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HOW TO USE THIS MONOGRAPH

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

Breast Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer.
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Develop and explain a management strategy for treatment of 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 aromatase inhibitors in the adjuvant setting.
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 8

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

- Evaluate clinical research data regarding the sequencing of fulvestrant in postmenopausal women with hormone receptor-positive, metastatic breast cancer and consider the clinical implications for the management of these patients.
- Provide a rationale for the selection of single chemotherapy agents and combination regimens in the metastatic setting.
- Describe the clinical trials of first-line trastuzumab in the metastatic setting and ongoing adjuvant clinical trials with trastuzumab in order to counsel appropriately selected patients about nonprotocol and clinical trial options.
- Discuss the postulated phases and mechanisms of resistance to hormonal therapies and potential strategies to overcome resistance.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

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

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As a provider accredited by the ACCME, it is the policy of Research To Practice to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Eric P Winer, MD	**Grants/Research Support:** Bristol-Myers Squibb Company, GlaxoSmithKline, Genentech Inc
Hope S Rugo, MD	**Grants/Research Support:** Genentech Inc, Roche Laboratories Inc
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Leroy M Parker, MD	**Honorarium:** AstraZeneca Pharmaceuticals LP
V Craig Jordan, PhD, DSc	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	Hoffman-LaRoche Inc
bevacizumab	Avastin®	Genentech Inc
capecitabine	Xeloda®	Hoffman-LaRoche Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
celecoxib	Celebrex®	Pfizer Inc
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
epirubicin	Ellence®	Pfizer Inc
erlotinib (OSI-774)	Tarceva™	Genentech Inc, OSI Pharmaceuticals, Hoffman-LaRoche Ltd
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
flavopiridol	Alvocidib, HMR1275	Aventis Oncology
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
irinotecan	Camptosar®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals Corporation
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pamidronate	Aredia®	Novartis Pharmaceuticals Corporation
pegfilgrastim	Neulasta®	Amgen Inc
raloxifene	Evista®	Eli Lilly & Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
toremifene citrate	Fareston®	Orion Pharma
trastuzumab	Herceptin®	Genentech Inc
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronic acid	Zometa®	Novartis Pharmaceuticals Corporation

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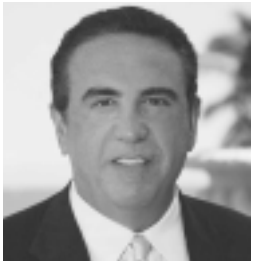


Editor's Note

Adjuvant Dilemmas

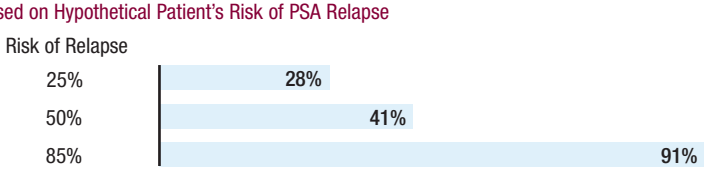
For the last two years, our education group has produced a prostate cancer audio series for urologists and radiation oncologists. We quickly appreciated a dramatic contrast in the approach to adjuvant endocrine therapy compared to breast cancer.

Reassured by the sensitivity of PSA testing to detect early recurrence, urologists rarely utilize adjuvant androgen suppression after radical prostatectomy, even in very high-risk situations. The strategy of waiting for PSA relapse has never been validated by randomized clinical trials, and older, more classic, adjuvant approaches utilizing endocrine treatment immediately after local therapy resulted in survival curves remarkably similar to what was seen with breast cancer. Prostate cancer research leaders and community-based physicians are justifiably concerned about exposing men who might be cured with surgery to therapies with substantial side effects. However, most patients are unaware that a leap of research "faith" has been taken when endocrine therapy is delayed.

In September 2002, we gathered more than 300 prostate cancer patients and their guests for a one-day town meeting. We presented a variety of clinical scenarios and asked participants to vote — using anonymous keypad polling — on what their theoretical treatment preference might be based on the information presented. This event produced remarkable findings with regard to androgen suppression. When Dr Mark Soloway, a urologic oncology research leader, presented the option of adjuvant endocrine therapy, many patients and guests believed it to be a rational and preferable choice even though Dr Soloway did not support that approach (Figure 1).

Figure 1: Immediate (adjuvant) versus delayed hormonal therapy after radical prostatectomy

A 59-year-old man with normal erectile function and an undetectable PSA after a bilateral, nerve-sparing radical prostatectomy. The patient's risk of relapse was varied for this scenario.



Compelled by the positive feedback and interesting data we received from this event, we conducted two similar "Breast Cancer Patient Perspectives Meetings" in New York and Florida this year. More than 700 breast cancer survivors and guests listened as a faculty of national research leaders presented a variety of common adjuvant case scenarios and described what they tell patients about the risks and benefits in these situations.

As with the prostate cancer meeting, the heterogeneity of perspectives was remarkable, but we discovered that most women were primarily interested in reducing the risk of recurrence regardless of treatment toxicity.

After hearing a description of the treatment schedules and toxicities for CA and CMF, more than half of the survivors indicated they would want to be treated with chemotherapy for a one percent improvement in survival. The greatest concern about CA was the potential cardiotoxicity, but alopecia was also an issue. Those preferring CA did so primarily because of the convenience in treatment scheduling compared to CMF. Patients also preferred anastrozole over tamoxifen, mainly because of concerns over endometrial cancer and thrombosis (Figure 2).

Figure 2: Breast cancer patients' perspectives about adjuvant chemotherapy and endocrine therapy*

How would you compare the acceptability of CA versus CMF?	
CA much more favorable	13%
CA slightly more favorable	19%
About the same	11%
CMF slightly more favorable	35%
CMF much more favorable	22%

Which factor influenced your choice the most?	
Cardiac effects	39%
Hair loss	11%
Treatment scheduling	28%
Nausea and vomiting	4%
Other	18%

How would you compare the acceptability of tamoxifen versus anastrozole?	
Tamoxifen much more favorable	14%
Tamoxifen slightly more favorable	12%
About the same	17%
Anastrozole slightly more favorable	39%
Anastrozole much more favorable	18%

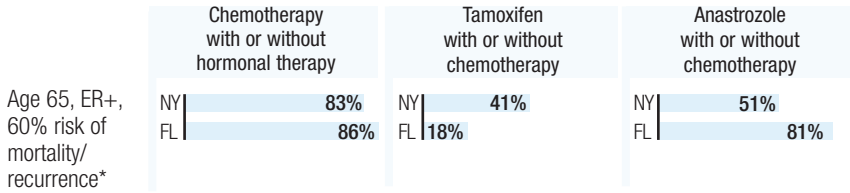
Which factor influenced your choice the most?	
Endometrial cancer/vaginal bleeding	31%
Blood clots	24%
Bone effects	5%
Joint pain	6%
Longer safety data with tamoxifen	27%
Other	7%

*Data collected at Florida meeting, 2003.

One of the most fascinating sidelights of these meetings was that in New York, the faculty presented qualitative estimates on the potential benefits of various interventions, but in Florida, the panel presented the absolute projected benefits for treatment based on Peter Ravdin's Adjuvant! computer model.

In a high-risk, node-positive situation, this dramatically changed how participants voted on endocrine therapy in a postmenopausal patient (Figure 3).

Figure 3: Breast cancer patients' preferences for adjuvant therapy in a hypothetical clinical scenario



*At New York meeting, percentages referred to 10-year risk of breast cancer mortality; in Florida, percentages referred to 10-year risk of recurrence.

Designing credible continuing education programs about adjuvant treatment is a challenge because our physician audience knows that the available data is often inconclusive. To this end, they regularly seek the perspectives of research leaders whose professional lives revolve around breast cancer. However, the patient meetings offer "food for thought" about another perspective that must enter the equation. Our simple, highly unselected CME needs assessment experiment with breast cancer survivors reinforces the importance of offering available information to women who wish to receive it.

We have concluded that absolute reductions in risk of relapse and death from breast cancer must be part of the menu of information options presented. It is not acceptable to tell an inquisitive patient that therapy will reduce her chance of relapsing by, for example, 30 percent, when this number refers to relative risk reduction. For a woman whose absolute risk of relapse is, for example, 10 percent, she must be advised that treatment will not change her outcome more than 95 percent of the time.

Similarly, we also firmly believe that one cannot simply ignore the ATAC trial data and only discuss tamoxifen as an option for adjuvant endocrine therapy in postmenopausal women. According to the Ravdin model, a postmenopausal woman with an ER-positive tumor and a 10-year relapse risk of 60 percent without treatment will have that risk lowered to 45 percent with tamoxifen but to 38 percent with anastrozole. This, of course, assumes that the 47-month ATAC data will continue its current trend, but in the face of these numbers, patient preferences were clear-cut.

Breast cancer has set an example for the rest of oncology in terms of patient advocacy and education. Prostate cancer research leaders frequently cite the breast cancer clinical research experience when they look into the future.

Our foray into patients' meetings clearly revealed that one cannot generalize or assume how a person with cancer will react to challenging decisions, such as those related to adjuvant systemic therapy. These dilemmas will always demand personalized and time-consuming consultations.

—Neil Love, MD

Eric P Winer, MD

Director, Breast Oncology Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, MA

Edited comments by Dr Winer

Treatment of patients with ER-positive metastatic breast cancer progressing on tamoxifen

In patients with hormone receptor-positive disease progressing on tamoxifen, one can switch to an aromatase inhibitor and there's a good chance the patient will respond. Three commercially available agents have been studied and are approved in this setting, so which agent to use is up to the individual oncologist.

Fulvestrant is also a good choice for these patients. In the two randomized studies comparing it to anastrozole, fulvestrant performed at least as well if not slightly better than anastrozole. Hopefully these patients would benefit from hormonal therapy for an extended period of time, and either fulvestrant followed by an aromatase inhibitor or the other way around would be reasonable alternatives.

Fulvestrant after progression on prior endocrine therapy

I'm concerned that physicians commonly give fulvestrant to patients with hormone receptor-positive metastatic disease who have received multiple chemotherapy regimens and hormonal therapies, and then judge fulvestrant to be a relatively inactive drug. This is probably not a fair evaluation.

In randomized trials of patients receiving fulvestrant or anastrozole in the metastatic setting, fulvestrant was at least as good as anastrozole, and I find the data quite persuasive. The one striking difference that favored fulvestrant was that there were fewer arthralgias and musculoskeletal complaints, and in our institution, the injection has not been a major issue.

Combined results from two multicenter trials comparing fulvestrant to anastrozole for the treatment of advanced breast cancer in postmenopausal women who progressed on prior endocrine therapy

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

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

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

Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma (ABC) in postmenopausal women

"Overall, these data demonstrate that fulvestrant, given as a 250-mg monthly i.m. injection, is at least as effective as daily oral anastrozole in the treatment of postmenopausal women with ABC who have been treated previously with endocrine therapy. With its proven efficacy and good tolerability profile, fulvestrant may provide a valuable new treatment option for postmenopausal women with ABC."

EXCERPT FROM: 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**

First-line chemotherapy following adjuvant anthracyclines

Outside of a clinical trial, a woman who has received an anthracycline as adjuvant therapy could potentially receive docetaxel, paclitaxel, capecitabine or vinorelbine as first-line therapy for metastatic disease. In my opinion, the

response rates for these agents are fairly similar. Some oncologists believe docetaxel is the most active agent, but I am not convinced that any of these agents have different activity. I tailor the treatment to the woman and base my decision on the types of side effects the woman would prefer to avoid.

Regarding toxicity, the best agents are probably capecitabine and vinorelbine. Alopecia is often an issue for women, and capecitabine is not associated with hair loss. If one is careful with the capecitabine dose, most side effects can be avoided. Over time, some women may experience chronic changes in their hands and feet, but that is the predominant toxicity encountered with capecitabine. In addition, I find when it's time for a patient to switch from hormonal therapy to chemotherapy, switching to capecitabine is not such a big step for them psychologically.

Capecitabine/docetaxel for metastatic breast cancer

I have occasionally given a patient capecitabine combined with docetaxel, and once the patient was stable, stopped the docetaxel. Fluid retention seen with higher doses of docetaxel makes it reasonable to stop the docetaxel and continue the capecitabine alone. I'm a little concerned about giving a combination for a short period of time, such as two months, and then moving on to capecitabine alone, because it's possible that giving very short courses of therapy may result in induction of resistance that may ultimately deny the patient benefits from the therapy.

The evolving role of capecitabine in breast cancer therapy

"The integration of capecitabine, either as a single agent or in combination with docetaxel, into adjuvant breast cancer therapy is justified due to its high antitumor activity in previously treated and untreated MBC [metastatic breast cancer], its tolerability, lack of cross-resistance with the anthracyclines and taxanes, and because combined docetaxel/capecitabine improves the overall survival of patients with MBC. Capecitabine is being evaluated as preoperative therapy in patients with operable breast cancer, as adjuvant therapy in patients with high-risk node-negative or node-positive disease, and as oral single-agent therapy in women ≥ 65 years of age."

EXCERPT FROM: O'Shaughnessy JA. **The evolving role of capecitabine in breast cancer.** *Clin Breast Cancer* 2003;4(Suppl 1):S20-5. **Abstract**

Trastuzumab/chemotherapy combinations

For the time being, trastuzumab should not be given with an anthracycline because of the potential cardiotoxicity. The standard of care is trastuzumab

plus paclitaxel, based on the FDA approval. Given the activity of docetaxel in women with metastatic breast cancer and the potential preclinical synergy, there are many physicians who administer trastuzumab plus docetaxel.

When we began studying trastuzumab plus vinorelbine in our first Phase II trial with about 40 women, the combination was well-tolerated and there was an overall response rate of approximately 70 percent. We then conducted a multicenter, Phase II trial of trastuzumab and vinorelbine in 55 patients and were again comforted by the safety and efficacy data.

Overall response rates in a Phase II trial of trastuzumab/vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer

	No. of patients	Response rate (%)
CR + PR	37	68%*
CR	4	7%
PR	33	61%
Stable disease for ≥ 6 months	9	17%

*95% confidence interval, 54-80%
CR = complete response; PR = partial response

EXCERPT FROM: Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.** *J Clin Oncol* 2003;21(15):2889-95. **Abstract**

Trastuzumab/vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer

"This multicenter phase II trial of combination therapy with trastuzumab and vinorelbine as first-line treatment for HER2-positive metastatic breast cancer demonstrated high rates of clinical activity achieved with limited acute toxicity. More than two thirds of patients had objective response, and nearly 40% of patients were without disease progression at 1 year. Prior adjuvant chemotherapy did not affect response rates."

EXCERPT FROM: Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.** *J Clin Oncol* 2003;21(15):2889-95. **Abstract**

Phase III trial of trastuzumab plus a taxane or vinorelbine

There is an ongoing, multicenter, Phase III study involving about 50 sites in the United States comparing the combination of vinorelbine and trastuzumab with a taxane and trastuzumab regimen in the metastatic setting. The choice

of which taxane to use, either weekly paclitaxel or weekly docetaxel, is left to the physician's discretion. Vinorelbine has not been one of the first-line agents in the treatment of patients with metastatic breast cancer, but we think that the vinorelbine and trastuzumab combination is a very promising regimen. If we want physicians to take this regimen seriously and consider incorporating it into an adjuvant program in the future, it has to be compared head-to-head with the taxanes.

Phase III Randomized Study of Trastuzumab (Herceptin) in Combination with Either Vinorelbine or Taxane-Based Chemotherapy in Patients with HER2-Overexpressing Metastatic Breast Cancer Open Protocol

Protocol IDs: GSK-2001-P-000473/2, DFCI-01087
Projected Accrual: 250

Eligibility: Stage IV, HER2-overexpressing breast cancer

ARM 1: Trastuzumab qw + vinorelbine qw
ARM 2: Trastuzumab qw + (paclitaxel qw or docetaxel on weeks 1, 2, 3, 5, 6, 7)*

*Choice of taxane is at physician's discretion
Courses in both arms repeat every 8 weeks in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, September 2003.

Trastuzumab for patients with ER-positive, HER2-positive metastatic disease

I still strongly consider hormonal therapy in these women, however, there is suggestive evidence that patients with HER2-positive disease may be less likely to respond to hormonal therapy. For that reason, if I were on the fence about using hormonal therapy or moving on to chemotherapy, I would switch to chemotherapy more readily in patients with HER2-overexpressing disease.

When it is time to switch to chemotherapy in patients with HER2-positive disease, most of us believe trastuzumab is the standard of care. The question is whether to use trastuzumab plus chemotherapy or trastuzumab alone. I think in the United States, and certainly in my own practice, trastuzumab plus chemotherapy is more commonly given. The survival benefit with trastuzumab in the pivotal trial was seen when the combination of chemotherapy and trastuzumab was given up front. Also, there's a sense that response rates, and therefore control of tumor-related symptoms, are higher when chemotherapy is added to trastuzumab.

I don't believe there are many right and wrong choices in the treatment of metastatic breast cancer, but at this time, a woman who has metastatic,

HER2-positive, ER-negative disease, who has never received chemotherapy, should receive a regimen that includes trastuzumab. I am impressed by the survival benefit seen with trastuzumab in Dennis Slamon's study. If anything, that survival benefit was minimized by the crossover in the group of women who didn't receive trastuzumab initially and by the fact that the HER2 assay was an imperfect assay.

Trastuzumab has actually changed the natural history of HER2-positive, metastatic breast cancer. We have women living far longer than they used to, and the unfortunate manifestation is that we are seeing an increasing number of patients with central nervous system metastases.

Nonprotocol adjuvant trastuzumab

I try not to use trastuzumab in patients with Stage II and IIIA breast cancer outside of a trial, because it's not an established therapy. In patients with inflammatory breast cancer, I don't know that we're ever going to have a randomized study, and at least 50 percent of the time the tumor is HER2-positive. I would be hard-pressed to criticize a physician who wanted to use a trastuzumab-based regimen in a patient with HER2-positive, inflammatory breast cancer.

I feel patients who are eligible for the randomized adjuvant trials should be encouraged to participate. Outside of those trials, I think that the standard adjuvant treatment is a non-trastuzumab-containing combination.

Importance of accurate HER2 testing

Whenever we have a new therapy requiring a predictive test, how that therapy performs is dependent on how good the test is at identifying the appropriate target. Both the NSABP adjuvant trial and the Intergroup trial indicated that HER2 testing in centers around the country — both community centers and academic centers — appeared to be less than perfect. Approximately 25 percent of the time, the test that was done in the local hospital — nonacademic institutions and academic institutions alike — couldn't be confirmed at a central testing site.

We need to be careful about where the HER2 testing is performed and view results from less-experienced labs with caution. This is especially important in the adjuvant setting where, unlike the metastatic setting, we have no way of knowing if the treatment is working, and we're committing the patient to a course of therapy.

Also, when we are banking on results from clinical trials, it is critical that we know the testing is accurate. Currently there's no established adjuvant role for trastuzumab, but I suspect in the next three to five years we'll learn whether it's an effective adjuvant therapy. Then accurate testing will be important to correctly identify the patients who will receive the maximum benefit from therapy.

When HER2 retesting is indicated

In metastatic disease when the initial HER2 test results and the clinical situation are inconsistent, one should consider retesting the patient. I've had a number of patients whose tumors were IHC zero, but their clinical presentation was consistent with HER2 amplification, so I retested. In each one of those cases there was not a discrepancy, but still I think it's worth doing. Even if I find a discrepancy only two out of 100 times, I'm doing those two patients a huge service.

Changes in HER2 status following exposure to trastuzumab

We recently published a study of 40 patients with Stage II and III breast cancer who had HER2-overexpressing (IHC 2+ or 3+) disease and were treated preoperatively with a combination of trastuzumab and paclitaxel. Of the patients who had residual tumor and could be assessed postoperatively, approximately 20-25 percent had a change in the IHC status. While the numbers are extraordinarily small, it looks like the change in IHC status might be a little more common in patients who were initially 2+ rather than 3+; the IHC typically changed from 2 or 3+ to 0 or 1+.

We don't know exactly what is going on in these cases — perhaps it's just variability in testing or perhaps it's an effect of trastuzumab. We don't have FISH data on these patients yet, and it's possible some of these patients have FISH-negative tumors. Also, in our current study we have one patient in whom IHC and FISH testing has revealed a HER2-negative and a HER2-positive tumor side-by-side. Although most of us think of HER2 as more homogeneous than heterogeneous, it is possible that some patients have both types of tumor.

HER2 status following preoperative combination of trastuzumab and paclitaxel

HER2 status after preoperative therapy	Baseline HER2 status			
	3+ (n=32)		2+ (n=8)	
	No. of patients	%	No. of patients	%
3+	17	53	1	13
2+	2	6	0	0
1+ or 0	4	13	3	37
Not assessable	3	9	3	37
Pathologic complete response	6	19	1	13

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

HER2 status following preoperative combination of trastuzumab and paclitaxel

"For most patients with residual tumor after 12 weeks of neoadjuvant treatment, HER2 expression as measured by immunohistochemistry was unchanged. However, a subset of patients whose initial tumors were 3+ were found, on testing after induction therapy, to have lost immunohistochemical expression of HER2. The clinical significance of this finding is not known. It may represent downregulation of HER2 expression following anti-HER2 antibody exposure, as reported in preclinical tumor models. It may also represent intrinsic heterogeneity of HER2 expression and tumor response, or an artifact of tumor sampling or testing. It is not clear whether this finding implies resistance or sensitivity to trastuzumab."

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

Select publications

Publications discussed by Dr Winer

Burstein HJ et al. **Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2001;19(10):2722-30. **Abstract**

Burstein HJ et al. **Multicenter Phase II study of trastuzumab (herceptin; H) and vinorelbine (navelbine; N) as first-line therapy for HER2 overexpressing metastatic breast cancer (HER2+ MBC).** *Proc ASCO* 2002;**Abstract 211.**

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

Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.** *J Clin Oncol* 2003;21(15):2889-95. **Abstract**

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

Mauriac L et al. **Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: Combined results from two multicentre trials.** *Eur J Cancer* 2003;39(9):1228-33. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. **Abstract**

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**

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**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** J Clin Oncol 2002;20(3):719-26. **Abstract**

Endocrine therapy in the metastatic setting

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Carlson RW. **Sequencing of endocrine therapies in breast cancer—Integration of recent data.** *Breast Cancer Res Treat* 2002;75(Suppl 1):S27-32; discussion S33-5. **Abstract**

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Parker L, Webster A. **Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex').** *Proc ASCO* 2002;**Abstract 160.**

Perey L et al. **Fulvestrant ('faslodex') as hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and aromatase inhibitors.** *Breast Cancer Res Treat* 2002;**Abstract 249.**

Piccart M et al. **Oestrogen receptor downregulation: An opportunity for extending the window of endocrine therapy in advanced breast cancer.** *Ann Oncol* 2003;14(7):1017-25. **Abstract**

Rose C. **A comparison of the efficacy of aromatase inhibitors in second-line treatment of metastatic breast cancer**. *Am J Clin Oncol* 2003;26(4 Suppl):S9-S16. **Abstract**

Steger GG et al. **Fulvestrant beyond the second hormonal treatment line in metastatic breast cancer.** *Proc ASCO* 2003;**Abstract 78.**

Thuerlimann B et al. **Anastrozole ('arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: Results of the double-blind crossover SAKK Trial 21/95 – a sub-study of Anastrozole Trial 0027.** *Breast Cancer Res Treat* 2002;**Abstract 255.**

Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79(2):207-11. **Abstract**

Hope S Rugo, MD

Associate Clinical Professor of Medicine
Carol Franc Buck Breast Care Center
Co-Director, Breast Oncology Clinical Trials Program
University of California at San Francisco
Comprehensive Cancer Center
San Francisco, CA

Edited comments by Dr Rugo

Gene expression profiling and treatment outcome

Dr Lajos Pusztai's data from MD Anderson indicate that in the future we will be able to look at the genetic makeup of patients with breast cancer and have a better idea of their treatment outcome. Data already indicated that prognosis could be predicted from a gene array.

Dr Pusztai found that women who had a complete pathologic response to neoadjuvant chemotherapy — women who might have a better prognosis — were most likely to have a specific gene array. About 75 percent of the women with the specific gene array had a pathologic complete response. In contrast, only 20 percent of the women who did not fit into that particular pattern of gene expression had a pathologic complete response.

Resistance to systemic therapy

At UCSF, an NCI-funded study will look at tumor tissue obtained from women treated with trastuzumab alone, examining the genetic makeup of these tumors to try to understand what creates trastuzumab resistance. In women with HER2-positive breast cancer, resistance may include other pathways being activated.

Research in animal models and *in vitro* testing suggests that the effect of epidermal growth factor receptor (EGFR) upregulation on hormone resistance is important. Some patients have primary endocrine resistance because of upregulation of EGFR.

There are studies combining hormonal agents with agents that block EGFR. A study of fulvestrant and gefitinib — a very exciting combination — will look at the reversal of hormone resistance. It would also be interesting to look at blocking the production of estrogen in that setting with an aromatase inhibitor.

Fulvestrant in women with metastatic breast cancer

I tend to use fulvestrant as second- or third-line therapy. Because most of our patients have oral medications covered by insurance, coming in once a month for an injection is a bigger issue. I've also been interested in the pharmacokinetics of fulvestrant. The trial evaluating it in combination with gefitinib will administer fulvestrant every two weeks for the first few doses, because the pharmacokinetics indicate that it may take up to three months for fulvestrant to reach steady state serum concentrations. We've already seen that fulvestrant is effective, but it's not better than the aromatase inhibitors. It may just be a pharmacokinetic issue; by dosing fulvestrant more frequently, we may see improved efficacy in this trial.

Fulvestrant's tolerability

When using second- and third-line agents, we often don't see many side effects. Since these patients have advanced disease, they are more worried about response. I have seen very few side effects, other than hot flashes, with fulvestrant.

We usually use two 2.5-cc injections of fulvestrant, because many nurses in the United States are not comfortable giving the whole 5-cc injection.

2003 Survey of US Oncologists

Use and Tolerability of Fulvestrant

Have you used fulvestrant?

Yes	90%
No	10%

What percentage of your patients receiving fulvestrant reported difficulty tolerating the injection?

Mean	3%

83% of physicians stated that none of their patients receiving fulvestrant reported difficulty tolerating the injection.

What percentage of your patients receiving fulvestrant reported significant side effects?

Mean	3%

78% of physicians stated that none of their patients receiving fulvestrant reported significant side effects.

Algorithm for HER2 testing

At our institution, we perform HER2 testing by immunohistochemistry (IHC). If the patient's tumor scores 2+ on IHC, we perform a FISH test. For quality assurance purposes, some tumors scoring 1+ or 3+ are also tested by FISH, but we do not do this routinely. In our patients with tumors that score 2+, about 20 to 30 percent are truly HER2-positive. This is consistent with the results from the trastuzumab pivotal trial.

Percent of patients with HER-2 gene amplification according to Immunohistochemistry Score (IHC)

Author	IHC Antibody	N	0	1+	2+	3+
Mass	CTA	529	4.2%	6.7%	23.9%	89.3%
Mass	CTA	451	—	—	31.0%	89.0%
Schaller	A0485	142	0	0	25.0%	100.0%
Lebeau	A0485	79	—	—	25.0%	100.0%
	CB11		—	—	81.8%	100.0%
	TAB250		—	—	66.7%	100.0%
Buehler	A0485	142	0	0	30.5%	100.0%
Tubbs	A0485	145	—	—	12.5%	75.0%
	CB11		—	—	23.5%	85.0%
Hoang	A0485	100	0	0	16.7%	88.9%
	e2-4001		1.6%		5.9%	75.0%
Ridolfi	A0485	117	1.8%		35.9%	100.0%
Seidman	A0485	78	9.1%		82.2%	
	CB11		14.3%		94.4%	
Persons	A0485	100	1.3%		68.2%	

CTA = clinical trial assay (4D5 and CB11 antibodies)

Treatment of women with ER-positive, HER2-positive metastatic disease

If a postmenopausal woman with ER-positive, HER2-positive metastatic disease presents with a minimal tumor burden, I will treat her with an aromatase inhibitor initially and wait to use trastuzumab. I usually start with a nonsteroidal aromatase inhibitor — letrozole or anastrozole — and then move on to exemestane or fulvestrant in patients whose disease progresses.

In patients who need chemotherapy, we use a combination of chemotherapy and trastuzumab, because the pivotal trial data demonstrated an improvement in survival for the combination. When the patients are ready to discontinue chemotherapy, we use the next sequential hormonal agent as maintenance therapy in conjunction with trastuzumab. Studies are currently evaluating the effectiveness of trastuzumab in combination with the aromatase inhibitors, and the results will be very interesting.

Clinical trials combining trastuzumab plus hormonal therapy for patients with ER/PR-positive, HER2-positive, metastatic and locally advanced breast cancer

Chair	Trial setting	Menopausal status	Projected accrual	Treatment arms
J Mortimer	Phase III	pre/post	280	— trastuzumab + tamoxifen — trastuzumab
B Langer	Phase II/III	post	202	— trastuzumab + anastrozole — anastrozole
R O'Regan	Phase II	post	18-60	— trastuzumab + exemestane

SOURCES: NIH Clinical Trials Website, October 2003. NCI Physician Data Query, October 2003.

Trastuzumab monotherapy in patients with HER2-overexpressing metastatic breast cancer

If patients have fairly low-bulk disease — bone and soft-tissue — and are minimally symptomatic, we will try trastuzumab as a single agent. Trastuzumab monotherapy is a good transition therapy for patients who have just learned that they have metastatic disease.

I start with weekly trastuzumab because I want the serum concentrations to rise quickly. Thereafter, as long as they're doing fine, I switch to every-three-week trastuzumab. We have several women who have been on trastuzumab for more than two years as their only treatment for metastatic disease; this is really remarkable. We encouraged another woman, who initially received a taxane with trastuzumab, to subsequently be treated with trastuzumab alone, because she primarily had bone disease. She received chemotherapy because she was 32 years old. She's been on trastuzumab alone for three years, and in these patients, trastuzumab monotherapy is very reasonable.

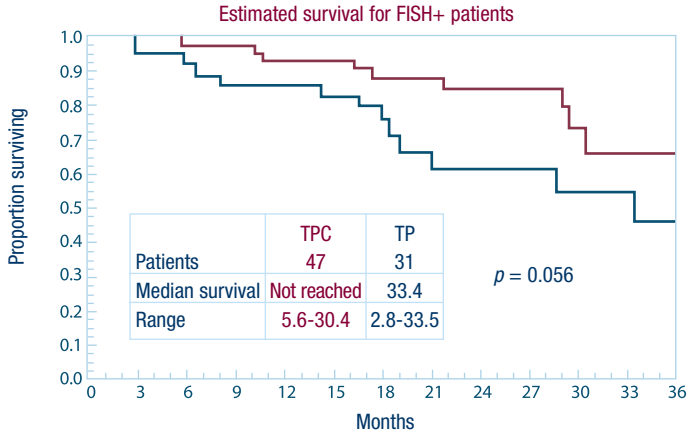
I recently treated a patient with lung nodules who had a lot of disease after neoadjuvant AC and paclitaxel. I wasn't very enthusiastic about starting chemotherapy too early because I believed she had relatively resistant disease. I started her on trastuzumab alone, which has controlled her disease for about eight months. She's now moving on to chemotherapy.

Trastuzumab in combination with chemotherapy

I use chemotherapy up-front in patients with life-threatening or very bulky HER2-positive disease. In these patients, chemotherapy selection depends on their adjuvant treatment. Traditionally, we'll start with a taxane and trastuzumab. For patients in visceral crisis or with bulky disease, I've been adding weekly carboplatin. Although Nick Robert's randomized trial evaluated an every-three-week schedule, we see a fair amount of thrombocytopenia with that treatment schedule, so we've been using weekly carboplatin, paclitaxel or docetaxel, and trastuzumab. Once the patients have a good response, we discontinue the chemotherapy and continue with every-three-week trastuzumab alone.

I also use capecitabine with trastuzumab, and it's been very effective. Patients with HER2-overexpressing disease are often very receptive to capecitabine. So it's important to use that drug as part of the treatment approach for these patients.

Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER2/neu-positive advanced breast cancer



TPC (% Survival)	93	85	65
TP (% Survival)	87	61	45

TPC = trastuzumab/paclitaxel/carboplatin; TP = trastuzumab/paclitaxel

ADAPTED FROM: Nicholas Robert, Presentation, San Antonio Breast Cancer Symposium, 2002.

UCSF Cancer Center Trial: Phase II Trial of Weekly Docetaxel Plus Capecitabine and Trastuzumab for Patients with HER2-Expressing Stage IV Breast Cancer

Eligibility: Patients with HER2-positive metastatic breast cancer

Treatment: docetaxel + capecitabine + trastuzumab

Study Contact:
UCSF Cancer Center
Hope Rugo, MD, Investigator; Telephone: 415-353-7213

SOURCE: UCSF Cancer Center Website. Available at http://cc.ucsf.edu/trials/007516.html Accessed on September 23, 2003.

Management of patients who progress on trastuzumab and chemotherapy

There are a whole host of drugs to try in women progressing on trastuzumab and chemotherapy. We certainly use vinorelbine and gemcitabine with trastuzumab. I've given one patient, who had particularly resistant disease,

the combination of gemcitabine and a taxane with trastuzumab. We're more comfortable using carboplatin early in the course of therapy. For patients who haven't been treated previously with an anthracycline, I'll stop the trastuzumab and use either weekly epirubicin or liposomal doxorubicin.

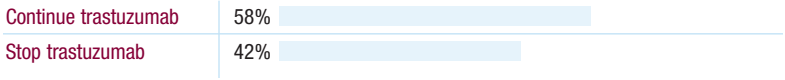
My colleagues in the community frequently ask whether to continue the trastuzumab as these patients progress, and we don't know the answer. The study presented by Debu Tripathy several years ago in San Antonio, of patients who continued trastuzumab, really didn't provide us with any definitive information. Interestingly, Dr Pusztai tried to conduct a multicenter trial in patients who progressed on a taxane and trastuzumab regimen. The trial design was to randomize patients to vinorelbine or vinorelbine with trastuzumab, but he couldn't enroll patients because they didn't want to discontinue trastuzumab.

Some patients may still benefit from trastuzumab beyond progression. There have been some anecdotal reports of radiation sensitivity and slowing of disease with trastuzumab, so that when trastuzumab is discontinued, the disease seems to grow faster. Although this is all anecdotal, it makes patients reticent to stop trastuzumab.

2003 Survey of US Oncologists

Continuation of Trastuzumab upon Disease Progression

57-year-old woman, treated two years ago with AC-paclitaxel for ER-negative, HER2-positive (by FISH) IDC. The patient then is diagnosed with asymptomatic bone metastases and rising tumor markers and is treated with trastuzumab (with or without chemotherapy). Upon disease progression, would you continue or stop the trastuzumab?



Central nervous system metastases

Brain metastases are a big issue in the control of breast cancer, and we really need drugs that can cross the blood-brain barrier. Novel taxanes are being studied, a variety of which cross the blood-brain barrier. Those are very exciting, because they can be used in the adjuvant setting as prophylaxis.

Other drugs get into the cerebral spinal fluid (CSF), such as capecitabine. One of the problems with capecitabine is that we don't know how much of it goes into the CSF because it's a prodrug. The other drug I've been interested in is irinotecan. It's been tested in combination with capecitabine for primary brain tumors, and it clearly goes into the CSF.

Sequential single-agent versus combination chemotherapy

Combination chemotherapy is important for patients in visceral crisis who need a rapid response. Combination chemotherapy improves response, and it is generally more toxic. It does not improve quality of life sufficiently to make up for the fact that it doesn't prolong survival. The capecitabine/docetaxel study published by Joyce O'Shaughnessy is the only study that has demonstrated some prolongation in survival. That trial was problematic because of the absence of sequential therapy in the women randomized to the docetaxel-alone arm. It may be that the survival benefit wouldn't have occurred if the patients on the docetaxel-alone arm had capecitabine available.

Phase III trials comparing single-agent and combination chemotherapy for metastatic breast cancer

	XT Trial: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	Docetaxel	Capecitabine/ docetaxel	Doxorubicin	Paclitaxel	Doxorubicin/ paclitaxel
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months	18.9 months	22.2 months	22.0 months

DERIVED FROM: 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**

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92. **Abstract**

Benefit of combination therapy in patients with significant tumor burden

"The early separation of the survival curves suggests that the combination therapy prevented early deaths in a subset of patients, the majority of whom had heavily pretreated disease and significant tumor burden in this trial. ...

"In addition, it should be taken into account that after failure of study chemotherapy in the current trial, only 60% to 70% of patients received further cytotoxic therapy. Therefore, 30% to 40% of patients did not have the opportunity to benefit from subsequent chemotherapy administered sequentially."

EXCERPT FROM: 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**

Select publications

Publications discussed by Dr Rugo

Mass RD et al. **The concordance between the clinical trials assay (CTA) and fluorescence in situ hybridization (FISH) in the Herceptin pivotal trials.** *Proc ASCO* 2000;**Abstract 291.**

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;**Abstract 36.**

O'Shaughnessy 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**

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

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 35.**

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**

Winer E et al. **Phase II multicenter study to evaluate the efficacy and safety of Tarceva™ (erlotinib, OSI-774) in women with previously treated locally advanced or metastatic breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 445.**

Trastuzumab

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

Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.** *J Clin Oncol* 2003;21(15):2889-95. **Abstract**

Christodoulou C et al. **Prolonged administration of weekly paclitaxel and trastuzumab in patients with advanced breast cancer.** *Anticancer Res* 2003;23(1B):737-44. **Abstract**

Esteva FJ et al. **Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(7):1800-8. **Abstract**

Jahanzeb M et al. **Phase II trial of weekly vinorelbine and trastuzumab as first-line therapy in patients with HER2(+) metastatic breast cancer.** *Oncologist* 2002;7(5):410-7. **Abstract**

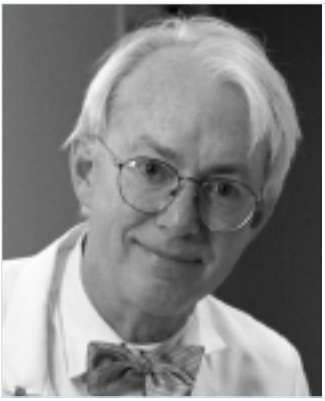
Montemurro F et al. **Safety and activity of docetaxel and trastuzumab in HER2 overexpressing metastatic breast cancer: A pilot Phase II study.** *Am J Clin Oncol* 2003;26(1):95-7. **Abstract**

O'Shaughnessy J. **Gemcitabine and trastuzumab in metastatic breast cancer.** *Semin Oncol* 2003;30(2 Suppl 3):22-6. **Abstract**

O'Shaughnessy J et al. **Phase II trial of gemcitabine plus trastuzumab in metastatic breast cancer patients previously treated with chemotherapy: Preliminary results.** *Clin Breast Cancer* 2002; Suppl 1:17-20. **Abstract**

Osoba D et al. **Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer.** *J Clin Oncol* 2002;20(14):3106-13. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**



Leroy M Parker, MD

Associate Professor of Medicine
Gillette Women's Cancer Program
Dana-Farber Cancer Institute
Harvard Medical School
Boston, MA

Edited comments by Dr Parker

Case discussion: 79-year-old woman with ER-positive metastatic disease following adjuvant tamoxifen

History

This patient was initially diagnosed in her late sixties with a 3-centimeter Stage II breast cancer. She was treated with breast conservation surgery and participated in NSABP-B-18, comparing preoperative versus postoperative doxorubicin/cyclophosphamide. She received AC postoperatively and tolerated it without any major difficulties. She received five years of adjuvant tamoxifen, which she also tolerated without complaints.

Following tamoxifen the patient was disease-free for three years. She was not under the care of an oncologist, but rather a primary care physician who didn't recognize that her increasing "arthritic" symptoms were actually the slow onset of bony metastases. This went on for a year and finally the appropriate studies were performed, including a bone scan, which revealed disease throughout her skeleton, but not in any visceral organ.

She was a vigorous and independent individual at the time I treated her adjuvantly and when she presented with progressive disease. When she returned to me with metastatic disease, her independence was threatened, and she was disappointed that the recurrence had not been detected earlier. Like many patients, she thought that after five years of being disease-free, there was no need to worry about breast cancer.

Follow-up

We discussed the possibility of enrolling her in a clinical trial comparing fulvestrant and anastrozole, but we needed to demonstrate whether her disease was sensitive or refractory to tamoxifen, so she was placed on tamoxifen and had objective progression in three months.

At that point, she entered the study and was randomized to what we later learned was fulvestrant. She began feeling better within about three months, her tumor markers — CEA and CA-27.29 — decreased from in the hundreds to the normal range; she had radiographic evidence of bone healing, and she no longer required pain medication.

She maintained this excellent response for three-and-a-half years, and then her tumor markers began to rise and she experienced increased discomfort. We unblinded the study and offered her the alternate drug, anastrozole. She once again responded to treatment, which lasted about 18 months.

This time when she progressed I chose to start her on chemotherapy rather than another hormonal agent because of the degree of her pain, and my interest in bringing the disease under control without resorting to radiation therapy. She received a series of single-agent chemotherapy regimens, including vinorelbine, which she tolerated very poorly. She experienced GI intolerance, which occurs in about 15 percent of my patients.

Discussion

This patient had a very dramatic response to fulvestrant that lasted nearly four years. I had the pleasure of participating in the double-blind, double-dummy trial in the United States comparing fulvestrant and anastrozole in patients with tamoxifen-resistant disease.

The results of the European and North American studies demonstrated that fulvestrant and anastrozole are equivalent in a controlled clinical trial, but there is a suggestion that duration of response may be somewhat longer in patients on fulvestrant. This is a tantalizing piece of data that needs to be looked at further.

It's great to have fulvestrant as another option for patients who progress following adjuvant tamoxifen, as well as for patients with whom compliance or availability of drugs is an issue. Also, in patients receiving drugs such as pamidronate or zoledronate for bone metastases, the fulvestrant injection can be administered when they are in for treatment, and we know they're receiving adequate care.

In terms of tolerability of the injections, I have observed absolutely no problems with them and have received almost no complaints from patients who are receiving the medication. Hot flashes can be difficult to control in many women who have had prior hormone replacement therapy, and I find they're equivalent whether the patient is taking anastrozole or fulvestrant in the metastatic setting. One of fulvestrant's most important qualities is that it does not have any agonist activity, so it doesn't adversely affect the endometrium.

Fulvestrant: A once-monthly, injectable estrogen receptor downregulator

"Although fulvestrant is the first commercially available injectable HT [hormonal therapy], complications such as injection-site pain or reactions were mild to moderate and led to treatment withdrawals in only 0.5% of patients. The rates of overall withdrawals due to a drug-related adverse event were 0.9% for fulvestrant and 1.2% for anastrozole. No evidence of endometrial tissue changes has been reported with fulvestrant or anastrozole. Fulvestrant has been shown to be at least as effective as anastrozole in postmenopausal women with advanced breast cancer, which is noteworthy because most patients had prior tamoxifen treatment."

EXCERPT FROM: Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24(Suppl C):c43-57. **Abstract**

Sequencing fulvestrant in women with hormone-responsive disease

A number of studies demonstrate that patients who have benefited from fulvestrant at the time of progression can respond to any number of other hormonal agents. Conversely, patients who have not benefited from it can also respond to other hormonal agents. In addition, we have some evidence that fulvestrant is an effective drug after progression on an aromatase inhibitor.

Studies of fulvestrant in patients with ER/PR-positive, metastatic breast cancer who have relapsed on prior antiestrogen therapy

	Steger et al Failure after two endocrine therapies* (n = 40) Patients (%)	Watanabe et al Failure after tamoxifen or toremifene** (n = 30) Patients (%)
Partial response	3 (7%)	7 (23%)
Stable disease ≥ 6 months	17 (43%)	11 (37%)
Clinical benefit rate	50%	60%

*Disease relapse followed at least two (adjuvant and/or palliative) hormone therapy modalities (tamoxifen, anastrozole and/or exemestane). Fulvestrant was second-line palliative treatment in 17 patients, third-line in 20 patients and fourth-line in 11 patients.

**Disease relapse after initial response (adjuvant or palliative) to antiestrogen therapy (tamoxifen or toremifene).

SOURCES: Steger GG et al. **Fulvestrant beyond the second hormonal treatment line in metastatic breast cancer.** *Proc ASCO* 2003;**Abstract 78.**

Watanabe T et al. **Fulvestrant provides clinical benefit to postmenopausal women with metastatic breast cancer who have relapsed on prior antiestrogen therapy: A Japanese study.** *Proc ASCO* 2003;**Abstract 274.**

Fulvestrant in the treatment of women with hormone-responsive disease

"The mechanism of action of fulvestrant is different from that of both tamoxifen and AIs, reducing the risk of cross-resistance, which should allow this drug to have an important role in the hormonal treatment of breast cancer. For patients who have progressed on tamoxifen, fulvestrant produces good response rates; moreover, in tamoxifen-resistant patients, fulvestrant is as effective as anastrozole. A retrospective analysis showed that women with advanced breast cancer progressing on fulvestrant remained sensitive to subsequent treatment with anastrozole and letrozole."

EXCERPT FROM: Piccart M et al. **Oestrogen receptor downregulation: An opportunity for extending the window of endocrine therapy in advanced breast cancer.** *Ann Oncol* 2003;14(7):1017-25. **Abstract**

Trials 20/21: Retrospective analysis of response to subsequent endocrine therapy in patients with progression on fulvestrant

	Patients who derived clinical benefit from fulvestrant (n=54)	Patients who did not derive clinical benefit from fulvestrant (n=51)
Partial response	4 (7%)	1 (2%)
Stable disease ≥ 24 weeks	21 (39%)	17 (33%)
Disease progression	29 (54%)	33 (65%)

DERIVED FROM: Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79:207-11. **Abstract**

Extending endocrine regimens with fulvestrant

"Following progression on tamoxifen, fulvestrant provides an effective treatment option in addition to the currently available endocrine therapies for advanced breast cancer. Progression following treatment with an SERM, and subsequent treatment with an anti-estrogen with pure antagonistic properties, does not appear to lead to complete cross-resistance with aromatase inhibitors."

EXCERPT FROM: Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79:207-11. **Abstract**

First-line trial of fulvestrant versus tamoxifen

Data have been presented demonstrating that fulvestrant is active in the first-line setting, but in the first-line study comparing it to tamoxifen, it did not prove to be more active. The primary endpoint was time to treatment failure, and tamoxifen was superior, although not statistically. One question that has been raised in this setting is whether the fulvestrant dose was adequate.

A number of investigators feel that some of the early failures seen in the comparison of fulvestrant and tamoxifen might indicate that patients were not brought up to their steady-state level, and that a loading dose of fulvestrant may be necessary.

This is currently being studied in a clinical trial that gives patients a loading dose in the first month of therapy. I would not recommend the concept of a loading dose in a nonprotocol setting at this time. We already know that when fulvestrant was compared to anastrozole as treatment for progression after tamoxifen, the current dose was adequate.

Fulvestrant in the adjuvant setting

I'm sure fulvestrant will be studied in the adjuvant setting at some point. There are a number of investigators who are quite interested in combining an aromatase inhibitor with fulvestrant to fully deplete estrogen. Despite the results of combined hormonal therapy in the ATAC trial, I'm convinced that there is a biologic basis for investigating an aromatase inhibitor and fulvestrant combination. It remains to be seen whether it's going to play out in a positive way in the metastatic setting.

CALGB-9741: Dose-dense chemotherapy

I participated in the CALGB-9741 trial and was very impressed by the results and the ease with which patients can be treated with dose-dense chemotherapy. I utilize the dose-dense approach in the nonprotocol setting, specifically the combination rather than the sequential regimen. I've been using filgrastim, but we are about to perform a study with pegfilgrastim to evaluate its safety and efficacy in a larger number of patients.

Three-year results of CALGB-9741, a Phase III randomized study comparing dose-dense versus conventional scheduling and sequential versus combination adjuvant chemotherapy for node-positive breast cancer

Parameters	Dose-dense scheduling	Conventional scheduling	*p* value
Disease-free survival	85%	81%	RR = 0.74 ($p = 0.010$)
Overall survival	92%	90%	RR = 0.69 ($p = 0.013$)

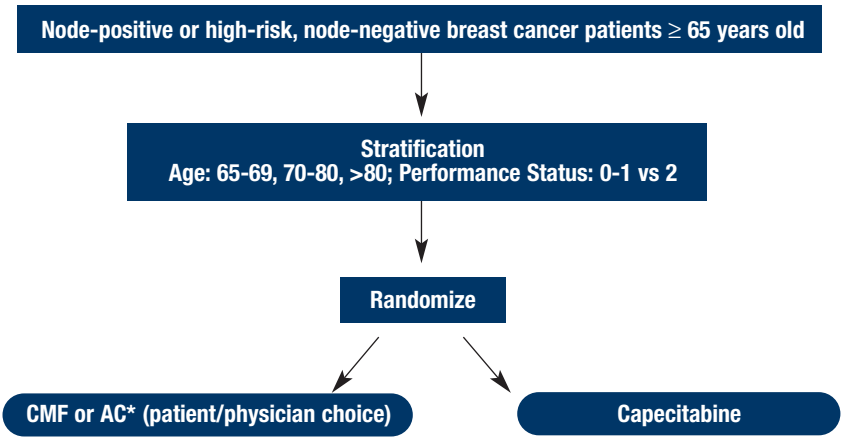
DERIVED FROM: Citron M et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-39. **Abstract**

Adjuvant chemotherapy in the elderly patient

I find that if an elderly patient's performance status is good when they begin treatment, they'll do just as well as younger patients in tolerating adjuvant chemotherapy. On the other hand, if they have significant comorbidities, I am more hesitant to embark on chemotherapy, particularly in patients with estrogen receptor-positive disease. I participate in the CALGB trial randomizing elderly patients to capecitabine versus CA or CMF.

Having used capecitabine in the metastatic setting, I can attest to the fact that it's a highly effective drug, and I believe it will have an impact on early breast cancer. Patients need to be a partner when using this drug, because they have to recognize when they're beginning to experience toxicities so that we can tailor the dose accordingly.

CALGB-49907: A randomized trial of adjuvant chemotherapy with standard regimens (CMF or AC) versus capecitabine in women 65 years and older with node-positive or high-risk, node-negative breast cancer



* Patients whose LVEF is not within lower limits of normal must receive CMF, not AC.
All ER+ or PR+ patients receive tamoxifen x 5 years.

SOURCE: CALGB 49907 Protocol.

Trastuzumab in combination with carboplatin and paclitaxel

In a patient with HER2-overexpressing, ER-negative breast cancer who is not eligible for a study, the data on the combination of carboplatin, paclitaxel and trastuzumab is very important. In these situations, the question always comes up as to whether the extra toxicity from a combination will be worth it and whether the sequential use of the drugs is just as good.

This hasn't been answered by the current trials. In a number of patients with ascites and other manifestations of breast cancer that mimic ovarian cancer, I have felt comfortable using the carboplatin/paclitaxel/trastuzumab combination. Generally, I give the paclitaxel on a weekly basis.

Trastuzumab/vinorelbine combination

At our institution, we've had tremendous experience with the combination of vinorelbine and trastuzumab and found it very useful. We are participating in a clinical trial comparing trastuzumab with either vinorelbine or a taxane, and I believe we'll find similar response rates but different side effects.

I don't know whether quality of life will be superior with any one combination, but my clinical impression is that trastuzumab/vinorelbine is extremely well-tolerated by the vast majority of patients. I believe at acceptable paclitaxel doses, trastuzumab with paclitaxel is also well-tolerated in most patients; I have observed more problems with weekly docetaxel and trastuzumab.

Management of HER2-overexpressing, ER-positive metastatic breast cancer

It's very clear to me that patients with HER2-overexpressing, ER-positive disease benefit from combining chemotherapy and trastuzumab. My first-line approach is to participate in a clinical trial, if possible, and the trial currently open at our institution is a Phase I/II study of trastuzumab plus flavopiridol, a cyclin inhibitor. At this point we don't have the data to say that we've made a lot of headway, but it's a very interesting concept.

Flavopiridol is not yet clinically available, and it's the first cyclin inhibitor to be studied in clinical trials. Some information is available on cyclin overexpression and prognosis in breast cancer. There's clear involvement of these factors in the biology of cancer, and this is our first attempt to block them. Most of the data on flavopiridol is derived from treatment of lung cancer.

Continuing trastuzumab in the metastatic setting beyond disease progression

Often I continue patients on trastuzumab beyond disease progression and switch the chemotherapy agent. I've had patients taking trastuzumab for three or four years, while switching the chemotherapy agents.

When a patient plateaus after an initial response to chemotherapy, I generally use trastuzumab alone. I continue the trastuzumab indefinitely or until progression, often using an every-three-week schedule.

Phase I Study of Trastuzumab (Herceptin) and Flavopiridol in Patients with HER2-Positive Metastatic Breast Cancer **Open Protocol**

Protocol IDs: DFCI-01177, NCI-5867
Projected Accrual: 30-50

Eligibility: Stage IV, HER2-positive breast cancer

Treatment: Trastuzumab days 1, 8 and 15 + flavopiridol days 1 and 8

Course repeats every 21 days in the absence of disease progression or unacceptable toxicity.

Cohorts of 3-6 patients receive escalating doses of flavopiridol until the maximum tolerated dose is determined (MTD). Then an additional cohort of 10 patients receives flavopiridol at the MTD and trastuzumab on the once weekly schedule and a second cohort of 10 patients receives flavopiridol at the MTD and trastuzumab once every 21 days.

Study Contact:
Lyndsay Harris, Chair, Tel: 617-632-6363
Dana-Farber Cancer Institute

SOURCE: NCI Physician Data Query, September 2003.

Combination trastuzumab/flavopiridol in the treatment of breast cancer

"ErbB2 and cyclin D1 are interacting oncogenes that are particularly important in breast cancer. We demonstrated previously synergy between two drugs that separately address each oncogene, trastuzumab and flavopiridol. ... Although both drugs are thought to alter cell cycle progression, the combination of trastuzumab and flavopiridol had little effect on G_1 progression or retinoblastoma protein phosphorylation. Instead, trastuzumab-flavopiridol synergistically enhanced apoptosis."

EXCERPT FROM: Nahta R et al. **Epidermal growth factor receptor expression is a candidate target of the synergistic combination of trastuzumab and flavopiridol in breast cancer.** *Cancer Res* 2003;63(13):3626-31. **Abstract**

Select publications

Publications discussed by Dr Parker

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** Erratum in: *J Clin Oncol* 2003;21(11):2226.

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. **Abstract**

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 35.**

Steger GG et al. Fulvestrant beyond the second hormonal treatment line in metastatic breast cancer. *Proc ASCO* 2003;**Abstract 78.**

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;98:1802-10. **Abstract**

Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79(2):207-11. **Abstract**

Watanabe T et al. **Fulvestrant provides clinical benefit to postmenopausal women with metastatic breast cancer who have relapsed on prior antiestrogen therapy: A Japanese study.** *Proc ASCO* 2003;**Abstract 274.**

Evaluation of flavopiridol's role in solid tumors

Buolamwini JK. **Cell cycle molecular targets in novel anticancer drug discovery.** *Curr Pharm Des* 2000;6(4):379-92. **Abstract**

Chen ZS et al. **Transport of methotrexate, methotrexate polyglutamates, and 17beta-estradiol 17-(beta-D-glucuronide) by ABCG2: Effects of acquired mutations at R482 on methotrexate transport.** *Cancer Res* 2003;63(14):4048-54. **Abstract**

Gries J-M et al. **Phase I study of flavopiridol 24 hour infusion monotherapy in solid tumors (HMR1275/1002).** *Proc ASCO* 2003;**Abstract 564.**

Li Y et al. **Induction of apoptosis and inhibition of c-erbB-2 in breast cancer cells by flavopiridol.** *Clin Cancer Res* 2000;6(1):223-9. **Abstract**

Li Y et al. **Induction of growth inhibition and apoptosis in prostate cancer cells by flavopiridol.** *Int J Oncol* 2000;17(4):755-9. **Abstract**

Lu K et al. **Expression of pRB, cyclin/cyclin-dependent kinases and E2F1/DP-1 in human tumor lines in cell culture and in xenograft tissues and response to cell cycle agents.** *Cancer Chemother Pharmacol* 2000;46(4):293-304. **Abstract**

Nahta R et al. **Epidermal growth factor receptor expression is a candidate target of the synergistic combination of trastuzumab and flavopiridol in breast cancer.** *Cancer Res* 2003;63(13):3626-31. **Abstract**

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Nahta R et al. **Signal transduction inhibitors in the treatment of breast cancer.** *Curr Med Chem Anti-Canc Agents* 2003;3(3):201-16. **Abstract**

V Craig Jordan, PhD, DSc

Diana, Princess of Wales Professor of Cancer Research
Director, Lynn Sage Breast Cancer Research Program
Robert H Lurie Comprehensive Cancer Center
Northwestern University, Feinberg School of Medicine
Chicago, IL

Edited comments by Dr Jordan

Tamoxifen resistance

Our model of drug resistance applies to all of the selective estrogen receptor modulators (SERMs), but tamoxifen is the example we have used. If estrogen is driving the tumor cell, tamoxifen will block that tumor's estrogen-stimulated growth for many years. Tamoxifen provides a strong antitumor effect in the patient with ER-positive disease.

Over the last 10 years, we've learned that there are things we wouldn't necessarily have anticipated happening at the cellular level. For example, with continuous tamoxifen exposure, one form of drug resistance is tamoxifen-stimulated growth. Hence, tamoxifen is exploiting the estrogen-receptor mechanism and causing these tumors to grow.

How does this happen? We think there is cell-surface signaling. The cell-surface receptors (e.g., epidermal growth factor receptor and HER2) produce a phosphorylation cascade. These cell-surface receptors are activated, and they transfer the phosphorylation of proteins into "superactivation" of the tamoxifen-estrogen-receptor complex; hence, turning it from an antiestrogenic complex to an estrogen-like complex that will promote tumor growth. This new way of looking at drug resistance, where an inhibitor stimulates cell growth, gives us insight into the future use of these agents.

During this first phase of drug resistance, if tamoxifen is discontinued, the tumors do not grow. In the clinical setting, tamoxifen-supported growth of advanced breast cancer has been seen for many years, and there can be a tamoxifen-withdrawal response. Tamoxifen is stopped, and the tumor stops growing. Tony Howell reported this in a series of patients in the *Annals of Oncology* in the early 1990s. In this type of drug resistance, a woman's endogenous estrogen can also bind to the estrogen receptor and take over where tamoxifen left off. An aromatase inhibitor is a good alternative as second-line therapy after tamoxifen resistance occurs, because it reduces the woman's endogenous estrogen.

Endocrine therapy withdrawal responses

"We assessed WR [withdrawal responses] in women after cessation of adjuvant therapy at first relapse, and after progression on first, second or third line endocrine therapy for advanced disease. One of seven patients (14%) responded after cessation of tamoxifen adjuvant therapy at relapse. Sixty-five of 72 patients were evaluable for WR after cessation of tamoxifen as first line therapy for advanced disease. There were five partial responses (8%) and 14 (22%) 'no change' with a median duration of WR of 10 months (range 3-40 months). WR were seen mainly in soft tissue disease but there were two responses in lung and two in bone."

EXCERPT FROM: Howell A et al. **Response after withdrawal of tamoxifen and progestogens in advanced breast cancer.** *Ann Oncol* 1992;3:611-7. Abstract

We've now described a second phase of tamoxifen resistance; if tamoxifen is stopped, instead of estrogen stimulating growth, it destroys the tumor cells. This is a laboratory model that we've replicated in many other breast cancer cell lines and endometrial cancer cell lines. Richard Santen also found the same thing with estrogen deprivation of breast cancer cell lines. If estrogen is taken away from breast cancer cell lines for a couple of years and then small amounts of estrogen are put back, the cells go through apoptosis and die. The general principle is supersensitivity. As part of the process of drug resistance, these cells become supersensitized to the negative effects of estrogen. They turn on death pathways and turn off survival pathways.

We've also started to describe a third form of drug resistance — the ER-positive breast cancer cell that will grow spontaneously after five or 10 years of antihormonal therapy. Fulvestrant, letrozole, anastrozole, tamoxifen or raloxifene will not work in these animal models. Nothing will control the growth of these tumor cells; they grow relentlessly. But if postmenopausal levels of estrogen are given to these animals, the tumors melt away. The survival mechanisms of the cells are so strong that they have subverted anything an antihormonal agent can do. The cells have learned to grow without any stimulus, and they appear to be hormone-independent. But estrogen can still destroy these tumor cells quite effectively by switching on death receptors and switching off survival pathways.

Extended endocrine deprivation

Clinically, there are a few sporadic reports that estrogen will destroy tumor cells after extended endocrine withdrawal. In the laboratory, we've shown that extended endocrine withdrawal followed by estrogen therapy will kill 90 percent of the tumors. Of the 10 percent of tumors that re-grow, when we transplant those, endocrine therapy works again. In women who have had extended endocrine therapy, we could plan clinical trials that utilize an estrogen "purge," and then consider antihormonal therapy to maintain patients for a

much longer period. Obviously, we'd have to try this in women with advanced disease as an interface before we go to chemotherapy.

In a retrospective analysis reported in Breast Cancer Research and Treatment 2001, Per Lonning and Tony Howell found that diethlystilbesterol (DES) produced four complete responses in 32 patients with ER-positive advanced breast cancer that had been treated with sequential endocrine therapies (i.e., tamoxifen and aromatase inhibitors). One of the complete responses lasted well over a year. These were women whose only other choice was chemotherapy.

Response to DES after resistance to conventional endocrine therapy

"The results shown here reveal that a substantial number of patients becoming resistant to conventional endocrine therapy respond to DES administered as 15 mg daily. ...

"In summary, we conclude that DES 15 mg daily may be a suitable and an effective treatment option of breast cancer patients with hormone-sensitive tumors heavily exposed to contemporary treatment regimens."

EXCERPT FROM: Lonning PE et al. **High-dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy.** *Breast Cancer Res Treat* 2001;67(2):111-6. **Abstract**

After prolonged endocrine therapy, if drug resistance has built up and the survival pathways are developed, the survival pathways will defend against the effects of chemotherapy. Therefore, the apoptotic responses that we anticipate with chemotherapy are potentially going to be blunted by the establishment of this long-term survival pathway with antihormonal therapy.

Can we change the environment? High doses of phytoestrogens may be able to pre-prime these cells for chemotherapy. This would start destruction of the survival pathways that could be built upon more effectively with chemotherapy. For 10 years, we've been working on how to go back and exploit the target — the estrogen receptor, as I call it, "the gift that keeps on giving."

Mechanism of action for DES

Dick Santen's paper in the *Journal of the National Cancer Institute* helped us understand why high-dose estrogens have an antitumor effect. He has been very interested in aromatase inhibitor drug resistance. He asked the questions: Is drug resistance to an aromatase inhibitor going to be related to supersensitivity to estrogen? Are very small amounts of estrogen going to keep these tumors growing?

In his paper, Santen said, "This is giving us our first insight into what happens with DES." He made the argument that older, postmenopausal women in their seventies have been estrogen-deprived for a long time, and

DES worked great in those ER-positive patients. In contrast, DES hardly worked in perimenopausal women in their fifties. Hence, long-term estrogen deprivation is required for estrogen to cause this death cycle.

Long-term estradiol deprivation supersensitizes cells to estradiol

"In summary, our data on breast cancer cells adapted to growth under conditions of estrogen deprivation demonstrate that additive estrogen causes a paradoxical reduction in breast cancer cell number in vitro that is associated with enhancement of apoptosis. …

"These findings suggest that long-term estradiol deprivation sensitizes cells to the proapoptotic effects of high doses of estradiol."

EXCERPT FROM: Song RX et al. **Effect of long-term estrogen deprivation on apoptotic responses of breast cancer cells to 17beta-estradiol.** *J Natl Cancer Inst* 2001;93(22):1714-23. **Abstract**

Predicting which patients will respond to estrogen

We need to develop some sort of test to ensure that we give estrogen to the right patients. If we can screen various human tumor models, gene array profiling may be able to tell us with a high probability which cells estrogen will kill and which cells estrogen will allow to survive. Maybe we can get some idea in advanced disease, where there is accessible tissue, whether gene profiling will work.

Another idea would be to evaluate patients with noninvasive techniques. In a patient treated with long-term endocrine therapy who is probably in the "estrogen death scenario," maybe PET or some other detection technique can monitor over a period of weeks whether there is any change in the viability of the tumor when their diet is changed to high-estrogen-containing foods — phytoestrogens. Once no growth is documented with this dietary change, then the patient may be treated with estrogen and appropriate chemotherapy to obtain a far bigger cell kill than imagined.

Hormonal therapy after disease progression on an aromatase inhibitor

I wouldn't rush off and give those patients DES. There's laboratory data suggesting that destroying the estrogen receptor with fulvestrant works after long-term estrogen deprivation with anastrozole. In cell culture, tamoxifen works, but I would use fulvestrant because of the possibility that cell-surface signaling is enhanced by long-term estrogen deprivation.

Selecting drug therapy in the future

We need to examine breast tumors and determine the top ten things that go wrong with the cell-surface signal transduction pathways. Then, we will be able, better than ever before, to profile patients. We'll be able to pick a combination of agents to prevent cell survival and promote cell death. In the

next 10 years, that's going to be a reality. It's not going to be the same drug for everybody. There will be 10 drugs that we can apply effectively, and we'll choose three or four for a particular patient that will promote apoptosis and close down as many cell-survival pathways as possible.

Select publications

Publications discussed by Dr Jordan

Howell A et al. **Response after withdrawal of tamoxifen and progestogens in advanced breast cancer.** *Ann Oncol* 1992; 3: 611-7. **Abstract**

Lonning PE et al. **High-dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy.** *Breast Cancer Res Treat* 2001;67(2):111-6. **Abstract**

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Tamoxifen resistance

Ali S, Coombes RC. **Endocrine-responsive breast cancer and strategies for combating resistance.** *Nat Rev Cancer* 2002;2(2):101-12. **Abstract**

de Lima GR, Facina G, Shida JY, Chein MB, Tanaka P, Dardes RC, Jordan VC, Gebrim LH. **Effects of low dose tamoxifen on normal breast tissue from premenopausal women.** *Eur J Cancer* 2003 May;39(7):891-8.

Goss PE and Strasser K. **Tamoxifen resistant and refractory breast cancer: The value of aromatase inhibitors.** *Drugs* 2002;62(6):957-66. **Abstract**

Hendrich AB, Michalak K. **Lipids as a target for drugs modulating multidrug resistance of cancer cells.** *Curr Drug Targets* 2003;4(1):23-30. **Abstract**

Hutcheson IR, Knowlden JM, Madden TA, Barrow D, Gee JM, Wakeling AE, Nicholson RI. **Oestrogen receptor-mediated modulation of the EGFR/MAPK pathway in tamoxifen-resistant MCF-7 cells.** *Breast Cancer Res Treat.* 2003 Sep;81(1):81-93.

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Johnston SR et al. **Integration of signal transduction inhibitors with endocrine therapy: An approach to overcoming hormone resistance in breast cancer.** *Clin Cancer Res* 2003;9(1 Pt 2):524S-32S. **Abstract**

Kurokawa H, Arteaga CL. **ErbB (HER) receptors can abrogate antiestrogen action in human breast cancer by multiple signaling mechanisms.** *Clin Cancer Res* 2003;9(1 Pt 2):511S-5S. **Abstract**

Murphy LC, Leygue E, Niu Y, Snell L, Ho SM, Watson PH. **Relationship of coregulator and oestrogen receptor isoform expression to de novo tamoxifen resistance in human breast cancer.** *Br J Cancer.* 2002 Dec 2;87(12):1411-6.

Osborne CK, Bardou V, Hopp TA, Chamness GC, Hilsenbeck SG, Fuqua SA, Wong J, Allred DC, Clark GM, Schiff R. **Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer.** *J Natl Cancer Inst.* 2003 Mar 5;95(5):353-61.

Schapira M. **Pharmacogenomics opportunities in nuclear receptor targeted cancer therapy.** *Curr Cancer Drug Targets* 2002;2(3):243-56. **Abstract**

Schiff R et al. **Breast cancer endocrine resistance: How growth factor signaling and estrogen receptor coregulators modulate response.** *Clin Cancer Res* 2003;9(1 Pt 2):447S-54S. **Abstract**

Post-test: Breast Cancer Update, Issue 8, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Fulvestrant, an estrogen receptor downregulator, has no known agonist activity and, therefore, does not affect the endometrium.**
   a. True
   b. False

2. **Clinical trials evaluating fulvestrant after previous endocrine therapy demonstrated clinical benefit in 50 percent or more of patients.**
   a. True
   b. False

3. **Inflammatory breast cancer is rarely HER2-overexpressing.**
   a. True
   b. False

4. **Which trial(s) in the metastatic disease setting demonstrated an improved survival for combination chemotherapy?**
   a. ECOG trial E1193 comparing AC to sequential doxorubicin and paclitaxel
   b. US Oncology trial comparing capecitabine/docetaxel to docetaxel alone
   c. Both of the above
   d. None of the above

5. **In Phase III trials of fulvestrant versus anastrozole in the metastatic setting, fulvestrant was less efficacious and more toxic than anastrozole.**
   a. True
   b. False

6. **Capecitabine in combination with other chemotherapy agents is being evaluated in clinical trials in the preoperative and adjuvant settings.**
   a. True
   b. False

7. **In the ongoing Phase III study comparing vinorelbine/trastuzumab to a taxane/trastuzumab regimen in the metastatic setting, the taxane administered is determined by:**
   a. Random assignment
   b. Physician preference

8. **Both the NSABP adjuvant and the Intergroup trials indicate HER2 testing by IHC performed in local or community laboratories could not be confirmed at a central testing site in approximately what percentage of cases?**
   a. Less than 5 percent of cases
   b. One-quarter of cases
   c. Greater than one-half of cases

9. **One of the postulated mechanisms of drug resistance associated with tamoxifen involves tamoxifen stimulating breast cancer cell growth.**
   a. True
   b. False

10. **In a small retrospective study, treatment with DES did not provide clinical benefit in patients with ER-positive, advanced breast cancer who were treated with prior endocrine therapies.**
    a. True
    b. False

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

Evaluation Form: Breast Cancer Update, Issue 8, 2003

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

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment 5 4 3 2 1
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant setting 5 4 3 2 1
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 8

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

- Evaluate clinical research data regarding the sequencing of fulvestrant in postmenopausal women with hormone receptor-positive, metastatic breast cancer and consider the clinical implications for the management of these patients 5 4 3 2 1
- Provide a rationale for the selection of single chemotherapy agents and combination regimens in the metastatic setting 5 4 3 2 1
- Describe the clinical trials of first-line trastuzumab in the metastatic setting and ongoing adjuvant clinical trials with trastuzumab in order to counsel appropriately selected patients about nonprotocol and clinical trial options 5 4 3 2 1
- Discuss the postulated phases and mechanisms of resistance to hormonal therapies and potential strategies to overcome resistance 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Eric P Winer, MD	5 4 3 2 1	5 4 3 2 1
Hope S Rugo, MD	5 4 3 2 1	5 4 3 2 1
Leroy M Parker, MD	5 4 3 2 1	5 4 3 2 1
V Craig Jordan, PhD, DSc	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form: Breast Cancer Update, Issue 8, 2003

Please Print Clearly

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

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

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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:

n MD n DO n PharmD n RN n NP n PA n BS n Other _____

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