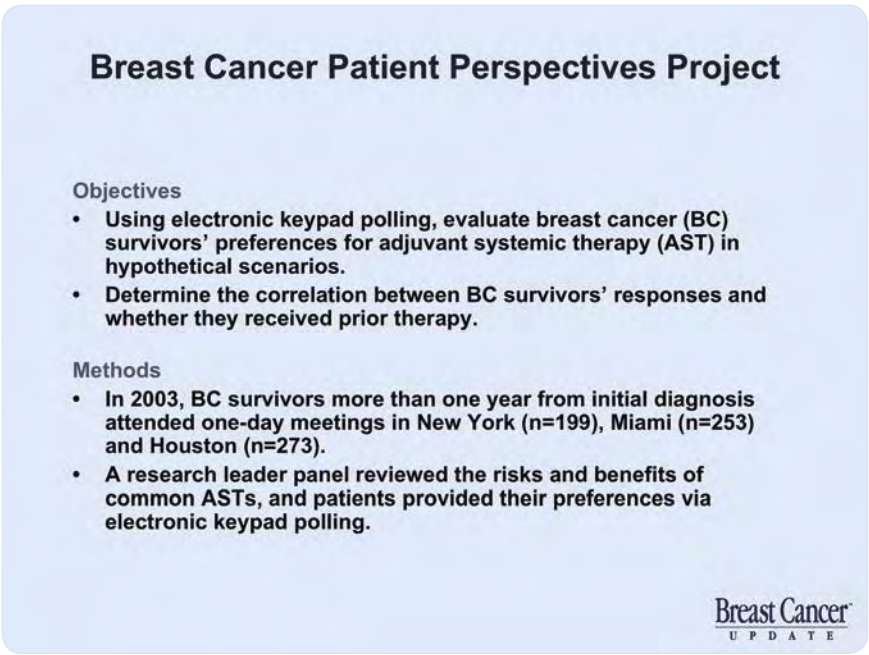
**Slide 1**



Slide 2

## Breast Cancer (BC) Survivors Attending the Meetings

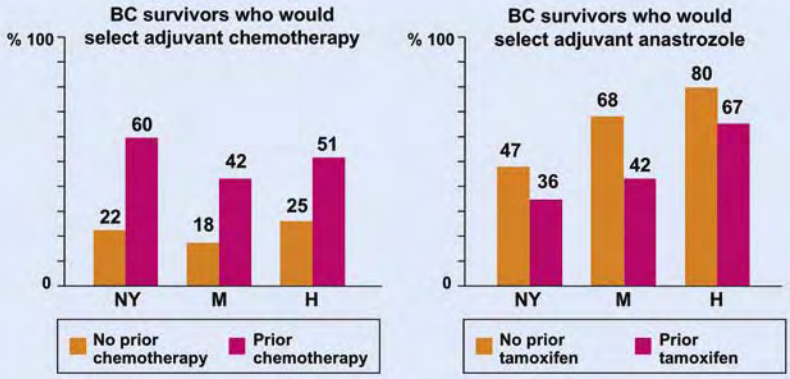
| | New York | Miami | Houston |
|---|---|---|---|
| Number of BC survivors | 199 | 253 | 273 |
| BC survivors 41 to 70 years old | 87% | 84% | 85% |
| Initial diagnosis within the past five years | 63% | 71% | 67% |
| Prior systemic therapy | | | |
| Chemotherapy | 69% | 66% | 67% |
| Hormonal therapy | 71% | 74% | 65% |
| *Tamoxifen* | 57% | 61% | 49% |
| *Aromatase inhibitor* | 10% | 11% | 14% |
| Recurrent or metastatic disease | 23% | 22% | 13% |
| Participation in a clinical trial | 16% | 23% | 24% |

Breast Cancer UPDATE

Slide 3

## Influence of Prior Therapy on Choice of Chemotherapy and Endocrine Therapy

Case 1: Age 65, ER-positive, 10% risk of BC mortality/recurrence



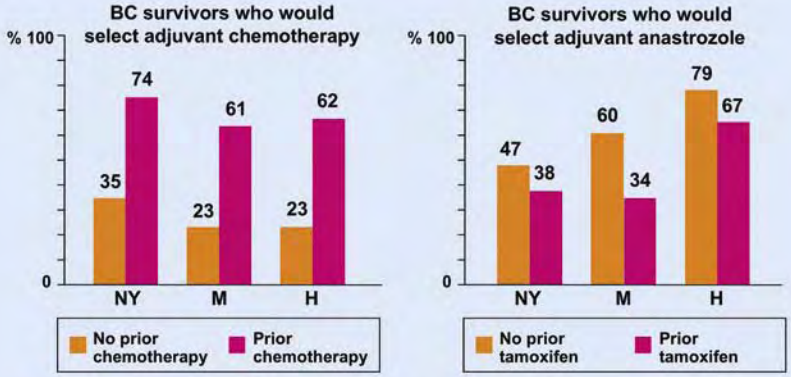

Data from the New York meeting refer to risk of 10-year breast cancer mortality. Data from the Miami and Houston meetings refer to risk of 10-year breast cancer recurrence.

Breast Cancer UPDATE

Slide 4

## Influence of Prior Therapy on Choice of Chemotherapy and Endocrine Therapy

Case 2: Age 65, ER-positive, 20% risk of BC mortality/recurrence



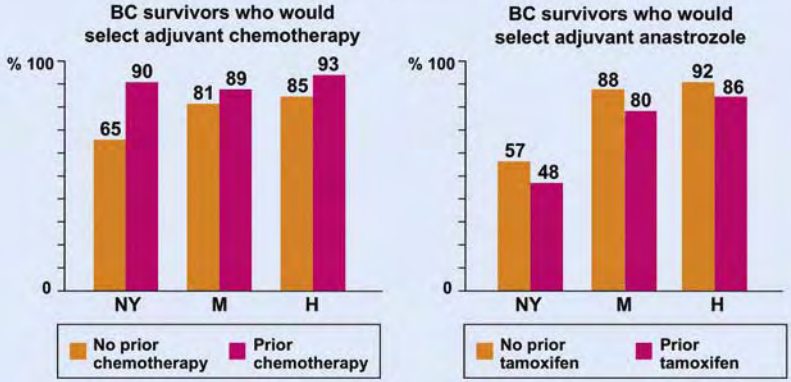

Data from the New York meeting refer to risk of 10-year breast cancer mortality. Data from the Miami and Houston meetings refer to risk of 10-year breast cancer recurrence.

Breast Cancer UPDATE

Slide 5

## Influence of Prior Therapy on Choice of Chemotherapy and Endocrine Therapy

Case 3: Age 65, ER-positive, 60% risk of BC mortality/recurrence



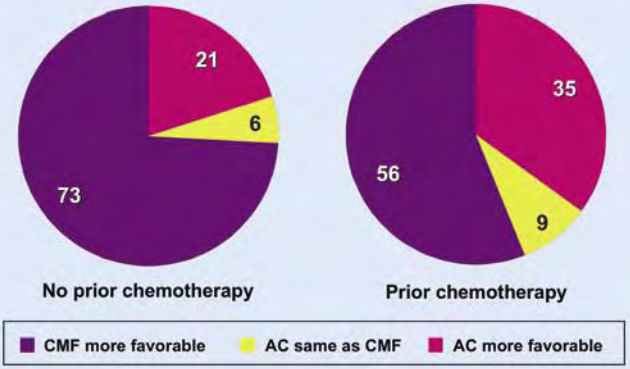

Data from the New York meeting refer to risk of 10-year breast cancer mortality. Data from the Miami and Houston meetings refer to risk of 10-year breast cancer recurrence.

Breast Cancer UPDATE

Slide 6

## Influence of Prior Chemotherapy on Perception of Toxicity

Preference for Adjuvant Chemotherapy (AC versus CMF)




After hearing the faculty describe the relative risks of CMF and AC chemotherapy, and assuming equivalent antitumor effect, survivors preferred CMF, mainly because of concerns about the cardiotoxicity of doxorubicin.

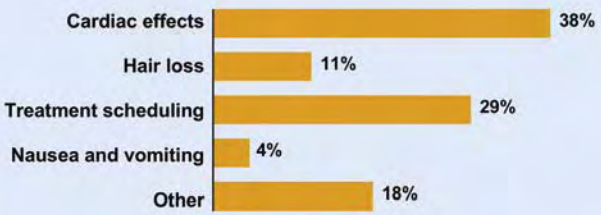
Data collected at the Miami and Houston meetings.

Breast Cancer UPDATE

Slide 7

## Influence of Side Effects on Choice of Chemotherapy

Which factor influenced your choice of AC versus CMF the most?



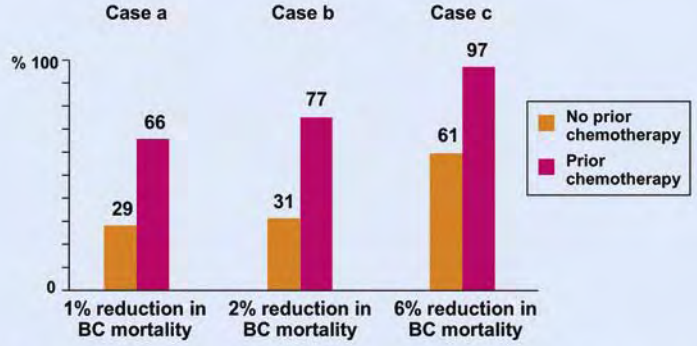

Data collected at the Miami meeting.

Breast Cancer UPDATE

Slide 8

## Influence of Prior Chemotherapy on Benefit Required from Chemotherapy

BC Survivors Who Would Select Adjuvant Chemotherapy




Magnitude of benefit associated with adjuvant chemotherapy

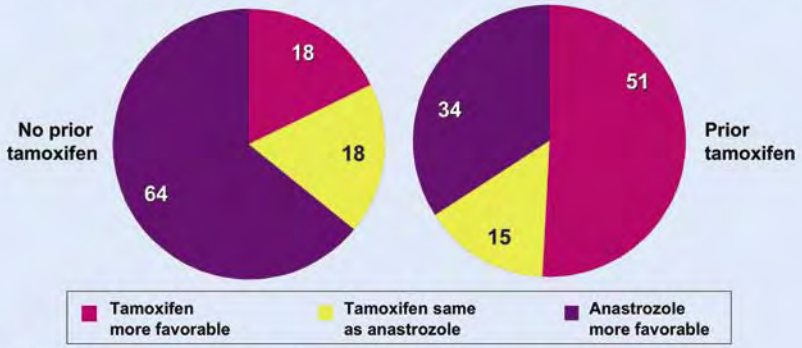
Data collected at the New York meeting.

Breast Cancer UPDATE

Slide 9

## Influence of Prior Hormonal Therapy on Perception of Toxicity

Preference for Adjuvant Hormonal Therapy (Tamoxifen versus Anastrozole)




When just the side effects of tamoxifen and anastrozole were compared (assuming equivalent antitumor effect), women who did not receive prior tamoxifen therapy preferred the side effects of anastrozole; however, women who received prior tamoxifen preferred the side-effects profile of this agent.

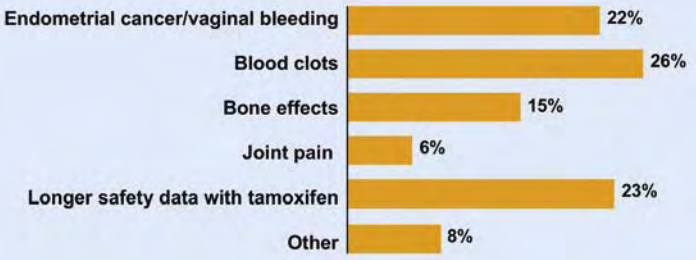
Data collected at the Miami and Houston meetings.

Breast Cancer UPDATE

Slide 10

## Breast Cancer Patients' Perspectives about Side Effects of Adjuvant Hormonal Therapy

**Which factor influenced your choice of tamoxifen versus anastrozole the most?**

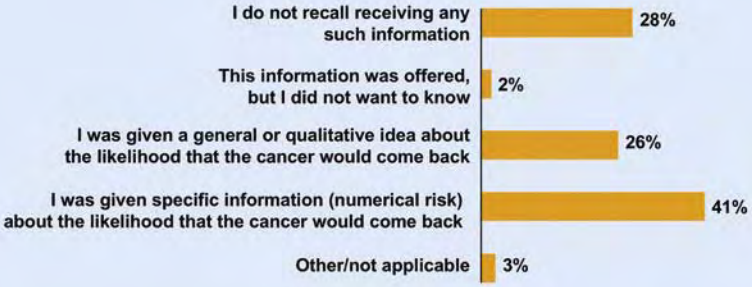



Data collected at the Miami and Houston meetings.

Breast Cancer UPDATE

Slide 11

## At the time of your diagnosis, what do you recall that your doctor told you about the chance of the cancer coming back or progressing?

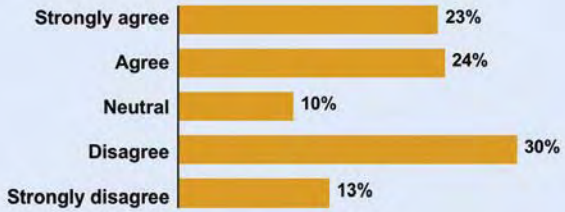



Data collected at the Miami and New York meetings.

Breast Cancer UPDATE

Slide 12

## When I was first diagnosed with breast cancer, I was so upset that I had a very difficult time understanding what the doctor was explaining to me about treatment.

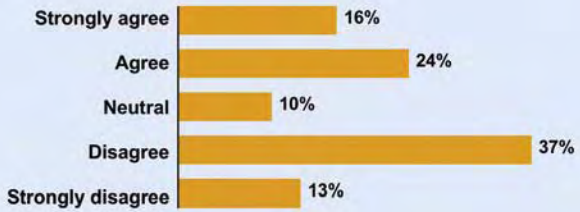



Data collected at the Miami meeting.

Breast Cancer UPDATE

Slide 13

## When I was first diagnosed with breast cancer, I had a very difficult time understanding what the doctor was explaining to me because it was too complex.




Data collected at the Miami meeting.

Breast Cancer UPDATE

# Post-test:
## *Breast Cancer Update* — Issue 6, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Dose-dense (F)AC plus G-CSF resulted in a five-year event-free survival that was comparable to or better than the standard NSABP AC regimen.**
   a. True
   b. False

2. **SWOG-S0221 will evaluate every two-week versus weekly AC plus:**
   a. Weekly paclitaxel
   b. Every two-week paclitaxel
   c. Every three-week paclitaxel
   d. Either a or b

3. **The lifetime risk of developing anthracycline-associated acute leukemia is:**
   a. One percent or less
   b. Two percent
   c. Three percent

4. **In NSABP-B-14, what percentage of patients with node-negative, ER-positive disease were found to have a favorable risk profile using the Genomics Health assay?**
   a. 10 percent
   b. 25 percent
   c. 50 percent
   d. 80 percent

5. **In a trial conducted by Anne Schott, the dose of docetaxel was selected based on the patient's body surface area and which of the following:**
   a. Age
   b. Race
   c. Comorbidities
   d. Metabolic phenotype

6. **SWOG's planned study of patients who progressed on trastuzumab and a taxane, randomizing to vinorelbine or vinorelbine plus trastuzumab, will help determine whether synergy exists between trastuzumab and chemotherapy.**
   a. True
   b. False

7. **In the randomized trial comparing docetaxel versus paclitaxel in patients with metastatic disease, reported by Stephen Jones at the 2003 San Antonio Breast Cancer Symposium, which agent resulted in greater survival?**
   a. Docetaxel
   b. Paclitaxel

8. **The IMPACT neoadjuvant trial randomly assigned patients to which of the following treatments?**
   a. Tamoxifen
   b. Anastrozole
   c. Tamoxifen and anastrozole
   d. Either a or b
   e. Either a, b or c

9. **In the IMPACT neoadjuvant trial, which of the following surrogate endpoints paralleled the results from the ATAC adjuvant trial?**
   a. Clinical response
   b. Ki67
   c. All of the above
   d. None of the above

10. **In the neoadjuvant setting, at least two trials have suggested that patients with HER2-positive disease may respond better to an aromatase inhibitor than to tamoxifen.**
    a. True
    b. False

11. **In a subgroup analysis of the patients with ER-positive and PR-negative disease in the ATAC adjuvant trial, adjuvant tamoxifen significantly reduced the risk of relapse compared to adjuvant anastrozole.**
    a. True
    b. False

12. **The SoFEA trial will randomly assign patients who have failed therapy with a nonsteroidal aromatase inhibitor to which of the following treatments?**
    a. Exemestane
    b. Fulvestrant
    c. Fulvestrant and anastrozole
    d. Either a, b or c
    e. None of the above

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

# Evaluation Form:
## *Breast Cancer Update* — Issue 6, 2004

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

**Please answer the following questions by circling the appropriate rating:**

| 5 = Outstanding | 4 = Good | 3 = Satisfactory | 2 = Fair | 1 = Poor | 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 on breast cancer treatment. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 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 relevance to patients considering adjuvant chemotherapy regimens. . . . . 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
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer. . . . . 5 4 3 2 1 N/A

### EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

| Faculty | Knowledge of Subject Matter | Effectiveness as an Educator |
|---|---|---|
| Daniel F Hayes, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Robert B Livingston, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Mitchell Dowsett, PhD | 5 4 3 2 1 | 5 4 3 2 1 |

### OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity . . . . . 5 4 3 2 1
Related to my practice needs . . . . . 5 4 3 2 1
Will influence how I practice . . . . . 5 4 3 2 1
Will help me improve patient care . . . . . 5 4 3 2 1
Stimulated my intellectual curiosity . . . . . 5 4 3 2 1
Overall quality of material . . . . . 5 4 3 2 1
Overall, the activity met my expectations . . . . . 5 4 3 2 1
Avoided commercial bias or influence . . . . . 5 4 3 2 1

# Evaluation Form:
## *Breast Cancer Update* — Issue 6, 2004

**REQUEST FOR CREDIT — Please Print Clearly**

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

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

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

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

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

**Degree:**

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

**FOLLOW-UP**

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

☐ Yes, I would be interested in participating in a follow-up survey.

☐ No, I'm not interested in participating in a follow-up survey.

**Additional comments about this activity:**

.....

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

# Breast Cancer™ UPDATE




| | |
|---|---|
| Contact Information | Neil Love, MD<br>Research To Practice<br>One Biscayne Tower<br>2 South Biscayne Boulevard, Suite 3600<br>Miami, FL 33131<br>Fax: (305) 377-9998<br>Email: NLove@researchtopractice.net |
| For CME Information | Margaret Peng, CME Administrator<br>Email: MPeng@researchtopractice.net |





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# Breast Cancer™

## U P D A T E


This program is supported by education grants from AstraZeneca Pharmaceuticals LP,
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