

# Breast Cancer™

U P D A T E

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

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## *Breast Cancer Update*

### A CME Audio Series and Activity

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#### STATEMENT OF NEED/TARGET AUDIENCE

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

#### GLOBAL LEARNING OBJECTIVES

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

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

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

#### ACCREDITATION STATEMENT

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

#### CREDIT DESIGNATION STATEMENT

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

#### HOW TO USE THIS MONOGRAPH

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

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**Dr Sledge – Consultant:** Genentech BioOncology. **Dr Romond –** No financial interests or affiliations to disclose. **Dr Cuzick – Consultant:** AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Pfizer Inc.

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## UPCOMING EDUCATIONAL EVENTS

### 2005 American Society for Therapeutic Radiology and Oncology Annual Meeting

October 16-20, 2005

Denver, Colorado

Event website: [www.astro.org/annual\\_meeting](http://www.astro.org/annual_meeting)

### European Cancer Conference

October 30-November 3, 2005

Paris, France

Event website: [www.fecs.be](http://www.fecs.be)

### Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow

November 2-5, 2005

New York, New York

Event website: [www.mssm.edu/tcf/](http://www.mssm.edu/tcf/)

### Oncology World Congress

November 16-19, 2005

New York, New York

Event website: [www.oncologycongress.com](http://www.oncologycongress.com)

### 28<sup>th</sup> Annual San Antonio Breast Cancer Symposium

December 8-11, 2005

San Antonio, Texas

Event website: [www.sabcs.org/Index.asp](http://www.sabcs.org/Index.asp)

### Miami Breast Cancer Conference

February 22-25, 2006

Miami Beach, Florida

Event website: [www.cancerconf.com](http://www.cancerconf.com)

### Fifth European Breast Cancer Conference

March 21-25, 2006

Nice, France

Event website: [www.fecs.be](http://www.fecs.be)



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## Editor's Note

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### *Novus ordo seclorum*

*I would like to conclude this session with a photo. For those of you who have a dollar bill in your pocket, this is the Great Seal of the United States that dates back to the 1780s, when the founding fathers were first putting together the United States after the American Revolution. The Great Seal includes two curious mottos, which I'll share with you, for those of you who were not Latin scholars in school.*

*First, Annuit Cœptis, which translates as "Providence has favored our endeavor." Below that is Novus Ordo Seclorum. This has a number of possible translations but the standard one is, "A new order for the ages." The historian Paige Smith has given a slightly different translation, which I prefer, "A new age now begins."*

*Ladies and gentlemen, I propose this toast to you, Novus Ordo Seclorum.*

*— George W Sledge Jr, MD  
ASCO "Education Session"  
May 16, 2005  
Orlando, Florida*



The morning after George Sledge sent a stunned ASCO audience into the Orlando sunshine to contemplate six fascinating presentations on monoclonal antibody therapy for breast cancer with trastuzumab and bevacizumab, he met with me to begin the process of making these revolutionary data sets understandable and applicable to physicians in practice. This interview is featured on this program, along with a discussion with the NSABP's Ed Romond, who presented the combined NCCTG-NSABP adjuvant trastuzumab data at ASCO, and a chat with Jack Cuzick, one of the central figures in the evolution of our other major targeted therapy for breast cancer, endocrine treatment.

When George showed the ASCO multitudes his closing slide of a dollar bill and proposed that "Toto, we're not in Kansas anymore," I had the sense that no

one in that huge meeting room would disagree with his contention that clinical research in oncology had achieved an unprecedented milestone.

A new age of molecular targeted therapy of cancer has indeed begun, and perhaps the most important take-away from May 16<sup>th</sup> is that “the system works.” Specifically, it has been possible to:

1. Identify a molecular target for an antitumor strategy (HER2 via Dennis Slamon)
2. Develop a relatively nontoxic systemic agent to attack that target (trastuzumab)
3. Demonstrate that the targeted agent added benefit in the treatment of metastatic disease (Slamon and others)
4. Demonstrate robust response rates as monotherapy or with chemotherapy in the neoadjuvant setting (Aman Buzdar, Jenny Chang and others)
5. Prove that it substantially reduces relapses and deaths when used as adjuvant therapy (NSABP-B-31, NCCTG-N9831, HERA)

Of equal if not greater importance is that these data once again validate the profound utility of large, well-designed Phase III randomized trials, not only in moving the field forward but also in offering direct benefit to trial participants. This point was made evident during a CME meeting our group hosted in New York immediately after ASCO. An oncologist from Connecticut presented the case of a 35-year-old woman who had initially joined NSABP-B-31 and was randomly assigned to chemotherapy with trastuzumab.

Several weeks later, after researching her options more extensively, the patient decided to drop out of the study because she wished to receive dose-dense AC followed by paclitaxel, which was not part of the NSABP trial design. The patient subsequently developed disease recurrence and is now receiving chemo-trastuzumab as palliative treatment for metastatic disease.

While one cannot accurately predict the course of an individual patient, the recent ASCO data suggest that this woman’s statistical likelihood of relapse might have been cut in half had she remained in the study and received trastuzumab.

Like all important clinical research databases, NSABP-B-31, NCCTG-N9831, HERA and ECOG-E2100 have raised as many questions as they have answered, and based on my initial interactions with both clinical investigators and community-based oncologists since ASCO, it is clear that the practical application of these data will be a source of enormous controversy for some time.

Undoubtedly, there will be a sense of urgency to optimize adjuvant trastuzumab algorithms, particularly in patients with pre-existing clinical and subclinical cardiac disease. However, this agent seems to follow the paradigm of other adjuvant therapies, and the classic risk-benefit calculations learned with chemotherapy and endocrine treatment apply to this agent. Peter Ravdin has already begun the process of factoring in the effect of trastuzumab on the very popular website Adjuvant! ([www.adjuvantonline.com/online.jsp](http://www.adjuvantonline.com/online.jsp)).

Bevacizumab is another story. While in some ways, the data from E2100 are similar to what was seen when the “other” monoclonal antibody (trastuzumab) was added to chemotherapy in the metastatic setting, bevacizumab does not have an identified target to separate out a patient population for treatment as HER2 does for trastuzumab. This has economic implications, but the situation with bevacizumab goes beyond dollars.

The E2100 data arrive at a time when there has been widespread support among clinical investigators for a minimalist approach to chemotherapy for metastatic breast cancer. Much of this is the result of ECOG-E1193, for which George was the principal investigator. This classic study revealed that while combination chemotherapy improved response rate and short-term tumor control, long-term survival was the same as with sequential single agents. These data were often cited when subsequent combination chemotherapy trials — for example, Joyce O’Shaughnessy’s US Oncology study evaluating capecitabine/docetaxel — demonstrated improved progression-free survival and overall survival.

E2100 did show an overall survival benefit when bevacizumab was added to paclitaxel, although these data will be more mature and interpretable later this year. However, this study — as with Joyce’s “XT” trial — did not mandate a crossover to the second agent, and this leaves room for controversy. On the other hand, bevacizumab seems to have considerably less adverse impact on quality of life than cytotoxic therapy. So perhaps what seems like some confusion about practical implications of this data set will quickly resolve if future studies demonstrate that in some way, this unique agent is a general potentiator of all cytotoxic regimens. In the future, we may be routinely combining bevacizumab with chemo just as routinely as we now add in anti-emetics. If this happens, there will undoubtedly be even more challenging questions about who will pick up the tab for this considerable investment, although it is clear that most patients desperately value any extension of the time of disease control and their survival, particularly as the result of a relatively nontoxic treatment.

Our group is about to conduct another patterns of care study on randomly selected US-based medical oncologists, and it will be very interesting to see what people are doing about adjuvant and neoadjuvant trastuzumab and bevacizumab for metastatic disease. With regards to the anti-VEGF agent, docs might just end up in the future choosing the exact same first-line chemo regimen they chose before ASCO — and just add bevacizumab. It is also likely that — as with trastuzumab in metastatic disease — there will be considerable discussion about whether to continue bevacizumab and switch chemo agents on disease progression.

In terms of adjuvant trastuzumab, by the grace of whatever or whomever you believe in, one in four or five breast cancer patients will now walk out of their initial consultation with a medical oncologist knowing that on May 16<sup>th</sup>, their risk of cancer recurrence was further lowered by 50 percent.

Like George says, *Annuit Cæptis*.

— Neil Love, MD  
NLove@ResearchToPractice.net

## ECOG-E2100: Phase III randomized trial of paclitaxel with or without bevacizumab as first-line chemotherapy for metastatic disease

### *Background*

ECOG-E2100 (E2100) was based on preclinical work from our laboratory and a number of others. In our group, Dr Chris Sweeney conducted a study in which he evaluated the ability of the taxanes to interact with bevacizumab against endothelial cells and found that the taxanes are good anti-angiogenic agents themselves.



We were able to show synergistic activity between bevacizumab and taxanes against endothelial cells, and we reasoned that the best way to use those data in the clinic was to administer a weekly taxane along with bevacizumab. We used paclitaxel because our experience — and I think that of many — is that weekly paclitaxel is better tolerated than weekly docetaxel.

### *Trial design*

E2100 was a randomized trial of weekly paclitaxel with or without every two-week bevacizumab (Miller 2005a; [1.1]). Patients could receive up to 18 courses of therapy. Each course consisted of a four-week cycle of therapy in which patients received three weeks of paclitaxel followed by a one-week rest. If the patients became tired of chemotherapy, they could discontinue paclitaxel and continue bevacizumab.

The primary endpoint was progression-free survival, and secondary endpoints included overall survival and the usual toxicity parameters. As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for discontinuing this trial if we saw an excess number of patients developing Grade IV hypertension or bleeding (Miller 2005a). When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer. Fortunately, early analyses demonstrated that was not an issue.



## 1.1 ECOG-E2100: Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100  
Accrual: 715 (Closed)

### Eligibility

Locally recurrent or metastatic breast cancer  
HER2-positive only if prior treatment with or contraindication to trastuzumab  
No prior chemotherapy for metastatic disease  
Adjuvant taxane allowed if disease-free interval >12 months; PS 0 or 1; no CNS metastases

R

Paclitaxel (days 1, 8 and 15)  
+ bevacizumab (days 1 and 15)

Paclitaxel (days 1, 8 and 15)

**SOURCE:** Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.**

Presentation. ASCO 2005a. No abstract available

### Safety

The side effects were relatively minimal. Predominantly, we saw mild to moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we'll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a low incidence of serious bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy (Miller 2005a; [1.2]).

To a certain extent, I wonder whether many of the toxicities observed with bevacizumab are, in fact, relatively tumor specific. For instance, the bowel perforations in patients with colorectal cancer and the bleeding problems in patients with lung cancer have not been an issue in patients with breast cancer.

Evaluating the literature, one could say that bevacizumab increases thrombotic events. In E2100, we saw a low level of thrombotic events (Miller 2005a; [1.2]). I suspect you can't do a lot to blood vessels without altering the risk of thrombotic episodes. Going along with that is the increase in migraines seen in almost every trial conducted with bevacizumab.

These are classic migraines, which in my experience tend to occur more commonly in patients who have a prior history of migraines. In the initial Phase I/II breast cancer trial in which we dose escalated, migraines were the dose-limiting toxicity once we reached a dose of 20 mg/kg (Cobleigh 2003).

In E2100, we haven't analyzed whether age or pre-existing risk factors influence the incidence of thrombosis. Patients who enroll in large cooperative group trials tend to be younger than the general population of patients with breast cancer. For instance, in E2100, the median age was approximately 55 (Miller 2005a), which is close to a decade younger than the age of the average patient with breast cancer in the United States. So it's entirely possible that in a more elderly group, we'll see more toxicity.

## 1.2 ECOG-E2100 Safety Results

	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy††		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

\*  $p < 0.0001$ ; †  $p = 0.0004$ ; ††  $p = 0.01$

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

### *Efficacy*

Progression-free survival went from just over six months for paclitaxel alone to almost 11 months for paclitaxel plus bevacizumab — a 4.5- to five-month improvement in progression-free survival (Miller 2005a; [1.3]). If we were to evaluate the randomized trials in metastatic breast cancer conducted over the past 20 years outside of HER2-positive disease, I would say that I cannot remember any trial showing this significant of an improvement in progression-free survival.

### *Effects on survival*

It's still too early to evaluate overall survival. The  $p$ -value is statistically significant for overall survival, but I see a certain amount of choppiness in the overall survival curves (Miller 2005a). We don't have enough events and haven't followed patients long enough. In six to 12 months, we'll have a lot more events and the curves will be more believable. We're encouraged because the early data suggest an overall survival advantage.

### **Implications of the results from E2100**

Bevacizumab ought to be considered for use along with taxane-based therapy as front-line therapy for patients with metastatic breast cancer. I certainly would not argue with those who suggest we need safety data for bevacizumab in combination with docetaxel or nanoparticle albumin-bound (*nab*) paclitaxel. However,

much of our preclinical testing was with docetaxel, and I would expect docetaxel to work well with bevacizumab.

I would not be surprised if nanoparticle taxane therapy would also work well. In fact, the nanoparticle taxanes have — as a possible mechanism of action — an effect on endothelial cells. We might see some synergistic activity there also. I'm not aware of any safety data for *nab* paclitaxel in combination with bevacizumab, but I suspect it would be safe. I would not have a problem with someone using the combination, and I would not expect any unusual toxicity.

### 1.3 ECOG-E2100 Efficacy Results

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	<i>p</i> -value
Response rate	28.2%	14.2%	<0.0001
Progression-free survival	10.97 months	6.11 months	<0.001
Overall survival	Hazard ratio = 0.674 (CI 0.495-0.917)		0.01

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

### Dosing of bevacizumab

The dose we choose is based on our Phase I/II dosing in patients with breast cancer (Cobleigh 2003). Colon and lung cancer had different paths based on randomized Phase II trials conducted in those diseases. I don't know what represents the right dose of bevacizumab. We know 20 mg/kg is too much because of the dose-limiting toxicity of migraines (Cobleigh 2003).

In the Phase I trials, once we got past approximately one mg/kg, all circulating, free VEGF was bound. So somewhere in between one and 20 mg/kg is the right dose. We used 10 mg/kg in E2100. In the Phase I/II breast cancer trial, we looked at doses of three mg/kg, 10 mg/kg and 20 mg/kg. Even though the numbers were small, we had a sense that when we went from three to 10 mg/kg, the responses were more brisk, and we saw relatively more patient benefit (Cobleigh 2003).

### Trials combining bevacizumab and trastuzumab

When we launched E2100, literally no data existed concerning the use of combination monoclonal antibody therapy in patients with breast cancer for any antibody, let alone bevacizumab and trastuzumab. Since that time, Mark Pegram and his colleagues at UCLA, based on some wonderful preclinical work, combined bevacizumab and trastuzumab in a Phase I trial that was recently reported (Pegram 2004), and they now have an ongoing Phase II trial.

The Phase I trial enrolled a total of nine patients because the combination was fairly nontoxic, and the trial zipped through the dose levels. Five of the nine patients receiving bevacizumab and trastuzumab had an objective response, and

other patients had prolonged stabilization of their disease (Pegram 2004). You don't want to make too much of a Phase I trial or a trial with nine patients, but for a treatment with no chemotherapy involved, this is a respectable response rate. If bevacizumab plus trastuzumab plays out in the larger Phase II trial, it will be a felicitous combination.

## **Combining bevacizumab with a taxane and capecitabine**

It would be reasonable to evaluate a combination of a taxane, capecitabine and bevacizumab despite the negative second-line trial of capecitabine and bevacizumab (Miller 2005b), which was conducted in a population of patients with very advanced disease.

I am the principal investigator for a new trial called XCalibr, which will evaluate the combination of bevacizumab and capecitabine as front-line therapy for patients with metastatic breast cancer who have relapsed after an adjuvant anthracycline/taxane combination. We don't have data about the use of capecitabine plus bevacizumab as first-line therapy, and we have negative second-line data (Miller 2005b). It's incumbent on us to generate some positive front-line data before we say it's the right thing to do.

## **Adjuvant bevacizumab trials**

An ECOG pilot trial of adjuvant bevacizumab, which will be primarily evaluating safety issues, will involve over 200 patients and will open within the next few months. Our belief is that given adequate safety data in the adjuvant setting — which we hope to have within 12 to 18 months — we'll be able to go directly to a large Phase III trial comparing chemotherapy to chemotherapy plus bevacizumab.

Of course, many questions can be asked in the adjuvant setting with bevacizumab (eg, which combination chemotherapy or what duration of therapy), which may require more than one trial. We will also need more than one trial because we'll have to evaluate both HER2-negative and HER2-positive disease.

## **Clinical impact of adjuvant trastuzumab trial data**

As a result of the data presented at ASCO in 2005, trastuzumab became a standard of care in the adjuvant setting for HER2-positive breast cancer. We saw a stunning validation of the biology of HER2 and the concept that we could diminish the likelihood of recurrence and improve overall survival through the use of targeted therapy. This validates 15 years of preclinical and clinical research, from Slamon's initial observation in the late 1980s that HER2 was a bad actor in breast cancer (Slamon 1987) to the pivotal metastatic trial led by Slamon (Slamon 2001) and now the adjuvant trial data (Piccart-Gebhart 2005; Romond 2005). We have consistently seen that when HER2 is overexpressed or amplified, it markedly increases a patient's risk of early relapse.

In the HERA trial, we saw that by two years after randomization, one quarter of the patients in the control arm had relapsed. In the joint analysis of NCCTG-N9831 and NSABP-B-31, around 25 percent had relapsed by approximately three

years (Piccart-Gebhart 2005; Romond 2005). This is a bad disease, and partly because of that, we see a high event rate early in these trials. A striking benefit was seen with trastuzumab, including survival with a median follow-up of just two years. That is unprecedented in any adjuvant trial.

It's interesting to imagine what the impact of the estrogen receptor trials would have been if we had enrolled 3,000 patients on those studies two or three decades ago. The data probably would have been similar to the adjuvant trastuzumab trial data. The message is that if we understand biology and target it appropriately, we obtain a great result, whereas when we use relatively nonspecific therapies, we can tweak them — changing dose duration, dose density and dose intensity — and obtain slightly better results, but we'll never achieve the revolutionary results that we saw in the adjuvant trastuzumab trials.

### Distant disease recurrence reduction with adjuvant trastuzumab

In the joint analysis of NCCTG-N9831 and NSABP-B-31, the hazard rates for distant disease recurrence in patients who received trastuzumab appeared to improve with time. It's still early to analyze these data because few patients in either trial are four years out; however, the distant disease-free survival curve appears to plateau in the trastuzumab arm. If that's the case, it's astonishing. We've never seen a true plateau in any adjuvant trial. When we examine disease-free survival curves like this, we need to ignore a fair amount of the right side of the curve because there are so few numbers, but if that is maintained it will be an exciting finding.

#### 1.4 NCCTG-N9831 and NSABP-B-31 Adjuvant Trastuzumab Trials: Disease-Free Survival Data

Joint analysis pairwise comparison	Number of events	Log rank <i>p</i> -value*	HR* (95% CI)
Concurrent versus control <sup>1</sup>	395	3 x 10 <sup>-12</sup>	0.48 (0.39-0.60)
N9831 analysis pairwise comparison	Number of events	Log rank <i>p</i> -value*	HR* (95% CI)
Sequential versus control <sup>2</sup>	220	0.2936	0.87 (0.67-1.13)
Concurrent versus sequential <sup>3</sup>	137	0.0114	0.64 (0.46-0.91)

\* Stratified — nodal and receptor status

<sup>1</sup> AC → T + H → H versus AC → T

<sup>2</sup> AC → T → H versus AC → T

<sup>3</sup> AC → T + H → H versus AC → T → H

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

## Concurrent or sequential trastuzumab administration with chemotherapy

In the HERA trial, all the patients received trastuzumab after rather than concurrent with chemotherapy, and those data were positive with an impressive 45 percent reduction in hazard rate (Piccart-Gebhart 2005). On the other hand, in the Intergroup trial, it appears that concurrent therapy is superior to the sequential schedule (Perez 2005; [1.4]). These are different data sets, and both trials have a short median follow-up and a relatively small number of events, so we shouldn't make too much of this yet.

Concurrent therapy after the anthracycline is probably better. I base that belief on the results of the pivotal trials and on a large body of preclinical data that suggest trastuzumab is a good amplifier of chemotherapy-induced apoptosis. Also, considering how rapidly the efficacy curves separate in the joint analysis data, it almost makes one want to start trastuzumab about 10 seconds after a core biopsy is obtained.

## Assessment of HER2 status

I believe every patient with primary breast cancer should be tested for HER2 by FISH, although not everyone agrees with me. The NCCTG-N9831 trial required tumors to be either FISH-positive or IHC 3+ with central review; however, we know that even with central review of IHC 3+ results, a certain number of tumors were found to be HER2-negative when a FISH assay was performed. If we analyzed the data for only the FISH-positive population in this study, the results might be even more impressive. The BCIRG 006 trial accepted only FISH-positive cases, so it's possible that the results of that trial will be even more positive.

Clearly, many hospitals report inaccurate FISH and IHC results. We know this because of the analyses done by the NSABP and NCCTG, in which comparisons of central lab testing with local hospital testing demonstrated a shocking degree of difference in some cases (Perez 2005; [1.5]). It's frightening to think that some patients will lose a chance of being cured of breast cancer because the laboratory results were wrong. We need to develop strong national or international standards for testing HER2. We don't have standardization for testing estrogen receptor either.

The FISH positivity rate in patients whose tumors are reported as IHC 0 and 1+ is low, but it's real. In the data generated by Genentech as part of the initial suite of trials, the rates for both 0 and 1+ tumors being FISH-positive were under 10 percent — I believe it was seven percent for 1+ and two percent for 0. That sounds like a low number, but given that most tumors are IHC 0 or 1+ in a general population, seven percent represents a fair number of untreated patients. We need to revisit the issue of whether to retest IHC scores of 0 and 1+ now that it appears adjuvant treatment may lead to a cure in patients with HER2-positive disease.

## 1.5 Concordance of HER2 Testing in NCCTG-N9831

### Concordance between local and central laboratories for IHC and FISH positivity

With HercepTest®	81% (78-83%)
With FISH	87% (84-90%)

### High level of agreement between central and reference laboratory results for HER2-negative tumors

For IHC (0, 1+, 2+)	94.5%
For FISH (not amplified)	95.1%

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

## Combining adjuvant trastuzumab with chemotherapy regimens

The carboplatin/docetaxel/trastuzumab regimen will be an important issue in the future. The first planned analysis of the BCIRG 006 trial could take place within the next few months. This is a crucial trial because the third arm — carboplatin/docetaxel plus trastuzumab — is compared to two more or less standard arms seen in the joint analysis. The trial will provide important data regarding cardiotoxicity versus efficacy with these regimens.

Dr Slamon shared some interesting cardiac data from an analysis of approximately 3,000 patients on the BCIRG 006 trial. A lower incidence of congestive heart failure (CHF) and fewer declines in left ventricular ejection fraction (LVEF) were seen when trastuzumab was given with carboplatin/docetaxel versus in proximity to doxorubicin (1.6). This raises the question of whether we need an anthracycline at all with trastuzumab-based therapy.

If carboplatin/docetaxel/trastuzumab has similar efficacy to AC followed by docetaxel/trastuzumab, it would probably become the de facto standard in a short period of time. Also, Robert's study comparing paclitaxel/trastuzumab with or without carboplatin as front-line therapy for metastatic breast cancer resulted in a doubling in time to progression for patients who received all three agents in a true HER2-positive population (Robert 2002). That was impressive, and if we see anything like it in the adjuvant setting, it's also likely to be a good combination.

## Role of delayed adjuvant trastuzumab

The HERA trial suggests administering trastuzumab after chemotherapy may be beneficial, so the question becomes, *how long* after chemotherapy will it be beneficial? In the case of estrogen receptors, we have two European randomized trials that evaluated the late use of tamoxifen in patients with estrogen receptor-positive breast cancer, and both were positive. Will we see a similar benefit with delayed adjuvant trastuzumab? It's a reasonable and important question, particularly for those patients in the control arms of N9831 and B-31 who are 18 months

out from treatment. I'm not going to be dogmatic about this, but I do believe it's reasonable to discuss the option of trastuzumab with such patients.

## 1.6 LVEF Declines by NYHA Class in BCIRG 006

	AC/T	AC/TH	TCH
>10%, <LLN	9	34	7
>15%, <LLN	6	25	4
Grade III/IV CHF	1	18	1

Implication: trastuzumab per se is not cardiotoxic; it becomes so when it keeps company with DOX.

A = doxorubicin; C = cyclophosphamide; T = docetaxel; H = trastuzumab; LLN = lower limits of normal

**SOURCE:** Slamon DJ. **Antibody-based therapeutics: More than a one-trick pony.** Presentation. ASCO 2005. No abstract available

## Select publications

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

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

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

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005b;23(4):792-9. [Abstract](#)

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

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

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

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

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** San Antonio Breast Cancer Symposium 2002; [Abstract 35](#).

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

Slamon DJ et al. **Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene.** *Science* 1987;235(4785):177-82. [Abstract](#)

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



### Combined analysis of NSABP-B-31 and NCCTG-N9831: Disease-free and overall survival data

In the combined analysis of the NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials, disease-free survival was the primary endpoint, but we also examined distant disease-free survival because it's a good surrogate for overall survival. What's impressive about the data is that the absolute difference in disease-free survival is 12 percent at three years, favoring trastuzumab, and those data are quite firm because many women are now three years out (Romond 2005; [2.1]). The estimate at four years is a striking 18 percent.



In addition, even though the median follow-up in the combined data set was only two years, a statistically significant difference in survival was already evident. That partly reflects the adverse prognosis of this disease — if the patient relapses, it occurs earlier rather than 10 years later. In the control arm, the recurrence rate was 25 percent at three years, which demonstrates the aggressiveness of this disease.

We never expected to see a survival benefit so early in this trial, yet at three years, the difference in overall survival was statistically significant with 3,351 women.

### Combined analysis of NSABP-B-31 and NCCTG-N9831: Distant disease-free survival data

The distant disease-free survival data are also compelling. At three years of follow-up, distant disease-free survival in the trastuzumab arm is 90 percent versus 81 percent in the control arm. At four years, it drops to 74 percent in the control arm, whereas in the trastuzumab arm, it stays at 90 percent (Romond 2005; [2.1]). This indicates that we are not yet seeing late recurrences in the trastuzumab-treated patients. Currently, only a few hundred women are four years out, so those data have more wiggle room than the three-year data. However, if this continues for another year, we may be seeing a plateau in the breast cancer survival curve for the first time.

*Dr Romond is an Associate Professor of Medicine in the Division of Hematology/Oncology at the University of Kentucky in Lexington, Kentucky.*

In both the control and trastuzumab-treated arms, the highest rate of recurrences and distant recurrences occurred in the second year. It was 90 per 1,000 women per year versus approximately 40 per 1,000 women per year in the control and trastuzumab arms, respectively. However, in the control arm, the rate of distant recurrence was essentially the same in the third and fourth years, whereas the rate plummeted in the third year and went down even further in the fourth year in the trastuzumab-treated arm.

If the data hold over time, it will completely change the ballgame in HER2-positive breast cancer. It may mean these patients are being cured early. We can't say that with confidence yet, but if the data hold up, it could be exciting.

### 2.1 Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data

Parameters	Chemotherapy* (n = 1,679)	Chemotherapy* with trastuzumab (n = 1,672)	Hazard ratio	p-value
Disease-free survival				
Three-year disease-free survival	75%	87%		
Four-year disease-free survival	67%	85%	0.48	3 x 10 <sup>-12</sup>
Time to first distant recurrence				
Three years from randomization	81%	90%		
Four years from randomization	74%	90%	0.47	8 x 10 <sup>-10</sup>
Overall survival				
Three years from randomization	92%	94%		
Four years from randomization	87%	91%	0.67	0.015

\* Chemotherapy = AC → paclitaxel

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

### Sequential versus concurrent trastuzumab with chemotherapy: Cardiac toxicity

The Intergroup trial NCCTG-N9831 did not just replicate NSABP-B-31; it was also designed to examine whether trastuzumab is better given concurrently or sequentially with chemotherapy and to evaluate the risk of cardiac events in each schedule. Patients were randomly assigned to one of three arms: chemotherapy without trastuzumab, trastuzumab given with paclitaxel and then continued for a total of one year or trastuzumab given after paclitaxel for one year. Perez presented data at ASCO in 2005 that showed cardiac events occurred in both schedules of trastuzumab, but they occurred more often in patients who received concurrent rather than sequential trastuzumab (Perez 2005).

In the NSABP trial B-31, 30 patients treated with adjuvant trastuzumab experienced NYHA Class III and IV CHF, and this correlated with age and even more

so with the patient’s post-AC ejection fraction measurement (Romond 2005; [2.2]). If the ejection fraction was over 65 percent, it was unusual for them to experience clinical CHF.

This measurement was highly statistically significant, and it may be a clinically useful parameter when deciding whether to administer trastuzumab with paclitaxel or to give the cardiac muscle a break by finishing paclitaxel and then giving trastuzumab in patients who have already received AC.

## 2.2 NSABP-B-31: Incidence of Trastuzumab-Associated Congestive Heart Failure (TACHF) Correlated with Age and Post-AC LVEF

Post-AC LVEF(%) <sup>1</sup>	TACHF	
	Age <50 years <sup>2</sup> n (%)	Age >50 years <sup>2</sup> n (%)
50-54	3/48 (6.3%)	9/47 (19.1%)
55-64	5/229 (2.2%)	10/194 (5.2%)
65+	1/160 (0.6%)	2/159 (1.3%)

<sup>1</sup> LVEF =  $p$ -value < 0.0001; <sup>2</sup> Age =  $p$ -value = 0.04

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

## Adjuvant trastuzumab in patients with node-negative disease

The NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials were initially limited to patients with node-positive disease. However, in May 2003, the Intergroup amended their protocol to include patients with high-risk, node-negative disease, which were basically ER-negative/HER2-positive or ER-positive/HER2-positive tumors that were larger than two centimeters. As a result, in the overall data set, approximately 100 patients in each arm had node-negative disease.

The relative risk reduction in the combined data analysis of patients with node-negative disease was approximately 0.48 — the same as the entire data set. The problem is that with 100 or less patients with node-negative disease in the arms of the N9831 protocol, the confidence interval goes out forever and crosses one. That does not mean there is no biologic effect; it probably exists, but it’s difficult to pin down how much benefit we gain by using trastuzumab in patients with node-negative disease. The HERA trial may be a better data set to examine the benefit of adjuvant trastuzumab in that population, because one third of those patients had node-negative disease (2.3).

## Importance of reliable HER2 testing

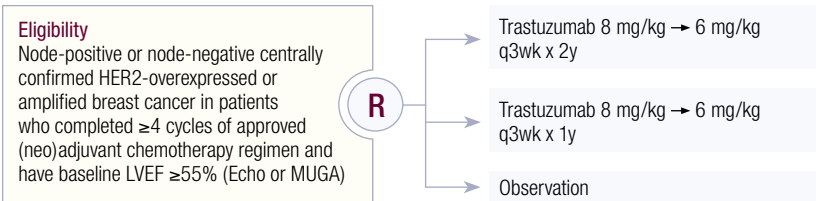
The NSABP-B-31 and NCCTG-N9831 trials were designed to require confirmatory HER2 testing in approximately the first 100 patients. However, we found

that over 20 percent of the IHC tests reported as 3+ by community hospitals were not HER2-positive when evaluated centrally by FISH or repeat IHC. We found that when the IHC was performed in laboratories with a lot of experience, such as reference laboratories that do 100 or more assays a month, the results correlated with FISH positivity in over 95 percent of cases. Therefore, we put a constraint in the protocol that IHC assays performed at community hospitals had to be confirmed at a good reference laboratory.

From an economic and toxicity standpoint, it's extremely important that HER2-positive results are really HER2-positive and the target is there. IHC 2+ results should have a FISH assay performed, and a few patients with IHC 1+ results will have gene amplification by FISH also. Off protocol, I would use adjuvant trastuzumab in patients with positive nodes who have FISH-confirmed, HER2-positive disease. Another alternative is to perform a FISH assay, although that's not 100 percent reliable in the community either (Perez 2004).

### 2.3 HERceptin Adjuvant (HERA) Trial

Protocol ID: BIG-01-01  
 Accrual: 5,090 (Closed)



#### Disease-Free Survival Benefit in the HERA Adjuvant Trastuzumab Trial by Nodal Status: One Year of Trastuzumab versus Observation

Nodal status	N	Hazard ratio
Node-negative	1,100	0.52
1-3 positive	972	0.51
>4 positive	953	0.53

“In conclusion, at one-year median follow-up, trastuzumab given every three weeks for one year following adjuvant chemotherapy significantly prolongs disease-free survival and relapse-free survival for women with HER2-positive early breast cancer. Trastuzumab significantly reduces the risk of distant metastasis. Trastuzumab’s clinical benefits are independent of patients’ baseline characteristics and of type of adjuvant chemotherapy received. Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure, but, clearly, longer follow-up is needed to better quantify this risk.”

— *Martine Piccart-Gebhart, ASCO 2005*

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

## Select publications

Altundag O et al. **Adjuvant targeted therapy with trastuzumab may decrease metastatic capacity in specific group of oropharyngeal cancer patients: Downregulation of E-cadherin-catenin complex by cooperative effect of erbB-2 and human papillomavirus type 16 E6/E7 protooncogenes.** *Med Hypotheses* 2004;63(2):277-80. [Abstract](#)

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

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

Emens LA. **Trastuzumab: Targeted therapy for the management of HER-2/neu-overexpressing metastatic breast cancer.** *Am J Ther* 2005;12(3):243-53. [Abstract](#)

Gasparini G et al. **Therapy of breast cancer with molecular targeting agents.** *Ann Oncol* 2005;16(Suppl 4):iv28-iv36. [Abstract](#)

Hampton T. **Monoclonal antibody therapies shine in breast cancer clinical trials.** *JAMA* 2005;293(24):2985-9. No abstract available

Hortobagyi GN. **Opportunities and challenges in the development of targeted therapies.** *Semin Oncol* 2004;31(1 Suppl 3):21-7. [Abstract](#)

Montemurro F, Aglietta M. **Incorporating trastuzumab into the neoadjuvant treatment of HER2-overexpressing breast cancer.** *Clin Breast Cancer* 2005;6(1):77-80. [Abstract](#)

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

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

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

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

Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab.** *J Clin Oncol* 2004;22(2):322-9. [Abstract](#)

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

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

Sledge GW Jr. **HERe-2 stay: The continuing importance of translational research in breast cancer.** *J Natl Cancer Inst* 2004;96(10):725-7. No abstract available

Theodoulou M, Seidman AD. **Cardiac effects of adjuvant therapy for early breast cancer.** *Semin Oncol* 2003;30(6):730-9. [Abstract](#)

Lottner C et al. **Simultaneous detection of HER2/neu gene amplification and protein overexpression in paraffin-embedded breast cancer.** *J Pathol* 2005;205(5):577-84. [Abstract](#)

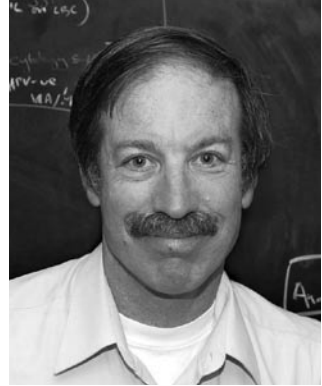
Rueckert S et al. **A monoclonal antibody as an effective therapeutic agent in breast cancer: Trastuzumab.** *Expert Opin Biol Ther* 2005;5(6):853-66. [Abstract](#)

Youssef G, Links M. **The prevention and management of cardiovascular complications of chemotherapy in patients with cancer.** *Am J Cardiovasc Drugs* 2005;5(4):233-43. [Abstract](#)

## ATAC trial: 68-month results

### *Efficacy*

The most important results were that the effects were maintained up to and beyond the five years of active treatment. Evidence exists of a “carryover” effect with tamoxifen, which isn’t surprising. The initial results from the ATAC trial suggest that the effect will be even larger for anastrozole. The fact that the six-year absolute difference in recurrence rates between anastrozole and tamoxifen is larger than the five-year difference and the curves are still separating is particularly exciting.



At 68 months of follow-up, no difference in overall mortality and a 12 percent nonsignificant ( $p = 0.2$ ) reduction in breast cancer deaths were noted with adjuvant anastrozole compared to tamoxifen (Howell 2005; [3.1]). It is early to expect a difference in survival. The significant improvement in distant disease-free survival with anastrozole will likely translate into a reduction in breast cancer mortality in a few more years.

Of course, the mortality benefit will be attenuated because — just as with tamoxifen — the mortality benefit is about half the recurrence benefit, as women take treatment upon recurrence if they haven’t received it as adjuvant therapy. The same will be true in this situation; women who didn’t receive an adjuvant aromatase inhibitor will receive it upon recurrence. You’d expect the mortality benefit to be about half of the recurrence benefit. A 10 to 15 percent reduction in relative mortality is what one might anticipate.

### *Safety*

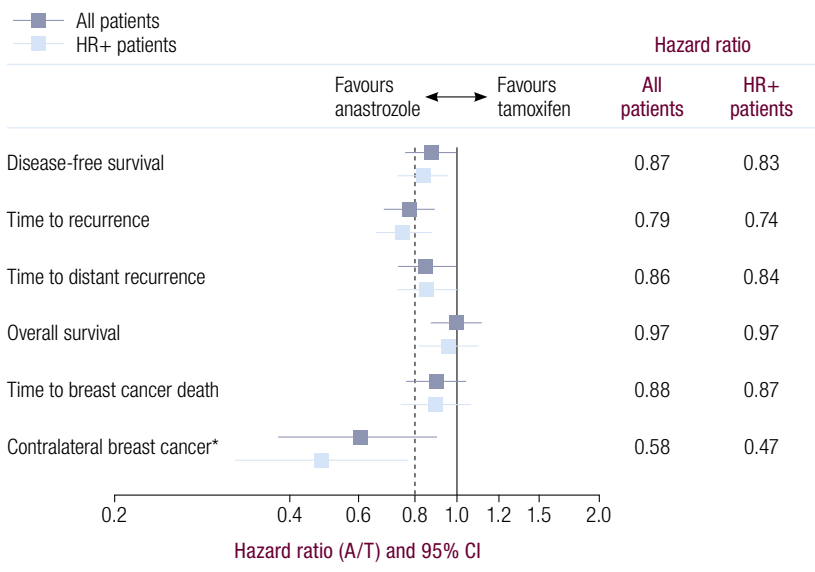
In the IBIS-1 trial, we found an increase in the hysterectomy rate for patients treated with tamoxifen (Cuzick 2002), thus it wasn’t surprising to find the same in the ATAC trial. The actual magnitude was surprising, however. The hysterectomy rate was about four times as high with tamoxifen in the ATAC trial (Howell 2005; [3.2]), whereas we saw roughly a doubling in the prevention trial (Cuzick 2002). We’re looking at the hysterectomy rates in different countries. One might suspect it’s going to be high in the United States, where more endometrial monitoring occurs.

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### 3.1 ATAC Trial 68-Month Analysis

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



**SOURCE:** Reprinted from The Lancet, 365, ATAC Trialists' Group, Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer, 60-2, 2005, with permission from Elsevier. [Abstract](#)

### Potential effect of tamoxifen on the progesterone receptor

My belief is that when patients with ER- and PR-positive disease receive adjuvant tamoxifen, the first negative event for them is the loss of the progesterone receptor. Of course, we don't actually see that, because it occurs in the micrometastases. The loss of the progesterone receptor occurs progressively at a high rate over the first two to three years of tamoxifen use, and once it happens, the rate of metastases is about double what it would be in patients who have both receptors.

In the patients with ER-positive and PR-negative disease in the ATAC trial, the recurrence rate was about half for those treated with anastrozole compared to those treated with tamoxifen (Dowsett 2003; [3.3]). For patients with ER-positive and PR-negative disease, tamoxifen doesn't work well, but anastrozole works as well as in the patients with ER- and PR-positive disease. This is just a model, however; we need more data to flesh this out.

If the model is correct, it suggests that starting with an aromatase inhibitor is best for all patients because you don't have the priming effect that tamoxifen causes. Tamoxifen is pushing some patients into a poorer prognosis group. You're always better off using the best treatment first. That will be particularly apparent if the patient has PR-negative disease initially. If the patient has PR-

positive disease initially, it may take longer for that effect to be demonstrated, but I believe that it's never better to use tamoxifen first.

### 3.2 ATAC Trial 68-Month Analysis: Adverse Events\*

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

AE = adverse events; SAE = serious adverse events

\* Adverse events on treatment or within 14 days of discontinuation

† Fractures occurring before recurrence (includes patients no longer on treatment)

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

Howell A, on behalf of the ATAC Trialists' Group. "Arimidex", Tamoxifen, alone or in combination (ATAC) trial: Completed treatment analysis. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 1](#).

### Recent adjuvant aromatase inhibitor trials

The German/Austrian studies (ARNO 95/ABCSG-8) evaluated the use of anastrozole after two years of adjuvant tamoxifen (Jakesz 2004; [3.4]). The results were almost exactly in line with the exemestane study (Coombes 2004), suggesting that after two to three years of adjuvant tamoxifen, exemestane and anastrozole have essentially equivalent efficacy. In the BIG 1-98 trial comparing initial adjuvant therapy with letrozole to tamoxifen (Thürlimann 2005a, 2005b), the efficacy results in patients with ER-positive disease were almost identical to the results from the ATAC trial (Howell 2005).



### 3.3 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](#).

### 3.4 Efficacy Data from the Combined Results of the ABCSG-8 and ARNO 95 Trials

Localization of events	Total (n = 3,224)	Tamoxifen [T] (n = 1,606)	Anastrozole [A] (n = 1,618)	Hazard ratio (A/T)	p-value
<b>Events*</b>					
Locoregional	44	24	20		
Contralateral breast cancer	28	16	12	—	—
Distant recurrences	121	75	46		
<b>Event-free survival</b>					
Events	177	110	67		
3-year event-free survival	—	92.7%	95.8%	0.6	0.0009
<b>Overall survival</b>					
Deaths	104	59	45		
3-year overall survival	—	96.4%	97.1%	0.76	0.16

\* Events occurring simultaneously are included twice.

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

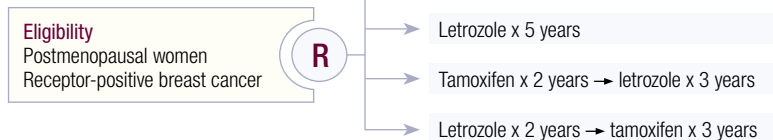
## BIG 1-98 trial

Originally, the BIG 1-98 trial, which accrued about 1,800 patients, was going to compare five years of adjuvant therapy with letrozole or tamoxifen. However, at a later stage, the IBCSG decided to evaluate the crossover. In the remaining 6,000 patients, the trial was essentially a two-by-two design. Patients began adjuvant therapy with either tamoxifen or letrozole and after two years, they were randomly re-assigned to continue with their initial treatment or switch to the other treatment (Thürlimann 2005a, 2005b; [3.5]).

### 3.5 Phase III Trial Comparing Letrozole and Tamoxifen as Adjuvant Endocrine Therapy (Median Follow-Up = 25.8 Months)

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

Accrual: 8,028 (Closed)



	HR (95% CI)	p-value
Disease-free survival (DFS)	0.81 (0.70-0.93)	0.003
Overall survival	0.86 (0.70-1.06)	0.16
Time to recurrence	0.72 (0.61-0.86)	0.0002
Time to distant metastases	0.73 (0.60-0.88)	0.0012

HR = hazard ratio for letrozole versus tamoxifen

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

We don't know anything about the switch. Strong evidence is emerging that at some stage, an aromatase inhibitor is a good idea; the only arm in question is the one in which patients start and remain on tamoxifen. In my view, it would be difficult to justify continuing with five years of tamoxifen; however, the other three arms are important and will provide the first evidence about switching from an aromatase inhibitor to tamoxifen.

The initial results from BIG 1-98 have been reported — a comparison between tamoxifen and letrozole in which all patients who were switched are censored. The efficacy results were essentially the same as those in the ATAC trial at the 30-month point. The hazard reduction was similar, and the side-effect profile was by and large the same, although it was reported differently (Thürlimann 2005a, 2005b).

A few differences were seen. They found a benefit for letrozole only in patients with node-positive disease, which is difficult to understand. It's probably a chance finding, but we need to follow that. At this stage, they've found no difference in efficacy between the patients with PR-positive and PR-negative disease (Thürlimann 2005a, 2005b). We have to acknowledge that the data are different from what's been observed in other trials.

The third and most worrying finding is the substantial excess in cardiovascular deaths for letrozole compared to tamoxifen (Thürlimann 2005a, 2005b), which hasn't been observed in the trials with anastrozole. Whether this is due to chance

or differences in cardiovascular mortality is important to know. Letrozole is a slightly more potent aromatase inhibitor, and it is not clear whether that has an impact.

### **ATAC trial: Cardiovascular mortality**

In the IBIS prevention trials, I'm glad we are using anastrozole because there's no worry about cardiovascular safety. If one were to consider letrozole for prevention now, I would be concerned about proceeding until I could see how the data panned out.

We have cardiovascular mortality data from the 68-month follow-up of the ATAC trial that have not yet been presented; they are in a paper about to be submitted. In fact, the data were in the paper of the 68-month follow-up we initially offered for publication, but *The Lancet* and the *New England Journal of Medicine* wanted a shorter publication, and we only presented the headline results.

### **Incidence of contralateral breast cancer in trials of adjuvant aromatase inhibitors**

The study results have been mixed in terms of the aromatase inhibitors' effects on overall recurrence, primarily because of the different designs. The studies that have sequenced aromatase inhibitors after tamoxifen have shown bigger relative effects, but that may be explained by the effects on the receptors.

Overall, when you consider the incidence of contralateral tumors, the trials are remarkably similar. The trials are showing nearly a 50 percent reduction in the incidence of contralateral tumors for patients treated with an aromatase inhibitor compared to those treated with tamoxifen (Howell 2005; Coombes 2004). However, in the MA17 trial, letrozole was compared to a tamoxifen carryover effect (Goss 2003).

This bodes well for prevention. First of all, I'm excited that the effect on the incidence of contralateral tumors is consistently larger than the effects on the incidence of recurrence (50 percent versus 25 to 40 percent). Aromatase inhibitors are expected to only have an effect on new tumors that are ER-positive. We don't have data on the receptor status of the contralateral tumors, although the data will be available soon from the ATAC trial. Overall, a 50 percent reduction above and beyond tamoxifen's ability to reduce the incidence of ER-positive tumors by 50 percent would suggest a 75 percent reduction in new ER-positive tumors. Eradicating 75 percent of ER-positive breast cancer would be fantastic.

### **Optimal duration of therapy with adjuvant aromatase inhibitors**

We know virtually nothing about the optimal duration of adjuvant therapy with the aromatase inhibitors. That will be the major question in the next round of trials. Many of the trials have reported large effects after a couple years of aromatase inhibitors. The ATAC trial has gone out to five years. There's no reason to stop at five years. The side-effect profile looks good. If they are used

longer, a DEXA scan will be needed to keep an eye on the bones. The issue of longer duration of therapy is both important and useful.

No direct evidence suggests that five years is better than two years. Many believe that 10 years is going to be better than five. The MA17 trial is the one example in which the duration of therapy is being evaluated. All of those patients had five years of tamoxifen, and the patients who were treated with letrozole after five years of tamoxifen will be randomly re-assigned at 10 years to stop or continue letrozole. Hence, it will be a trial of five years of tamoxifen followed by either five or 10 years of letrozole.

## Managing bone loss associated with the aromatase inhibitors

Great strides have been made in terms of the new bisphosphonates. The oral weekly preparations are well tolerated. I am optimistic that bone loss is completely manageable, and it may actually lead to a greater public health benefit by paving the way for having osteoporosis dealt with routinely in all postmenopausal women. That could be one of the more beneficial effects of this issue. With the new bisphosphonates and the potential availability of DEXA scans, osteoporosis may be a disease of the past in another decade.

## Select publications

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

Cuzick J et al; IBIS Investigators. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial.** *Lancet* 2002;360(9336):817-24. [Abstract](#)

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Proc SABCs* 2003;[Abstract 4](#).

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

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

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

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

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

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

# PowerPoint Journal Club

This PowerPoint Journal reviews recently published clinical research articles and presentations. In this issue, we review a study by Buzdar et al evaluating the addition of trastuzumab to neoadjuvant chemotherapy versus chemotherapy alone in patients with HER2-positive breast cancer; a report by Bajetta et al on a Phase II clinical trial evaluating doses of capecitabine in the treatment of elderly women with advanced breast cancer; and a review paper by Dellapasqua et al of adjuvant endocrine therapy for premenopausal patients.

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

Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy with Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer

Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Puzstai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN.

*J Clin Oncol* 2005;23(16):3676-85.

Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy with Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer

Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Puzstai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN.

*J Clin Oncol* 2005;23(16):3676-85.

Breast Cancer  
JOURNAL

## 4.1

### Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy with Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer

Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Puzstai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN.

*J Clin Oncol* 2005;23(16):3676-85.

**SLIDE 4.1** Trastuzumab in combination with standard chemotherapy has resulted in improvement in time to progression, overall response, duration of response and survival in patients with HER2-positive metastatic breast cancer. No randomized preoperative study has previously been performed with trastuzumab.

4.2

### Objectives

- Compare pathologic complete response (pCR) rates in breast and axilla following six months of preoperative paclitaxel (P) + FEC alone and the same chemotherapy + trastuzumab (H)
- Compare the safety of the two regimens

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*SOURCE:* Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. [Abstract](#)

4.3

### Trial Design

Arm I: Paclitaxel 225 mg/m<sup>2</sup> q3wk x 4

→ FEC (500/75/500 mg/m<sup>2</sup>) x 4

→ Local therapy

Arm II: Paclitaxel 225 mg/m<sup>2</sup> q3wk x 4 + H qwk x 12

→ FEC (500/75/500 mg/m<sup>2</sup>) x 4 + H qwk x 12

→ Local therapy

Patients with hormone receptor-positive disease received appropriate endocrine therapy after local therapy.

H = trastuzumab 4 mg/kg day 1, then 2 mg/kg weekly

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*SOURCE:* Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. [Abstract](#)

**SLIDE 4.3** The dose and schedule of paclitaxel was based on information available at the study's inception in 1999. Based on more current evidence, a weekly schedule may be more effective. Epirubicin was chosen in an attempt to reduce the cardiotoxicity attributed to trastuzumab/doxorubicin.

## 4.4

## Tumor Characteristics

	P → FEC (n = 19)	P + H → FEC + H (n = 23)
Hormone receptor status		
ER+/PR+	6	6
ER+/PR-	4	4
ER-/PR+	1	3
ER-/PR-	8	10
HER2 status		
FISH+	17	19
IHC 3+ only	1	3
IHC 3+, FISH-	1	1

P = paclitaxel; H = trastuzumab

**SOURCE:** Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.4** Approximately half of the patients had hormone receptor-positive tumors. Most patients had HER2 status of tumors confirmed by FISH. For four patients, HER2 status was determined by IHC only. One patient in each arm was subsequently found to be HER2-negative by FISH.

## 4.5

## Pathologic Complete Response Rates

	P → FEC (n = 19)	P + H → FEC + H (n = 23)	p-value
pCR (95% CI)	26.3% (9.1-51.2)	65.2% (43.0-84.0)	0.016
pCR by hormone receptor status			
Positive	27.2%	61.5%	—
Negative	25.0%	70.0%	—

P = paclitaxel; H = trastuzumab

Note: Unscheduled Data Monitoring Committee review stopped study due to high pCR rate

**SOURCE:** Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.5** Among the total patients, 26.3 percent of patients in the chemotherapy alone arm achieved pCR compared to 65.2 percent of the patients treated with trastuzumab plus chemotherapy. Patients with hormone receptor-positive and -negative disease had similar pCR rates compared to the overall population.

## 4.6

## Extent of Residual Disease

	P → FEC (n = 19)	P + H → FEC + H (n = 23)	p-value
Residual disease in breast			
None	5	15	0.01
<1 cm	3	5	
1-3 cm	9	1	
>3 cm	2	2	
Number of positive nodes			
0	15	20	0.25
1-3	2	3	
4-10	2	0	
>10	0	0	

P = paclitaxel; H = trastuzumab

**SOURCE:** Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.6** For patients treated with trastuzumab plus chemotherapy, the size of residual tumors in the breast was significantly smaller compared to tumors of patients treated with chemotherapy alone. The difference in the extent of residual disease in the lymph nodes was not statistically significant.

## 4.7

## Adverse Events

Events	P → FEC (n = 19)	P + H → FEC + H (n = 23)
Neutropenia (Grade IV)*	11	21
Neutropenic fever	8	8
Neutropenic infections	3	5
Hospitalization	1	3
Non-neutropenic infections	4	7
Chemotherapy dose reduction secondary to neutropenia	5	10

P = paclitaxel; H = trastuzumab

\*  $p = 0.03$

**SOURCE:** Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.7** A higher fraction of patients treated with trastuzumab plus chemotherapy experienced Grade IV neutropenia while receiving paclitaxel. A small number of patients had neutropenic fever requiring hospitalization. There were no treatment-related deaths.



4.8

## Adverse Events Cardiac Safety Data

Events	P → FEC (n = 19)	P + H → FEC + H (n = 23)
CHF	0	0
>10% decrease in ejection fraction	5	7
Decrease on P	0	4
Decrease on FEC	5	3
Improvement in ejection fraction on follow-up evaluation	2	3
Abnormal troponin-T	0	1

P = paclitaxel; H = trastuzumab

*SOURCE:* Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.8** None of the patients developed clinical congestive heart failure. A greater than 10 percent decrease in the left ventricular ejection fraction occurred in five and seven patients in the chemotherapy alone and trastuzumab plus chemotherapy arms, respectively.

4.9

## Conclusions

- The addition of trastuzumab to P + FEC significantly increased pCR rates (65.2%) in patients with HER2-positive breast cancer compared to those receiving P + FEC alone (26.3%).
- No clinical cardiac toxicity was observed.

P = paclitaxel

*SOURCE:* Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

**SLIDE 4.9** These results represent the highest reported pCR rate in this patient population. The most logical explanation for this high pCR rate is the use of two potentially noncross-resistant chemotherapies in combination with trastuzumab. Another possibility is the longer duration of neoadjuvant therapy.

## Select publications

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

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

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

Gennari R et al. **Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2.** *Clin Cancer Res* 2004;10(17):5650-5. [Abstract](#)

Griggs JJ et al. **Safety and effectiveness of primary systemic therapy with docetaxel and trastuzumab in HER-2 positive breast cancer.** *Proc ASCO* 2005;[Abstract 793](#).

Jahanzeb M et al. **Dose-dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support.** *Proc ASCO* 2005;[Abstract 591](#).

Kostler WJ et al. **Monitoring of serum Her-2/neu predicts histopathological response to neoadjuvant trastuzumab-based therapy for breast cancer.** *Anticancer Res* 2004;24(2C):1127-30. [Abstract](#)

Mehta RS et al. **Phase II study of neoadjuvant biweekly doxorubicin and cyclophosphamide (AC) with GM-CSF followed by weekly paclitaxel, carboplatin +/- trastuzumab (TC +/- H) in the treatment of breast cancer (BC).** *Proc ASCO* 2005;[Abstract 826](#).

Montemurro F, Aglietta M. **Incorporating trastuzumab into the neoadjuvant treatment of HER2-overexpressing breast cancer.** *Clin Breast Cancer* 2005;6(1):77-80. [Abstract](#)

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

Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab.** *J Clin Oncol* 2004;22(2):322-9. [Abstract](#)

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

Ries LM et al. **Neoadjuvant q4week carboplatin and weekly paclitaxel + trastuzumab in resectable and locally advanced breast cancer: A Brown University Oncology Group (BrUOG) study.** *Proc ASCO* 2005;[Abstract 759](#).

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

Rueckert S et al. **A monoclonal antibody as an effective therapeutic agent in breast cancer: Trastuzumab.** *Expert Opin Biol Ther* 2005;5(6):853-66. [Abstract](#)

Van Pelt AE et al. **Neoadjuvant trastuzumab and docetaxel in breast cancer: Preliminary results.** *Clin Breast Cancer* 2003;4(5):348-53. [Abstract](#)

Wenzel C et al. **Preoperative therapy with epidoxorubicin and docetaxel plus trastuzumab in patients with primary breast cancer: A pilot study.** *J Cancer Res Clin Oncol* 2004;130(7):400-4. [Abstract](#)

5.1

### Safety and Efficacy of Two Different Doses of Capecitabine in the Treatment of Advanced Breast Cancer in Older Women

Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, Catena L, Ricotta R, Longarini R, Zilembo N, Buzzoni R.

*J Clin Oncol* 2005;23(10):2155-61.

**SLIDE 5.1** This study sought to determine the safety and efficacy of capecitabine monotherapy in the treatment of advanced breast cancer in older women.

5.2

### Palliative Chemotherapy for Breast Cancer in the Elderly

- Elderly patients are at a greater risk for excessive chemotherapy-associated toxicity.
- Greater toxicity potential for combination regimens supports the use of sequential single-agent therapy.
- Favorable safety profile of capecitabine monotherapy makes it an attractive chemotherapeutic agent for this patient population.

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**SOURCE:** Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

## 5.3

## Methods

- Capecitabine administered sequentially to patients  $\geq 65$  years with metastatic breast cancer
  - Standard-dose cohort (n = 30): 1,250 mg/m<sup>2</sup> BID for 2 wk q3wk
  - Low-dose cohort (n = 43): 1,000 mg/m<sup>2</sup> BID for 2 wk q3wk
- Primary objective: Evaluate safety profile
- Secondary objective: Evaluate response rate and time to disease progression

*SOURCE:* Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

**SLIDE 5.3** Patients age 65 or older with metastatic breast cancer received either standard- or low-dose capecitabine therapy. The primary objective was to assess the safety profile of capecitabine. The secondary objective was to determine efficacy in terms of response rate and time to disease progression.

## 5.4

## Cohort Baseline Differences

- More patients with hormone receptor-negative tumors in standard- versus low-dose cohort (40% vs 14%;  $p = 0.03$ )
- More patients with no prior systemic treatments for advanced disease in standard- versus low-dose cohort (70% vs 49%;  $p = 0.09$ )

*SOURCE:* Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

**SLIDE 5.4** Baseline characteristics were similar between cohorts with the exceptions that the standard-dose cohort had a greater percentage of patients with hormone receptor-negative tumors and a greater percentage of patients not having received prior systemic treatments for advanced disease.

## 5.5

## Grade III/IV Events, Dose Reductions and Lethal Toxicities

	Standard-dose cohort (n = 30)	Low-dose cohort (n = 43)
Fatigue	7%	12%
Diarrhea	13%	2%
Dyspnea	10%	5%
Nausea	7%	5%
Dose reductions required	30%	5%
Lethal toxicities	7%	2%

*SOURCE:* Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

**SLIDE 5.5** The initial planned dose of capecitabine for this study was 1,250 mg/m<sup>2</sup> BID. Due to the occurrence of two toxic deaths, the dose was subsequently reduced to 1,000 mg/m<sup>2</sup> BID.

## 5.6

## Efficacy

	Standard-dose cohort (n = 30)	Low-dose cohort (n = 43)
Median survival	10 months	16 months
Overall response	36.7%	34.9%
Median duration of response	4.3 months	4.3 months
Stable disease	33%	46%
Median time to progression	3.9 months	4.1 months

*SOURCE:* Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

**SLIDE 5.6** The response rate was 36.7 percent for the standard-dose cohort. Seven patients had disease stabilization at  $\geq 24$  weeks. The response rate was 34.9 percent in the low-dose cohort. An additional 15 patients had prolonged stabilization. Median time to disease progression was approximately four months in each group.

## Conclusion

- Low overall incidence of severe toxicity
- Majority of AEs in both cohorts were mild to moderate in intensity
  - Tolerability profile more satisfactory in low-dose group
  - Attention to diarrhea is important in patients >70 years, as it may be fatal
- Similar rates of tumor response in both cohorts
- Capecitabine at 2,000 mg/m<sup>2</sup> per day is a more appropriate starting dose for older women and merits consideration as a “standard” for metastatic breast cancer therapy in women ≥70 years old without severely impaired renal function

*SOURCE:* Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61. [Abstract](#)

**SLIDE 5.7** Due to the more favorable tolerability profile and similar rate of tumor response, low-dose capecitabine merits consideration as “standard” therapy in this patient population.

## Select publications

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

Hennessy BT et al. **Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: Retrospective analysis of patients treated at MD Anderson Cancer Center and a review of capecitabine toxicity in the literature.** *Ann Oncol* 2005;[Epub ahead of print]. [Abstract](#)

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

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

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

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9. [Abstract](#)

Pierga JY et al. **Efficacy and safety of single agent capecitabine in pretreated metastatic breast cancer patients from the French compassionate use program.** *Breast Cancer Res Treat* 2004;88(2):117-29. [Abstract](#)

Walko CM, Lindley C. **Capecitabine: A review.** *Clin Ther* 2005;27(1):23-44. [Abstract](#)

## 6.1

### Adjuvant Endocrine Therapy for Premenopausal Women with Early Breast Cancer

Dellapasqua S, Colleoni M, Gelber RD, Goldhirsch A.

*J Clin Oncol* 2005;23(8):1736-50.

**SLIDE 6.1** One third of new invasive breast cancer diagnoses are in women under 50 years old. This trend may increase because of changes in lifestyle, demographics and screening. In this review, Dellapasqua S et al discuss the current status of adjuvant endocrine therapy for premenopausal women with early breast cancer.

## 6.2

#### Data Review Considerations

- Contribution of ovarian function suppression (OFS) to effects of adjuvant chemotherapy in premenopausal women
- No data on use of aromatase inhibitors (AIs) with OFS
- Type and duration of OFS
- Optimal combination of endocrine therapies with selective estrogen receptor modulators (SERMs), AIs and selective estrogen receptor downregulators (SERDs)
- Investigations into tailored therapies for younger premenopausal patients

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.2** This review considered treatment effects of adjuvant chemotherapy, use of AIs combined with OFS, the type and duration of OFS, endocrine therapy combined with SERMs, AIs and SERDs and tailored treatments for younger versus older premenopausal women.

6.3

### Adjuvant Therapies for Younger Patients

- Breast cancer prognosis unfavorable in young women
- Chemotherapy alone not sufficient for younger premenopausal patients with ER-positive disease
- Tamoxifen ± OFS usually offered to premenopausal women with ER-positive disease
- AIs, effective in postmenopausal women, are ineffective at premenopausal estrogen levels

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.3** Adjuvant chemotherapy is usually prescribed before endocrine therapy for women with hormone-responsive disease with a high risk of relapse. Younger patients have a poorer prognosis, and AIs, effective in postmenopausal women, are ineffective in the presence of premenopausal estrogen levels.

6.4

### Ovarian Function Suppression/Ablation

- Younger women benefit similarly from ablation, adjuvant chemotherapy or tamoxifen
- Ovarian ablation in women ≤50 years old significantly improved survival (from EBCTCG)
- LHRH for OFS is safe and reversible
  - No permanent ovarian dysfunction
  - Similar response rates as oophorectomy
- OFS by chemotherapy may cause ovarian dysfunction

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.4** Adjuvant therapy of ovarian ablation with surgery or radiation improves recurrence-free and overall survival among breast cancer patients ≤50 years old. OFS is achievable with LHRH agonists and chemotherapy. Whether or not chemotherapy benefits are due entirely to endocrine effects is unknown.



## 6.5

## Tamoxifen

- EBCTCG overview analysis of tamoxifen trials with women <50 years old with ER-positive tumors
  - 45% risk reduction in recurrence
  - 32% risk reduction in mortality
- Recommended duration of tamoxifen treatment: Five years
  - Tamoxifen treatment beyond five years
    - Increased risk of endometrial cancer
    - No demonstrated benefit
- Side effects: Endometrial cancer, thromboembolic disorders

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.5** Results of many trials evaluating adjuvant tamoxifen support its use as adjuvant therapy for both pre- and postmenopausal women, especially those with hormone receptor-positive breast cancer. Side effects of tamoxifen include endometrial cancer and thromboembolic disorders.

## 6.6

## OFS + Tamoxifen ± Chemotherapy

- LHRH agonists can suppress tamoxifen-induced stimulation of ovarian function
- Significant survival benefit from combined LHRH + tamoxifen versus LHRH agonist alone
- OFS + tamoxifen safe and as effective as chemotherapy in premenopausal women with ER-positive disease
- Unknown efficacy of sequential combination of OFS and chemotherapy
- PERCHE trial compares combined endocrine therapy versus the addition of chemotherapy to OFS plus tamoxifen

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.6** LHRH agonists suppress ovarian function stimulation by tamoxifen. Combined, these two agents significantly benefit survival while being safe and as effective as chemotherapy in premenopausal women with ER-positive disease. At present, the efficacy of combined OFS and chemotherapy is unknown.

6.7

## Aromatase Inhibitors

Study	Intervention
IBCSG-24-02 (SOFT trial)	Tamoxifen Ovarian suppression + tamoxifen Ovarian suppression + exemestane
IBCSG-25-02 (TEXT trial)	Triptorelin + tamoxifen Triptorelin + exemestane
IBCSG-26-02 (PERCHE trial)	Ovarian suppression + tamoxifen or exemestane Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.7** Aromatase inhibitors in combination with GnRH analogs may be effective as adjuvant therapy for premenopausal women with endocrine-responsive breast cancer. This is being investigated in the ongoing SOFT, TEXT and PERCHE trials coordinated by the International Breast Cancer Study Group (IBCSG).

6.8

## Special Issues

- GnRH analogs as adjuvant therapy option not routinely offered to premenopausal women
- Women prefer goserelin over chemotherapy
- Preservation of ovarian function during chemotherapy
- Ovarian tissue preservation
- Safety of endocrine therapies for grown children of mothers who conceived after tamoxifen and other endocrine agents

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.8** There are special issues to consider: when provided with the option, premenopausal women would prefer a GnRH analog over chemotherapy; preservation of ovarian function during chemotherapy, including ovarian tissue preservation; and safety of endocrine therapies in specific subgroups of women.

## 6.9

## Additional Research

- Amenorrhea as a determinant for premenopausal women with early-stage breast cancer
- Optimal duration of OFS with LHRH analogs
- Value of OFS/OFA after chemotherapy
- Combination endocrine therapies
- Use and long-term side effects of AIs
- Value of chemotherapy for patients at low risk for relapse who receive optimal endocrine therapy
- Targeted chemotherapies combined with endocrine treatments
- Endocrine therapies and effects on child bearing

*SOURCE:* Dellapasqua S et al. *J Clin Oncol* 2005;23(8):1736-50. No abstract available

**SLIDE 6.9** Premenopausal women with ER-positive breast cancer need adjuvant endocrine therapy that is tailored to their group. However, despite many advances in adjuvant hormonal therapy, further research is required.

## Select publications

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

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 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](#)

Castiglione-Gertsch M et al; International Breast Cancer Study Group. **Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial.** *J Natl Cancer Inst* 2003;95(24):1833-46. [Abstract](#)

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation in early breast cancer: Overview of the randomised trials.** *Lancet* 1996;348(9036):1189-96. [Abstract](#)

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

Goldhirsch A et al. **Adjuvant therapy for very young women with breast cancer: Need for tailored treatments.** *J Natl Cancer Inst Monogr* 2001;30:44-51. [Abstract](#)

Goldhirsch A et al. **Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer.** *J Clin Oncol* 2003;21(17):3357-65. [Abstract](#)

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

## Post-test:

*Breast Cancer Update* — Issue 6, 2005

### QUESTIONS (PLEASE CIRCLE ANSWER):

- In E2100, the addition of bevacizumab to \_\_\_\_\_ as first-line therapy was found to significantly increase progression-free survival in patients with metastatic breast cancer.
  - Capecitabine
  - Docetaxel
  - Paclitaxel
  - Nab* paclitaxel
  - All of the above
- In E2100, the dose of bevacizumab was \_\_\_\_\_.
  - 1 mg/kg
  - 5 mg/kg
  - 10 mg/kg
  - 20 mg/kg
  - None of the above
- In a small Phase I trial of bevacizumab and trastuzumab, five out of nine patients had an objective response.
  - True
  - False
- Based on the joint analysis of NCCTG-N9831 and NSABP-B-31, which schedule appears to be superior in terms of disease-free survival?
  - Sequential trastuzumab given after chemotherapy
  - Concurrent trastuzumab/chemotherapy
- A cardiac data analysis of approximately 3,000 patients on the BCIRG 006 trial showed which of the following in patients who received trastuzumab in combination with carboplatin/docetaxel versus trastuzumab in proximity to doxorubicin:
  - Lower incidence of CHF
  - Lower incidence of reduced LVEF
  - Both a and b
  - None of the above
- In the combined analysis of the NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials, which of the following were improved with the addition of trastuzumab?
  - Disease-free survival
  - Distant disease-free survival
  - Overall survival
  - Both a and b
  - All of the above
- In the combined analysis of the NSABP-B-31 and NCCTG-N9831 trials, the rate of distant recurrence was essentially the same in the third and fourth years in the control arm, whereas in the trastuzumab-treated arm, the rate \_\_\_\_\_ in the third and fourth years.
  - Increased
  - Decreased
- In the NSABP-B-31 and NCCTG-N9831 trials, a statistically significant correlation was seen between patients' post-AC ejection fraction measurements and the incidence of clinical CHF in patients who received trastuzumab.
  - True
  - False
- Whereas the reliability of HER2 testing by immunohistochemistry can vary depending on the laboratory where it is performed, FISH testing is 100 percent reliable.
  - True
  - False
- In the ATAC trial, the hysterectomy rate was about four times as high with tamoxifen compared to anastrozole.
  - True
  - False
- ARNO 95 and ABCSG-8 evaluated the use of \_\_\_\_\_ following two years of adjuvant tamoxifen.
  - Exemestane
  - Letrozole
  - Anastrozole
  - All of the above
- The initial results from BIG 1-98 demonstrated an excess number of cardiovascular deaths for letrozole compared to tamoxifen.
  - True
  - False

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

# Evaluation Form:

## Breast Cancer Update — Issue 6, 2005

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

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

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

### GLOBAL LEARNING OBJECTIVES

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

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

### EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
George W Sledge Jr, MD	5 4 3 2 1	5 4 3 2 1
Edward H Romond, MD	5 4 3 2 1	5 4 3 2 1
Jack Cuzick, 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 N/A
- Related to my practice needs. . . . . 5 4 3 2 1 N/A
- Will influence how I practice. . . . . 5 4 3 2 1 N/A
- Will help me improve patient care. . . . . 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
- Overall quality of material. . . . . 5 4 3 2 1 N/A
- Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
- Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

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## Evaluation Form:

*Breast Cancer Update* — Issue 6, 2005

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**REQUEST FOR CREDIT** — please print clearly

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

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

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

Yes  No

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

.....

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

.....

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

.....

**Additional comments about this activity:**

.....

**Degree:**

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

### FOLLOW-UP

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

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

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

# Breast Cancer™

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