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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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GRAND ROUNDS SLIDE PRESENTATION

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 9 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Hortobagyi, Pegram, Miller and Brufsky on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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

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

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

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FACULTY AFFILIATIONS AND DISCLOSURES

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Consultant: Eli Lilly and Company
Honorarium: Genentech BioOncology, Novartis Pharmaceuticals

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FACULTY AFFILIATIONS AND DISCLOSURES (CONT)

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Pharmaceutical agents discussed in this program

anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
bevacizumab	Avastin®	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
epirubicin hydrochloride	Ellence®	Pfizer Inc
estradiol	Various	Various
exemestane	Aromasin®	Pfizer Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
irinotecan	Camptosar®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals Corporation
leucovorin calcium	Various	Various
megestrol acetate	Megace®	Bristol-Myers Squibb Company
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene hydrochloride	Evista®	Eli Lilly and Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
toremifene citrate	Fareston®	Orion Corp
trastuzumab	Herceptin®	Genentech BioOncology
vinorelbine	Navelbine®	GlaxoSmithKline

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ERRATUM

In the previous issue of *Breast Cancer Update* (Volume 3, Issue 8), the Grand Rounds slide 4.22 contained an inverted color key. The dark blue color should represent XT (n=255) and the light blue color should represent docetaxel (n=256). For a replacement slide, please visit the website at **www.breastcancerupdate.com/erratum**.

Editor's Note

Long and winding road

In 1979 I was a junior faculty member in the oncology department at the University of Miami Sylvester Comprehensive Cancer Center. Having somehow landed in the education division, I had the dubious honor of teaching the cancer segment of the sophomore med student pathophysiology course. Education was a welcome relief from the demands of patient care, and this pursuit took on greater momentum when I received a call from a neurology resident friend of mine who said, "Our department just bought a portable video camera for training. Let's tape something." My "Spielbergian" genes immediately sprang to attention and I decided to produce a series of video sound bites from patient interviews to assist in teaching the mechanisms of cancer-related symptomatology. I always liked Frank Netter's CIBA collection of medical illustrations; this would become the video version.

To begin, I sought a patient with esophageal cancer — looking for a classic story of progressive dysphagia. I soon met Mr J, a very asthenic, reserved, indigent African-American man in his late sixties. With my buddy neurologist as the cameraperson, we taped away. The result was initially somewhat disappointing. The patient had a difficult time explaining his symptoms, which were in no way similar to classic teaching. Try as I might, the interview remained awkward at best, but just when I was preparing to pull the plug, we struck educational gold.

"They didn't tell me I had cancer," he said. The patient's face was contorted with rage. "I found out when I realized that everyone in the radiation therapy waiting room had cancer. The doctors never told me." The man was quiet but angry as hell, as he issued a blistering indictment of the medical care he received, eloquently elaborating on this in great detail. In later years, even when I was regularly producing educational videos with the UM audiovisual staff using much more sophisticated hardware, I continued to show med students that grainy camcorder video of Mr J, because they needed to know that physicians have particularly serious responsibilities for effective patient communication when cancer is involved.

In 1988, I shifted my emphasis to audio production, figuring that real people are too busy to watch TV, and all of us are stuck in our cars. (I also subsequently learned that television is best watched without sound, particularly during election years.) It was with considerable enthusiasm that I conducted my first audio interview with the "father of breast cancer clinical research," Dr Bernard

Fisher. Much to my dismay, Bernie, in his burly and inimitable way, informed me that "researchers do research and are not in the business of telling people how to practice." Nothing I did or asked could prompt this legendary figure to comment on the clinical implications of the then groundbreaking NSABP trials demonstrating an advantage to adjuvant chemotherapy and tamoxifen in patients with node-negative tumors. Fortunately for me and our series, subsequent interviewees began to chat openly about how they take care of patients and what they really think about emerging clinical research. Now, on a good day, I can even get Bernie to open up a bit.

One of the coolest things about my unexpected career is that I can directly observe oncology history evolve. Sometimes things happen very quickly. Consider the following two audio interviews with Gabe Hortobagyi this year, in which I posed the same query:

> Question: Right now, in your own clinical practice in a nonprotocol setting, if you see a postmenopausal woman who's been on adjuvant tamoxifen for two or three years, how do you approach the decision about whether or not to switch to an aromatase inhibitor?
>
> Answers from Dr Hortobagyi:
>
> ***February 26, 2004, Miami Breast Cancer Conference***
>
> I raise the issue with all of my patients who are currently on adjuvant tamoxifen, but I am not yet prepared to switch because of the immaturity of the data. I'm starting to talk to them about the promising new data, but I will wait for more mature reports before I start switching.
>
> ***October 18, 2004,* Breast Cancer Update *Working Group Meeting***
>
> For patients who are on tamoxifen for any length of time, our practice today is to switch to an aromatase inhibitor.

Gabe reiterated these views at a recent CME conference our group held in Chicago. After the meeting I asked Jay Harris, another panel member, about these provocative comments. "People have tremendous respect for Gabe and listen very carefully to him," Jay told me. "We have learned over the years that what Gabe says usually comes to pass."

This December marks my 25th year as a professional listener, and I truly love my work. People have so much to say, and there is so much to learn. On this "golden anniversary" of what has become a fascinating educational path, the traditional Hebrew greeting "Mazel Tov" seems very appropriate. The phrase means "good luck" and reflects the truth that one must be blessed with great opportunity to do great things. A recent external independent survey demonstrated that more than two thirds of oncologists in the United States listen to our various audio programs, including this one, the grandmother of the others. It's an honor and privilege to pose the questions I think you might ask if placed in the same situation.

— Neil Love, MD
NLove@ResearchToPractice.net

Randomized trial of neoadjuvant paclitaxel and FEC with or without trastuzumab in women with HER2-positive disease

Background

In the late 1990s, the adjuvant trastuzumab trials were being developed. My group had been working on neoadjuvant trials for the previous 15 to 20 years, so we wanted to evaluate trastuzumab-containing combinations in that setting. A substantial number of women had larger tumors when we developed this protocol, and we wanted to obtain biological information through multiple biopsies in the neoadjuvant setting.

Our initial proposal in 1998 followed shortly after the reports of cardiac toxicity associated with trastuzumab administered in combination with chemotherapy, especially the anthracyclines. We encountered a fair amount of resistance with respect to the use of an anthracycline with trastuzumab. We hypothesized — based on preclinical data from Dennis Slamon's laboratory — that the temporal association between chemotherapy and trastuzumab was important to obtain maximal cytotoxicity and that the anthracyclines were clearly an important component of the treatment for women with HER2-positive tumors.

Trial design

Our trial (Buzdar 2004) was different from all others using trastuzumab either sequentially following the completion of adjuvant chemotherapy or in combination with chemotherapy regimens that excluded anthracyclines. We were criticized by our colleagues because we decided to pursue a trial in which trastuzumab was administered simultaneously with an anthracycline.

Our trial involved the best regimen at that time — every three-week paclitaxel followed by FAC; however, to minimize cardiac toxicity we elected to use epirubicin instead of doxorubicin. The neoadjuvant chemotherapy regimen was four cycles of paclitaxel followed by four cycles of FEC. Patients, mostly with T2 or T3 disease, were randomly assigned to receive neoadjuvant chemotherapy

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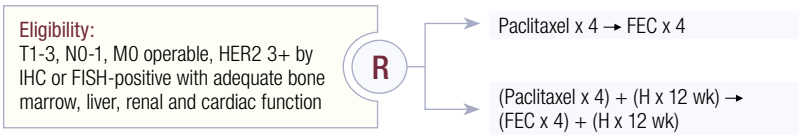
with or without simultaneous trastuzumab (1.1). Postoperative therapy was left to each investigator's discretion.

The primary endpoint of the trial was the pathological complete response (pCR) rate, which was defined as no evidence of residual invasive disease either in the breast or the regional lymph nodes. Our trial was based on the assumption that the chemotherapy regimen would lead to a 21 percent pCR rate and that the addition of trastuzumab would improve the pCR rate by another 20 percent to 41 percent. Because of the potential for cardiac toxicity, we wanted to demonstrate a large difference. We believed a smaller difference would not be convincing enough to make this regimen generally accepted.

1.1 Randomized Study of Neoadjuvant Chemotherapy versus Chemotherapy plus Trastuzumab

Protocol ID: MD Anderson
Accrual: 42/164 planned (Early termination by DSMB)



Note: After local therapy, patients with ER/PR-positive disease receive endocrine therapy.

Paclitaxel = 225 mg/m^2 24 hour IV infusion every 3 weeks
FEC = fluorouracil 500 mg/m^2 IV day 1 and 4; epirubicin 75 mg/m^2 IV day 1; cyclophosphamide 500 mg/m^2 IV day 1 every 3 weeks
H = trastuzumab 4 mg/kg IV day 1, then 2 mg/kg IV weekly

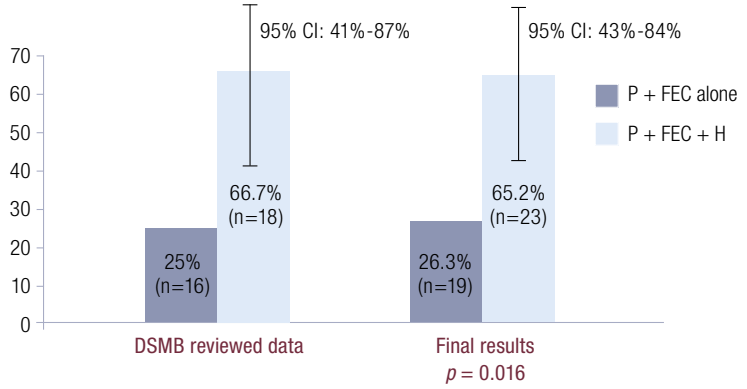
SOURCE: Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline-containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004;**Abstract 520**.

Trial results

We enrolled 42 patients over three years. We did not notice any adverse cardiac events during the trial, and as the trial went on we became more comfortable with the combination. Eventually, we began to see high pCR rates in our patients, and the Data Safety Monitoring Board (DSMB) was alerted to analyze the data. They recommended the randomization be discontinued, and a formal analysis was performed.

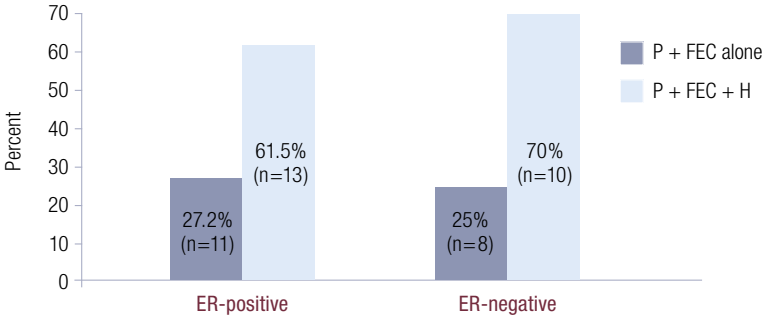
We exceeded the projected improvement in the pCR rate. In the subset of patients who had undergone surgery at the time of the DSMB's analysis, the pCR rate was about 67 percent. After all 42 patients had undergone surgery, the data were similar except that the 95 percent confidence interval had narrowed (1.2 a and b). Long-term follow-up data are not yet available but we felt obligated to present the data and did so at the 2004 ASCO meeting.

1.2a Pathological Complete Response Rates



SOURCE: Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline-containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004;**Abstract 520**.

1.2b Pathological Complete Response Rates by Estrogen Receptor Status



SOURCE: Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline-containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004;**Abstract 520**.

We are now performing the correlative studies on the pretreatment and post-treatment biopsies from patients with residual disease. Ironically, the high pCR rate doesn't leave any tissue; hence, the correlative studies are restricted to the pretreatment biopsies in those patients. In addition to the clinical examination for cardiac toxicity, we also monitored troponin levels and MUGA scans. In the entire group of patients, we did not see any episodes of congestive heart failure or cardiac-related deaths (1.3).

1.3 MD Anderson Neoadjuvant Trial: Adverse Events

Neutropenic events	P → FEC (n=19)	P + H → FEC + H (n=23)
Neutropenia Grade IV	11	21 ($p = 0.03$)
Neutropenic fever Neutropenic infections Hospitalization	8 3 1	8 5 3
Non-neutropenic infections	4	7
Neutropenia-related chemotherapy dose reduction	5	8

Cardiac safety data	P → FEC (n=19)	P + H → FEC + H (n=23)
Congestive heart failure	0	0
10% decrease in ejection fraction (EF) Decrease on paclitaxel Decrease on FEC	5 0 5	7 4 3
Improvement in EF on follow-up	2	3
Abnormal troponin-T level	0	1

SOURCE: Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline-containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004;**Abstract 520**.

Nonprotocol use of neoadjuvant and adjuvant trastuzumab

Our results were very surprising, but very important. If you consider that a patient with a T3 tumor with palpable lymph nodes, to whom you administer adjuvant chemotherapy with trastuzumab, is a reasonable choice off protocol, why wouldn't you do that if surgery was done up front and that same patient presents with 10 positive nodes *de novo*? All kinds of scientific and ethical questions arise about how to deal with this. Currently, we have a single-arm trial running to expand our database. We are considering opening that up for larger tumors, to include the locally advanced and inflammatory tumors, until additional trial concepts become available. We'd rather treat those patients within the safety of a clinical trial that requires extensive monitoring than treat them with adjvant trastuzumab off trial.

Nevertheless, we have agreed as a group that, if a patient with HER-2-positive primary breast cancer is considered for neoadjuvant chemotherapy and is not a candidate for, or does not agree to participate in, the ongoing trial, we would discuss and offer trastuzumab with the same regimen used in the study. Although we have discussed this extensively in my group, we have not extrapolated it to the adjuvant setting for the time being. It's difficult to legislate what goes on between an individual patient and her physician, but as a group, we have agreed that it is generally not appropriate to start adjuvant trastuzumab outside of a clinical trial.

Randomized neoadjuvant trial comparing weekly paclitaxel and every three-week docetaxel plus capecitabine both followed by FEC

In a current trial, we are comparing two regimens — our previous best neoadjuvant regimen of weekly paclitaxel followed by FEC, and every three-week docetaxel plus capecitabine followed by FEC. Even though no direct comparisons have yet been reported, every three-week docetaxel is probably equivalent to weekly paclitaxel. One trial in patients with metastatic disease suggests that every three-week docetaxel is more effective, although more toxic, than every three-week paclitaxel (Jones 2003). On that basis, I believe the capecitabine plus docetaxel regimen will have greater efficacy than weekly paclitaxel.

Adjuvant aromatase inhibitors as initial therapy in postmenopausal women

Since the third generation aromatase inhibitors are better than tamoxifen, my postmenopausal patients with ER-positive disease who have not yet started adjuvant hormonal therapy will initially receive an adjuvant aromatase inhibitor — preferably anastrozole. We started to using adjuvant anastrozole instead of tamoxifen after the first presentation of the ATAC trial results.

Even if tamoxifen and anastrozole had been therapeutically equivalent, anastrozole would still be preferable because it was better tolerated. For us, the issue of osteopenia was always secondary. We already had experience with the bisphosphonates and monitoring patients for osteoporosis, because chemotherapy and ovarian ablation produce premature menopause and accelerated bone resorption. We felt quite comfortable in switching our front-line adjuvant therapy to anastrozole.

Aromatase inhibitors as crossover therapy in postmenopausal women treated with adjuvant tamoxifen

Our current practice in postmenopausal women who are taking adjuvant tamoxifen for any length of time is to switch to an aromatase inhibitor. We try to conform to the data from the randomized trials evaluating a crossover to the aromatase inhibitors, but taken together, those data appear to have a class effect.

A year ago, I would have said, "If the woman had received adjuvant tamoxifen for five years, I would switch to letrozole. If the woman had received adjuvant tamoxifen for two or three years, I would switch to exemestane." Right now, I feel comfortable with any of the aromatase inhibitors at any point in time of switching. In addition to the MA17 trial with letrozole (Goss 2003) and the Intergroup Exemestane Study (Coombes 2004), the Italian trial (Boccardo 2003) with anastrozole reported similar results. In the absence of a head-to-head comparison, the toxicity profiles of these three drugs are very similar.

Aromatase inhibitors following five years of adjuvant tamoxifen

We base the decision to give aromatase inhibitors to women who have completed five years of adjuvant tamoxifen on the patient's risk. In some patients the

residual risk is so small that the benefit of additional therapy is marginal. Yet some of these patients have difficulty letting go of tamoxifen — it's a safety net and they want to continue on adjuvant therapy. Others can't wait to finish the treatment.

At ASCO 2004, I presented an abstract on the prognosis of patients with operable breast cancer five years after diagnosis (Hortobagyi 2004) (1.4). We pooled our adjuvant data dating back to 1974 from approximately 2,500 patients who had received adjuvant therapy and re-plotted the survivors' disease-free survival five years after diagnosis.

We studied the pattern of relapse in the second five years and found that for most patients with Stage II and Stage III disease, the residual risk is sufficient to justify additional therapy, including patients with ER-positive tumors who received five years of tamoxifen.

If I believe a patient has a sufficiently high risk, I will consider offering an aromatase inhibitor six or even 18 months after she completed five years of tamoxifen. Where to draw the line is gray, because we don't have good data on how to calculate residual risk at the end of five years of tamoxifen. We are rather proficient at calculating risk at the time of initial diagnosis by using Chuck Loprinzi's model or Peter Ravdin's Adjuvant! program, but we're not very good at determining risk five years later.

1.4 Five- and 10-Year Disease-Free Survival in Patients on Adjuvant Systemic Therapy Trials who Remained Recurrence-Free Five Years after Diagnosis

Group	5-year disease-free survival	10-year disease-free survival
Stage I (n=101)	94%	NR
Stage II (n=1,104)	87%	79%
Age <50 years (n=637)	88%	83%
Age ≥50 years (n=467)	85%	74%
0 positive nodes (n=149)	95%	86%
1-3 positive nodes (n=573)	89%	82%
4-10 positive nodes (n=303)	82%	74%
>10 positive nodes (n=79)	78%	68%
Stage III (n=202)	83%	71%

SOURCE: Hortobagyi S et al. **What is the prognosis of patients with operable breast cancer (BC) five years after diagnosis?** *Proc ASCO* 2004;Abstract 585.

Fulvestrant versus aromatase inhibitors in the metastatic setting

Assuming an aromatase inhibitor and fulvestrant are equivalent in efficacy, the choice of which agent to use may come down to patient preference. Some of my patients are perfectly happy with a monthly injection while others prefer an

oral agent. For many patients, fulvestrant is financially favorable because of our arcane reimbursement system. We know that responses can be seen with either sequence — an aromatase inhibitor followed by fulvestrant or the opposite — but I believe it's important we determine which is superior.

I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too low because by the time steady state was reached, many patients were off-study, presumably because of progression. In my group, we administer loading doses of 500 mg of fulvestrant, followed by 500 mg two weeks later and then 250 mg monthly.

The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population might not have revealed the true efficacy of fulvestrant (Robertson 2003). It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior. We may need to repeat some of these studies with a more appropriate dosing schedule.

Select publications

Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *The Lancet* 2002;359(9324):2131-9. Erratum in: *The Lancet* 2002;360(9344):1520. **Abstract**

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

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

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 520**.

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

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**

Hortobagyi GN. **What is the prognosis of patients with operable breast cancer (BC) five years after diagnosis?** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 585**.

Jones SE et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2003;82(Suppl 1):9;**Abstract 10**.

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

Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients. Results from GONO MIG1 study.** *Breast Cancer Res Treat* 2003;**Abstract 12**.

Trial of neoadjuvant docetaxel, carboplatin and trastuzumab

We are conducting a neoadjuvant study of docetaxel, carboplatin and trastuzumab in women with locally advanced breast cancer. Patients with HER2-negative disease receive docetaxel/carboplatin, while patients with HER2-positive disease are randomly assigned to docetaxel/carboplatin with or without trastuzumab.

Locally advanced breast cancer behaves more like metastatic than early-stage disease. Klaus Pantel's work (Pantel 2004) suggests that these patients probably have many micrometastases, so I am more inclined to consider trastuzumab off-protocol in these cases or in patients with high-risk, Stage II HER2-positive disease.

Our trial mimics Judith Hurley's study at the University of Miami (Hurley 2003) and we have already seen impressive pathologic complete response rates similar to those reported by Dr Hurley (2.1). We are able to collect tissue before and after treatment, so a number of biochemical and molecular biologic correlates will be examined. The primary endpoints are molecular correlates of pathologic complete response.

Neoadjuvant chemotherapy with or without trastuzumab

I was impressed by the MD Anderson study examining trastuzumab, paclitaxel and anthracycline-containing chemotherapy in the neoadjuvant setting. The pCR rate in the trastuzumab-treated subjects was approximately 65 percent, which is extraordinary — in fact, it's the highest I've ever seen in any primary breast cancer study (Buzdar 2004).

Although I believe the results are probably correct, a new standard of care has not been established and larger confirmatory trials are needed. The BCIRG adjuvant trastuzumab trial has accrued 3,150 FISH-positive cases and the European HERA study has accrued approximately 4,000 patients. We'll have data from these studies and the North American Cooperative Group efforts in a couple of years.

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Pathological complete response may prove to be a very important surrogate for future studies. Data from NSABP-B-27, being presented at the next San Antonio meeting, will tell us how well pCR correlates with long-term disease control. If indeed pCR proves to be a robust surrogate in the analysis of early-stage breast cancer, then the pCR data from the MD Anderson study may forecast the results of these larger adjuvant studies with regard to survival.

2.1 Platinum Salts and Docetaxel as Primary Therapy for Locally Advanced and Inflammatory Breast Cancer: Response Rates of 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**.

Rationale for combining trastuzumab and bevacizumab

We conducted a study evaluating the effect of HER2 overexpression on VEGF expression in cell lines and found overexpression of HER2 yields an increase in VEGF expression. The next step was to determine the effect of HER2 overexpression in human tumors, so we examined 612 primary breast tumors and found the HER2-positive tumors were more likely to be VEGF-positive (2.2) (Konecny 2003).

When we evaluated clinical outcome, patients with tumors that had expression of both HER2 and VEGF had the worst prognosis. This data confirmed a connection between HER2 and VEGF in human subjects with primary breast cancer and provided one rationale for combining therapeutic approaches targeting both HER2 and VEGF.

Another rationale for combining these approaches involves the ability of VEGF to increase interstitial oncotic pressure within a solid tumor. Trastuzumab is a macromolecule unlikely to diffuse easily into a bulky solid tumor because of the high interstitial oncotic pressures.

However, treating that tumor with bevacizumab and reducing the VEGF levels could lower the interstitial oncotic pressure and potentially improve the delivery of trastuzumab and afford a better response.

2.2 Association between HER2 and Vascular Endothelial Growth Factor (VEGF) Expression in Patients with Primary Breast Cancer

VEGF status	HER2-status		
$VEGF_{165-206}$	Negative	Positive	*p*-value
Negative	29.0%	12.3%	<0.001
Positive	71%	87.7%	

$VEGF_{121-206}$	Negative	Positive	*p*-value
Negative	45.5%	22.8%	<0.001
Positive	54.5%	77.2%	

"Conclusion: The positive association between HER-2/neu and VEGF expression implicates VEGF in the aggressive phenotype exhibited by HER-2/neu overexpression, and supports the use of combination therapies directed against both HER-2/neu and VEGF for treatment of breast cancers that overexpress HER-2/neu."

SOURCE: Konecny GE et al. **Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients.** *Clin Cancer Res* 2004;10(5):1706-16. **Abstract**

Clinical response to bevacizumab in patients progressing on trastuzumab

We have seen anecdotal responses to bevacizumab in patients who are progressing on trastuzumab. Our experience mimics that of Sledge, Miller and Cobleigh in the Phase I trials of single-agent bevacizumab. These patients probably still have circulating trastuzumab even though a washout occurred since their last dose, and it may be that bevacizumab facilitates the penetration of trastuzumab into the tumors. We are conducting a Phase I/II trial evaluating bevacizumab and trastuzumab in patients with relapsed or metastatic breast cancer. If the results are favorable we will design a Phase III trial — possibly docetaxel, carboplatin and trastuzumab with or without bevacizumab in the metastatic setting.

Continuing trastuzumab at the time of disease progression

At ASCO 2004, Christina Haeyoung Yeon (Yeon 2004) presented some very provocative data developed at UCLA regarding the clinical benefit of trastuzumab among nonresponders in the pivotal trastuzumab trial (2.3). Oddly enough, the nonresponding subset of patients had a statistically significant longer time to progression than patients who received chemotherapy alone, suggesting continued biologic activity of trastuzumab even in the nonresponding subset. If indeed that's the case, it reinforces the rationale for continuing trastuzumab beyond progression, especially if we can exploit other synergies with salvage cytotoxic agents.

The determination about when to discontinue trastuzumab is a clinical decision. I generally continue the agent in patients with a good performance status as long as they are not experiencing any long-term side effects and have adequate IV access, even though no randomized, controlled trials support continuation.

2.3 Median Time to Progression for Patients with HER2-Positive, Metastatic Breast Cancer Who Did Not Achieve Objective Responses When Treated with Chemotherapy Plus Trastuzumab in the Pivotal Trial

Parameter	Chemotherapy alone	Chemotherapy + trastuzumab	Paclitaxel alone	Paclitaxel + trastuzumab	AC alone	AC + trastuzumab
All nonresponders	2.8 months	4.1 months	2.1 months	3.9 months	4.3 months	4.4 months
p-value	0.0027		0.0007		0.35	
FISH-positive	3.0 months	4.1 months	2.0 months	3.9 months	4.4 months	4.4 months
p-value	0.025		0.014		0.44	
FISH-negative	2.7 months	3.9 months	2.2 months	3.9 months	3.3 months	5.3 months
p-value	0.09		0.16		0.29	

SOURCE: Yeon CH et al. **Clinical benefit of trastuzumab (H) among patients with HER2-positive metastatic breast cancer (MBC) not achieving objective responses when treated with H plus chemotherapy (CT).** Presentation. ASCO, 2004;**Abstract 680**

Trastuzumab in combination with hormonal therapy

In the *Journal of the National Cancer Institute* in 2003, we published a paper in collaboration with the Munich group showing a quantitative decrease in ER expression in over 900 patients with primary breast cancer when HER2 was amplified (Konecny 2003). Even in HER2-positive disease that was scored as ER-positive by IHC, quantitative measurement indicates a statistically significant lower level of ER than in HER2-nonamplified, ER-positive disease.

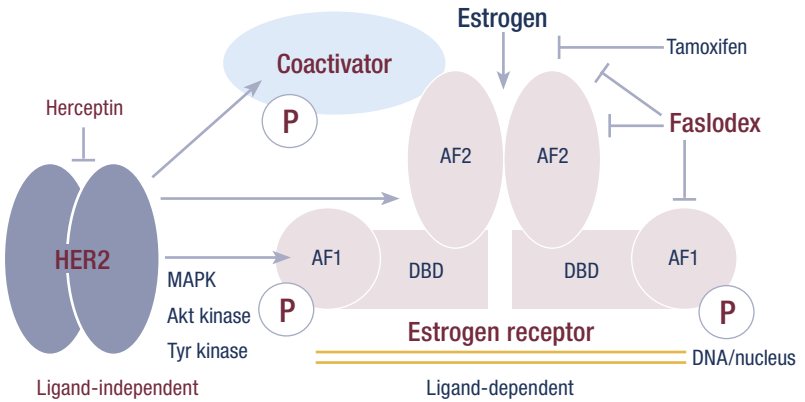
Therefore, inasmuch as the predicted response to any hormone manipulation is directly proportional to the abundance of the target, we would predict *a priori* that patients with ER-positive, HER2-positive disease would be less likely to respond to hormonal therapy than patients with ER-positive, HER2-negative disease.

Randomized trials evaluating the strategy of combining hormonal therapy and trastuzumab are ongoing in Europe, including the study of anastrozole with or without trastuzumab, and some active Phase II nonrandomized studies, such as Matt Ellis' trial of letrozole plus trastuzumab. We'll have to wait for the data to determine the efficacy of combined receptor blockade, but it appears very promising in the preclinical models. We are about to launch a randomized clinical trial evaluating fulvestrant with or without trastuzumab based on the rationale that fulvestrant degrades the estrogen receptor and may eliminate

any potential for cross talk between HER2 signaling pathways and the estrogen receptor (2.4) (Pietras 2004).

When treating patients with ER-positive, HER2-positive disease on first relapse, I generally begin with a combination of trastuzumab and chemotherapy. I have used trastuzumab and hormonal therapy in a nonprotocol setting; however, I always inform patients that the trials are ongoing and we have no data — although the emerging pattern appears promising. I believe we'll see a survival advantage in first-line hormone-based regimens combined with trastuzumab in metastatic disease, as we have seen with first-line chemotherapy-based regimens combined with trastuzumab, and that we'll find trastuzumab to be more active as first-line rather than salvage therapy.

2.4 Hypothesis: Dual Inhibition of HER2 and Estrogen Receptor Signaling Improves Antitumor Efficacy



SOURCE: With permission from Pietras RJ. **Antitumor therapy with Herceptin and Faslodex for dual targeting of HER-2 and estrogen receptors in breast cancer with HER-2 overexpression.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 22**

Select publications

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER-2 positive disease.** *Proc ASCO* 2004;**Abstract 520**.

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**.

Konecny G et al. **Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer.** *J Natl Cancer Inst* 2003;95(2):142-53. **Abstract**

Pietras RJ. **Antitumor therapy with Herceptin and Faslodex for dual targeting of HER-2 and estrogen receptors in breast cancer with HER-2 overexpression.** Presentation. San Antonio Breast Cancer Symposium, 2003.

Kathy D Miller, MD

EDITED COMMENTS

Clinical trials of bevacizumab in women with metastatic breast cancer

I believe the differences in the trial results of bevacizumab in breast cancer (Miller 2002) and colon cancer (Hurwitz 2004) trials were attributable to where during the course of the disease patients were treated, not some inherent difference in the biology of the cancers.

Our breast cancer ECOG trial evaluating bevacizumab with capecitabine enrolled patients with very advanced disease that was refractory to anthracycline and taxane therapy. Those patients could have received up to two other chemotherapy regimens for metastatic disease if they had received both an anthracycline and a taxane as adjuvant therapy (Miller 2002).

Dr Hurwitz's trial of bevacizumab with IFL was conducted in patients with metastatic colon cancer who had not received previous chemotherapy for metastatic disease but could have had adjuvant chemotherapy (Hurwitz 2004). Likewise, our ECOG-2100 breast cancer trial enrolled patients with breast cancer who had not received chemotherapy for metastatic disease but could have had adjuvant chemotherapy.

Patients were randomly assigned to weekly paclitaxel with or without bevacizumab. The primary endpoint for ECOG-2100 is time to progression (3.1). Hopefully, the first interim efficacy analysis will be available within the next six to eight months; the final efficacy analysis is probably at least a year and a half away.

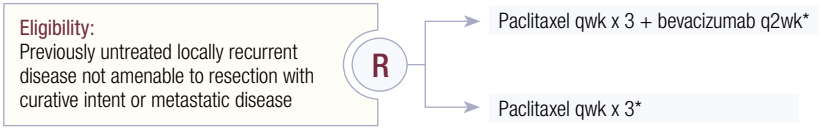
Proposed ECOG pilot trial of adjuvant bevacizumab in women with breast cancer

Because the effect of bevacizumab is expected to be greater in the adjuvant setting, a pilot adjuvant bevacizumab trial in patients with breast cancer has been proposed through the Eastern Cooperative Oncology Group. As much as I would like to conduct a full-scale study, we're not ready to launch a definitive 3,000-patient adjuvant trial until the results from ECOG-2100 are available.

Dr Miller is a Sheila D Ward Scholar of Medicine and Assistant Professor of Medicine in the Department of Hematology/Oncology at the Indiana University School of Medicine in Indianapolis, Indiana.

3.1 Phase III Randomized Study of Paclitaxel with or without Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol ID: ECOG-2100, CTSU, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 316-650 patients (Closed)



* In both arms, treatment repeats q4wk in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, November 2004.

The purpose of the pilot adjuvant bevacizumab trial is to determine: (1) whether patients will be able to take the drug long term; (2) whether patients will be willing to continue therapy, because bevacizumab is administered intravenously and in some patients requires antihypertensive therapy; (3) whether patients treated with adjuvant therapy can maintain target serum drug concentrations comparable to those achieved in patients with metastatic disease; and (4) cardiac safety.

In our randomized trial of capecitabine with or without bevacizumab, an increase in the number of patients with either heart failure or cardiomyopathy was seen in those treated with bevacizumab. The total number of events was extremely small and not significantly different. All of those patients previously received anthracycline therapy and many, though not all, had received left chest wall radiation.

Two other trials — one in patients with refractory leukemia and the other in patients with sarcoma — evaluated bevacizumab concurrent with an anthracycline. Those two trials also reported cases of congestive heart failure and cardiomyopathy; however, trials in patients with diseases for which anthracyclines are not typically used have not reported cardiomyopathy.

If our pilot adjuvant bevacizumab trial demonstrates an incidence of clinical congestive heart failure of 10 percent or more, we would not move ahead with a full-scale adjuvant trial. Patients in the pilot adjuvant bevacizumab trial will be randomly assigned to receive bevacizumab concurrent with dose-dense AC followed by paclitaxel or dose-dense AC followed by bevacizumab concurrent with paclitaxel. The duration of therapy with bevacizumab for both groups will be six months.

Neoadjuvant capecitabine/docetaxel trial

In one of our ongoing neoadjuvant studies, we're trying to take advantage of genomics and proteomics to improve the individualization of therapy. The trial is based on the capecitabine/docetaxel (XT) regimen that Joyce O'Shaughnessy evaluated in the metastatic setting (3.2) (O'Shaughnessy 2002). For their first

cycle of chemotherapy, patients will be randomly assigned to either capecitabine or docetaxel monotherapy. After that initial cycle, all patients will receive four cycles of both drugs in combination.

We're collecting fresh tissue and a serum sample for serum proteomic analyses before the start of chemotherapy, after the first cycle of monotherapy and after the combination at the time of surgery. We are hopeful that the serum proteomics will be useful in predicting response because for many patients it is difficult to obtain a fresh tumor sample.

Investigators have predominantly evaluated the role of serum proteomics in identifying patients at risk of developing a malignancy or segregating patients with cancer from those with some benign condition. We're trying to take proteomics a step further and determine if it will predict for response to individual therapies. We're also performing tumor proteomic analyses in those patients. If we identify proteins in the serum that predict for response, we'll also be able to determine whether those same proteins are actually in the tumor.

3.2 Efficacy of Capecitabine/Docetaxel versus Docetaxel in Patients with Anthracycline-pretreated Metastatic Breast Cancer

	Capecitabine/docetaxel (n=255)	Docetaxel (n=256)	*p*-value
Median time to progression	6.1 months (95% CI: 5.4-6.5)	4.2 months (95% CI: 3.4-4.5)	Log rank $p = 0.0001$
Objective tumor reponse	42% (95% CI: 36-48)	30% (95% CI: 24-36)	$p = 0.006$
Stable disease	38% (95% CI: 32-44)	44% (95% CI: 38-50)	—
Median survival	14.5 months (95% CI: 12.3-16.3)	11.5 months (95% CI: 9.8-12.7)	Log rank $p = 0.0126$

SOURCE: O'Shaughnessy J et al. **Superior survival with capecitabine and docetaxel combination chemotherapy in anthracycline-pretreated patients with advanced breast cancer.** *J Clin Oncol* 2002;20(12):2812-2823. **Abstract**

Sequential versus combination chemotherapy for women with metastatic disease

I am a confirmed "sequentialist." In the metastatic setting, combination chemotherapy is appropriate for very few patients. The trials of the combination regimens of capecitabine/docetaxel (O'Shaughnessy 2002) and paclitaxel/gemcitabine (Albain 2004) tell us that capecitabine and gemcitabine are active drugs in breast cancer and that patients with breast cancer are better off if they receive those drugs as part of their treatment. The trials, however, don't tell us how to optimally use the drugs in the metastatic setting.

First-line therapy for a patient with asymptomatic ER-negative, HER2-negative metastatic disease

In my clinic, many patients with previously untreated, asymptomatic ER-negative, HER2-negative metastatic disease are treated first line with capecitabine monotherapy because it fits best with the goals of therapy. Capecitabine is by far the most convenient for patients. In my experience, it's one of the most tolerable agents as chronic chemotherapy. Patients on capecitabine see me every nine or 12 weeks, and they don't lose their hair.

Role of adjuvant aromatase inhibitors in postmenopausal women

Three aromatase inhibitors have been tested in the adjuvant setting in three different ways (Baum 2003; Coombes 2004; Goss 2003). Each of those three strategies demonstrated a decrease in early recurrences. We don't have overall survival data yet because the trials aren't mature enough. It's possible that these strategies may not translate into an overall survival advantage because they were studied in postmenopausal elderly women who are more likely to die of other causes.

In a postmenopausal elderly woman, however, I'm not sure that overall survival is necessarily the most important outcome. If I can keep a 75-year-old patient from experiencing the physical pain and the emotional angst of a breast cancer recurrence before she dies of something else at age 79, I've done her well, even though I may not have altered her overall survival. I believe it will be important to obtain information from the long-term follow-up of those trials, including quality of life and the risk of heart disease and osteoporosis.

Of the postmenopausal women with newly diagnosed ER-positive early breast cancer in my practice, about 60 or 70 percent start on an adjuvant aromatase inhibitor, and about 30 or 40 percent start on adjuvant tamoxifen (3.3). If they're starting on an adjuvant aromatase inhibitor, it's always anastrozole because that's the one for which we have data. I would use adjuvant tamoxifen for postmenopausal patients with low-risk breast cancer (eg, a Grade I, 1.2 cm tumor) who already have significant osteoporosis. In those patients, I worry that osteoporosis will have more of an impact than breast cancer on their overall health.

3.3 Actual Cases from Practice: Choice of Adjuvant Endocrine Therapy

Which adjuvant endocrine therapy did you use in the last postmenopausal patient you evaluated with an ER-positive breast cancer?

Therapy	Node-positive	Node-negative
Tamoxifen	42%	28%
Anastrozole	50%	60%
Letrozole	6%	10%
Exemestane	2%	2%

SOURCE: *Breast Cancer Update* National Survey of 150 Medical Oncologists, April 2004.

Extended adjuvant hormonal therapy with an aromatase inhibitor following five years of adjuvant tamoxifen

We talk about this to all of our patients who are finishing five years of adjuvant tamoxifen. Interestingly, one third of those women are concerned about stopping tamoxifen and would have badgered me to continue it. They believe additional therapy with an adjuvant aromatase inhibitor is the greatest thing and can't wait to switch. Another third, I believe, have been taking their adjuvant tamoxifen to humor me, rather than because they believe they need it. They were counting the days until their therapy with tamoxifen was over and they are not interested in continuing therapy. The last third of the women are looking forward to completing therapy, but if an adjuvant aromatase inhibitor provides additional benefit, they want to consider it.

It's a tough decision for many women, and we suggest they re-check their cholesterol and bone mineral density and consider those factors when making their decisions. I often suggest they stop taking tamoxifen and then see me in three months. I have them start taking the aromatase inhibitor about one month before they see me. This way, their personal experience with the toxicity can be considered in their decision-making.

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.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 510**.

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

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

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**

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Miller KD et al. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;76(Suppl 1);**Abstract 36**.

O'Shaughnessy J et al. S**uperior 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**

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

Grand Rounds: Adam M Brufsky, MD, PhD*

*Originally presented at a *Breast Cancer Update* Working Group meeting, Naples, October 2, 2004. For the audio portion of this presentation and the PowerPoint slides, please see accompanying CDs.

4.1

Optimal Sequencing of Hormonal Therapy in Metastatic Disease

Adam M Brufsky, MD, PhD
Co-Director, Breast Cancer Program of the UPMC Cancer Centers
University of Pittsburgh

4.2

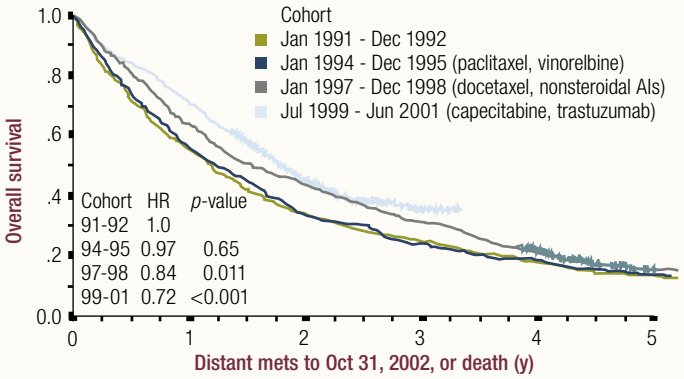
Breast Cancer

- It is estimated that in the United States during 2004
  - 215,990 new cases will be diagnosed in women
  - 44,110 women will die
- Second-leading cause of cancer death in women
- Survival — 5 years
  - Stage 0/I disease — 97%
  - Stage II/III disease — 79%
  - Stage IV disease — 23%

SOURCE: Jemal A et al. *Ca Cancer J Clin* 2004;54:8-29. **Abstract**

4.3

Improvements in Outcomes in Metastatic Breast Cancer: Overall Survival



AI = aromatase inhibitor; HR = hazard ratio

SOURCE: With permission from Chia SKL et al. Presentation. ASCO, 2003;**Abstract 22**

SLIDE 4.2 I'm not sure there is an optimal sequence of hormonal therapy in metastatic disease. From recently updated SEER data, we know that approximately 23 percent of women with metastatic breast cancer survive at least five years. Many of them have slowly progressing disease that can be adequately controlled with hormones. I think the art of this is to decide which hormones to use and how.

SLIDE 4.3 It's gratifying that systemic therapy is doing better. The British Columbia group evaluated their database of patients with metastatic breast cancer and found the median survival actually improved by about 28 percent over a 10-year period. This median survival benefit continues to improve in metastatic disease. The supportive care we're providing is better, and we're diagnosing metastatic disease earlier in its course. On the other hand, the addition of novel and more improved systemic therapies has had something to do with this improvement in survival, particularly the introduction of nonsteroidal aromatase inhibitors in the mid 1990s.

4.4

Endocrine Therapy for Metastatic Breast Cancer

- Tamoxifen was the preferred first-line endocrine therapy for more than two decades
- Objective response rates of 20%-35% in women with receptor-positive breast cancer; clinical benefit in up to 60%
- Favorable quality of life compared to chemotherapy
- Other hormonal agents are likely superior to tamoxifen

SLIDE 4.4 Tamoxifen was the preferred agent for the treatment of metastatic breast cancer for more than two decades. Because the vast majority of women with metastatic breast cancer have bone and soft-tissue disease, it's often difficult to measure objective response to hormonal therapies. Presently, the objective response of these women to endocrine therapy is about 35 percent. A study of an aromatase inhibitor versus megesterol demonstrated that a clinical benefit that is a partial response, complete response or stable disease greater than six months is a good surrogate endpoint for survival. A lot of us say, "Gosh, if a woman's cancer didn't get better in six months, what are we really doing?"

A trial of anastrozole versus megesterol as second-line therapy for metastatic disease showed that the two-year survival rate was 85 percent in women who had stable disease for six months or greater — the same two-year survival rate seen in women who had complete or partial response. That's good to know when we try to evaluate the literature or counsel patients. I have patients with metastatic disease who come to me very upset and say, "My cancer didn't get any better. Let's switch therapy." I tell them, "On the other hand, you have had stable disease for more than six months, so your chance of survival at two years is the same as it would be if all your cancer went away." It's hard to convince them of that.

4.5

First-Line Trials: Are Aromatase Inhibitors Superior to Tamoxifen in Postmenopausal Metastatic Breast Cancer?

SLIDE 4.5 What about using aromatase inhibitors? Are they superior to tamoxifen?

4.6

Randomized Phase III Studies of Antiaromatase Agents versus Tamoxifen as Initial Therapy for Metastatic Breast Cancer

	Anastrozole vs tamoxifen	Anastrozole vs tamoxifen	Letrozole vs tamoxifen	Exemestane vs tamoxifen
Patients (n)	170 vs 182	340 vs 328	453 vs 454	182 vs 189
Overall response (%)	21 vs 17	33 vs 33	30 vs 20*	46 vs 31*
Clinical benefit (%)	59 vs 46*	56 vs 56	49 vs 38*	66 vs 49*
TTP (mo)	11 vs 6†	8 vs 8	9 vs 6*	10 vs 6*
ER unknown (%)	11 vs 11	56 vs 54	34 vs 33	15 vs 11

*Significantly superior to tamoxifen after protocol analysis
†Significantly superior to tamoxifen after nonprotocol analysis

SOURCES: Nabholtz JM et al. *J Clin Oncol* 2000;18:3758-67. Bonneterre J et al. *J Clin Oncol* 2000;18:3748-57. Mouridsen H et al. *J Clin Oncol* 2001;19:2596-606. Parideans R. Presentation. ASCO, 2004;**Abstract 515**.

SLIDE 4.6 The available data suggest that aromatase inhibitors are better than tamoxifen as first-line therapy for metastatic disease.

4.7

Implications for Clinical Practice

- Aromatase inhibitors are superior to tamoxifen as first-line therapy
- Benefits are not overwhelming
- Are aromatase inhibitors the best available first-line therapy in postmenopausal, metastatic, ER-positive breast cancer? (Yes)

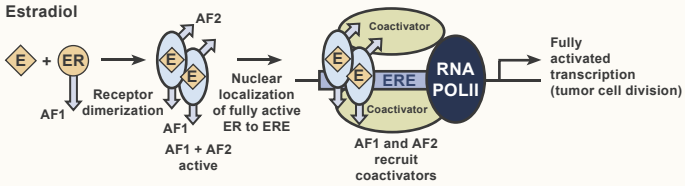
SLIDE 4.7 We know that aromatase inhibitors are likely superior to tamoxifen as first-line therapy. They're clearly superior to megesterol following tamoxifen failure. We know that patients can respond to a steroidal aromatase inhibitor after failing a nonsteroidal aromatase inhibitor, but what about the use of other agents such as the estrogen receptor downregulator fulvestrant.

4.8

Estrogen Receptor Downregulators: Novel Mechanism of Action

4.9

Mode of Action of Estradiol

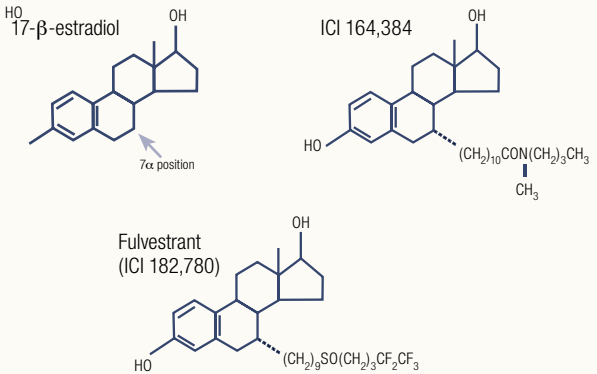


SOURCE: Adapted with permission from Wakeling AE et al. *Endocr Relat Cancer* 2000;7(1):17-28. **Abstract**

SLIDE 4.9 When estrogen binds to the estrogen receptor in the cytoplasm, the receptors dimerize and then go into the nucleus. In the nucleus, cofactors interact with the "business" end of the molecule, called AF1, to activate gene transcription. These cofactors are different depending on the tissue type. Miles Brown, whom I used to work for as a post-doc, elaborated on this a lot in the 1990s, and it is very interesting.

4.10

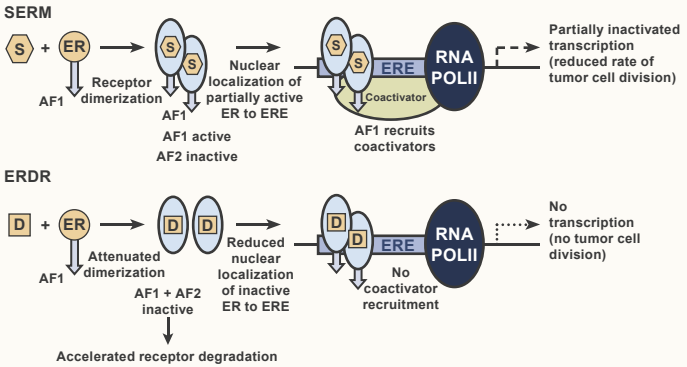
The First Nonagonist (Pure) Antiestrogens



SLIDE 4.10 To produce fulvestrant, estradiol is modified with a long side group at the seven alpha position.

4.11

Mode of Action of SERMS and ER Downregulators (ERDRs)

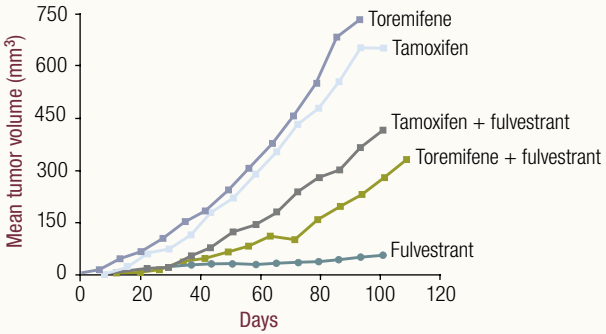


SOURCE: Adapted with permission from Wakeling AE et al. *Endocr Relat Cancer* 2000;7(1):17-28. **Abstract**

SLIDE 4.11 Estrogen receptor downregulators block dimerization in the cytoplasm and completely degrade the receptors. This is unlike SERMs, such as raloxifene, which allow the receptors to dimerize, but block the activation of cofactors in the nucleus, resulting in only a partial disruption of gene expression and cell growth.

4.12

Antitumor Effects of Fulvestrant in Tumors with Developed Resistance to Tamoxifen



SOURCE: With permission from Osborne CK et al. *Cancer Chemother Pharmacol* 1994;34(2):89-95 (copyright Springer-Verlag). **Abstract**

SLIDE 4.12 In animal experiments, when a breast cancer cell line is exposed to tamoxifen, immunohistochemical analysis shows the receptors are still present. After exposure to fulvestrant, all the receptors disappear in the nucleus. This seems to be a purer way of affecting estrogen receptor function.

Cells often become resistant to toremifene and tamoxifen over time and tend to grow when given these drugs. If given fulvestrant, they don't grow at all. When given fulvestrant and the supposed stimulus of tamoxifen/toremifene, the result is partial suppression. Clearly, some cross-resistance occurs, and perhaps something could be done to the existing receptor in the cell to overcome that resistance. One hypothesis is that the receptor becomes mutated in the cell. Fulvestrant can partially overcome this resistance, which suggests it can be used after tamoxifen failure.

4.13

Phase III Trials of Fulvestrant versus Anastrozole in Tamoxifen-Resistant Postmenopausal Patients with Advanced Breast Cancer

- Multicenter double-blind randomized North American and European Phase III trials
- Fulvestrant 250 mg IM qmo vs anastrozole 1 mg/d
- Primary objective: increase time to progression

SOURCES: Osborne CK et al. *J Clin Oncol* 2002;20(16):3386-95. **Abstract**
Howell A et al. *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

4.14

Phase III Trials of Fulvestrant versus Anastrozole in Tamoxifen-Resistant Postmenopausal Patients with Advanced Breast Cancer

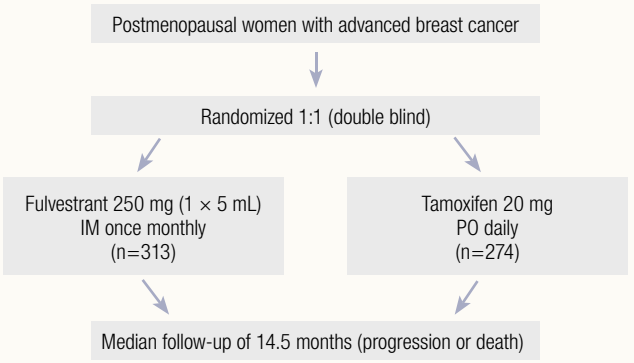
Trial		n	Median TTP (mo)	ORR (%)	Median DOR (mo)
North American[1]:	Fulvestrant	206	5.4	17.5	19.0
	Anastrozole	194	3.4	17.5	10.8
European[2]:	Fulvestrant	222	5.5	20.7	15.0
	Anastrozole	229	5.1	15.7	14.5

SOURCES: [1] Osborne CK et al. *J Clin Oncol* 2002;20(16):3386-95. **Abstract**
[2] Howell A et al. *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

SLIDES 4.13 - 4.14 Data from head-to-head Phase III trials of fulvestrant versus anastrozole following tamoxifen failure demonstrate overall response rates and duration of response to be similar. Such results suggest that in postmenopausal women with metastatic breast cancer following tamoxifen failure, aromatase inhibitors and fulvestrant are essentially equal.

4.15

Fulvestrant versus Tamoxifen: A Randomized First-Line Trial



SOURCE: Howell A et al. *J Clin Oncol* 2004;22(16):1605-13. **Abstract**

SLIDE 4.15 A recently published trial compared fulvestrant to tamoxifen as first-line therapy for metastatic breast cancer not yet treated with hormones. The median follow-up was about 15 months.

4.16

Fulvestrant versus Tamoxifen: Conclusions

- Fulvestrant is effective as first-line treatment of advanced breast cancer in postmenopausal women
- No statistical differences were seen between fulvestrant and tamoxifen in TTP and ORR
  – ER-positive and/or PgR-positive subset: No differences in TTP or ORR
  – ER-positive/PgR-positive subset: ORR favored fulvestrant
- Clinical benefit statistically favored tamoxifen
- Both treatments were generally well tolerated
  – Incidence of thromboembolic events
    – Fulvestrant 6% vs tamoxifen 3%; *p*-value not available
  – Significantly fewer hot flashes for fulvestrant (18% vs 25%, $p = 0.05$)

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(16):1605-13. **Abstract**

SLIDE 4.16 The trial found a lower incidence of hot flashes with fulvestrant. The two drugs were similar in terms of time to progression and overall response rate.

4.17

Fulvestrant after Failure of Tamoxifen and AIs

- Phase II open-label trial in metastatic breast cancer
- Progression after tamoxifen and aromatase inhibitors
- Accrued 20 patients: 14 bone, 9 liver, 4 skin, 2 lung, 3 breast metastases
- Median age 67 (45-86)
- Fulvestrant 250 mg monthly intramuscular injection
- Minimal side effects (nausea, chills, fatigue) in less than 10%
- 2 PR, 5 SD >24 wk (41% clinical benefit)

SOURCE: Perey L et al. Poster. San Antonio Breast Cancer Symposium, 2002;**Abstract 249**.

SLIDE 4.17 Choosing the right sequence of hormonal therapies can be difficult because these agents are essentially equivalent — although perhaps some are slightly better. Data from small trials presented at the San Antonio Breast Cancer Symposium and other meetings can help in clarifying the choices. In a Phase II trial presented in San Antonio, women with metastatic breast cancer all received fulvestrant after progression on tamoxifen and an aromatase inhibitor. Fulvestrant demonstrated a clinical benefit of about 41 percent with very few side effects; hence, fulvestrant has potential activity after tamoxifen and aromatase inhibitors.

4.18

Treatment after First-Line Fulvestrant

- Accrued 587 patients with previously untreated metastatic breast cancer
- Randomly assigned to fulvestrant 250 mg IM qmo (313) or tamoxifen 20 mg qd (274)
- 66 women had clinical benefit, progressed and were treated with another hormonal agent (usually an aromatase inhibitor, tamoxifen or megestrol acetate); of these, 35 were in the fulvestrant group and 31 were in the tamoxifen group
- Clinical benefit rate was 57% after fulvestrant failure and 61% after tamoxifen failure
  - Tamoxifen after fulvestrant (n=10): 1 PR, 7 SD >24 wk
  - Aromatase inhibitor after fulvestrant (n=22): 1 CR, 1 PR, 9 SD >24 wk
  - Aromatase inhibitor after tamoxifen (n=25): 2 CR, 1PR, 13 SD >24 wk

SOURCE: Howell A et al. Poster. San Antonio Breast Cancer Symposium, 2002;**Abstract 251**.

SLIDE 4.18 A more complicated question is whether fulvestrant should be given first line and what happens afterward. In the British study of tamoxifen versus fulvestrant, 66 women had clinical benefit from fulvestrant and then progressed and were treated with another hormonal agent. After fulvestrant failure, the clinical benefit rate was still 57 percent from other agents.

4.19

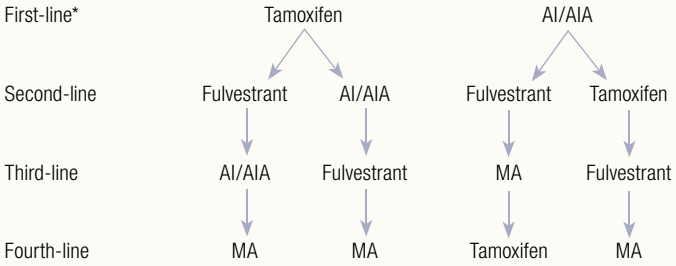
Implications for Clinical Practice

- Fulvestrant and anastrozole are equal after tamoxifen
- Fulvestrant and tamoxifen are equal as first-line therapy
- Should we be using fulvestrant? (Yes)
- As first-line therapy? (Maybe)
  – Cost considerations
  – Compliance considerations
- After failure of other hormonal agents? (Yes)

SLIDE 4.19 The implications, in terms of clinical practice, are that fulvestrant and anastrozole are equal after progression on tamoxifen. Should we be using fulvestrant? I think it is an option as first-line treatment despite its expense, because it's paid for by Medicare. You can give this to someone in your office, as opposed to her paying $300 a month for aromatase inhibitors. Compliance is another consideration — some patients just don't want to take pills and even though they tell you they're taking their pills all the time, they really don't. These are the patients for whom fulvestrant may be appropriate instead of an aromatase inhibitor. Data from small, Phase II studies suggest we can give fulvestrant after failure of other hormonal agents.

4.20

Proposed Sequence of Endocrine Therapies Postmenopausal Women with ER-Positive Advanced Breast Cancer



* Fulvestrant is also an option as first-line therapy

AI = aromatase inhibitor; AIA = aromatase inactivator; MA = megestrol acetate

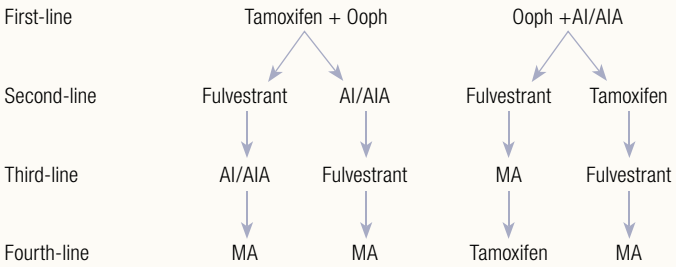
SLIDE 4.20 What are some options for sequencing endocrine therapies? One option is first-line tamoxifen followed by fulvestrant, an aromatase inhibitor or inactivator, and then megesterol. A second option is first-line tamoxifen followed by an aromatase inhibitor, fulvestrant and then megesterol. Or an aromatase inhibitor and then steroidal aromatase inhibitor, fulvestrant and megesterol.

Many of us start with an aromatase inhibitor in postmenopausal women and then either fulvestrant or tamoxifen followed by either megesterol and tamoxifen or fulvestrant and megesterol.

Many options are available. Clinically, if a woman has responded to one hormonal agent for a while — whether it's months or years — she will likely respond to another one later on.

4.21

Proposed Sequence of Endocrine Therapies in Premenopausal Women with ER-Positive Advanced Breast Cancer



Ooph = oophorectomy; AI = aromatase inhibitor; AIA = aromatase inactivator; MA = megestrol acetate

SLIDE 4.21 In premenopausal women, aromatase inhibitors as monotherapy should not be utilized. Aromatase inhibitors given to a premenopausal woman decrease the peripheral estrogen, signaling the ovary to increase estrogen production. This is the complete opposite of the desired effect.

I have seen premenopausal women with metastatic breast cancer treated up front with an aromatase inhibitor who have come to me because they had a flare of their disease and no one knew what to do. The simple thing to do was an oophorectomy.

Data from Europe suggest that the combination of tamoxifen and oophorectomy is probably superior to oophorectomy alone. Then one could continue with fulvestrant or an aromatase inhibitor or inactivator. If the patient progresses on fulvestrant, I would give an aromatase inhibitor or inactivator. At that point, if they progress on an aromatase inhibitor, I'd give fulvestrant, and then finally, megesterol.

The alternative first-line therapy is oophorectomy and an aromatase inhibitor or inactivator. Some antagonism may occur between the LHRH agonist (if the oophorectomy is nonsurgical) and an aromatase inhibitor or inactivator. Some patients who have rising tumor markers or develop symptoms (or both) when treated with this combination have been found to still have premenopausal estrogen levels. In that situation, surgical oophorectomy followed by an aromatase inhibitor is suggested. After that, the sequence is fulvestrant, tamoxifen or megesterol.

4.22

Hormonal Therapies: Summary

- Aromatase inhibitors are superior to megestrol acetate as second-line hormonal therapy for postmenopausal metastatic breast cancer
- Aromatase inhibitors are superior to tamoxifen for first-line therapy for postmenopausal metastatic breast cancer
- Estrogen receptor downregulation with fulvestrant is likely equivalent to an aromatase inhibitor or tamoxifen as first- or second-line hormonal therapy for metastatic breast cancer
- Third- and fourth-line responses to hormonal agents are not uncommon

SLIDE 4.22 To summarize the hormonal therapies in postmenopausal women with metastatic breast cancer, I think aromatase inhibitors are superior to megesterol as second-line therapy and probably superior to tamoxifen as first-line therapy. Fulvestrant is likely equal to aromatase inhibitors and tamoxifen as first- or second-line hormonal therapy for metastatic breast cancer. Third- and fourth-line responses to hormonal agents are not uncommon.

4.23

The Future: Prediction of Response and Survival Using Cellular Assays

SLIDE 4.23 I've talked about the past; now I'd like to briefly talk about the future — using cellular assays to predict response and survival in women with metastatic breast cancer.

4.24

Clinical Trial Results

Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer

SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351(8):781-91. **Abstract**

4.25

Hypothesis

Enumeration of circulating tumor cells in patients with metastatic breast cancer provides an early, reliable indication of the likelihood of success or failure of new systemic therapy.

SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351:781-91. **Abstract**

4.26

Eligibility

- Progressive metastatic breast cancer
- Commencing new systemic therapy
- Measurable disease
- ECOG performance status 0-2

SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351(8):781-91. **Abstract**

SLIDES 4.24 - 4.26 In a prospective trial sponsored by the Immunicon Corporation and spearheaded by Dan Hayes at the University of Michigan and colleagues from MD Anderson, the Cleveland Clinic, Duke University and the University of Arizona, a device developed by the Immunicon Corporation was clinically applied to measure circulating tumor cells and tumor cell burden. Their hypothesis was that such measurements could help predict whether a woman would relapse or progress on systemic therapy for metastatic breast cancer. The study participants were women with progressive, measurable, metastatic breast cancer who were starting a new systemic therapy. These women had a good ECOG performance status (0-2) and, therefore, were expected to live a reasonable amount of time.

4.27

Methods: CTC Enumeration

- Sample collection
  – *CellSave® Preservative Tube*
- Reagents
  *CellSearch™ Epithelial Cell Kit**
  – Immunomagnetic beads and buffers
  – Immunofluorescent stains
- Specimen mounting
  – *MagNest® Cell Presentation Chamber and Magnet*
- Sample preparation
  – *CellTracks® AutoPrep System*
- Sample analysis
  – *CellSpotter® Analyzer**

* Received FDA clearance for *in vitro* diagnostics, February 2004

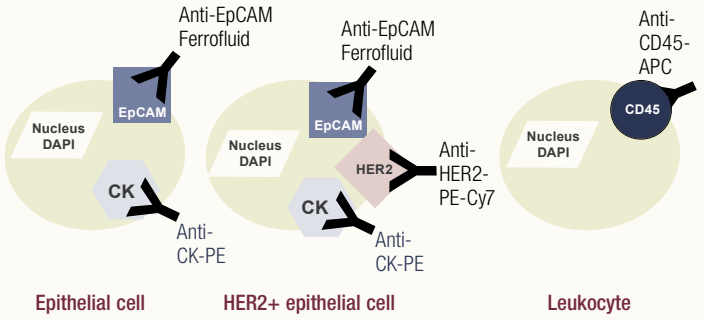
SOURCE: Allard WJ. Presentation. ASCO, 2004;**Abstract 9552**.

SLIDE 4.27 A brief explanation of the cell-counting procedure will help in understanding the concept of measuring the tumor cells. The

patients had 7.5 cc's of blood drawn in a CellSave® tube, which uses a proprietary preservative that allows the cells to be immunohistochemically stained.

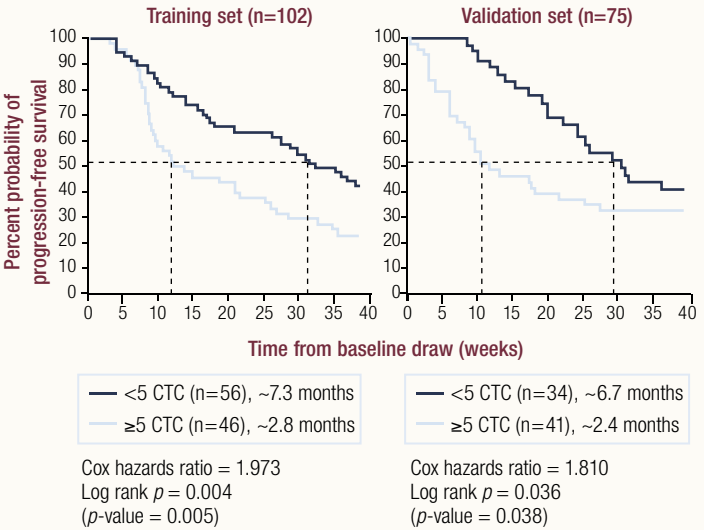
4.28

Immunomagnetic Labeling and Immunofluorescent Identification of Cells



4.29

Baseline Circulating Tumor Cells Predict Progression-Free Survival



SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351(8):781-91. **Abstract**

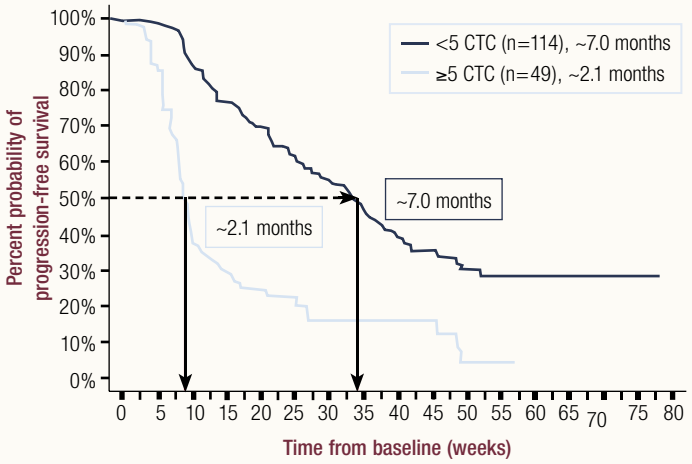
SLIDE 4.28 Circulating tumor cells (CTC) can be easily read by antibody staining. An automated machine, the CellSpotter®, is used to do the reading. A cartridge is placed into the scanning micro-

scope, which will scan the entire scope to identify potential circulating tumor cell candidates, which are then given to a technician or a pathologist to read.

SLIDE 4.29 The results of the Immunicon study were published in the *New England Journal of Medicine*. They initially did a training set to establish the number of circulating tumor cells that would best differentiate patients who will progress early from patients who will progress late. They found that the number of cells reached a plateau at about five. Applying this five circulating tumor cell cut-off, they noted that patients with less than five circulating tumor cells in their 7.5-cc blood sample had a progression-free survival of about 7.3 months. Patients with five or greater circulating tumor cells had a progression-free survival of a little less than three months. A doubling of progression-free survival occurred with less than five circulating tumor cells at baseline. In a validation set, the researchers drew blood from another 75 randomly selected patients. In the validation set, the progression-free survival of patients who had five or more circulating tumor cells was about 2.4 months; patients with less than five had progression-free survival of about 6.7 months.

4.30

CTC at First Follow-Up Predict PFS



First follow-up (3-4 wk), n=163, Log rank $p < 0.001$

SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351(8):781-91. **Abstract**

SLIDES 4.30 Ideally, we would like to not only predict progression-free survival at baseline but also be able to predict whether therapy affected this progression-free survival. To test whether this was viable, the Hayes group drew blood at various intervals throughout therapy.

They found that at about one month after the initiation of new systemic therapy, patients with greater than five circulating tumor cells had a progression-free survival rate of 2.1 months, suggesting that their initial therapy was probably not going to work. However, participants with five or less circulating tumor cells had a progression-free survival rate of about seven months.

4.31

Multivariate Analysis

	Category		PFS		OS	
Prognostic factor	(+)	(-)	HR	*p*-value	HR	*p*-value
Baseline CTC	≥5	<5	1.76	0.001	4.26	<0.001
Line of therapy	≥2nd	1st	1.73	0.002	2.38	0.01
Type of therapy	Chem	Horm	1.61	0.02	2.54	0.02
ECOG	2 vs 1 vs 0		ns	ns	1.48	0.02
Time to metastasis	Time in years		ns	ns	0.92	0.03
First follow-up CTC	≥5	<5	2.52	<0.001	6.49	<0.001
ER/PR status	+	–	ns	ns	0.35	<0.001
Line of therapy	≥2nd	1st	1.58	0.01	2.29	0.006
ECOG	2 vs 1 vs 0		ns	ns	1.53	0.03

CTC = circulating tumor cells; HR = hazard ratio; ns = not significant

SOURCE: Cristofanilli M et al. *N Engl J Med* 2004;351(8):781-91. **Abstract**

4.32

Metastatic Breast Cancer: Conclusions

- At baseline, 50% of patients had circulating tumor cells ≥5 and independent prognostic indicators of favorable and unfavorable outcomes (progression-free and overall survival)
- At first follow-up, 30% of patients had circulating tumor cells ≥5; when elevated, circulating tumor cells predict short progression-free and overall survival and may indicate patient is on a futile therapy

SLIDE 4.31 In a multivariate analysis of all the factors that went into determining progression-free survival and overall survival, one of the best predictors for progression-free survival was less than five circulating tumor cells. Patients with less than five circulating tumor cells at baseline had about 75 percent improvement in progression-free survival. At first follow-up, less than five circulating tumor cells after therapy seemed to predict for a very good progression-free and overall survival.

SLIDE 4.32 From this cell count study, researchers concluded that in metastatic breast cancer, 50 percent or more of patients have greater than five circulating tumor cells at baseline. These circulating tumor cells are an independent prognostic indicator for favorable and unfavorable outcomes. At first follow-up, 30 percent of patients had five or greater circulating tumor cells, so 20 percent of the patients derived benefit from chemotherapy or hormonal therapy.

But in patients in whom the tumor cells were still elevated, it predicted a short progression-free and overall survival, and potentially indicated that therapy should be changed. Not only do we have clinical judgment and other parameters, but we also may have this independent assay to consider. These findings need to be validated in larger studies but in the future will likely prove to be a good adjunct to standard staging modalities for us to predict recurrence.

4.33

Implications for Clinical Practice

- Do these data apply to all patients?
  - All patients had measurable disease
  - Data appear less robust for patients on endocrine therapy
- Ongoing or planned clinical trials:
  - Accruing patients with nonmeasurable disease
  - A prospective randomized trial is being designed to determine if changing therapy at 3 to 4 weeks improves outcome
- Ready for prime time?
  - Await results of confirmatory clinical trials
  - Has great potential (especially in nonmeasurable disease)

SLIDES 4.33 What are the implications of a cell-counting tool in clinical practice? The patients studied by Hayes and colleagues had measurable disease, but the majority of patients with metastatic breast cancer have nonmeasurable disease (evaluable disease). Trials are now accruing patients with nonmeasurable disease to determine whether these data will be as robust for patients on endocrine therapy alone.

Dan Hayes is organizing a prospective randomized trial, called the BRATS study, designed to determine if a change in therapy after three to four weeks, based on a circulating tumor cell assay, will improve a patient's outcome. Patients who have five circulating tumor cells after a month of therapy will be randomly assigned to a change of therapy or continued therapy. As I said before, we need to await the results of confirmatory clinical trials, but I'm presenting this now because it has great potential for the future.

Post-test:

Breast Cancer Update — Issue 9, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In the MD Anderson study examining chemotherapy with or without trastuzumab in the neoadjuvant setting, pCR rates favored which treatment?
   a. Chemotherapy alone
   b. Chemotherapy plus trastuzumab

2. According to Hortobagyi's ASCO abstract on the prognosis of patients who had received adjuvant therapy, five years after diagnosis most patients with Stage II and Stage III disease have residual risk sufficient to justify additional adjuvant therapy.
   a. True
   b. False

3. In the current MD Anderson neoadjuvant trial, weekly paclitaxel followed by FEC is being compared to what regimen?
   a. Paclitaxel plus capecitabine followed by FAC
   b. Docetaxel plus capecitabine followed by FEC
   c. Paclitaxel plus capecitabine followed by FEC

4. Clinical trials comparing fulvestrant to anastrozole for the second-line treatment of advanced breast cancer in postmenopausal women showed fulvestrant to be at least as effective as anastrozole.
   a. True
   b. False

5. ECOG-E2100 will randomly assign patients with metastatic breast cancer to:
   a. Paclitaxel
   b. Bevacizumab and capecitabine
   c. Bevacizumab and paclitaxel
   d. Both a and b
   e. Both a and c

6. In the pilot adjuvant bevacizumab trial being proposed through ECOG, which adjuvant chemotherapy regimen will be evaluated?
   a. TAC
   b. Dose-dense AC followed by paclitaxel
   c. FEC
   d. All of the above
   e. None of the above

7. The Genomic Health Onco*type* DX™ breast cancer assay was developed to predict the risk of recurrence in patients on adjuvant anastrozole.
   a. True
   b. False

8. In postmenopausal women with early breast cancer, three aromatase inhibitors have been evaluated in three different sequence strategies. All three strategies have demonstrated that adjuvant aromatase inhibitors improve disease-free survival.
   a. True
   b. False

9. In the NSABP-B-31 adjuvant trial comparing AC followed by paclitaxel with or without trastuzumab, the absolute difference in protocol-defined cardiac events between the two arms:
   a. Exceeded 4 percent and accrual was terminated
   b. Was less than 4 percent and accrual continued

10. In the subset of nonresponders in the pivotal trastuzumab trial, patients who received chemotherapy plus trastuzumab had a significantly longer median time to progression than those who received chemotherapy alone.
    a. True
    b. False

11. In the randomized trial of neoadjuvant paclitaxel and FEC with or without trastuzumab in women with HER2-positive disease, at this point, no cases of congestive heart failure or cardiac-related deaths have occured.
    a. True
    b. False

12. The positive association demonstrated between HER2 and VEGF supports the use of combination therapies directed against both targets, such as trastuzumab and bevacizumab, for treatment of HER2-positive breast cancer.
    a. True
    b. False

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

Evaluation Form:

Breast Cancer Update — Issue 9, 2004

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Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Gabriel N Hortobagyi, MD	5 4 3 2 1	5 4 3 2 1
Mark D Pegram, MD	5 4 3 2 1	5 4 3 2 1
Kathy D Miller, MD	5 4 3 2 1	5 4 3 2 1
Adam M Brufsky, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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Breast Cancer Update — Issue 9, 2004

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