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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 3 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs O'Shaughnessy, Geyer, Jakesz and Paik on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

29th Annual Symposium of the American Society of Breast Disease: Practical Issues in Multidisciplinary Management of Breast Cancer
April 14-16, 2005
Las Vegas, Nevada
Event website: **www.asbd.org**

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

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

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

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

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

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

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

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

Editor's Note

Overture

Just before boarding a peanut-and-pretzels-only flight to Atlanta for the Society of Surgical Oncology meeting, I received an email from our scientific director, Rick Kaderman. Attached were two interesting *JCO* articles* that had just become available online. The first was the formal publication of Aman Buzdar's neoadjuvant trastuzumab study, which was initially presented at the 2004 ASCO meeting. The second was the accompanying editorial by Harold Burstein and Eric Winer.

That evening, while my wife Adriana and I were dining at the somewhat unappetizing Atlanta Hyatt lobby buffet, Aman — who was to join me the next morning on a tumor panel discussion at the ungodly surgical hour of 6:00 AM — dropped by our table. He had just arrived back from Japan where he was doing a visiting professorship, during which he spent some time in Hiroshima. All he could talk about was the emotional enormity of being in the place where so many people died instantly. While I listened intently to his travel-related stories, I was also curious about the *JCO* paper. "The editors contacted me right after ASCO," he said. "They wanted to see it published quickly."

No wonder. The importance of Aman's study was eloquently discussed by Hal and Eric in an extended editorial, which noted that the day is soon coming when HER2-positive breast cancer will truly be considered a separate disease, and the remaining HER2-negative patient subset will look a lot different. Very specifically, Aman's study sets the stage for the most anticipated group of trials in breast cancer clinical research in the last decade: the four large randomized studies evaluating adjuvant trastuzumab (1.1).

The next issue of our series includes an extraordinary interview with Edith Perez, the principal investigator of one of these landmark studies, NCCTG-9831. After major prodding on my behalf (which made me feel like a prosecuting attorney), Edith spilled some major beans: The NCI and FDA have

* 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);[Epub ahead of print]. **Abstract**

Burstein HJ, Winer EP. **HER2 or not HER2: That is the question.** *J Clin Oncol* 2005;23(16); [Epub ahead of print]. **Abstract**

just agreed to allow the data from the two common randomization arms of N9831 and NSABP-B-31 to be combined into one analysis.

According to Edith, this data set will be analyzed in April and has enough events to provide an initial evaluation of the risks and benefits of adjuvant trastuzumab. With more arm twisting (sorry, Edith!), she told me that the results could become publicly available as early as this summer, although it could also be much longer before we hear anything due to very stringent statistical boundaries for revealing the data at this point. The other two major trastuzumab trials (HERA and BCIRG-006) might not have results for a year or two.

1.1 Phase III Clinical Trials of Adjuvant Trastuzumab

Trial (target accrual)	Eligibility	Randomization
NSABP-B-31 (2,700 patients)	Node-positive IHC 3+ or FISH-positive	AC x 4 → paclitaxel q3wk x 4 or paclitaxel qwk x 12 AC x 4 → (paclitaxel q3wk x 4 or paclitaxel qwk x 12) + H qwk x 1 year
Intergroup N9831 (3,300 patients)	Node-positive IHC 3+ or FISH-positive	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 1 year AC x 4 → (paclitaxel + H) qwk x 12 → H qwk x 40
BCIRG-006 (3,150 patients)	Node-positive FISH-positive	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H (qwk x 12 weeks) → H (qwk x 40 weeks) (Docetaxel + C) x 6 + H (qwk x 18 weeks) → H (qwk x 34 weeks)
BIG-01-01 HERA* (4,924 patients)	Node-positive or node-negative IHC 3+ or FISH-positive	H q3wk x 1 year H q3wk x 2 years No H

* Post-chemohormonal therapy randomization
H = trastuzumab; C = cisplatin or carboplatin; AC = doxorubicin + cyclophosphamide

SOURCES: NCI Physician Data Query, March 2005; BCIRG website, March 2005.

The eternal optimist in me (and all oncologists) says that things won't be the same in breast cancer after the unprecedented NCCTG-NSABP analysis. This situation reminds me of the months leading up to the first presentation of the ATAC data in December 2001. As with the discussion with Edith, I received an early "heads up" about ATAC during an interview with Mike Baum in February 2001 at the Miami Breast Cancer Conference. At that time, no one had a clue when the initial data would be analyzed, but Mike revealed that the trialists had just determined that enough events had transpired to perform a data analysis that November and present the findings the following month in San Antonio.

From that point on, one of my standard questions during any interview for this series was, "What do you think the ATAC trial will show?" All but one person, who now lives in infamy (sorry, Bob!), predicted without much hesitation that anastrozole would be superior to tamoxifen, and that indeed, is exactly what occurred. Most of these investigators also commented that bone would likely be

an issue because bone density monitoring and the use of bisphosphonates were not included in the ATAC protocol.

Of course, many other times in the history of breast cancer clinical research our hopes and expectations have been crushed by trial results — witness the rise and fall of stem cell transplantation — but ATAC and the other aromatase inhibitor trials have provided renewed confidence that advances in metastatic disease will translate to the adjuvant setting.

As the little ball on the adjuvant trastuzumab roulette wheel is slowly coming to a halt, and we hold our collective breaths in anticipation, I have adopted a new favorite interview question, "What do you think the adjuvant trastuzumab trials will show?" So far, the results have been unanimously optimistic, and I am also fully on the adjuvant H bandwagon.

Nothing in oncology will make sense anymore if these trials don't show at least a significant reduction in the short-term recurrence rate with trastuzumab, particularly in view of studies like Aman's neoadjuvant trial, which clearly demonstrates a major bump in tumor control by adding this landmark targeted agent.

Even with a three to four percent rate of cardiac toxicity with trastuzumab, a relative reduction in relapse rate of even 20 to 30 percent will result in a positive benefit-to-risk ratio for patients with HER2-positive, node-positive tumors, particularly those lacking estrogen and progesterone receptors.

The answers will start appearing soon, and if things transpire as expected, Hal and Eric's concept of HER2-positive breast cancer as a separate disease entity will be fully on the table. I can't imagine that it won't be quickly embraced, but it is also fascinating to consider how the residual non-HER2 tumors will be reconceptualized and how all of this ties in with new classification systems such as those related to the Genomic Health Onco*type* DX™ assay and to the work of Charles Perou. All four speakers in this issue of *Breast Cancer Update* comment on this issue, which is perhaps the most discussed topic in breast cancer research today.

With all this being said, it is clear that the HER2 overture is over and the symphony is about to begin. Patients and physicians will be on the edge of their seats and I hope and pray they will not be disappointed.

— Neil Love, MD
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Select publications

Carey LA et al. **The triple negative paradox: Primary tumor chemosensitivity of the basal-like breast cancer (BBC) phenotype.** San Antonio Breast Cancer Symposium 2004;**Abstract 1023**.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Perou CM et al. **Molecular portraits of human breast tumors.** *Nature* 2000;406(6796):747-52. **Abstract**

Rouzier R et al. **Basal and luminal types of breast cancer defined by gene expression patterns respond differently to neoadjuvant chemotherapy.** San Antonio Breast Cancer Symposium 2004;**Abstract 201**.

Phase II trial of capecitabine and paclitaxel

We conducted this clinical trial in two different cohorts of about 50 patients with metastatic disease: taxane naïve and taxane pretreated.

If you're going to administer capecitabine with any other agent (eg, paclitaxel, docetaxel or vinorelbine) in the adjuvant, neoadjuvant or metastatic setting, a dose of 1,650 mg/m^2 per day seems to be well tolerated.

On a 21-day cycle, we administered paclitaxel 80 mg/m^2 on days one and eight and capecitabine 1,650 mg/m^2 per day in two divided doses, 14 days on and seven days off (Blum 2004).

The data from the taxane-naïve patients with metastatic breast cancer demonstrated a response rate of about 50 percent (2.1), and the toxicity was mild (Blum 2004). It was an easy clinical trial to conduct because many of us were already utilizing the combination of capecitabine and paclitaxel in our practices; however, we didn't have any data for weekly paclitaxel and capecitabine.

2.1 Results from a Phase II Trial of First-Line Therapy with Capecitabine and Weekly Paclitaxel in 55 Women with Taxane-Naïve Metastatic Breast Cancer

Efficacy in evaluable patients	
Partial response	27/54 (50%)
Stable disease	16/54 (30%)
Disease progression	11/54 (20%)
Median duration of response	6.3 months
Median progression-free survival	12.1 months

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

Dr O'Shaughnessy is Co-Director of the Breast Cancer Research Program at Baylor-Charles A Sammons Cancer Center, US Oncology in Dallas, Texas.

This regimen was extremely well tolerated. Some side effects were associated with capecitabine, and about one fourth of the patients required a dose reduction. I particularly like combinations like this that are well tolerated and allow us to treat patients for long periods of time. I think capecitabine/paclitaxel is a good regimen; it's active and has manageable toxicity.

Dr Gradishar also reported in the *Journal of Clinical Oncology* on a regimen of capecitabine and every three-week paclitaxel with a response rate of 52 percent (Gradishar 2004). Of course, more myelosuppression occurs with paclitaxel administered at 175 mg/m^2 every three weeks per day, but it is a well-tolerated regimen that has efficacy similar to our paclitaxel/capecitabine regimen.

Like all combination chemotherapies, fatigue occurs over time; however, many patients can continue for long treatment periods. I often stop the intravenous part of the regimen — in this case, paclitaxel — after six or eight cycles and continue with capecitabine alone.

Comparing capecitabine/docetaxel and capecitabine/paclitaxel

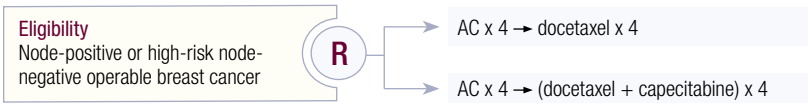
These two regimens have similar efficacy. The response rates and percentage of patients with prolonged stable disease are similar. With regard to toxicity, I think every three-week docetaxel is similar to every three-week paclitaxel — both cause more myelosuppression than weekly paclitaxel.

Patients develop a bit more asthenia with docetaxel. With capecitabine/docetaxel, lifting off of the nail beds is a prominent but reversible toxicity. In our adjuvant trial comparing AC followed by docetaxel to AC followed by capecitabine/docetaxel (2.2), the nail toxicities are more common with the combination of capecitabine/docetaxel.

Additionally, docetaxel sometimes causes epiphora, which is not observed with weekly paclitaxel. With just four cycles of docetaxel or capecitabine/docetaxel in the adjuvant setting, the epiphora, which is fairly ubiquitous, is almost always completely reversible. In the metastatic setting, where patients receive more cycles of docetaxel, the epiphora may not be reversible without stenting.

2.2 Phase III Trial Comparing AC Followed by Either Docetaxel or Capecitabine Plus Docetaxel

Protocol ID: US Oncology 01-062
Accrual: 1,810 (Open)



Note: ER-positive and/or PR-positive patients receive tamoxifen or anastrozole (postmenopausal only) for 5 years.

SOURCE: Protocol 01-062 synopsis, June 2002.

The VINOCAP regimen (vinorelbine/capecitabine)

I've used capecitabine in combination with vinorelbine administered on a day one and day eight schedule. VINOCAP does not cause alopecia, and Phase II trial data with this regimen indicate response rates in the 40 percent to 60 percent range (2.3). With that regimen, I stop the vinorelbine after a while and keep using capecitabine alone. That is a bit of a gamble because you don't know if the woman is responding to one or the other or both agents. It's rather imprecise but I think we have to make decisions based on toxicity.

2.3 Phase II Clinical Trials of Vinorelbine and Capecitabine (VINOCAP) Reported in Patients with Metastatic Breast Cancer

Study	No. of patients	Doses of VINOCAP	Objective response CR + PR	SD	Grade III/IV neutropenia	Grade III/IV hand-foot syndrome
[1] Ahn JH Sr et al, 2002	19	25 mg/m^2 2,500 mg/m^2	53%	NR	22%	0%
[2] Ghosn M et al, 2003	30	25 mg/m^2 1,650 mg/m^2	68%	NR	13%	0%
[3] Hess DD et al, 2002*	36	20-25 mg/m^2 800-1,250 mg/m^2	50%	28%	8%	0%
[4] Domenech G et al, 2001	12	18 mg/m^2 2,000 mg/m^2	58%	25%	25%	NR
[5] Gligorov J et al, 2003	16	60 mg/m^2 2,000 mg/m^2	31%	NR	25%	NR
[6] Stuart N et al, 2003	80	25 mg/m^2 2,000 mg/m^2	40%	7%	NR	0%
[7] Estevez LG et al, 2004	15	25 mg/m^2 2,000 mg/m^2	50%	20%	53%	53%
[8] Xu B et al, 2004	23	25 mg/m^2 2,000 mg/m^2	44%	26%	22%	NR

* Phase I/II dose-finding study
CR = complete response; PR = partial response; SD = stable disease > 6 months; NR = not reported

DERIVED FROM: [1] Ahn JH Sr et al. *Proc ASCO* 2002;**Abstract 2030**. [2] Ghosn M et al. *Proc ASCO* 2003;**Abstract 270**. [3] Hess DD et al. *Proc ASCO* 2002;**Abstract 2915**. [4] Domenech G et al. *Proc ASCO* 2001;**Abstract 1939**. [5] Gligorov J et al. *Proc ASCO* 2003;**Abstract 351**. [6] Stuart N et al. *Proc ASCO* 2003;**Abstract 183**. [7] Estevez LG et al. *Proc ASCO* 2004;**Abstract 748**. [8] Xu B et al. *Proc ASCO* 2004;**Abstract 741**.

Adjuvant clinical trials incorporating capecitabine

The vinorelbine/capecitabine combination is one of numerous capecitabine combinations being evaluated in European adjuvant trials. I'm not aware of any adjuvant or neoadjuvant studies evaluating capecitabine/paclitaxel; however, a number of neoadjuvant and adjuvant trials are evaluating capecitabine/docetaxel.

Even if I had data with capecitabine/paclitaxel, I probably would not have considered evaluating that combination — as opposed to capecitabine/docetaxel — in our adjuvant trial. In metastatic disease, docetaxel 75 mg/m^2 in combination with capecitabine has a clear survival advantage compared to docetaxel 100 mg/m^2 (O'Shaughnessy 2002). Usually, we try to take that advantage in survival in metastatic disease and immediately move it into the adjuvant setting.

US Oncology neoadjuvant trial of FEC 100 followed by capecitabine/docetaxel

In women with T2, T3 or T4 clinical breast cancer who have been diagnosed by a core biopsy, we're treating the patients preoperatively with four cycles of FEC 100 followed by four cycles of capecitabine in combination with weekly docetaxel 35 mg/m^2 on day one and day eight. Then, the patients undergo surgery. Pretreatment tumor specimens are sent to Dr Lajos Pusztai at MD Anderson for microarray analysis to predict who's going to have a pathologic complete response (pCR).

Since Dr Aman Buzdar presented the exciting data from MD Anderson at ASCO 2004 — indicating a 67 percent pCR rate with FEC, paclitaxel and trastuzumab (Buzdar 2004) — we have been working hard to expand our current trial by adding an additional cohort of patients with HER2-positive disease. We will still use FEC followed by capecitabine/docetaxel but, like Dr Buzdar, we'll drop the epirubicin dose to 75 mg/m^2 and add trastuzumab. We will see if we can reproduce his high pCR rate and obtain additional cardiac safety data.

I usually use AC followed by docetaxel in the preoperative setting but I am impressed with FEC 100, which is very effective in treating primary breast lesions. My colleagues in US Oncology who have been using FEC 100 preoperatively say it is highly effective, and I've recently seen that for myself. FEC followed by capecitabine/docetaxel results in a fair number of pCRs.

Trastuzumab in the neoadjuvant and adjuvant settings

From the cardiac safety perspective, I think it's a bit soon to utilize Dr Buzdar's neoadjuvant trastuzumab regimen in a nonprotocol setting. Although he has accrued additional patients and the cardiac safety is holding up, I think we need more data.

Mark Pegram has data with a preoperative regimen of docetaxel, carboplatin and trastuzumab (TCH; [2.4]), which is showing a pCR rate in the same range as that seen by Judith Hurley with a similar regimen (Hurley 2003). We do not yet have Phase III data with regard to safety and efficacy, but I think it's beginning to emerge as a reasonable option.

I tend to treat women with locally advanced disease preoperatively without trastuzumab. If they don't have a pCR after surgery, then I start trastuzumab. For example, I might use preoperative FEC or CAF for four cycles, send the patient to surgery and evaluate the antitumor response. If the woman still has a lot of cancer in her lymph nodes or breast and has strongly HER2-positive and ER/PR-

negative disease, then I'll treat her with four cycles of TCH afterward. In women with inflammatory breast cancer, I use a similar approach — preoperative CAF or FEC, surgery and then TCH.

I've done this judiciously and only in patients with the highest-risk disease. The NSABP-B-31 cardiac safety data (Geyer 2003) allows us to provide information about the cardiac risks associated with a taxane and trastuzumab following four cycles of doxorubicin. I administer four cycles of TCH, then stop the chemotherapy and continue trastuzumab. I switch the trastuzumab to an every three-week regimen and continue it for one year.

2.4 Platinum Salts and Docetaxel as Primary Therapy for Locally Advanced and Inflammatory Breast Cancer: Response Rates in Three Sequential Studies

Regimen	pCR (breast)	pCR (breast and axilla)	Node negative
Regimen 1 (n=56)	27%	20%	29%
Regimen 2 (n=44)	20%	16%	43%
Regimen 3 (n=44)	20%	18%	39%
Total (n=144)	23%	18%	36%

pCR = pathological complete response
Regimen 1 = cisplatin/docetaxel + G-CSF → surgery → AC + radiotherapy ± tamoxifen
Regimen 2 = cisplatin/docetaxel + trastuzumab + G-CSF + EPO → surgery → AC + radiotherapy ± tamoxifen
Regimen 3 = carboplatin/docetaxel → surgery → AC + radiotherapy ± tamoxifen

SOURCE: Hurley J et al. **Platinum salts and docetaxel as primary therapy of locally advanced and inflammatory breast cancer: The final report of three sequential studies.** *Breast Cancer Res Treat* 2003;**Abstract 238**.

Synergy between the anthracyclines and trastuzumab

From a molecular standpoint, about 40 percent to 50 percent of patients with HER2 overexpression will have topoisomerase II alpha (topo-II) gene amplification, which increases sensitivity to the anthracycline. Most HER2-driven breast tumors are highly proliferative. Even if they don't have topo-II gene amplification, they have a lot of protein because they're so highly proliferative. Doxorubicin targets these highly proliferative cells. Adding trastuzumab creates a highly synergistic combination.

In the pivotal trial by Dr Slamon, a regimen of an anthracycline and cyclophosphamide with trastuzumab was highly effective but was associated with significant cardiac toxicity. The survival advantage associated with the addition of trastuzumab was higher with an anthracycline and cyclophosphamide than with paclitaxel (Slamon 2001).

Interestingly, a lot of work is ongoing with epirubicin and trastuzumab. Dr PierFranco Conte is conducting a trial in Italy that combines FEC with trastuzumab as either adjuvant or neoadjuvant therapy. The German groups are evaluating EC for four cycles with trastuzumab, and they're doing quite well.

The Europeans, however, are utilizing 90 mg/m^2 of epirubicin with four cycles of trastuzumab, and they're not running into cardiac problems. It's encouraging.

Select publications

Ahn JH Sr et al. **Phase II study of combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002;**Abstract 2030**.

Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005 Feb 14;[Epub ahead of print]. **Abstract**

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

Buzdar AU et al. **Significantly higher pathological 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);[Epub ahead of print]. **Abstract**

Domenech G et al. **Vinorelbine/capecitabine (VINOCAP) combination remission induction therapy for metastatic breast cancer (MBC).** *Proc ASCO* 2001;**Abstract 1939**.

Estevez LG et al. **Phase II study with the combination of capecitabine (C) and vinorelbine (V) in metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes.** *Proc ASCO* 2004;**Abstract 748**.

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

Ghosn M et al. **Final results of a phase II study of vinorelbine in combination with capecitabine as first line chemotherapy for metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 270**.

Gligorov J et al. **Capecitabine and oral vinorelbine in metastatic breast cancer: Preliminary experience.** *Proc ASCO* 2003;**Abstract 351**.

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**

Hess DD et al. **Phase I-II trial of capecitabine and vinorelbine in elderly patients (pts: > 65y) with metastatic breast cancer (MBC): SAKK 25/99 for the Swiss Group of Clinical Cancer Research, Berne, Switzerland.** *Proc ASCO* 2002;**Abstract 2915**.

Hurley J et al. **Platinum salts and docetaxel as primary therapy of locally advanced and inflammatory breast cancer: The final report of three sequential studies.** San Antonio Breast Cancer Symposium 2003;**Abstract 238**.

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

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**

Stuart N et al. **Vinorelbine and capecitabine (VX) for advanced breast cancer — A phase II study showing good activity and potential for further development.** *Proc ASCO* 2003;**Abstract 183**.

Xu B et al. **Capecitabine (X) combined with vinorelbine (V) in Chinese patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2004;**Abstract 741**.

Cardiotoxicity in the NSABP trial B-31 evaluating adjuvant trastuzumab

In the cardiac safety study, we waited until we had the 18-month follow-up on most patients because recoverability is clearly an important issue (Geyer 2003). Certainly, we need to identify the rates and severity of toxicity, but with the appreciation that the cardiotoxicity is, to a large degree, reversible.

In patients receiving trastuzumab, we continue to have approximately a four and a half percent incidence of symptomatic heart failure and about one percent in the control arm. That's less than the four percent incidence attributable to trastuzumab that we needed to see to continue the study (3.1). We also found that approximately 25 percent of patients weren't completing the full year of trastuzumab due to asymptomatic drops in LVEF that mandated discontinuation.

Approximately four percent of patients who received trastuzumab are still taking medications to manage heart failure, but they're not symptomatic. We tracked the patients carefully, following up every six months to determine whether their symptoms persisted, the status of their LVEF and whether they were still on medication. Only one of the patients who developed symptoms remains symptomatic.

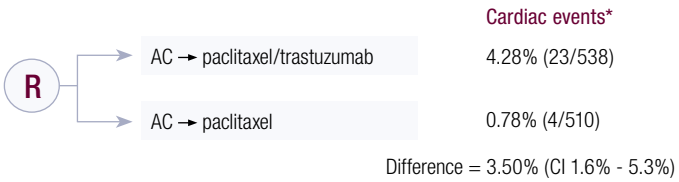
Approximately nine and a half percent of patients on the trastuzumab arm and four and a half on the control arm had ejection fractions lower than 50 at 18 months, so we've learned that sequential AC → paclitaxel has some impact on long-term cardiac function, which is why the control arm is so critical in this trial.

Reversibility of declines in LVEF

A substantial improvement in ejection fractions occurs across the board, with virtually all patients then moving back toward baseline. A slight downward shift of the distribution occurs in a small number of patients with LVEFs in the 40 to 50 percent range, and a couple of patients in the upper 30 percent range. Many of the patients with LVEFs less than 40 percent had recent events and have not yet had time to recover; however, the ejection fractions do recover substantially.

Dr Geyer is the Director of Medical Affairs of the National Surgical Adjuvant Breast and Bowel Project and Director of Breast Medical Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania.

3.1 NSABP-B-31 Cardiac Safety Study



* Cardiac events = definite or probable cardiac death, symptomatic congestive heart failure confirmed by MUGA or Echo

DERIVED FROM: Geyer CE Jr. Presentation. San Antonio Breast Cancer Symposium 2003;**Abstract 23**.

Potential implications for nonprotocol treatment

We collected information on known cardiac risk factors for all patients enrolled in the study. Patients had to have a normal EKG and no history of cardiac events. On the cardiac safety study, only 15 percent of patients were older than age 60.

This is a select group of healthy patients with normal cardiac function, which will be one of the many dilemmas when we start seeing patients who would not have met the eligibility criteria of the study, but whom we know would benefit from trastuzumab. It will be challenging to figure out how to extrapolate the data to patients who might have some pre-existing cardiac dysfunction.

MD Anderson clinical trial of neoadjuvant trastuzumab

The pCR rate of 65 percent is phenomenal (Buzdar 2004; [3.3]). Interestingly, the rationale for doing the study was that they disagreed with the decision to not continue studying trastuzumab combined with anthracyclines.

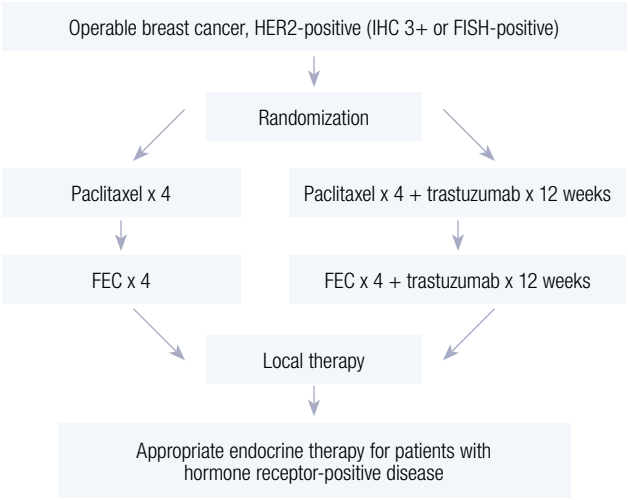
They adapted their backbone regimen of paclitaxel followed by FAC and utilized FEC 75. They also made the decision to truncate trastuzumab to 24 weeks (3.2). In a number of other neoadjuvant trastuzumab studies — primarily with vinorelbine but also with carboplatin/paclitaxel — the typical pCR was 20 percent to 30 percent. Steve Limentani pushed it up to 35 percent with vinorelbine/docetaxel, but clearly the MD Anderson regimen dramatically outperforms those combinations.

It intrigues me that they took two sequential regimens that presumably interact well with trastuzumab and administered them sequentially. Their regimen was much longer in duration than the other regimens. If you evaluate the nontrastuzumab data, you see the same trend of higher pCR rates associated with longer duration of therapy.

I can't help but wonder whether their results are due to the epirubicin/trastuzumab combination or the two sequential approaches? That's an extremely important question. I would bet the combination is important for some patients — perhaps those who co-overexpress topoisomerase II and HER2. But, is it good

for all patients? The MD Anderson study probably generates more questions than it answers.

3.2 MD Anderson Randomized Trial of Neoadjuvant Trastuzumab and Chemotherapy



SOURCE: Buzdar AU et al. *J Clin Oncol* 2005 Feb 28;[Epub ahead of print]. **Abstract**

3.3 Pathologic Complete Response Rates for Neoadjuvant Therapy

	Trastuzumab + P + FEC	P + FEC	*p*-value
Overall (n=23, 19)	65.2%	26.3%	0.016
Hormone receptor-positive (n=13, 11)	61.5%	27.2%	—
Hormone receptor-negative (n=10, 8)	70.0%	25.0%	—

P = paclitaxel; FEC = 5-fluorouracil, epirubicin and cyclophosphamide

SOURCE: Buzdar AU et al. *J Clin Oncol* 2005 Feb 28;[Epub ahead of print]. **Abstract**

NSABP trial B-27: Neoadjuvant AC/docetaxel

This was a three-arm study in which all patients received neoadjuvant therapy. The control group was AC for four cycles followed by surgery. The second group was AC followed by docetaxel followed by surgery. The third group had surgery between the AC and the docetaxel (Bear 2003, 2004).

We previously reported a doubling of pCR rates in the second group of patients who received docetaxel before surgery. Earlier this year, a sufficient number

of events had occurred on study to proceed with the final definitive survival analysis. Surprisingly, overall survival was no different among the three arms. In terms of disease-free survival, slightly fewer events occurred among the patients receiving docetaxel, but it was not statistically significant — and this was mature data with approximately 700 events (3.4). In evaluating B-27, according to our planned analysis, it was a negative trial.

The pCR has not yet been shown to be a surrogate for long-term outcome. I believe pCR remains a valid investigational tool for trying to sort out improved therapies, but we still have to investigate these therapies in large adjuvant trials.

3.4 NSABP-B-27: 68-Month Update of Study Endpoints

	Hazard ratios compared to AC	
Variable	AC → T → surg (n=803)	AC → surg → T (n=799)
Overall survival	0.94 ($p = 0.57$)	1.07 ($p = 0.53$)
Disease-free survival	0.86 ($p = 0.10$)	0.91 ($p = 0.27$)
Relapse-free survival	0.81 ($p = 0.03$)	0.91 ($p = 0.32$)

No significant difference in overall survival or disease-free survival by treatment, but improved relapse-free survival in Arm 2 (preoperative docetaxel) vs Arm 1 (AC)
T = docetaxel

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

NSABP-B-38: Phase III adjuvant trial comparing three chemotherapy regimens in women with node-positive breast cancer

Two key adjuvant trials have been BCIRG-001, evaluating TAC versus FAC (Martin 2003), and the CALGB dose-dense trial 9741 of AC → paclitaxel (Citron 2003). Currently, our view is that TAC appears to be the optimal way to administer an anthracycline/docetaxel regimen and dose-dense AC → paclitaxel is the optimal way to administer those agents.

Which is better? It's impossible to answer that question without performing a clinical trial, which is why we developed trial NSABP-B-38. It's a pragmatic design in which we regard TAC as our control arm (3.5).

A clear advantage of dose-dense therapy is that it is so well tolerated, and it clearly affords the opportunity to add a fourth drug to the paclitaxel. TAC is a maximally tolerated regimen. You really can't push it much more, so we sought a candidate drug to combine with paclitaxel. The study of paclitaxel/gemcitabine versus paclitaxel in metastatic breast cancer reported at ASCO demonstrated an improved response rate, time to progression and overall survival (Albain 2004).

Obviously, those results peaked our interest, but a number of investigators have been evaluating dose-dense paclitaxel with gemcitabine. Dr Colomer from Spain performed a Phase II study in patients with untreated metastatic breast cancer

and demonstrated an overall response rate of 71 percent, with a 26 percent complete response rate and a remarkable safety profile (Colomer 2004).

He used 2,500 mg/m^2 of gemcitabine every two weeks combined with 150 mg/m^2 of paclitaxel, and it was well tolerated. Those two data sets suggested it would be ideal to bring into the adjuvant setting because it could be added to Dr Norton's dose-dense regimen.

3.5 Phase III Randomized Trial of Three Different Adjuvant Chemotherapy Regimens

SOURCE: NCI Physician Data Query, March 2005.

NSABP-B-40 neoadjuvant trial

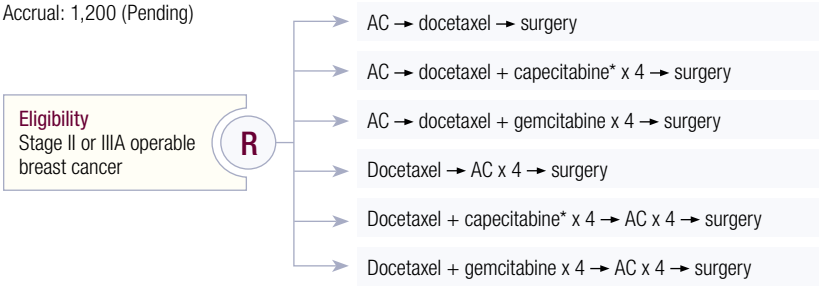
NSABP-B-40 is the replacement trial for NSABP-B-27. We will continue using sequential AC followed by docetaxel as our control, with a second arm utilizing capecitabine/docetaxel following AC and a third arm with gemcitabine/docetaxel also following AC (3.6). The data with capecitabine/docetaxel in the metastatic setting is compelling because survival advantages in metastatic disease usually translate into benefit in the adjuvant setting.

The notion that docetaxel is better than paclitaxel has changed with the results of B-27, but we believe continued investigation is warranted. We would like to continue to work with docetaxel combined with capecitabine in the neoadjuvant setting.

Our problem is we have so many drugs that are active, but we need to figure out how to identify predictive factors. Docetaxel is an extremely important drug for some patients, but others derive no benefit. Our neoadjuvant program is attempting to identify those predictive factors so we can utilize the right drug in the right patient.

3.6 Preoperative Capecitabine or Gemcitabine Plus Docetaxel in Sequence with AC

Protocol IDs: NSABP-B-40, CTSU
Accrual: 1,200 (Pending)



* Capecitabine dose = 825 mg/m^2 BID days 1-14 q3wk

SOURCE: NSABP Protocol Summary, November 2004.

Select publications

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

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

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

Buzdar AU et al. **Significantly higher pathological 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);[Epub ahead of print]. **Abstract**

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

Colomer R et al. **Biweekly paclitaxel plus gemcitabine in advanced breast cancer: Phase II trial and predictive value of HER2 extracellular domain.** *Ann Oncol* 2004;15(2):201-6. **Abstract**

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

Limentani SA et al. **Dose dense neoadjuvant treatment of women with breast cancer utilizing docetaxel and vinorelbine with growth factor support.** *Proc ASCO* 2003;**Abstract 131**.

Martin M et al. **AC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** San Antonio Breast Cancer Symposium 2003;**Abstract 43**.

Raimund V Jakesz, MD

EDITED COMMENTS

Rationale for sequencing endocrine therapies in the adjuvant setting

When a patient experiences resistance to one endocrine agent, that doesn't mean the cancer has become endocrine resistant. We know from the metastatic setting that a hormone-responsive tumor that responds to tamoxifen, but then progresses a year later, has a high likelihood that it will respond to another endocrine agent and again to third- and fourth-line endocrine treatments.

The tumor may become resistant to one drug, but we do not abolish the tumor's hormone dependency. We are now transferring that knowledge gained in the metastatic palliative setting to the adjuvant setting by evaluating trials of switching endocrine agents.

ABCSG-8 and ARNO-95: Switching to anastrozole after two years of adjuvant tamoxifen

In the combined trials of ABCSG-8 and ARNO-95, more than 3,200 postmenopausal patients, all with receptor-positive disease, were exposed to two years of adjuvant tamoxifen after primary surgery. We then randomly assigned them to tamoxifen or anastrozole for three years. The tumors were generally moderately well differentiated, and 95 percent were T1 or T2 lesions, 75 percent were node negative, and none of the patients received chemotherapy. It was clean, informative data.

With a median follow-up of 28 months, we found that switching to anastrozole reduced the likelihood of developing an event by 40 percent, which was highly significant (Jakesz 2004; [4.1]).

Most of the difference seen in event rate with anastrozole was due to a huge reduction in distant metastases. In the group treated with tamoxifen for five years, 75 patients developed distant metastases, whereas only 46 patients did so in the sequenced group. Perhaps in two or three years, this might translate to an improvement in overall survival.

Dr Jakesz is a member of the Department of Surgery at the Vienna Medical School and President of the Austrian Breast and Colorectal Cancer Study Group in Vienna, Austria.

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

Localization of events	Total	Tamoxifen	Anastrozole
Events*			
Locoregional	44	24	20
Contralateral breast cancer	28	16	12
Distant recurrences	121	75	46
Event-free survival			
Events	177	110	67
3-year event-free survival	—	92.7%	95.8%
Overall survival			
Deaths	104	59	45
3-year overall survival	—	96.4%	97.1%

* 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 3,224 women enrolled in the ABCSG Trial 8 and the ARNO 95 trial.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 2**.

ABCSG-8/ARNO-95: Safety data

Anastrozole is well tolerated and no treatment-related deaths occurred in these trials. Anastrozole did not cause an increase in cardiovascular disease or pulmonary disease, but a significant increase in fractures occurred. The fracture rate in the anastrozole group was 2.4 percent versus 1.2 percent in patients who received tamoxifen (Jakesz 2004). That's much lower than what we've seen in the ATAC trial, but that's because all the patients in our study were initially treated with tamoxifen, which, due to its partial agonistic effect, protects bone.

We didn't see many gynecological side effects probably because we counted side effects only after randomization. In patients on tamoxifen, gynecological side effects usually start in the first two years.

Switching from tamoxifen to either exemestane or anastrozole

ABCSG-8 and ARNO-95 — utilizing anastrozole — serve as confirmatory trials for the IES study, which used exemestane. I believe anastrozole and exemestane are similar in efficacy but have a different safety profile.

In the IES trial, exemestane resulted in a risk reduction of approximately 35 percent (Coombes 2004), whereas in the combined trials the risk of an event was reduced by 40 percent with anastrozole.

It was hoped that exemestane would have a protective effect on bone, but that is obviously not true.

ATAC trial: 68-month efficacy and safety data

The 68-month follow-up of the ATAC trial was presented at the San Antonio Breast Cancer Symposium and also recently published in *The Lancet* (Howell 2004, Howell 2005). An impressive trend for the reduction in the cancer-specific recurrences is seen with anastrozole, and the five-year recurrence-free survival differed by 3.3 percent. A carryover effect obviously exists and the curves diverge, which is a nice result.

On the other hand, the lack of improvement in overall survival is important. The ATAC trial was not as clean as the ABCSG-8 and ARNO-95 trials in that the ATAC study included patients with estrogen receptor-negative tumors and patients who received chemotherapy.

The safety profile in the update still favors anastrozole. The incidence of endometrial cancer is 0.2 percent with anastrozole and 0.8 percent with tamoxifen. The new data revealed a 5.1 percent rate of hysterectomy with tamoxifen and only slightly over one percent with anastrozole. Also, with anastrozole we seldom see gynecological side effects, such as bleeding or discharge, and we see no increased risk of strokes or pulmonary embolism.

Switching endocrine therapies to avoid subclinical resistance

Anastrozole is certainly more potent than tamoxifen, and it significantly reduces the incidence of contralateral breast cancer; however, we don't know the best sequence for the various endocrine agents. We need more sequencing trials. I believe the longer a tumor is exposed to a specific drug, the more likely it will develop subclinical resistance and eventually metastasize.

ABCSG-12: Zoledronic acid

ABCSG-12 is an adjuvant trial comparing goserelin plus tamoxifen to goserelin plus anastrozole in premenopausal patients with ER-positive disease. It's similar to the ATAC trial but studies premenopausal patients. We were concerned about the impairment of the bone mineral density, so both groups are further randomized to receive zoledronic acid or not. We have recruited approximately 1,400 patients and have approximately 1,200 bone mineral density measurements.

The trial is ongoing and we need to accrue approximately 400 more patients. Although we don't know the mechanism, it's well known that tamoxifen causes bone loss in premenopausal women, whereas it strengthens bone in postmenopausal women. As expected, patients on goserelin/anastrozole have a higher reduction in bone mineral density in the lumbar spine than patients receiving the goserelin/tamoxifen combination — approximately a 17 percent versus 11 percent reduction, respectively (Gnant 2004); however, we have seen that the bone loss for both groups can be entirely prevented by the administration of zoledronic acid.

This is a remarkable trial. I don't know what we will see with long-term follow-up, but I hope we can further improve the prognosis for these patients by administering anastrozole instead of tamoxifen. We are continuing to randomly assign

patients to the arms without zoledronic acid, but every other year we perform a bone mineral density measurement and treat patients according the ASCO guidelines as advised by an independent data monitoring committee. Whether zoledronic acid has an oncological benefit, we don't know yet, but I believe this is likely — and that would be a landmark finding.

Anastrozole following five years of adjuvant tamoxifen

We have submitted an abstract to the 2005 ASCO meeting and hope to present data from a trial in which, after five years of adjuvant tamoxifen, patients were randomly assigned to three years of anastrozole versus no further treatment. In the MA17 trial, patients received letrozole for five years after tamoxifen, but in our trial the anastrozole exposure was only three years. The results are important and are still confidential at this time. Currently, I discuss the MA17 data with patients and recommend that they take letrozole for at least two or three years after tamoxifen.

Estrogen receptor status and response to chemotherapy in postmenopausal patients

In estrogen receptor-negative tumors, we use chemotherapy in all patients with lesions greater than one centimeter; however, in estrogen receptor-positive tumors, we use chemotherapy only in high-risk cases such as undifferentiated, HER2-overexpressing tumors with five or more positive nodes.

It is important to separate estrogen receptor-positive and receptor-negative tumors when considering chemotherapy and when conducting clinical trials. To lump all these patients together doesn't reflect the biology of the tumor. These are different types of cancer. The patients should be treated differently and studied separately.

I believe that postmenopausal patients do not respond as well to chemotherapy and that receptor status affects response. Tumors proliferate more slowly in patients with estrogen receptor-positive disease; however, this is not well studied. We conducted a retrospective analysis of 250 patients who received preoperative chemotherapy, and we found no cases of pCR in tumors that were estrogen and progesterone receptor-positive.

Select publications

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

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

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

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

Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer.** *Cochrane Database Syst Rev* 2001;(1):CD000486. **Abstract**

Fallowfield LJ et al. **Intergroup exemestane study: Results of the quality of life sub-protocol.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 4**.

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

Fuqua SA, Cui Y. **Estrogen and progesterone receptor isoforms: Clinical significance in breast cancer.** *Breast Cancer Res Treat* 2004;87(Suppl 1):3-10. **Abstract**

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

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

Goss PE. **Changing clinical practice: Extending the benefits of adjuvant endocrine therapy in breast cancer.** *Semin Oncol* 2004;31(6 Suppl 12):15-22. **Abstract**

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

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

Henderson IC. **Aromatase inhibitors in the management of early breast cancer: Optimizing the clinical benefit.** *Semin Oncol* 2004;31(6 Suppl 12):31-4. **Abstract**

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

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

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

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

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

Lipton A. **Toward new horizons: The future of bisphosphonate therapy.** *Oncologist* 2004;9(Suppl 4):38-47. **Abstract**

Lower EE et al. **Impact of metastatic estrogen receptor and progesterone receptor status on survival.** *Breast Cancer Res Treat* 2005;90(1):65-70. **Abstract**

Rosen LS. **New generation of bisphosphonates: Broad clinical utility in breast and prostate cancer.** *Oncology (Huntingt)* 2004;18(5 Suppl 3):26-32. **Abstract**

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

Oncotype DX multigene assay as a prognostic factor in patients treated with tamoxifen

At the 2003 San Antonio meeting, when I presented the initial data on this assay, Dr Osborne raised a question about whether the recurrence score is a prognostic or predictive factor. Frankly, we didn't really care, as long as it's a prognostic factor in that specific setting of tamoxifen-treated patients, so that we can identify a cohort of patients who don't need chemotherapy.

Using the NCCN or St Galen criteria, in the tamoxifen-treated cohort in NSABP-B-14, we would identify about eight percent of patients who don't need chemotherapy. If we use the Genomic Health assay, we identify 50 percent — a huge increase in the number of patients categorized as low risk and not requiring chemotherapy.

The median 10-year distant failure rate was about 6.8 percent in patients who received tamoxifen with low-risk disease based on the recurrence score, but the individual risk ranged from three percent to 12 percent, which is another strength of this test.

Although the NSABP usually refrains from subset analyses, supplementary information accompanying the *New England Journal of Medicine* paper (Paik 2004a) details several subset analyses. Questions arose about whether the Oncotype DX assay would work in patients with tumors less than one centimeter, patients older than 60 years old, and other subsets in which the statistical power is much less; however, the overall trends seem to show that the assay works in every subset we evaluated. It always seemed to divide patients into low- or high-risk categories, regardless of histology grade or tumor size.

Oncotype DX assay to predict response to chemotherapy

NSABP-B-20 included women with node-negative, ER-positive disease. It was a three-arm design, and patients were randomly assigned to tamoxifen alone or tamoxifen concurrent with either CMF or methotrexate followed by 5-FU. Our study was a retrospective analysis of that completed trial.

Dr Paik is the Director of the Division of Pathology at the NSABP Foundation Inc in Pittsburgh, Pennsylvania.

We only had tissue blocks available for approximately 30 percent of the entire study cohort, so it's a subset; however, the subset and the entire cohort were comparable. We repeated the Onco*type* DX assay on the tamoxifen arm to ensure the assay was reproducible, and we demonstrated that it is reproducible, which is encouraging.

Importantly, we evaluated the NSABP-B-20 chemotherapy arms to address whether the assay predicted chemotherapy responsiveness. We went into that study with an a priori hypothesis, based on the data presented at the 2004 ASCO by Dr Luca Gianni's group in Milan evaluating samples from a neoadjuvant trial they performed with paclitaxel and doxorubicin.

They demonstrated a correlation between the Genomic Health recurrence score and pCR rate (Gianni 2004). The higher recurrence rate correlated strongly with the higher pCR rate. The overall pCR rate was approximately 25 percent in the patients with high-risk disease, and there was no pCR occurred in patients with low-risk disease.

We hypothesized that the benefit from chemotherapy in NSABP-B-20 would be almost negligible in patients with low-risk disease and high in patients with high-risk disease. The results of this study are actually quite striking and unlike anything I've ever seen (Paik 2004b). The absolute benefit from chemotherapy is actually negative in the low-risk group and zero in the intermediate-risk group. In high-risk group, the absolute improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent (5.1).

The data in the low-risk group are, in a sense, not relevant, because the baseline risk after tamoxifen is so low — 6.8 percent — so it's a moot point of whether they need chemotherapy or not. In the intermediate-risk group the confidence interval overlaps with one, so whether patients with intermediate-risk disease gain any benefit or not remains a question.

5.1 Ten-Year Distant Recurrence-Free Survival According to a 21-Gene Recurrence Score

Risk group	Tamoxifen (n=227)	Tamoxifen + chemotherapy (n=424)	*p*-value
Low (RS < 18)	96%	95%	0.76
Intermediate (RS = 18-30)	90%	89%	0.71
High (RS ≥ 31)	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Implications of the Onco*type* DX assay study results

These data provide an important paradigm shift in the way we think about clinical trial design and patient management. So far, in most clinical trial

designs, we presumed that the proportional benefit or incremental gain would be the same degree in patients with low-risk and high-risk disease. All statistical sample size calculations are based on that assumption, but now we have to change that.

It forces us to think about the clinical trial designs in which we preselect patients who are at high risk, because those are the patients who will benefit. We already knew from other studies that ER-positive patients do not benefit much from chemotherapy. In the neoadjuvant trials, the pCR rate is much lower in ER-positive tumors. This study definitely shows that, based on genes related to proliferation or estrogen receptor, we can actually select patients who are the best candidates for chemotherapy trials.

Benefit of chemotherapy in patients with ER-positive versus ER-negative tumors

In the NSABP-B-14 trial of placebo versus tamoxifen, patients had more than 10 fmol/mg of estrogen receptor by ligand binding assay, so these are all ER-positive tumors. We found that based on estrogen receptor messenger RNA quantitation by RT-PCR, we could actually identify patients who don't gain any benefit from tamoxifen, and they were the patients with low levels of estrogen receptor. It actually correlates well with recurrence score because it's heavily driven by the estrogen receptor pathway. Patients with a high recurrence score — approximately 25 percent of patients — do not gain any benefit from tamoxifen; however, we certainly need more studies before determining whether we can use the assay to rule out administering tamoxifen to those patients.

Clinical trials for patients with intermediate recurrence scores

Whether patients with intermediate recurrence scores will benefit from chemotherapy remains questionable. The Intergroup is designing a megastudy — the Program for the Assessment of Clinical Cancer Tests (PACCT) trial — with a sample size of 5,000 to 6,000 patients in the intermediate group. Patients will be randomly assigned to hormonal therapy alone versus hormonal therapy plus chemotherapy.

Predictive markers for specific chemotherapeutic agents

The Genomic Health assay does not identify any markers that predict response to specific chemotherapeutic agents. It will be interesting to see whether that can be done. I've been working with the NSABP trial in the neoadjuvant setting to determine whether we can use microarray gene expression profiling to predict treatment response. The Genomic Health study of neoadjuvant docetaxel by Luca Gianni's group showed that proliferation markers are predictive.

Surprisingly, immune-related pathways — histocompatibility genes, the chemokines and immunoglobulin genes — are also somehow predictive. Our neoadjuvant study identified a specific subset of breast cancer that has a high fraction of this so-called immune pathway. I don't know if it's expressed by cancer cells or stroma cells, but they seem to have a high pCR rate. It will be inter-

esting to see whether we can use these "blunt tools" of high-surface screening of gene expression or proteomics to sort out markers for response to specific chemotherapies. I suspect that may not be possible with these tools.

The hypothesis-driven studies, like those evaluating topoisomerase II, seem to be generating more interesting data. For example, the Danish group demonstrated that topoisomerase II actually predicts a relative benefit from CEF versus CMF. The MD Anderson study based on microarray analysis has identified a marker, Tau, which might predict response to paclitaxel (Pusztai 2004). We'll need to determine the reproducibility of those types of markers, but I believe those hypothesis-driven studies will generate more individualized data for each drug.

Onco*type* DX data and Ravdin's Adjuvant! model

Peter Ravdin notes that, in the Adjuvant! Program, the relative benefit of chemotherapy is presumed to be equal for patients at higher and lower risk, but it's likely that the estimation of chemotherapy benefit in the group with low-risk disease is an overestimation. Conversely, the benefit in the group with higher-risk disease may be underestimated. I believe our studies with Onco*type* DX demonstrate this, and Ravdin's model may need to be modified slightly.

My prediction is that when people see these data, they will want the assay performed because nobody wants to receive chemotherapy when it will not work. I'm sure a lot of competing assays are being developed that will claim to do the same thing. As a clinical trial group, we are interested in supporting all of those studies. In my lab, we are trying to develop competing assays that will be much less expensive and will be based on factors such as histology and estrogen receptors. We must demonstrate — in a clinical study in a stepwise fashion as we did with Genomic Health — that a marker is reliable and reproducible clinically so that patients will have confidence in the result.

Select publications

Gianni L et al. **Gene expression profiles of paraffin-embedded core biopsy tissue predict response to chemotherapy in patients with locally advanced breast cancer.** *Proc ASCO* 2004;**Abstract 501**.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004a;351(27):2817-26. **Abstract**

Paik S et al. **Expression of the 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** San Antonio Breast Cancer Symposium 2004b;**Abstract 24**.

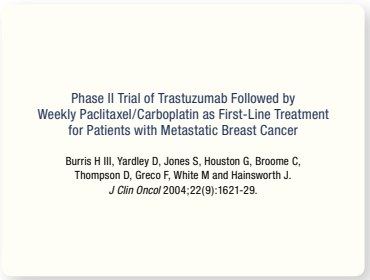
Paik S et al. **Risk classification of breast cancer patients by the recurrence score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade.** San Antonio Breast Cancer Symposium 2004c;**Abstract 104**.

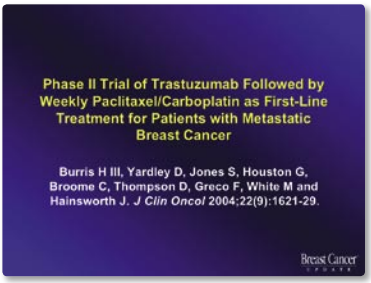
Pusztai L et al. **Microtubule associated protein Tau is a predictive marker and modulator of response to paclitaxel-containing preoperative chemotherapy in breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 112**.

PowerPoint Journal Club

This PowerPoint Journal reviews recently published clinical research articles and presentations. In this issue, we review papers by Howard Burris, MD and colleagues evaluating a Phase II study of trastuzumab followed by weekly paclitaxel and carboplatin as first-line therapy for patients with metastatic breast cancer and a status report by Eric Winer, MD et al on the ASCO Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer.

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





6.1

Phase II Trial of Trastuzumab Followed by
Weekly Paclitaxel/Carboplatin as First-Line Treatment
for Patients with Metastatic Breast Cancer

Burris H III, Yardley D, Jones S, Houston G, Broome C,
Thompson D, Greco F, White M and Hainsworth J.
J Clin Oncol 2004;22(9):1621-29.

SLIDE 6.1 Preclinical studies have demonstrated that platinum and taxanes are additive or synergistic with trastuzumab and increase the response rate over that which was reported with either agent alone. The current Phase II trial evaluates this triplet regimen as first-line therapy.

6.2

Study Objectives

Evaluate

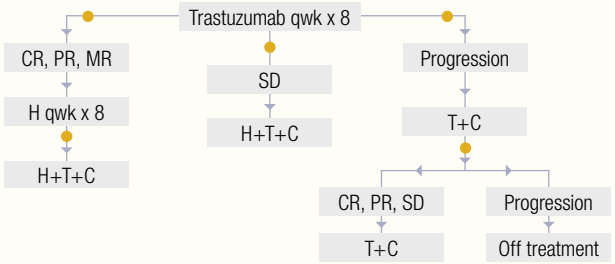
- Response rate to trastuzumab (H) in previously untreated patients
- Activity of a weekly carboplatin/paclitaxel (CT) regimen in patients not responding to H
- Activity, feasibility and toxicity of weekly TCH

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.2 This study sought to determine the feasibility of single-agent trastuzumab (H) as first-line therapy in patients with HER-2 positive metastatic breast cancer, the activity of weekly carboplatin/paclitaxel in patients unresponsive to H, and the activity and toxicity of trastuzumab/carboplatin/paclitaxel.

6.3

Schema



● = Disease assessment; H = trastuzumab; T = paclitaxel; C = carboplatin; CR = complete response; PR = partial response; MR = minor response; SD = stable disease

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.3 Trastuzumab (H) was administered weekly for the first eight weeks. Responders (CR, PR or MR) continued H for another eight weeks, after which weekly paclitaxel/carboplatin (TC) was added. Patients who had stable disease received eight-week cycles of six-weekly TCH.

6.4

Patient Characteristics

- 61 patients enrolled
- Assessable for response (n=52)
- Median age: 51
- ER/PR-positive (n=34)
- HER2-positive
  – IHC 3+ (n=41)
  – IHC 2+ (n=20)

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.4 Sixty-one patients were enrolled in the study, and all were assessable for survival and safety. Six patients did not meet criteria for measurable disease and three patients prematurely discontinued the study, resulting in 52 patients assessable for disease response.

6.5

Results: Overall Response, Progression and Survival

- Overall response rate (n=52) = 69% (9 CRs, 27 PRs)
  – IHC 3+ (n=34): Overall response rate = 78.6%
  – IHC 2+ (n=18): Overall response rate = 50%
- Median duration of CR = 18.8 months
- Median duration of PR = 8.5 months
- Median time to progression for all patients was 10 months
- Median overall survival of all patients was 26.7 months

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.5 The overall response rate including all treatments was 69 percent, with a median duration of complete response of 18.8 months and a median duration of partial response of 8.5 months.

6.6

Disease Response for Patients with Measurable Disease

	Best overall response	Post 8-weeks trastuzumab	Post 16-weeks trastuzumab	Post CT	Post TCH
	(n=52)	(n=52)	(n=16)	(n=16)	(n=31)
Complete response	17%	0%	0%	6%	26%
Partial response	52%	17%	50%	63%	58%
Minor response	—	15%	25%	—	—
Overall response	69%	32%	75%	69%	84%
Stable disease	14%	29%	6%	6%	10%
Progressive disease	17%	38%	19%	25%	6%

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.6 Approximately 32 percent of patients had a minor/partial response to trastuzumab (H) and received eight more weeks of H, and 29 percent of patients had stable disease and received TCH, with an overall response rate of 84 percent. Patients treated with CT after progression on initial H had an overall response rate of 69 percent.

6.7

Results: Response to CT and TCH

- Patients with stable disease or responding to weekly trastuzumab (H) had an 84 percent response rate to TCH. TTP was 14.2 months, and OS was 32.2 months.
- Patients failing to respond to weekly trastuzumab (H) had a 69 percent response rate to the addition of carboplatin/paclitaxel (CT). TTP was 8.3 months, and OS was 22.2 months.

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.7 Treatment of patients with TCH resulted in a response rate of 84 percent with median time to progression (TTP) and overall survival (OS) of 14.2 and 32.2 months, respectively. Sixteen of the 20 nonresponders to weekly H were treated with CT, with resulting response rates of 69 percent.

6.8

Toxicity

- Hematologic toxicity
  - Grade III/IV neutropenia = 28%
  - Grade III thrombocytopenia = 3%
  - Grade III/IV anemia = 5%
- No Grade IV nonhematologic toxicities
  - Weakness and fatigue most common
  - Carboplatin hypersensitivity = 7 patients
  - Grade III neuropathy = 3 patients

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.8 Chemotherapy was well tolerated. Nineteen patients had doses held primarily due to myelosuppression. Anemia, neurotoxicity, fatigue and edema were the other causes of delayed doses. No febrile neutropenia was reported.

6.9

Cardiotoxicity

- LVEF decline > 20% = 5/61 (8.2%)
  - LVEF in 3 patients > 20% but asymptomatic and continued trastuzumab
  - Two patients discontinued therapy due to declines in LVEF
    - One patient exhibited symptoms of CHF
    - One patient was asymptomatic but had a 40% decline in LVEF

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.9 Five of 61 patients experienced a decline in ejection fraction. One patient with a 40 percent decline continued on carboplatin and paclitaxel without trastuzumab. Her ejection fraction subsequently recovered to 50 percent. The overall cardiotoxicity rate was eight percent.

6.10

Conclusions

- Single-agent H is safe and effective initial therapy in patients with HER2-positive metastatic disease
- The addition of CT to weekly H increases the response rate
- Weekly CT is a highly active, well-tolerated regimen in metastatic breast cancer
- Lack of response to H did not interfere with sensitivity to weekly CT

SOURCE: Burris H III et al. *J Clin Oncol* 2004;22(9):1621-29. **Abstract**

SLIDE 6.10 This study confirmed the single-agent activity of trastuzumab and the benefit of carboplatin/paclitaxel with or without trastuzumab in patients with HER-positive metastatic disease.

Select publications

Baselga J et al. **HER2 overexpression and paclitaxel sensitivity in breast cancer: Therapeutic implications.** *Oncology* 1997;11(3 Suppl 2):43-8. **Abstract**

Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20:3857-64. **Abstract**

Pegram MD et al. **Trastuzumab and chemotherapeutics: Drug interactions and synergies.** *Semin Oncol* 2000;27(6 Suppl 11):21-5. **Abstract**

Pegram MD et al. **The effect of HER-2/neu overexpression on chemotherapeutic drug sensitivity in human breast and ovarian cancer cells.** *Oncogene* 1997;15(5):537-47. **Abstract**

Perez EA et al. **A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.** *Cancer* 2000;88:124-31. **Abstract**

Robert N et al. **Randomized phase III study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An update including survival.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 573**.

Rowland KM et al. **NCCTG 98-32-52:Randomized phase II trial of weekly versus every 3-week administration of paclitaxel, carboplatin and trastuzumab in women with HER2 positive metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 31**.

Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20:1215-21. **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**

7.1

American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors as Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-Positive Breast Cancer: Status Report 2004

Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA, Mamounas EP, Goldstein LJ, Whelan TJ, Powles TJ, Bryant J, Perkins C, Perotti J, Braun S, Langer AS, Browman GP, Somerfield MR.
J Clin Oncol 2005;23(3):619-29.

SLIDE 7.1 The ASCO technology assessment is conducted by a multidisciplinary panel of experts who review and synthesize the latest available data in order to make recommendations on therapeutic approaches in clinical practice.

7.2

Technology Assessment

- Describes practice procedures and therapies based on a review and synthesis of latest literature
- Identifies important questions
- Identifies settings for future research
- Reviewed annually and updated as needed
- Voluntary adherence

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.2 The technology assessment is a process that follows defined ASCO policies and procedures for determining whether a procedure is appropriate for broad-based conventional use in clinical practice. It is reviewed and updated annually. Adherence to the guidelines is voluntary.

7.3

Technology Assessment Timeline

Dec 2001	First results of ATAC trial, 33 months
May 2002	Initial technology assessment panel report on adjuvant use of aromatase inhibitors
Dec 2002	ATAC results at 47 months
May 2003	First technology assessment update
Dec 2003-Mar 2004	Results of ITA, MA17 and IES studies
Dec 2004	ATAC 68-month results; ARNO-95/ABCSG-8 results
Jan 2005	Second technology assessment update

SOURCES: Winer EP et al. *J Clin Oncol* 2002;20(15):3317-27. Winer EP et al. *J Clin Oncol* 2003;21(13):2597-9. Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. Howell A. Presentation. SABCS 2004. Jakesz R. Presentation. SABCS 2004.

SLIDE 7.3 The first results of the ATAC trial presented the oncology community with a new approach to the adjuvant therapy of postmenopausal women with hormone-responsive breast cancer. The ASCO technology assessment was formed soon after in order to review the data and provide recommendations on the adjuvant use of aromatase inhibitors.

7.4

Phase III Randomized Adjuvant Trials Comparing Third-Generation Aromatase Inhibitors to Tamoxifen or Placebo

Trial	Design	N
ATAC	T vs A vs T+A in newly diagnosed patients	9,366
MA17	Letrozole vs placebo in patients after 5 years of tamoxifen	5,187
ITA	T vs A in patients after 2 to 3 years of tamoxifen	426
IES	T vs E in patients after 2 to 3 years of tamoxifen	4,742
ARNO-95 ABCSG-8*	T vs A in patients after 2 years of tamoxifen	3,123

* Presented after tech assessment

SOURCES: Jakesz R. Presentation. SABCS 2004. **Abstract**
Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.4 Since the publication of the last panel update in 2003, the results of five randomized trials comparing third-generation aromatase inhibitors (AI) to tamoxifen were presented. As in the ATAC trial, they demonstrated improved benefit of AIs over tamoxifen in rates of disease recurrence.

7.5

Are There New Data to Prompt a Recommendation for an Aromatase Inhibitor as Initial Adjuvant Therapy in Unselected Postmenopausal Patients with Hormone Receptor-Positive Breast Cancer?

"...treatment with an aromatase inhibitor is a reasonable alternative to tamoxifen following primary surgery for any women with a hormone receptor-positive breast cancer."

"An aromatase inhibitor is the treatment of choice as initial adjuvant therapy for any postmenopausal women with hormone receptor-positive invasive breast cancer with a contraindication to tamoxifen."

"...For women who do not have a contraindication to tamoxifen, it remains unclear if initial treatment with an aromatase inhibitor is superior, equivalent, or inferior to a planned cross-over from tamoxifen to an aromatase inhibitor after a fixed point in time."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.5 Based on the results of multiple large randomized trials, the panel recommends the inclusion of an aromatase inhibitor as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer.

7.6

Do the Results of the MA17 Trial Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer who have Completed a 5-Year Course of Tamoxifen?

"... postmenopausal women finishing 5 years of tamoxifen for ER-positive, early-stage breast cancer should consider treatment with an aromatase inhibitor. ...At present, a minimum of 2.5 years of therapy can be recommended based on the median follow-up from MA-17."

"The survival advantage in the subset of women with node-positive disease is noteworthy and strengthens the argument for use of an aromatase inhibitor after tamoxifen in this patient population."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.6 Based on the 2.5 years median follow-up of the MA17 study, the panel recommends that postmenopausal women with ER-positive breast cancer finishing five years of adjuvant tamoxifen should consider treatment with an aromatase inhibitor for a minimum of 2.5 years.

7.7

Do the Results of the IES and ITA Trials Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer Who Have Received Tamoxifen for 2 to 3 Years?

"Both studies showed that a change in treatment from tamoxifen to an aromatase inhibitor reduced the risk of breast cancer recurrence."

"...the optimal moment of transition from tamoxifen to an aromatase inhibitor is not known."

"... postmenopausal women concluding 2 to 3 years of tamoxifen therapy may consider cross-over to an aromatase inhibitor. ...such patients should plan on a total of 5 years of adjuvant endocrine therapy..."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.7 Both the IES and ITA trials showed a reduction in breast cancer recurrence risk following a change in treatment from tamoxifen to an aromatase inhibitor. However, the optimal time of treatment transition is unknown.

7.8

- What is the Optimal Duration of Therapy with an Aromatase Inhibitor in the Adjuvant Setting?
- Should an Aromatase Inhibitor Be Continued for Longer than 5 Years Outside of a Clinical Trial?
- In Women Who are Switched from Tamoxifen to an Aromatase Inhibitor after 2 to 3 Years, Should Treatment with the Aromatase Inhibitor Continue Beyond the 5-Year Point?

"...Treatment with more than a 5-year course of an aromatase inhibitor should only be administered as part of a clinical trial."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.8 While there are studies underway, there is no present data to support the continuation of aromatase inhibitors beyond five years. The panel does not recommend treatment with an aromatase inhibitor for longer than five years outside of a clinical trial.

7.9

Unresolved Issues: Tamoxifen after AI and AI Use in Hormone Receptor-Negative Breast Cancer

- **Are there any studies that support the use of tamoxifen after an aromatase inhibitor?**

  "...there are no clinical data at this time that would support the initiation of tamoxifen after a course of therapy with an aromatase inhibitor in the adjuvant setting."

- **Is there any role for the aromatase inhibitors in women with hormone receptor-negative breast cancer?**

  "...women whose tumors are known to be hormone receptor-negative should not receive an aromatase inhibitor as adjuvant therapy."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.9 No existing data support the use of tamoxifen after an AI, and women completing initial adjuvant therapy with an AI should not be crossed over to tamoxifen outside of a clinical trial. However, if a woman develops toxicity on initial treatment with an AI, it is not unreasonable to switch to tamoxifen.

7.10

Unresolved Issues: AI Use in Premenopausal Women

- **Is it reasonable to use an aromatase inhibitor as initial hormonal therapy in a woman who is premenopausal at diagnosis and who appears to have gone through menopause with chemotherapy?**

  "...there are serious reasons for concern regarding the use of an aromatase inhibitor in women who are functionally premenopausal."

- **Is it reasonable to use an aromatase inhibitor in combination with a luteinizing hormone-releasing hormone agonist or oophorectomy in a woman who is premenopausal at diagnosis?**

  "Until such evidence is available, aromatase inhibitors should not be used in premenopausal women outside of a clinical trial."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.10 Because of the lack of evidence for adequate estrogen suppression and the potential for increased gonadotropin release stimulating the ovaries, aromatase inhibitors should not be used either as monotherapy or in combination with ovarian function suppression in premenopausal women outside of a clinical trial.

7.11

Unresolved Issues: Effects of Aromatase Inhibitors on Bone; Musculoskeletal Toxicity

- **What is known about bone and musculoskeletal toxicity associated with the aromatase inhibitors?**

  "...The ASCO bisphosphonate guideline identifies post-menopausal breast cancer patients who receive aromatase inhibitors to be at high risk for osteoporosis and recommends that they have baseline bone mineral density evaluation.

  "Overall, these three large studies support the conclusion that there is a small but statistically significant increase in arthralgias and/or myalgias with aromatase inhibitors compared with either tamoxifen or placebo."

SOURCES: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**
Hillner B et al. *J Clin Oncol* 2003;21(21):4042-57. **Abstract**

SLIDE 7.11 In all the studies reviewed by the technology assessment panel, the use of AIs was associated with increases in fractures, arthralgias and/or myalgias. The ASCO bisphosphonate guidelines recommend that breast cancer patients with a high risk of osteoporosis have bone mineral density evaluated.

7.12

Unresolved Issues: Vascular and Gynecological Side Effects of AI

- **What is known about vascular complications and endometrial cancer in women treated on the adjuvant aromatase inhibitor trials?**

  "Both anastrozole and exemestane were associated with significantly fewer endometrial cancers, as well as venous and arterial vascular events, when compared with tamoxifen."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.12 There were significantly fewer occurrences of endometrial cancers, pulmonary emboli and stroke in women treated with anastrozole or exemestane when compared to women treated with adjuvant tamoxifen.

7.13

Unresolved Issues: Quality of Life with AIs

- **What is known about overall quality of life and sexual functioning in women on aromatase inhibitors?**

  "In general there have been no major differences in symptoms influencing quality of life comparing anastrozole with tamoxifen or letrozole with placebo."

  "Anastrozole, exemestane, and letrozole are all well tolerated, with small numbers of women discontinuing treatment in comparison to women on placebo or tamoxifen."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.13 Comparison of patient-perceived symptoms with AIs is difficult due to a lack of standard criteria for data collection and the differences in clinical situations. In general, there do not seem to be major differences in the quality of life when comparing anastrozole with tamoxifen or letrozole with placebo.

7.14

Unresolved Issues: Tailoring Adjuvant Therapy to Individual Patient Risk/Benefit

- **To what extent can physicians individualize decisions about adjuvant hormonal therapy? How can physicians better quantify the risks of relapse and/or second primary in women who have taken a course of tamoxifen for either two to three or five years?**

  "Tailoring decisions about adjuvant hormonal therapy requires an understanding of disease and patient characteristics associated with relapse and toxicity of each approach."

  "Future studies will need to address the differences in disease outcome and toxicity across patient and tumor subtypes."

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.14 The differences in absolute benefit that a woman may expect are important considerations in the decision-making process and the technology assessment panel recommends that each patient's individual circumstance be considered when making recommendations.

7.15

2004 ASCO Technology Assessment Panel Recommendations

- Adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence.
- Neither optimal timing nor duration of aromatase inhibitor therapy is established.
- Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen.
- Treatment options include five years of an aromatase inhibitor or sequential therapy of tamoxifen for either 2 to 3 years or 5 years, followed by aromatase inhibitors for 2 to 3 years or 5 years.
- Patients intolerant of aromatase inhibitors should receive tamoxifen.

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.15 These points summarize the recommendations of the 2004 ASCO technology assessment panel.

7.16

2004 ASCO Technology Assessment Panel Unresolved Issues

- There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting.
- Women with hormone receptor-negative tumors should not receive adjuvant endocrine therapy.
- The role of progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial.

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.16 A number of important questions and issues remain unresolved at this time mainly because of a lack of data.

7.17

2004 ASCO Technology Assessment Panel Unresolved Issues

- Aromatase inhibitors are contraindicated in premenopausal women.
- There are limited data on the role of aromatase inhibitors in women with treatment-related amenorrhea.
- The side-effect profiles of tamoxifen and aromatase inhibitors differ.
- The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized.

SOURCE: Winer EP et al. *J Clin Oncol* 2005;23(3):619-29. **Abstract**

SLIDE 7.17 Many of these unresolved issues will be addressed by ongoing studies and additional follow-up. As more data become available, their impact will be reflected in future technology assessment updates.

Select publications

Baum M et al. **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;98:1802-1810. **Abstract**

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

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

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

Jakesz R, on behalf of the ABCSG, the GABG. **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**

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

Howell A, on behalf of the ATAC Trialists' Group. **The ATAC ('Arimidex', Tamoxifen, alone or in Combination) trial in postmenopausal women with early breast cancer-updated efficacy results based on a median follow of 5 years.** Presentation. San Antonio Breast Cancer Symposium 2004. **Abstract**

Post-test:

Breast Cancer Update — Issue 3, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The VINOCAP regimen usually does not cause alopecia.
   a. True
   b. False
2. A US Oncology neoadjuvant trial is evaluating FEC 100 followed by _____.
   a. Capecitabine
   b. Docetaxel
   c. Vinorelbine
   d. Both a and b
   e. Both a and c
3. Recent results from Dr Buzdar's neoadjuvant trial demonstrated a high pCR rate with which regimen?
   a. FEC + trastuzumab
   b. Paclitaxel + trastuzumab
   c. Paclitaxel + FEC + trastuzumab
   d. Trastuzumab
   e. None of the above
4. The NSABP-B-31 cardiac safety study demonstrated that the cardiotoxicity attributable to trastuzumab was:
   a. Approximately nine percent, but mostly reversible
   b. Less than four percent, but mostly reversible
   c. Less than four percent, but most of these patients required continued medical management for CHF
5. In contrast to NSABP-B-31, SWOG-9831 and the HERA trial are evaluating the sequential administration of chemotherapy and trastuzumab.
   a. True
   b. False
6. The MD Anderson neoadjuvant study evaluating chemotherapy plus trastuzumab demonstrated a pCR rate of:
   a. 26 percent
   b. 35 percent
   c. 65 percent
7. A recent analysis of mature data from the NSABP-B-27 neoadjuvant study demonstrated a disease-free and overall survival advantage for AC followed by docetaxel compared to AC alone.
   a. True
   b. False
8. Which of the following chemotherapy regimens will be evaluated in the NSABP-B-38 adjuvant trial for patients with node-positive breast cancer?
   a. TAC x 6
   b. AC x 4 → paclitaxel q2wk x 4
   c. AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4
   d. All of the above
   e. Both a and b
9. In ABCSG-8 and ARNO-95, postmenopausal patients exposed to two years of adjuvant tamoxifen had a significantly higher three-year event-free survival when switched to anastrozole versus tamoxifen.
   a. True
   b. False
10. The data from ABCSG-12, an ongoing adjuvant trial in premenopausal patients, shows which of the following?
    a. Reduction in bone mineral density is greater with goserelin/anastrozole than with goserelin/tamoxifen
    b. Reduction in bone mineral density is less with goserelin/anastrozole than with goserelin/tamoxifen
    c. Bone loss from either combination can be largely prevented with zoledronic acid
    d. Both a and c
11. The 10-year distant recurrence rate in tamoxifen-treated patients with low recurrence scores from the Genomic Health Onco*type* DX assay was approximately:
    a. 7%
    b. 14%
    c. 30%
12. The Intergroup PACCT trial will randomly assign patients with _____ recurrence scores by the Genomic Health assay to hormonal therapy versus hormonal therapy plus chemotherapy.
    a. Low
    b. Intermediate
    c. High

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

Evaluation Form:

Breast Cancer Update — Issue 3, 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
Joyce O'Shaughnessy, MD	5 4 3 2 1	5 4 3 2 1
Charles E Geyer Jr, MD	5 4 3 2 1	5 4 3 2 1
Raimund V Jakesz, MD	5 4 3 2 1	5 4 3 2 1
Soonmyung Paik, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form:

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

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

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Degree:

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

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

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

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Additional comments about this activity:

.....

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Breast Cancer™ UPDATE

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