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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 9

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

- Evaluate adjuvant chemotherapy options for patients at high risk for relapse, including ongoing clinical research trials.
- Discuss the implications of recent and ongoing clinical trials evaluating docetaxel and paclitaxel in the management of breast cancer.
- Develop an algorithm for sequencing hormonal agents in the management of estrogen receptor-positive metastatic breast cancer.
- Describe the clinical implications of ongoing clinical trials and emerging research on biologic therapies targeting HER2, VEGF and EGFR.
- Counsel patients with metastatic breast cancer about combination versus sequential single-agent chemotherapy.

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George W Sledge, MD	Consultant: Aventis Pharmaceuticals, Genentech Inc, Pfizer Inc
Sandra Swain, MD	No financial interests or affiliations to disclose
Stephen E Jones, MD	Honorarium: AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals Corporation
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
bevacizumab	Avastin™	Genentech Inc
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
celecoxib	Celebrex®	Pfizer Inc
cisplatin	Platinol®	Bristol-Myers Squibb Company
clodronate	Various	Various
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
exemestane	Aromasin®	Pfizer Inc
5-fluorouracil, 5-FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
irinotecan	Camptosar®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals Corporation
leucovorin	Various	Various
megestrol acetate	Megace®	Bristol-Myers Squibb Company
paclitaxel	Taxol®	Bristol-Myers Squibb Company
risedronate	Actonel®	Procter & Gamble Pharmaceuticals
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech Inc
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronic acid/zoledronate	Zometa®	Novartis Pharmaceuticals Corporation

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Editor's Note

Vulcan Oncology

When an oncologist talks to a patient with metastatic breast cancer, one of the first questions should be, "What are your goals?" Not what are my goals as the physician, but what are your goals as the patient? And women will tell you very different things. Some will say, "My daughter is graduating from college next spring, and I don't care how ill I am, I want to be at her graduation." Others will say, "Quality of life is all I care about. I don't want to live longer if I'm not going to live well." And there is, of course, a whole spectrum of patients in between.

In Star Trek, Mr Spock gives the Vulcan hand salute and says, "Live long and prosper." Perhaps we should be thinking more in terms of "Vulcan oncology." In the long run, our job as doctors is to both lengthen our patients' lives and improve their quality of life. Everything else is of secondary importance. This almost borders on the philosophic, but my bias, and I will admit it's my bias and it doesn't have to be anyone else's, is that the major interest of patients is how long they live and how well they live.

George W Sledge, MD

George Sledge and his colleague Kathy Miller have spent so much time pondering challenging decisions in breast cancer management that I sometimes think of them as the "Indiana University School of Oncologic Philosophy." However, unlike ivory tower thinkers, these two remarkable physicians regularly bring their well-thought-out viewpoints into practice, and it is no wonder that the theme of focusing on interventions that either improve survival or offer quality-of-life benefits permeates their management strategies as it does this series.

For this issue, that theme has particular relevance as Dr Sledge cites his own data from the classic ECOG-1193 trial to argue against combination chemotherapy for most patients with metastatic disease. This study demonstrated that long-term survival was equivalent when sequential single agents were utilized, and like most breast cancer research leaders, George uses the most effective, least toxic single agent available except in very symptomatic patients or those with visceral disease, in whom he employs combinations.

Capecitabine is among the first single agents he regularly uses, capitalizing on the oral administration, lack of alopecia and favorable toxicity profile of this drug. He also frequently utilizes vinorelbine and gemcitabine early on, particularly because so many relapsing patients have had prior anthracyclines and taxanes.

When I interviewed Sandra Swain, my primary goal was to learn of her perspective on current clinical trials of adjuvant systemic chemotherapy, including the NSABP-B-30 trial that she is chairing. However, our discussion drifted into metastatic disease, and a case she presented reinforced the "Vulcan" philosophy described by

Dr Sledge. Faced with the daunting task of managing treatment in a woman in her thirties with a supraclavicular, HER2-positive recurrence, Dr Swain recommended single-agent trastuzumab, hoping to avoid the toxicity but retain the survival benefit this agent has demonstrated when combined with chemotherapy.

Trusting Dr Swain's judgment, the woman embarked on treatment and had a complete response that now exceeds one year. One might argue that unlike the combination of trastuzumab and chemotherapy, trastuzumab monotherapy has not demonstrated a survival advantage; however, no randomized clinical trial has directly compared these two options. Dr Swain's presumption of efficacy certainly seems justified in this woman's case, and the patient was spared the toxicity of chemotherapy.

Stephen Jones discusses another facet of the "Vulcan" approach to metastatic disease as he delves into the emerging role of fulvestrant, a unique endocrine agent he believes offers a significant prolongation of response in a subset of patients. With the plethora of treatment options available in metastatic disease, it is becoming difficult to detect survival advantages in clinical trials because effective treatments may be given after the patient is treated in a study protocol.

While the randomized trial of fulvestrant versus anastrozole did not demonstrate a survival difference, there was a time to progression benefit for fulvestrant. As Dr Jones explains, this is completely in sync with his clinical impression. Most oncologists dread the moment when they inform a woman with metastatic disease that progression has occurred and therapy must be switched. Treatments that delay this event present an important potential benefit.

Mr Spock's purely scientific perspective often left him perplexed about human behavior, and oncologists face a similar challenge in providing care for patients with end-stage cancer who realistically cannot benefit from additional therapy, but cling to further interventions.

This is the art of oncology where science, empathy and experience intersect. Our series attempts to provide a window into the thoughts and feelings of experienced practitioners like Drs Sledge, Swain and Jones, and I often visualize a first-year oncology fellow — perhaps overwhelmed as many of us were with the burden of counseling patients with no effective options — listening to these and other experienced clinicians and realizing that there are no perfect answers, only our dedication to walk with our patients down this difficult path.

—Neil Love, MD

Select publications

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**

Robertson JFR 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**

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**

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**

George W Sledge, MD

Professor of Medicine
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Edited comments by Dr Sledge

Bevacizumab in the treatment of breast cancer

Although we do not have complete follow-up, the trial of bevacizumab in advanced colorectal cancer demonstrated approximately a five-month median improvement in overall survival. Will this translate to other diseases, including breast cancer? We don't know.

We do know that in breast cancer — in an anthracycline and taxane-refractory setting — adding bevacizumab to capecitabine nearly doubles the response rate but does not appear to improve time to progression or overall survival. So, while there is clearly a biologic impact in that setting, it is not clear that this is translated to real clinical benefit. It will be interesting to see whether using bevacizumab earlier in the metastatic breast cancer setting — as is being done in E-2100 — will provide a real clinical benefit, as opposed to just the response rate benefit seen in the trial of capecitabine and bevacizumab.

Phase III Randomized Study of Bevacizumab with Capecitabine versus Capecitabine Alone in Women with Previously Treated Metastatic Breast Cancer

Closed Protocol

Protocol IDs: Genentech-AVF2119g, GUMC-00299, MSKCC-01008, UAB-0028, UAB-F001009003
Accrual: 462 patients

Eligibility: Metastatic breast cancer previously treated with 1-2 chemotherapy regimens for metastatic disease or no prior chemotherapy for metastatic disease if previously treated with an adjuvant anthracycline and taxane regimen and relapsed within 12 months

ARM 1: Capecitabine (days 1-14) q3w

ARM 2: Capecitabine (days 1-14) q3w + bevacizumab (day 1) q3w

Treatment repeats for up to 35 courses in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, October 2003.

Efficacy and Toxicity of Capecitabine + Bevacizumab versus Capecitabine Alone

Efficacy	Capecitabine n=230	Capecitabine + bevacizumab n=232
Objective response rate	19.1%	30.2%
Duration of response	6.7 months	4.96 months
Progression-free survival	4.2 months	4.9 months
Toxicity	**n=215**	**n=229**
Hypertension (grade 3)	0.5%	17.9%
Thromboembolic	5.6%	7.4%
PE	1.4%	1.3%
DVT	2.3%	6.1%
Bleeding	11.2%	28.8%
Grade ≥ 3	1.4%	0.4%
Proteinuria	7.4%	22.3%
Cardiac (Grade 3 or 4)	0.9%	3.1%

SOURCE: Miller K. **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.** Presented at: San Antonio Breast Cancer Symposium, 2002. *Breast Cancer Res Treat* 2002;**Abstract 36.**

Relationship between Vascular Endothelial Growth Factor (VEGF) and HER2

Data has emerged suggesting that patients with HER2-positive tumors are more likely to have tumors that are positive for VEGF. Based on preclinical data, HER2 is upstream of VEGF, so a reasonable therapeutic hypothesis might be that co-blockade of HER2 and VEGF might result in greater benefit than blocking HER2 alone. This is currently being investigated at UCLA in a Phase I/II trial of bevacizumab and trastruzumab. I suspect that within a couple of years, we'll have some sense of whether this is a safe combination and whether it might provide some extra benefit.

Potential for bevacizumab in the adjuvant breast cancer setting

I believe it is reasonable to consider examining bevacizumab in the adjuvant setting. Approximately 30 to 50 percent of patients with breast cancer appear to have primary tumors that overexpress VEGF compared to surrounding normal tissue. In fairly large, albeit retrospective analyses, this population of patients had a higher rate of relapse, so there's a clear biologic hypothesis and rationale for exploring this strategy.

A major issue is whether or not we have the safety data yet to bring bevacizumab into the adjuvant setting. Should we wait for the results of E-2100? Should we start evaluating pilot approaches in the adjuvant setting? Should we start planning adjuvant trials? We are certainly considering these issues in the Eastern Cooperative Oncology Group.

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

Protocol IDs: E-2100, CTSU
Accrual: 316-650 patients

Eligibility: Locally recurrent disease not amenable to resection with curative intent or metastatic disease

ARM 1: Paclitaxel qw x 3 + bevacizumab q2w
ARM 2: Paclitaxel qw x 3

In both arms, treatment repeats q4w x 18 in the absence of disease progression or unacceptable toxicity.

Study Contacts:

Kathy Miller, Chair, Tel: 317-274-0920, ECOG
Edith Perez, Chair, Tel: 507-266-4997, NCCTG
Tamara Shenkier, Chair, Tel: 604-877-6000, NCIC
Melody A Cobleigh, Chair, Tel: 312-942-3240, NSABP

SOURCE: NCI Physician Data Query, October 2003.

Combination versus sequential chemotherapy

ECOG-1193 compared doxorubicin followed by paclitaxel, paclitaxel followed by doxorubicin, and the combination of the two agents at initial relapse. The overall response rate for the combination of agents was better than that of either single agent. The time to treatment failure was approximately two months longer for the combination than for either single agent, but overall survival and quality of life were identical between the three arms.

My personal bias is this data provided support for the use of sequential single-agent chemotherapy. In my clinic, I find single agents to be less toxic in many cases, and I frequently offer the average patient with metastatic disease single-agent chemotherapy.

Phase II/III Randomized Trial of DOX versus TAX versus DOX/TAX/G-CSF in Patients with Metastatic Breast Cancer **Closed Protocol**

Protocol IDs: E-1193, NCCTG-923252, SWOG-9332, E-10292
Accrual: 739 patients

Eligibility: Regionally progressing or metastatic breast cancer, hormone status not specified. No prior chemotherapy for overt metastatic disease, no prior systemic anthracyclines, anthracenes, paclitaxel or docetaxel

ARM 1: Doxorubicin
ARM 2: Paclitaxel
ARM 3: Doxorubicin + paclitaxel + G-CSF

SOURCE: NCI Physician Data Query, October 2003.

Efficacy of Combination versus Sequential Therapy in Intergroup Trial E1193

"Trial E1193 tested whether the combination of two active drugs, representing what are arguably the two most active classes of agents (anthracycline and taxanes) used in breast cancer, might prove superior to sequential, single-agent therapy with the same agents. Combination therapy resulted both in a superior overall response rate and a superior TTF, two frequent measures of efficacy in metastatic chemotherapy trials. Despite this superiority, combination therapy failed to improve overall survival. Perhaps more importantly, given the usually fatal nature of the disease, combination therapy did not improve quality of life."

SOURCE: 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**

Joyce O'Shaughnessy's trial demonstrated a survival advantage of approximately three months for the addition of capecitabine to docetaxel in the metastatic setting for anthracycline-refractory patients. This was a well-conducted, statistically rigorous trial, and the results are certainly believable.

Capecitabine provides a real benefit for patients with metastatic breast cancer, but I don't conclude that combination therapy is superior to sequential single-agent therapy, and this trial did not test that hypothesis. There was no crossover arm from docetaxel to capecitabine or from capecitabine to docetaxel. In most cases, patients did not cross over to capecitabine. This trial is not comparable to ECOG-1193, which specifically looked at that question.

Phase III Trial of Docetaxel/Capecitabine (XT) Combination Therapy versus Docetaxel Monotherapy (T) in Metastatic Breast Cancer **Closed Protocol**

Accrual: 511 patients

Eligibility: Metastatic breast cancer patients resistant to or relapsing after anthracycline-based therapy

ARM 1:	Capecitabine 2500 mg/m^2 po in 2 daily divided doses days 1-14 + docetaxel 75 mg/m^2 IV q 3 weeks
ARM 2:	Docetaxel 100 mg/m^2 IV q 3 weeks

"The significantly superior survival, including a 3-month improvement in median survival, achieved with combined docetaxel plus capecitabine and the manageable toxicity should establish this regimen as an important treatment option for patients with anthracycline-pretreated metastatic breast cancer."

SOURCE: 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**

Efficacy of Capecitabine/Docetaxel versus Docetaxel Alone

"The present trial provides clear evidence that combination therapy offers a survival advantage compared with single-agent therapy. However, the relative merits of sequential versus combination therapy with these two agents were not addressed in the present trial... .

"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. Whether combination capecitabine/docetaxel will provide superior benefit compared with sequential administration of the same agents (docetaxel followed by capecitabine or capecitabine followed by docetaxel) in the treatment of metastatic breast cancer is not known and was not addressed in this trial."

SOURCE: 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**

Fluoropyrimidines in adjuvant chemotherapy regimens

In the early 1990s, based on absolutely no data whatsoever, we dropped fluorouracil from adjuvant chemotherapy regimens in prospective randomized trials throughout the United States. There was a massive switch in clinical practice from FAC-type regimens to AC-type regimens.

Looking at the capecitabine data in the metastatic setting, one has to wonder whether or not that was an appropriate decision. Might an agent that improved survival in the metastatic setting also improve the cure rate in the adjuvant setting?

Management of patients with ER-negative, HER2-negative, metastatic disease

The majority of my patients have received adjuvant anthracycline-based chemotherapy. I am likely to offer single-agent sequential therapy — typically starting with a taxane — particularly if the patient relapsed fairly shortly after adjuvant therapy.

Based on the O'Shaughnessy data, I generally use capecitabine upon progression. If the patient wishes to continue chemotherapy after capecitabine, both gemcitabine and vinorelbine are capable of inducing remission in some patients in that setting and are reasonable options.

I also offer patients enrollment in clinical trials testing new concepts, including enrollment in E-2100, randomly assigning patients to weekly paclitaxel with or without bevacizumab. For patients who have received an anthracycline and a taxane in the adjuvant setting, we have little or no data. If the patient has relapsed within a year or so of adjuvant therapy, I am likely to offer single-agent capecitabine as first-line therapy.

Dosing and scheduling of capecitabine

The FDA-approved dose of 2,500 mg/m^2 in two divided doses, daily, is associated with a fair degree of hand-foot syndrome. I typically start patients at about 1,000 mg/m^2 BID for 14 days on and seven days off.

We don't have much data to guide us here. Anecdotally, we've tried just about every dosing schedule imaginable to reduce toxicity. We've reduced administration from 14 out of 21 days down to 10 out of 21 days. We've lowered the dose and had patients receive treatment on weekdays with the weekends off. Depending on the patient, all three of these dosing schedules result in a lowering of toxicity.

2003 National Patterns of Care Survey of US Oncologists: Dosing and Scheduling of Capecitabine

55-year-old asymptomatic woman with lung metastases was started on capecitabine 1,000 mg/m^2 BID (two weeks on, one week off).

After three cycles, there is no change in the lesions and no side effects of therapy. Which of the following would you generally do?

Continue therapy at the same dose	58%
Increase the dose to 1,250 mg/m^2 BID	23%
Continue capecitabine, add another agent	2%
Stop capecitabine, switch therapy	17%

After three cycles, there is an objective response in her lung lesions, but the patient complains of mild pain and redness in her hands and feet. Which of the following would you generally do?

Continue therapy at the same dose	45%
Reduce dose	30%
Change schedule to 2 weeks off therapy	18%
Stop capecitabine, switch therapy	3%
Switch therapy	4%

Efficacy and tolerability of fulvestrant

Like many of my colleagues, I'm not quite sure where to use fulvestrant, partly because we have limited clinical trial data. My interpretation of the results of the large North American and European trials is that fulvestrant and anastrozole are roughly equivalent agents in terms of survival.

In the North American trial, fulvestrant appeared to have some advantage over anastrozole in response and time to progression. My approach to therapy is to use survival to guide how I treat patients. The trials didn't demonstrate a survival difference, so I don't feel strongly that one agent is better than the other.

I use fulvestrant fairly regularly in my patients with steroid receptor-positive, metastatic breast cancer. I have patients who prefer receiving an injection once a month to taking pills every day. I have other patients who would prefer a pill to a shot. Aside from the acute discomfort of the injection itself, I've found fulvestrant to be an exceptionally well-tolerated medication.

2003 National Patterns of Care Survey of US Oncologists: Use and Tolerability of Fulvestrant

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.

Efficacy of Fulvestrant Compared to Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy

	Combined analysis[1]		European trial (0020)[3]		North American trial (021)[5]	
	Fulvestrant (n=428)	Anastrozole (n=423)	Fulvestrant (n=222)	Anastrozole (n=229)	Fulvestrant (n=206)	Anastrozole (n=194)
Disease progression			82.4%	83.4%	83.5%	86.1%
Median time to progression	5.4 months	4.1 months	5.5 months	5.1 months	5.4 months	3.4 months
Treatment failures			84.7%	85.6%	79.6%	84%
Objective response	19.2%[2]	16.5%[2]	20.7%	15.7%	17.5%	17.5%
Clinical benefit (CR + PR + SD ≥ 24 w)	43.5%[2]	40.9%[2]	99 (44.6%)	103 (45.0%)	87 (42.2%)	70 (36.1%)
Median duration of response in those responding	16.7 months*	13.6 months*	15.0 months	14.5 months	19.0 months	10.8 months
Median time to death			26.5 months[4]	24.3 months[4]		

* In addition to reporting median duration of response (DOR) in those responding, a newly developed statistical analysis of DOR was performed, defined for responders as the time from onset of response to disease progression and for non-responders as zero. In this analysis, DOR was significantly greater (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; p=0.0003) for fulvestrant versus anastrozole.

SOURCES: [1]Parker LM et al. *Proc ASCO* 2002;**Abstract 160**. [2]Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. **Abstract** [3]Howell A et al. *J Clin Oncol* 2002;20:3396-403. **Abstract** [4]Howell A et al. *Proc ASCO* 2003:**Abstract 178.** [5]Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. **Abstract**

Counseling postmenopausal patients with ER-positive disease about adjuvant endocrine therapy

I routinely present the ATAC data when I counsel postmenopausal patients about adjuvant endocrine therapy. I say that both tamoxifen and anastrozole are FDA-approved drugs, and I consider both to be very reasonable options.

These discussions are more like negotiations than mandates, and patients frequently tell me what they prefer. To my surprise, I find that patients often make choices based on factors that would not have had a significant impact on my decision.

Women vary tremendously with regard to the toxicities they're willing to accept, and often their decisions are based on personal and family history.

Breast Cancer Survivors' Perspectives on Adjuvant Hormonal Therapy Based on Verbal Description from Faculty of Treatment Side Effects and Toxicities

How would you compare the side effects and toxicity 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%

SOURCE: 2003 Breast Cancer Patient Perspectives Meeting, Hollywood, Florida.

Trials of combined blockade of growth factor receptors

We have a fair amount of preclinical data suggesting that combined blockade of growth factor receptors may be superior to blockade of one receptor. In the Eastern Cooperative Oncology Group, we're evaluating the combined blockade of both the epidermal growth factor receptor (EGFR) and HER2 using trastuzumab with gefitinib.

We're also evaluating combined blockade of both the EGFR and the estrogen receptor using gefitinib with either fulvestrant or anastrozole. We have good preclinical data for both of those approaches. Similarly, since we now know that patients with HER2-positive disease are more likely to overexpress VEGF, and studies in the metastatic setting are combining HER2 with VEGF blockade, using monoclonal antibodies for both.

Clinical Trials Evaluating Combined Growth Factor Blockade

Protocol IDs	Target accrual	Eligibility criteria	Randomization arms
CTRC-IDD-0228, CTRC-IDD-1839US, CTRC-IDD-0219	36-78	Postmenopausal women with ER/PR+, hormone refractory, metastatic or unresectable locally advanced breast cancer	Anastrozole x 14 d → [anastrozole + gefitinib] x 28 d
EORTC-10021, IDBBC-10021	108	Postmenopausal women with ER/PR+, metastatic or locally recurrent breast cancer that has failed tamoxifen therapy	ARM 1: anastrozole + gefitinib ARM 2: anastrozole + placebo
E-4101	148	Postmenopausal women with ER/PR+, recurrent or metastatic breast cancer	ARM 1: [anastrozole + gefitinib] x 28 d ARM 2: fulvestrant IM day 1 + gefitinib x 28 d
E-1100	34-132	HER2+ (IHC 3+/FISH+) metastatic breast cancer	Gefitinib daily + [trastuzumab weekly x 24 → trastuzumab q 3 weeks]

SOURCE: NCI Physician Data Query, October 2003.

Clinical trials of adjuvant trastuzumab

In the adjuvant setting, the most interesting issue to me is HER2 blockade. We have four major ongoing randomized trials internationally, evaluating trastuzumab in combination with different chemotherapies or as a solitary blockade. If I were asked to place a bet, I would say that of the adjuvant trials we have available now, the HER2 trials are most likely to yield a positive result for overall survival.

Breast Cancer Survivors' Perspectives on Adjuvant Trastuzumab Based on Faculty Recommendations against Nonprotocol Use of Adjuvant Trastuzumab

40-year-old woman with ER+, HER2+ breast cancer and 60% 10-year risk of breast cancer mortality/recurrence*	NY	FL
Would want trastuzumab off protocol	15%	35%
Would participate in a randomized adjuvant trastuzumab trial	21%	44%

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

SOURCE: 2003 Breast Cancer Patient Perspective Meetings, New York, New York and Hollywood, Florida.

Open Trials of Adjuvant Trastuzumab in the Treatment of Breast Cancer

Study name	Target accrual	Arms
BCIRG-006	3,150	ARM 1: AC x 4 → docetaxel x 4 ARM 2: AC x 4 → docetaxel x 4 + H (qw x 12 weeks) → H (qw x 40 weeks) ARM 3: (docetaxel + C) x 6 + H (qw x 18 weeks) → H (qw x 34 weeks)
NCCTG-N9831 CLB-49909 E-N9831 SWOG-N9831	3,300	ARM 1: AC x 4 → paclitaxel qw x 12 ARM 2: AC x 4 → paclitaxel qw x 12 + H (qw x 52 weeks) ARM 3: AC x 4 → (paclitaxel + H) qw x 12 → H qw x 40
BIG-01-01 EORTC-10011 HERA	3,192	(Randomization after approved neoadjuvant or adjuvant chemotherapy) ARM 1: H q3w x 1 y ARM 2: H q3w x 2 y ARM 3: No H
NSABP-B-31	1,000-2,700	ARM 1: AC x 4 → paclitaxel x 4 ARM 2: AC x 4 → paclitaxel x 4 + H qw x 1 y

AC = doxorubicin/cyclophosphamide; C = cisplatin or carboplatin; H = trastuzumab

SOURCE: NCI Physician Data Query, November 2003.

Evolution of dose-dense chemotherapy

In the Intergroup, we are currently involved in a CALGB-led trial randomizing patients to one of the dose-dense arms of C-9741 versus another dose-dense regimen originally pioneered at the University of Washington by Bob Livingston and Julie Gralow. This dose-dense regimen, in essence, gives continuous chemotherapy during the course of the trial and looked very promising in an early, small dataset. So, we will be comparing two different forms of dose densification.

Adjuvant bisphosphonates

I'm fascinated by the trials of adjuvant bisphosphonate therapy. Two of the three European trials evaluating adjuvant clodronate suggested that it could lower the incidence of bony metastases. An interesting observation from the German trial was that bisphosphonates also diminished the likelihood of developing visceral metastases. This led to the hypothesis that, for some patients, bony metastases may represent a place from which other metastases may develop.

The NSABP has an ongoing, randomized trial assigning patients to receive adjuvant clodronate or not. In the very near future, an Intergroup trial will compare clodronate to other, more recent generation and more potent bisphosphonates.

From a toxicity prevention standpoint, adjuvant bisphosphonates may be very important. If, as the ATAC trial data suggests, use of an aromatase inhibitor results in perhaps a somewhat higher rate of fractures than tamoxifen, and if

bisphosphonates prevent that problem, we might use them even if they don't improve survival. This is a very interesting strategy that needs to be pursued.

Phase III Trials of Adjuvant Clodronate (1600 mg PO qd) for Early Stage Breast Cancer

Author	Reduction in skeletal metastases	Reduction in nonskeletal metastases	Survival advantage
Diel et al.	Yes	Yes	Yes
Powles et al.	Yes during Rx only	No	Yes
Saarto et al.	No	No	Decreased survival in clodronate arm

SOURCE: NSABP-B-34 Protocol background.

Ongoing Adjuvant Bisphosphonate Trials in Breast Cancer

Study	N	Randomization
NSABP-B-34	3,200	Clodronate qd x 3 years Placebo qd x 3 years
CLB-79809	400	Zoledronate q 3 months (months 1-24) + daily calcium + vitamin D (months 1-36) Daily calcium + vitamin D (months 1-36) + zoledronate q 3 months (months 13-36)
CPMC-IRB-14069	120	Zoledronate q 3 months x 4 + daily calcium + vitamin D Placebo q 3 months x 4 + daily calcium + vitamin D
NCCTG-N02C1	220	(Oral risedronate q w + daily calcium + vitamin D) x 1 year (Oral placebo q w + daily calcium + vitamin D) x 1 year

SOURCE: NCI Physician Data Query, October 2003.

Intergroup trial of aromatase inhibitors and COX-2 inhibition

The first randomization of this trial is between the nonsteroidal aromatase inhibitor, anastrozole, and the steroidal aromatase inhibitor, exemestane. This trial asks whether or not there will be any efficacy, quality-of-life or toxicity differences between the aromatase inhibitors.

The second randomization of this trial is based on preclinical data suggesting COX-2 is upstream of aromatase in estrogen receptor-positive tumors. Tumors expressing a great deal of COX-2 have increased aromatase and are able to convert more androgens to estrogens. The same preclinical model system suggests that blocking both COX-2 and aromatase in mouse models results in greater benefits in treating existing cancers and preventing new cancers. This has led to a secondary randomization to either placebo or the COX-2 inhibitor, celecoxib.

Phase III Adjuvant Study of Exemestane versus Anastrozole ± Celecoxib in Postmenopausal Women with ER/PR-positive Primary Breast Cancer

Protocol IDs: CAN-NCIC-MA27, CLB-CAN-NCIC-MA27, NCCTG-CAN-NCIC-MA27
Projected Accrual: 6,830 patients

ARM 1:	(Exemestane x 5 y) + (celecoxib x 3 y)
ARM 2:	(Exemestane x 5 y) + (placebo x 3 y)
ARM 3:	(Anastrozole x 5 y) + (celecoxib x 3 y)
ARM 4:	(Anastrozole x 5 y) + (placebo x 3 y)

SOURCE: NCI Physician Data Query, October 2003.

Select publications

Publications discussed by Dr Sledge

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a Phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646.**

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

O'Shaughnessy J et al. **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* 200;21(4):588-92. **Abstract**

The role of VEGF expression in breast cancer

Dreisbach P et al. **Vascular endothelial growth factor (VEGF) plasma levels and tumor expression in breast cancer: A comparison of random pre-operative VEGF plasma levels in malignant and benign breast disease.** *Proc ASCO* 2002:**Abstract 2986.**

Ferrara N. **Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: Therapeutic implications.** *Semin Oncol* 2002;29(6 Suppl 16):10-4. **Abstract**

Folkman J. **Role of angiogenesis in tumor growth and metastasis.** *Semin Oncol* 2002;29(6 Suppl 16):15-8. **Abstract**

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003:**Abstract 825.**

Hoar FJ et al. **Co-expression of vascular endothelial growth factor C (VEGF-C) and c-erbB2 in human breast carcinoma.** *Eur J Cancer* 2003;39(12):1698-703. **Abstract**

Pegram MD, Reese DM. **Combined biological therapy of breast cancer using monoclonal antibodies directed against HER2/neu protein and vascular endothelial growth factor.** *Semin Oncol* 2002;29(3 Suppl 11):29-37. **Abstract**

Sledge GW Jr. **Vascular endothelial growth factor in breast cancer: Biologic and therapeutic aspects.** *Semin Oncol* 2002;29(3 Suppl 11):104-10. **Abstract**

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Edited comments by Dr Swain

NSABP-B-30: Adjuvant AC (doxorubicin/cyclophosphamide) followed by docetaxel (T) versus AT versus ATC

Trial rationale and design

When NSABP-B-30 was designed in 1997, taxanes were not routinely used in the adjuvant setting. Many of the investigators, including myself, believed that docetaxel was the most active agent in metastatic disease, and that it should be investigated in the adjuvant setting, which is why we included it in all three arms of B-30.

We also wanted to compare the various durations of treatment, so while the AC followed by docetaxel arm is a six-month treatment, the other arms are shorter in duration. The NSABP data showed four cycles of AC was effective, and we felt that four cycles of AT or TAC would be effective as well. Perhaps with hindsight, based on the TAC data, it would have been better to go with six cycles of TAC, but there's really no data showing six is superior to four cycles.

Initially we had several deaths in the ATC arm of B-30, probably due to the doses used — doxorubicin 60 mg/m^2, docetaxel 60 mg/m^2 and cyclophosphamide 600 mg/m^2. We changed the doses to those used in Nabholtz's regimen — doxorubicin 50 mg/m^2, docetaxel 75 mg/m^2, and cyclophosphamide 500 mg/m^2 — and since then we've had very few deaths.

We also changed the AT arm from doxorubicin 60 mg/m^2 and docetaxel 60 mg/m^2 to 50 mg/m^2 and 75 mg/m^2, respectively. The TAC regimen produced a high rate of febrile neutropenia — about 29 percent in the metastatic setting and 23 to 24 percent in the adjuvant trial — which we felt was unacceptable, so we added growth factors. It is up to the investigators whether they use the long- or shorter-acting growth factor.

Phase III Randomized Study of Adjuvant Doxorubicin and Cyclophosphamide Followed by Docetaxel versus Doxorubicin and Docetaxel versus Doxorubicin, Docetaxel and Cyclophosphamide in Women with Breast Cancer and Positive Axillary Lymph Nodes **Open Protocol**

Protocol IDs: NSABP-B-30, CTSU
Accrual: 5,300

Eligibility: Stage I, II or IIIA with at least one positive axillary lymph node

ARM 1:	Doxorubicin + cyclophosphamide q 3w x 4 → docetaxel q 3w x 4
ARM 2:	Doxorubicin + docetaxel q 3w x 4*
ARM 3:	Doxorubicin + cyclophosphamide + docetaxel q 3w x 4*

*Note: Primary prophylaxis with growth factors will be given.
Some patients may receive postmastectomy radiotherapy on SWOG-S9927 or NCIC-MA.20.

Study Contact:
National Surgical Adjuvant Breast and Bowel Project
Sandra Swain, Chair, Tel: 301-496-0901

SOURCE: NCI Physician Data Query, November 2003.

Menopausal status and benefits of adjuvant chemotherapy

One of the most exciting factors we are evaluating in NSABP-B-30 is the impact of the patient's menopausal status. We have accrued approximately 4,400 patients, 88 percent of our target, and about one-half of the women were premenopausal when they began the trial. We are following their menses for at least two years after treatment and, while we pretty much know what to expect with arms containing AC, I know of no data on how the taxanes will impact menstrual function.

A critically important question is whether patients who experience amenorrhea have a survival benefit. The SOFT and TEXT trials are evaluating whether ovarian ablation, with either an aromatase inhibitor or tamoxifen, is beneficial, but right now we just don't know.

Hormonal therapy in NSABP-B-30

Initially, the only hormonal therapy patients received was tamoxifen, but when the ATAC data came out, we added an amendment to the trial allowing anastrozole in postmenopausal women if there's a contraindication to tamoxifen or the physician otherwise prefers to utilize the aromatase inhibitor.

We're still recommending — consistent with the ASCO Technology Assessment — patients receive tamoxifen. We were concerned allowing anastrozole would confound the results, but the statistician believed that our numbers were large enough that it would not likely affect the results.

Dose density data

The dose-dense data are early, but I doubt the benefit will disappear. The CALGB used a taxane that I feel is less effective than docetaxel, and many of us think the scheduling of the paclitaxel every two weeks rather than every three weeks is why the "dose-dense" therapy actually worked. We discussed whether, based on the dose-dense data, we should discontinue our B-30 trial, but I don't think it negates the questions we're asking. In our discussions regarding the next replacement trial, we are proposing a three-arm trial, possibly TAC versus dose-dense TAC versus dose-dense AC followed by paclitaxel/gemcitabine.

We need to determine predictive factors, look at gene profiles and find answers to our research questions more quickly, which is why the neoadjuvant trials are critical. We began designing B-30 six years ago and we won't have results for another four years. That's an extremely slow process and in the interim, things change as we get results from new studies. The NSABP B-27 replacement trial, a neoadjuvant trial looking at the microarrays before and after as well as switching the treatment schedules around, looks very interesting and I believe we'll be doing more of these important trials.

Proposed NSABP-B-27 Preoperative Chemotherapy Replacement Trial

AC q 3w ↔ docetaxel q 3w → Surgery
AC q 3w ↔ docetaxel/capecitabine q 3w → Surgery
AC q 3w ↔ docetaxel/carboplatin q 3w → Surgery
AC q 3w ↔ docetaxel/vinorelbine q 3w → Surgery

↔ In this proposed 4 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

SOURCE: NSABP Annual Meeting, July 2003, Orlando, Florida.

Adjuvant chemotherapy options

Off protocol, my first choice for treatment of younger patients with node-positive disease is TAC, which most of my patients choose and that probably reflects my bias. My second choice is the dose-dense regimen because the Phase III data shows a benefit, but I am concerned about the reported 13 percent incidence of blood transfusions. I've spoken with physicians who say it's not that high in actual practice, so it may not be a real effect, rather just a result of limited data.

My third choice is AC followed by docetaxel, because in NSABP B-27 we saw a higher pathologic complete response rate, although not a survival benefit. I don't use anthracycline-based regimens like FEC or CAF because I prefer a regimen that includes a taxane. Although data supports using these regimens in the pre- or postmenopausal patient, I'm convinced the taxanes provide an additive benefit.

Efficacy data from NSABP-B-27 comparing tumor response of adding preoperative docetaxel following doxorubicin (A) and cyclophosphamide (C)

Endpoint	AC*	AC followed by preoperative docetaxel	*p*-value
Clinical complete response rate	40.1%	63.6%	$p < 0.001$
Overall clinical response rate	85.5%	90.7%	$p < 0.001$
Pathologic complete response rate	13.7%	26.1%	$p < 0.001$

*Pooled data from groups I (AC followed by surgery) and III (AC followed by surgery and then docetaxel), which had similar results.

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

NSABP-B-27: Improved Pathologic Complete Response Rate from Adding Sequential Preoperative Docetaxel to Preoperative AC

"If, in fact, the addition of docetaxel results in improved survival that is proportional to the increase in pCR rate reported here, it would confirm that the response of the primary tumor is a useful surrogate marker for survival. If this is the case, then perhaps the greatest promise for primary systemic chemotherapy will be the ability to carry out studies of new treatments using primary tumor response as an end point that is meaningful."

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

Adjuvant trastuzumab

Trastuzumab is a fabulous drug that has made a huge difference for a lot of patients with metastatic disease and a very poor prognosis. We don't have any efficacy data for adjuvant trastuzumab, so I think it's unwise to use it in that setting outside of a clinical trial. I'm concerned about the potential cardiac toxicity, and we need the studies to mature in order to analyze the toxicity data. On the other hand, there are cases in which I would consider using trastuzumab, such as inflammatory breast cancer, where more of the patients are HER2-positive and survival is poor.

Neoadjuvant bevacizumab trial

We're studying neoadjuvant bevacizumab in inflammatory breast cancer, which has a lot of angiolymphatic invasion. Significant angiogenic growth factors may be present and stimulated by VEGF. We hypothesize that if we disrupt that stimulation, we'll have improvement in efficacy.

We have accrued 13 out of 20 patients. The patients receive bevacizumab for one cycle up-front, and undergo biopsies before and after treatment to look for gene changes. MRIs have shown decreased tumor vascular permeability in patients taking bevacizumab alone, and these patients say they can feel a change in their breast.

Time to progression, the primary endpoint in the bevacizumab/capecitabine metastatic breast cancer study, was negative; however, the response rate was 10 percent better in the bevacizumab arm. That is the same benefit seen in the colon cancer study. I think we'll find bevacizumab is active, which is why I'm continuing our neoadjuvant trial. I am still hopeful that we will see an efficacy benefit with this agent.

NSABP-B-31: Adjuvant AC followed by paclitaxel with or without trastuzumab

After the NSABP designed the adjuvant trial B-31, the Intergroup designed a similar trial so that the data could be analyzed together. I think that's great because it will be a stronger analysis. I hope we'll see a benefit with trastuzumab, which has been a miracle drug in the metastatic setting. If this trial is positive, there will still be a lot of scheduling questions to be answered such as, "How long do you really need trastuzumab and can it be administered every three weeks rather than weekly?"

Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel with or without Trastuzumab (Herceptin) in Women with Node-Positive Breast Cancer that Overexpresses HER2 Open Protocol

Protocol IDs: NSABP-B-31
Projected Accrual: 1,000-2,700

Eligibility: Stage II or IIIA, HER2-positive breast cancer with at least one positive axillary lymph node

ARM 1: Doxorubicin + cyclophosphamide q 3w x 4 → paclitaxel q 3w x 4

ARM 2: Doxorubicin + cyclophosphamide q 3w x 4 → paclitaxel q 3w x 4 + trastuzumab qw x 52

Patients in all arms who are ER/PR-positive receive tamoxifen daily for 5 years. Patients who previously received tamoxifen for prevention may be treated with additional tamoxifen at the discretion of the principal investigator. Patients who are postmenopausal may receive anastrozole as a substitute for tamoxifen.

All patients may receive radiotherapy, administered daily for 5 to 6 weeks.

Study Contact:

National Surgical Adjuvant Breast and Bowel Project
Edward Romond, Chair, Tel: 859-323-8043

SOURCE: NCI Physician Data Query, November 2003.

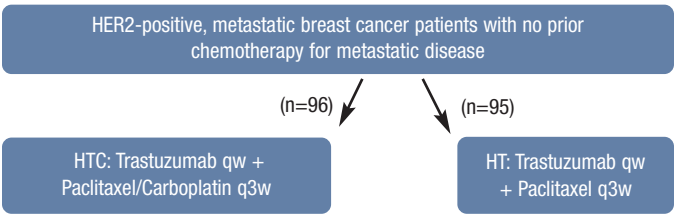
Management of patients presenting *de novo* with HER2-positive metastatic disease

Since trastuzumab was approved for use, I've changed the way I treat patients presenting *de novo* with HER2-positive, metastatic disease. I no longer use an anthracycline first-line. Instead, based on Nick Robert's data, I use a docetaxel or paclitaxel/carboplatin and trastuzumab regimen. After the patient completes that therapy, I continue the trastuzumab and may later add vinorelbine. After that, I use capecitabine with trastuzumab. There was a Japanese group that showed either an additive or synergistic effect with trastuzumab and 5-FU, which supports using the two together.

I'm anxious for the data from the current doxorubicin HCl liposome injection/trastuzumab trials. If there's no cardiac toxicity, we may move that combination up front. In Slamon's trial, doxorubicin with trastuzumab had the best benefit, however, it also had the highest risk of cardiac toxicity, which is why no one uses it.

It doesn't surprise me that some physicians treat these patients with an anthracycline without trastuzumab. We were always taught that anthracyclines were the best drugs available, but based on my general experience and Dennis Slamon's data showing a survival benefit with the addition of trastuzumab and paclitaxel, I don't believe an anthracycline is the best choice.

Phase III Study Comparing Trastuzumab and Paclitaxel with and without Carboplatin in Patients with HER2-positive, Advanced Breast Cancer



Study Results

Parameters	HTC Regimen	HT Regimen	*p*-Value
Response Rate (RR)	48/92 52%	34/94 36%	P = 0.04
RR in HER2 IHC 3+	35/61 57%	23/63 37%	P = 0.03
Time to progression (TTP)	11.2 months	6.9 months	P = 0.007
TTP in HER2 IHC 3+	13.5 months	7.2 months	P = 0.006

HTC = trastuzumab, paclitaxel, carboplatin; HT = trastuzumab, paclitaxel

SOURCE: 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.** Presented at San Antonio Breast Cancer Symposium 2002. *Breast Cancer Res Treat* 2002;**Abstract 35.**

Use of trastuzumab monotherapy

I've used single-agent trastuzumab in a couple of patients with limited metastatic disease, based on Chuck Vogel's data. One patient in her thirties with a cervical node recurrence experienced a complete remission in two or three months on trastuzumab. After almost a year of therapy, I took her off trastuzumab, hoping that if and when she had another recurrence, she would not be resistant to it. There's absolutely no data telling us how long one should remain on trastuzumab after a complete remission. You can make arguments either way, but we don't know the right answer.

Efficacy of Single-Agent Trastuzumab in First-Line Treatment of HER2-Overexpressing Metastatic Breast Cancer

"The results of this trial indicate that trastuzumab is active as a single agent and produces durable objective responses in women with HER2-overexpressing breast cancer who have not previously received chemotherapy for their metastatic disease. The response rate was 26%; the clinical benefit rate was 38% in all assessable patients and 48% in the subset whose tumors overexpressed HER2 at the 3+ level by IHC. Although an accurate assessment of the median duration of response was not possible because of censoring, 57% of the responding patients were known to be free of disease progression at 12 months or more of follow-up, underscoring the durability of the responses. These findings are noteworthy in view of the poor prognosis in this population."

SOURCE: 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**

Treatment of HER2-positive, ER-positive, metastatic breast cancer

I use hormonal therapy alone in these patients — generally an aromatase inhibitor if the patient is postmenopausal. I watch the patients carefully and if the disease progresses, then I move to trastuzumab. I've heard others say they would use trastuzumab up front, but we don't have any data showing a survival benefit in these patients. In addition, we know a lot of patients with hormone receptor-positive disease will do well for a long period of time, so I'm reluctant to add trastuzumab and make them come in every three weeks for IV therapy.

Advances in hormonal therapy

Aromatase inhibitors have dramatically changed hormonal therapy. I remember using aminoglutethimide, which had a lot of CNS toxicity, and megestrol acetate, which women hated because of weight gain. The aromatase inhibitors have very low toxicity, including exemestane, which may have a few more side effects but not much. I've used fulvestrant several times, but I used it later in the course of the disease so I've not seen as much efficacy with it. However, I think it's important to continue using this agent.

Treatment of HER2-negative metastatic breast cancer

I prefer sequencing single agents because I believe patients tolerate treatment better and live a better life. I want my patients to experience the most benefit with the least toxicity and, except for O'Shaughnessy's docetaxel/capecitabine trial, there's no evidence that combinations have a survival benefit. I've presented the docetaxel/capecitabine option to patients but they reject it saying they don't want all that toxicity for only a two-month median increase in survival. O'Shaughnessy also presented the gemcitabine/paclitaxel data showing a time-to-progression benefit with gemcitabine, but there's no survival data yet. In addition, neither of these two trials had a third arm where they sequenced the drugs.

In patients with HER2-negative, metastatic disease I often use capecitabine as my first-line therapy. It's a wonderful drug because it's very effective, and it's so well-tolerated. Patients don't mind taking a pill, and they love not losing their hair. It's important to watch the patients carefully and dose them appropriately to avoid hand-foot syndrome.

My second choice of therapy is a taxane. Like capecitabine, I think the taxanes have made a great contribution to improved survival in patients with metastatic disease. Paclitaxel came on board in 1992 and docetaxel in 1994, and, at least in the case of docetaxel, they are either equivalent or better than the anthracyclines.

I would also consider weekly doxorubicin or AC for the treatment of metastatic disease. I don't have a set treatment pattern, rather I look at the patient. If they don't have gastrointestinal symptoms, I consider capecitabine. If they do, then I consider an intravenous agent — probably AC or docetaxel.

Impact of improved supportive care

I've been practicing for 20 years, and I believe patients are surviving longer because we have more therapeutic options and better supportive care. Chemotherapy used to be miserable for patients, but now we have a number of antiemetics and growth factors that help patients tremendously. I'm not aware of any evidence that bisphosphonates increase survival, but they provide relief from fractures and pain. Zoledronate is easily administered in 15 to 30 minutes, relieves pain and it's great for the patients. Also, hair loss is a major issue for patients, especially in the metastatic setting where you just want to give them good quality of life. I use capecitabine as first-line therapy when I can, because patients don't experience alopecia and there's enough data showing good responses with the drug.

Select publications

Publications discussed by Dr Swain

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

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

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**

Hillan KJ et al. **The role of VEGF expression in response to bevacizumab plus capecitabine in metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 766.**

Mackey JR et al. **Final results of the Phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first-line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 137.**

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

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**

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20(15):3317-27. **Abstract**

Winer EP et al. **American Society of Clinical Oncology Technology Assessment Working Group update: Use of aromatase inhibitors in the adjuvant setting.** *J Clin Oncol* 2003;21(13):2597-99. **Abstract**

Adjuvant chemotherapy

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**

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

Gluck S. **The worldwide perspective in the adjuvant treatment of primary lymph node-positive breast cancer.** *Breast Cancer* 2001;8(4):321-8. **Abstract**

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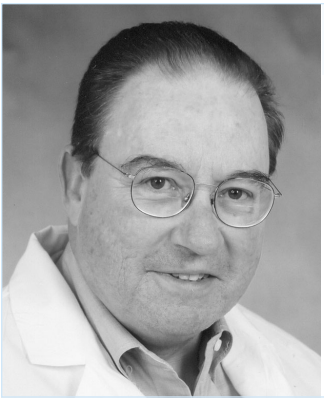
Hortobagyi GN. **Progress in systemic chemotherapy of primary breast cancer: An overview.** *J Natl Cancer Inst Monogr* 2001;30:72-9. **Abstract**

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

Norton L. **Theoretical concepts and the emerging role of taxanes in adjuvant therapy.** *Oncologist* 2001;6(Suppl 3):30-5. **Abstract**



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Clinical Professor, University of Texas Southwestern
Dallas, Texas

Edited comments by Dr Jones

Phase III randomized trial (Taxotere-311) comparing docetaxel to paclitaxel in patients with metastatic breast cancer

The Taxotere-311 trial started in 1993 and was completed in 2003. Peter Ravdin, the principal investigator, presented some of the data at the ECCO meeting in September 2003, and I presented the data at the 2003 San Antonio Breast Cancer Symposium.

With the approval of docetaxel, the FDA mandated a trial comparing docetaxel 100 mg/m^2 to paclitaxel 175 mg/m^2, each administered on an every-three-week schedule. Over 400 patients with relatively anthracycline-resistant disease were accrued; they had either relapsed on an anthracycline-containing regimen or within 12 months of receiving one.

The results were a bit surprising, and I didn't think they would be quite so dramatic. For the evaluable patients, there was a significant difference in the response rate, time to tumor progression and survival in favor of docetaxel. There was more toxicity associated with docetaxel than with paclitaxel, but it was the usual manageable toxicity.

This study basically confirmed that docetaxel was probably a more potent taxane, at least on an every-three-week schedule. The survival advantage was surprising. In fact, there aren't many regimens with a documented survival advantage in patients with metastatic breast cancer.

Obviously, adding trastuzumab to paclitaxel or to an anthracycline has a survival advantage relative to chemotherapy alone. Joyce O'Shaughnessy's trial, comparing capecitabine and docetaxel to docetaxel alone, also demonstrated a survival advantage.

Taxotere-311: A Phase III Randomized Trial Comparing Docetaxel to Paclitaxel in Patients with Metastatic Breast Cancer (n=449)

Overall response rate in the patients evaluable for response (n = 388)

Docetaxel	Paclitaxel	*p*-value
37.4%	26.4%	0.02

Efficacy: Intent-to-treat analysis

	Docetaxel (n = 225)	Paclitaxel (n = 224)	*p*-value
Overall response rate (CR + PR)	32.0%	25.0%	0.10
Median time to progression (months)	5.7	3.6	0.0001
Median overall survival (months)	15.4	12.7	0.03

Safety analysis: Grade III/IV toxicity

	Docetaxel (n = 222)	Paclitaxel (n = 222)
Neutropenia	93.3%	54.5%
Asthenia	23.9%	6.8%
Infection	14.0%	5.0%
Edema	11.3%	4.5%
Stomatitis	10.4%	0.5%
Neuromotor	9.0%	4.5%
Neurosensory	8.6%	4.5%

SOURCES:

Ravdin P et al. **Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer.** Presented at European Cancer Conference 2003. *European Journal of Cancer Supplements* 2003 1(5):S201;**Abstract 670.**

Jones S et al. *Breast Cancer Res Treat* 2003;**Abstract 10.**

Sequential single-agent versus combination chemotherapy in patients with metastatic breast cancer

The big question associated with the sequential single-agent versus combination chemotherapy trials is the effect of crossover therapy. In Joyce O'Shaughnessy's trial, we don't know what the effect on survival would have been if 60 or 70 percent of the patients treated with single-agent docetaxel were then treated with capecitabine. Maybe there would not have been a survival difference. Hence, the effect of crossover therapy remains a question in all of these trials comparing doublets to single-agent regimens.

Efficacy of XT vs T in Patients with Anthracycline-pretreated Metastatic Breast Cancer

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

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

XT versus T: Post-study Chemotherapy after Progression

	XT	T
% receiving postrandomization chemotherapy	72%	65%
Agent received*		
capecitabine	3%	18%
5-FU	20%	23%
vinorelbine	33%	28%
anthracyclines	11%	11%
docetaxel	21%	7%

* Reflects combination and single-agent chemotherapy regimens.

- Capecitabine versus all other chemotherapies resulted in a 50% decreased risk of death (HR=0.5, p<0.005).
- Vinorelbine-containing chemotherapy versus all other chemotherapy agents did not provide benefit (HR=1.0, p=0.94).
- Median survival was 21.0 months for single-agent capecitabine versus 13.5 months for vinorelbine versus 12.5 months for patients receiving any other chemotherapy regimen.

SOURCE: Miles D et al. **Survival benefit with Xeloda® (capecitabine)/Taxotere (docetaxel) (XT) versus Taxotere®: Analysis of post-study therapy.** Poster #442, San Antonio Breast Cancer Symposium 2001.

I generally prefer single-agent chemotherapy, but I discuss combination chemotherapy with my patients and offer them a choice. In clinical practice, my approach has been to use combination chemotherapy when I can't wait for a response.

In the patient with limited disease who needs chemotherapy, in whom I'm hoping to obtain a complete remission, consolidate the sites of disease with radiation or if there is a chance for a prolonged remission, I would probably also favor combination chemotherapy. If the treatment is strictly for palliation or to try to control the cancer, I'm probably going to use sequential single-agent chemotherapy.

2003 National Patterns of Care Survey of US Oncologists: Combination versus Sequential Chemotherapy in the Metastatic Setting

Would you generally use combination or sequential single-agent chemotherapy in women in their 50s with ER/PR-negative, HER2-negative breast cancer in each of the following metastatic situations?

Clinical Situation	Combination	Sequential single agents
Asymptomatic patients with bone metastases	23%	77%
Asymptomatic patients with several small lung metastases	30%	70%
Asymptomatic patients with several small hepatic metastases	38%	62%
Patients with moderate pain requiring oral narcotics with bone metastases	50%	50%
Very symptomatic patients with visceral metastases	85%	15%

US Oncology adjuvant capecitabine and docetaxel (XT) trial

NSABP conducted a neoadjuvant trial (NSABP-B-27) comparing four courses of AC to four courses of AC followed by docetaxel. In that trial, the addition of docetaxel doubled the pathologic complete response rate. Therefore, our Breast Committee at US Oncology has now assumed that four courses of AC followed by docetaxel is the standard treatment. In our adjuvant XT trial, patients will be randomly assigned to AC followed by docetaxel or AC followed by docetaxel and capecitabine.

A Randomized, Open-Label, Multicenter, Phase III Trial Comparing AC Followed by Either Docetaxel (T) or Capecitabine Plus Docetaxel (XT) as Adjuvant Therapy for Female Patients with High-Risk Breast Cancer **Planned Protocol**

Protocol ID: US Oncology 01-062
Accrual: 1,810 patients

Eligibility: Node-positive or high-risk node-negative operable breast cancer

ARM 1: AC x 4 → docetaxel x 4
ARM 2: AC x 4 → (docetaxel + capecitabine) x 4

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

SOURCE: Protocol 01-062 synopsis, June 2002.

US Oncology adjuvant docetaxel and cyclophosphamide trial

At ASCO 2003, I presented the first planned analysis of an adjuvant trial comparing four cycles of docetaxel and cyclophosphamide (TC) to four cycles

of doxorubicin and cyclophosphamide (AC). The trial was underpowered with 1,016 total patients and approximately 500 patients per treatment arm. The patients were pre- or postmenopausal and had either node-negative or node-positive disease. At 42 months of follow-up, there were fewer recurrences in the patients treated with TC than those treated with AC.

We had previously demonstrated that TC was a little better-tolerated than standard AC. Patients treated with TC had some of usual docetaxel-related side effects (e.g., arthralgias, peripheral neuropathy, etc.), but they had less mucositis, anemia, nausea and vomiting.

A Phase III Adjuvant Trial Comparing Docetaxel and Cyclophosphamide (TC) to Doxorubicin and Cyclophosphamide (AC)

	TC (n=506)	AC (n=510)	*p*-value
Relapses	9%	12%	0.13
Deaths (all causes)	7.5%	9%	0.47

SOURCE: Jones SE et al. **Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/ cyclophosphamide (AC) to 4 courses of docetaxel/cyclophosphamide (TC).** *Presented at ASCO* 2003;**Abstract 59.**

I use adjuvant TC for patients as an alternative to anthracycline-based regimens. I see little reason to use CMF, and I've used TC in patients with heart disease or those previously treated with doxorubicin. The TC regimen has no cardiac toxicity or long-term toxicities at 42 months.

For many patients with node-negative disease, four cycles of adjuvant AC is standard treatment, but if there were any hesitancy to use it because of heart disease or other issues, I would use four cycles of TC.

Recent adjuvant chemotherapy trials in patients with node-positive disease

We now have a number of adjuvant regimens that are better than the standard regimens. I'm intrigued by the dose-dense approach, but before I adopt it routinely, I want to see confirmation from a second trial. Two trials evaluating AC followed by paclitaxel have reported a significant improvement with that adjuvant regimen.

The NSABP-B-28 trial, which added four cycles of paclitaxel to AC, had results similar to the earlier study. Many oncologists have substituted docetaxel for paclitaxel, and the Taxotere-311 data lends support to that in the adjuvant setting. In a younger patient with node-positive disease who is not eligible for a trial, I am more likely use AC followed by docetaxel.

2003 National Patterns of Care Survey of US Oncologists: Impact of Age on Use of Adjuvant Chemotherapy

A woman with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: Would you recommend adjuvant chemotherapy?

Patient age	33	43	55	65	77
Percent recommending chemotherapy	93%	93%	98%	95%	85%

If you recommend adjuvant chemotherapy, which regimen would you select?

	Patient age				
Chemo	33	43	55	65	77
AC-docetaxel	46%	46%	44%	41%	15%
AC-paclitaxel	40%	35%	36%	35%	23%
AC	11%	13%	10%	16%	26%
CMF	—	3%	2%	—	21%
FAC/FEC	3%	3%	8%	8%	3%
Docetaxel	—	—	—	—	12%

The study comparing docetaxel, doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) is a very clean trial. It is often interpreted as TAC being more effective for patients with one to three positive nodes, but not those with four positive nodes. However, that is the way the data were presented, and TAC is pretty effective across the board. Some oncologists have expressed concern about the TAC regimen's toxicity, and it probably requires the use of growth factors.

BCIRG 001: Adjuvant TAC versus FAC

ARM 1: TAC (docetaxel, doxorubicin, cyclophosphamide 75/50/500 mg/m^2) q3w x 6

ARM 2: FAC (5-fluorouracil, doxorubicin, cyclophosphamide 500/50/500 mg/m^2) q3w x 6

SOURCE: Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** Presented at Proceedings of the American Society of Clinical Oncology, 2002;**Abstract 141.**

BCIRG 001: Adjuvant TAC versus FAC

	Risk ratio TAC/FAC	Absolute reduction %	*p*-value
DFS	0.68	8%	0.0011
by nodal status			
1-3	0.50	11%	0.0002
4+	0.86	2%	0.33
by receptor status			
HR-	0.62	—	0.005
HR+	0.68	—	0.02
Overall survival	0.76	5%	0.11
by nodal status			
1-3	0.46	7%	0.006
4+	1.08	2%	0.75

HR+ = ER/PR-positive tumors

SOURCE: Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** Presented at Proceedings of the American Society of Clinical Oncology, 2002;**Abstract 141.**

Fulvestrant in patients with metastatic breast cancer

Fulvestrant has a different mechanism of action than the other hormonal agents because it downregulates both the estrogen and progesterone receptors. It's a well-tolerated parenteral agent — a potential advantage for patients with compliance issues. There is a subset of patients who had an exceptionally long duration of response with fulvestrant, and this is not fully appreciated.

US Oncology participated in one of the trials comparing fulvestrant to anastrozole, and I personally enrolled 27 patients in the study. Five of those patients had responses lasting longer than three years, which is really extraordinary for any endocrine treatment; two of the patients had responses lasting longer than four years. Of those five patients, four have progressed and had their therapy unblinded; all four were on fulvestrant. I would bet the fifth patient, although her treatment remains blinded, is also on fulvestrant.

A reanalysis of the North American and the European fulvestrant trials used a different statistical model called the mean duration of response. In that statistical model, values were assigned to every patient: patients with disease that did not respond were assigned a value of zero and patients with disease that did respond were assigned a number to correspond with the number of months of the response. With those calculations, fulvestrant had a significantly longer duration of response. It was 36 percent longer in the North American trial and 27 percent longer in the European trial.

In this country, I see fulvestrant being used as a third- or fourth-line hormonal therapy; however, studies indicate that it might be better than anastrozole following disease progression on tamoxifen. I encourage physicians who are going to try fulvestrant to use it in women progressing on tamoxifen.

The paradigm will probably shift because more patients will be treated with adjuvant anastrozole. We don't know where fulvestrant will fit into that sequence in a patient who has never received tamoxifen whose disease relapses after adjuvant anastrozole.

2003 National Patterns of Care Survey of US Oncologists: Sequencing of Endocrine Therapy in Endocrine-Naïve Patients with Metastatic Disease

What sequence of hormonal therapy do you typically use in postmenopausal women with metastases who did not receive adjuvant endocrine therapy?

Agent	1st line	2nd line	3rd line	4th line
Anastrozole	38%	28%	5%	—
Tamoxifen	30%	37%	12%	7%
Letrozole	32%	12%	5%	2%
Fulvestrant	—	8%	38%	28%
Exemestane	—	15%	33%	18%
Megestrol acetate	—	—	7%	23%
Other	—	—	—	7%
None	—	—	—	15%

Sequencing hormonal agents in postmenopausal women

In a postmenopausal woman whose disease relapses on adjuvant tamoxifen, I would use fulvestrant because I've seen some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (e.g., aromatase inhibitors and megestrol acetate).

A couple of reports have looked at the response to fulvestrant in patients who have received an aromatase inhibitor. A fairly small Swiss study reported that about one-third of patients derived clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor. A compassionate-use study, reported at ASCO 2003, reported about 60 patients with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had a more than 50 percent clinical benefit rate in those patients.

2003 National Patterns of Care Survey of US Oncologists: Endocrine Therapy in Patients with Prior Adjuvant Tamoxifen

What sequence of hormonal therapy do you typically use in postmenopausal women with metastases who completed adjuvant tamoxifen four years ago?

Agent	1st line	2nd line	3rd line	4th line
Anastrozole	50%	15%	—	2%
Fulvestrant	—	33%	35%	15%
Letrozole	43%	10%	—	2%
Exemestane	—	33%	40%	5%
Tamoxifen	7%	7%	7%	8%
Megestrol acetate	—	2%	13%	25%
Other	—	—	—	8%
None	—	—	5%	35%

Adjuvant hormonal therapy for postmenopausal women

The ATAC trial has had a major impact across the country, and we are seeing more adjuvant anastrozole being used. The ATAC trial results must be discussed with patients, and patients should be aware of the two hormonal therapy options. Many factors go into making a decision about hormonal therapy, including the patient's ability to pay for the drug, her feelings and her history of thromboembolic events.

Change in Adjuvant Endocrine Therapy Use Since 2002

65-year-old woman with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: Which adjuvant endocrine therapy would you recommend?

	2002	2003
Tamoxifen	63%	35%
Anastrozole	31%	59%
Other aromatase inhibitor	6%	6%

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

I am more likely to use adjuvant anastrozole in the patient with higher-risk, node-positive disease. The woman with 10 positive nodes needs every percentage point possible to make sure her cancer doesn't recur. In that type of patient, I would try to encourage patients to receive anastrozole.

2003 National Patterns of Care Survey of US Oncologists: Tolerability of Tamoxifen

What percent of your patients has difficulty tolerating tamoxifen?

Difficulty tolerating tamoxifen	19%
No difficulty tolerating tamoxifen	81%

In the adjuvant setting, how many postmenopausal patients have you switched from tamoxifen to an aromatase inhibitor because the patient had difficulty tolerating tamoxifen?

Mean	11 patients

Adjuvant trastuzumab

Although I would use adjuvant trastuzumab for such a patient who enrolled in a clinical trial, I personally would not use it in such a patient not enrolled in a clinical trial. No studies have shown that adjuvant trastuzumab is safe or tolerable, and it may just put the patient at risk. We all think adjuvant trastuzumab is going to work, but until we have clinical trial data showing that, I would not use it. We think we can do better, and maybe adjuvant trastuzumab will be one of the answers.

2003 National Patterns of Care Survey of US Oncologists: Adjuvant Trastuzumab Outside the Clinical Trial Setting

Have you ever used trastuzumab in the adjuvant setting outside the context of a clinical trial?

Yes	18%
No	82%

In how many patients have you used adjuvant trastuzumab?

Mean	7 patients

Select publications

Publications discussed by Dr Jones

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

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**

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Heys SD et al. **Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial.** *Clin Breast Cancer* 2002;(3 Suppl 2):69-74. **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**

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

Jones SE et al. **Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/ cyclophosphamide (AC) to 4 courses of docetaxel/cyclophosphamide (TC).** *Proc ASCO* 2003;**Abstract 59.**

Mamounas EP et al. **Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *Proc ASCO* 2003;**Abstract 12.**

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

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**

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**

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 Can Res Treat* 2002;76 (Suppl 1):72;**Abstract 249.**

Ravdin P et al. **Phase III comparison of docetaxel (D) and paclitaxel (P) in patients with metastatic breast cancer (MBC).** *Eur J Cancer Suppl* 2003;1(5):201;**Abstract 670.**

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**

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**

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

Vergote I et al; Trial 0020 Investigators; Trial 0021 Investigators. **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.**

Post-test: Breast Cancer Update, Issue 9, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the study of bevacizumab/capecitabine in metastatic breast cancer, which of the following effects were seen:**
   a. Time to progression was superior in the combination
   b. Response rate was superior in the combination
   c. a and b

2. **The BIG-01-01 (HERA) adjuvant trial will evaluate one versus two years of trastuzumab.**
   a. True
   b. False

3. **Which of the following regimens were compared in the Taxotere-311 trial?**
   a. Docetaxel versus paclitaxel
   b. Docetaxel versus doxorubicin/cyclophosphamide
   c. Docetaxel versus epirubicin/cyclophosphamide
   d. All of the above

4. **Taxotere-311 demonstrated that patients with metastatic breast cancer treated with docetaxel have a better survival rate than those treated with paclitaxel.**
   a. True
   b. False

5. **The US Oncology adjuvant XT trial will compare which of the following regimens?**
   a. AC → docetaxel
   b. Docetaxel + capecitabine
   c. AC → docetaxel + capecitabine
   d. a and c
   e. b and c

6. **Ongoing clinical trials will evaluate the effectiveness of fulvestrant loading doses.**
   a. True
   b. False

7. **ECOG-2100 randomly assigns women with locally recurrent or metastatic breast cancer to paclitaxel alone or paclitaxel with bevacizumab as first-line therapy.**
   a. True
   b. False

8. **What percent of patients with breast cancer overexpress VEGF in their primary tumors compared to surrounding normal tissue?**
   a. <10%
   b. 30-50%
   c. 70-90%

9. **ECOG-1193 comparing doxorubicin followed by paclitaxel, paclitaxel followed by doxorubicin, and the combination demonstrated all of the following except?**
   a. Increased overall response rate for the combination
   b. Longer time to treatment failure for the combination
   c. Improved overall survival for the combination

10. **The European and North American trials of fulvestrant versus anastrozole in postmenopausal patients with metastatic disease demonstrated:**
    a. Equivalent survival
    b. Longer duration of response favoring fulvestrant
    c. Superior time to progression and response rate favoring anastrozole
    d. a and b

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

Evaluation Form: Breast Cancer Update, Issue 9, 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 9

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

- Evaluate adjuvant chemotherapy options for patients at high risk for relapse, including ongoing clinical research trials 5 4 3 2 1
- Discuss the implications of recent and ongoing clinical trials evaluating docetaxel and paclitaxel in the management of breast cancer 5 4 3 2 1
- Develop an algorithm for sequencing hormonal agents in the management of estrogen receptor-positive metastatic breast cancer 5 4 3 2 1
- Describe the clinical implications of ongoing clinical trials and emerging research on biologic therapies targeting HER2, VEGF and EGFR 5 4 3 2 1
- Counsel patients with metastatic breast cancer about combination versus sequential single-agent chemotherapy 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
George W Sledge, MD	5 4 3 2 1	5 4 3 2 1
Sandra Swain, MD	5 4 3 2 1	5 4 3 2 1
Stephen E Jones, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
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 9, 2003

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

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

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