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Errata:

On page 31 of Breast Cancer Update 2003, Issue 2, Marc L Citron was incorrectly identified as: Chief, Division of Oncology, Albert Einstein College of Medicine.

The correct information is:
Marc L Citron, MD
Chief, Oncology, ProHEALTH Care Associates, LLP; Clinical Professor of Medicine,
Albert Einstein College of Medicine of Yeshiva University

Roman Perez-Soler, MD
Professor of Medicine
Chairman, Department of Oncology, Montefiore Medical Center,
The University Hospital for the Albert Einstein College of Medicine;
Chief, Division of Medical Oncology, Department of Medicine,
Albert Einstein College of Medicine

We sincerely regret this error.

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 CD or tape, review the monograph and complete the post-test and evaluation form. This monograph contains edited comments, clinical trial schemas, graphics and references, which supplement the audio program and the website, BreastCancerUpdate.com, where you will find 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 utilizes 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 HER2-positive breast cancer patients.
- Develop and explain a management strategy for women with ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Develop and explain a management strategy for women with ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel ER-positive postmenopausal patients about the risks and benefits of aromatase inhibitors in the adjuvant setting.
- Evaluate the relevance of emerging data on dose-dense chemotherapy to patients.

Issue 3, 2003, of Breast Cancer Update consists of discussions with three research leaders on a variety of important topics including selection of single-agent versus combination chemotherapy in the metastatic setting, impact of the addition of carboplatin to trastuzumab plus paclitaxel, integration of the ATAC trial results into clinical practice and dose-dense chemotherapy.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 3

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

- Formulate a treatment plan for a postmenopausal woman with ER-positive breast cancer who develops asymptomatic metastatic disease while receiving adjuvant tamoxifen.
- Choose a first-line chemotherapeutic regimen for a woman with hormone refractory ER-positive metastatic breast cancer.
- Design a treatment plan for a woman with HER2-positive metastatic breast cancer who has not received any prior chemotherapy.
- Discuss the impact of dose-dense adjuvant chemotherapy on patient care.
- Assess the results of the clinical trial comparing trastuzumab plus paclitaxel with or without carboplatin.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

NL Communications 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 in the activity.

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Kathy Miller, MD	**Grants/Research Support:** AstraZeneca Pharmaceuticals LP; Genentech Inc.; Bristol-Myers Squibb Company; Aventis Pharmaceuticals Inc.; Sugen Inc.; Telik Inc.
	Consultant: Eli Lilly & Company
G Thomas Budd, MD	**Grants/Research Support:** Amgen Inc.; AstraZeneca Pharmaceuticals LP; Genentech Inc.
Nicholas J Robert, MD	**Grants/Research Support:** Merrimack Pharmaceuticals Inc.; Aventis Pharmaceuticals Inc.; Bristol-Myers Squibb Company; Genentech Inc.; Pharmacia Corporation; Roche Laboratories Inc.
	Consultant: AstraZeneca Pharmaceuticals LP; Aventis Pharmaceuticals Inc.; Bristol-Myers Squibb Company; Genentech Inc.
	Speakers' Bureau: AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Genentech 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
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®,	Bristol-Myers Squibb Company,
	Neosar®	Pharmacia Corporation
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc.
doxorubicin	Adriamycin®	Pharmacia Corporation
doxorubicin HCL liposome injection	Doxil®	Ortho Biotech Products Inc.
exemestane	Aromasin®	Pharmacia Corporation
filgrastim	Neupogen®	Amgen Inc.
fluorouracil, 5FU	—	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals Corporation
megestrol acetate	Megace®	Bristol-Myers Squibb Company
methotrexate	—	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc.
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech Inc.
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronate	Zometa®	Novartis Pharmaceuticals Corporation

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Editor's Note

Two Women

The plethora of "*P*" values and Kaplan-Meier curves permeating the oncology research literature sometimes makes it easy to forget that the building blocks of clinical trials are people — doctors, nurses and most importantly, patients. In this issue, Kathy Miller presents two women who participated in Phase III randomized trials that had a fundamental impact on our understanding of breast cancer treatment.

The first was a 62-year-old woman who enrolled in the ECOG-1193 trial. This classic trial, which was led by Kathy's colleague and mentor, George Sledge, addressed the critical question of combination versus sequential chemotherapy in women with metastatic disease. For years this study has been presented and mentioned at oncology meetings, but the definitive paper was only recently published in the February 15, 2003 issue of the *Journal of Clinical Oncology*. While the paper concludes that sequential single-agent chemotherapy results in the same overall survival as combination chemotherapy, Kathy's case reveals the challenges in incorporating data from a patient's individual course to a clinical trial.

This woman was randomized to the single-agent arm, and there was essentially no response to the first agent (doxorubicin) and a modest response to the crossover (paclitaxel), which also caused significant toxicity. However, after the primary randomization, major longstanding complete and near-complete responses were induced with anastrozole, and then capecitabine. The patient eventually died from an unrelated cerebrovascular event while experiencing excellent tumor control from capecitabine. Dr Miller noted that while this woman's extended survival contributed to the single-agent randomization arm of ECOG-1193, it was the post-trial therapy that seemed to have the greatest effect in prolonging her life.

One can argue that large numbers of patients accrued to a study will obviate outlying clinical events such as these, but any tumor board meeting will provide more than adequate testimony to the heterogeneity of breast cancer, particularly in the metastatic setting. Kathy's second case, presented at the 2002 San Antonio Breast Cancer Symposium "Meet the Professor" session, demonstrates another critical point about interpreting clinical research.

This 49-year-old woman was enrolled in a historic study — the first major randomized breast cancer clinical trial evaluating an antiangiogenic agent. Many attendees at the San Antonio Breast Cancer Symposium were disappointed that

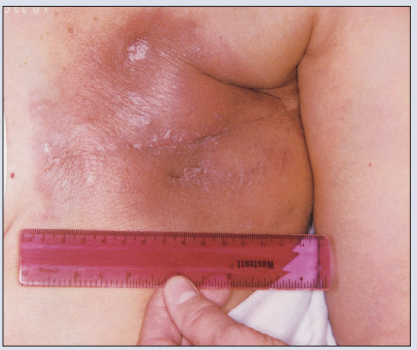
this trial failed to demonstrate its primary endpoint — a time to progression advantage for the combination of capecitabine and bevacizumab compared to capecitabine alone. In the interview for this program, Dr Miller presents the provocative course of her patient with chest wall recurrence to highlight the complexities of interpreting data from clinical trials in patients with metastatic disease.

To Dr Miller's eyes, this woman's tumor had a rapid and extremely impressive objective complete response to single-agent capecitabine (see photos below), and the symptoms from her aggressive tumor also completely abated. However, the external review board — evaluating the photos and clinical notes — called this "stable disease." Kathy concedes that based on the very conservative trial guidelines for external review, this was a correct interpretation, but this case vividly portrays the complexity of determining the antitumor effect of therapies in clinical trials.

In an era of "evidence-based" medicine, clinicians should consider that the foundation for clinical research is the individual patient and that complex biopsychosocial variables make clinical research a less exact science than laboratory investigation. Ultimately, patients and physicians in daily practice routinely confront a panoply of imperfect trial data that must be judiciously evaluated in the context of each patient's needs and values.

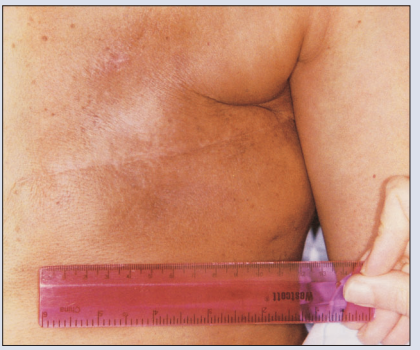
—Neil Love, MD

PRETREATMENT



A. Pretreatment: Massive erythematous cutaneous and subcutaneous tumor infiltration causing pruritus and pain.

POST-TREATMENT



B. Post-treatment with capecitabine: No tumor was visible, and the patient was asymptomatic. External trial review categorized this as "stable disease."

Kathy Miller, MD

Assistant Professor of Medicine,
Division of Hematology/Oncology,
Indiana University School of Medicine

Member, Eastern Cooperative Oncology Group

Edited comments by Dr Miller

CASE 1
62-year-old, postmenopausal woman with ER-positive, HER2-negative metastatic disease

1995: Modified radical mastectomy (node-negative), adjuvant tamoxifen.

1997: Pulmonary and hepatic metastases. Enrolled in the ECOG-1193 trial and randomized to single-agent doxorubicin. Received eight cycles with stable disease.

1998: Paclitaxel crossover on the trial; partial response. After nine cycles, progression to prestudy status.

1998: Treatment off-protocol with anastrozole: Complete response. During the remission, patient had breast reconstruction and contralateral breast reduction for symmetry.

2001: Bone metastases. Treatment with megestrol acetate, a bisphosphonate and radiation therapy for hip discomfort.

2001: Rapid progression in pulmonary nodules. Capecitabine administered with near complete response.

2002: Death from cerebrovascular event unrelated to the breast cancer.

Treatment alternatives after progression on adjuvant tamoxifen

If I were to treat this woman today, I would probably start with hormone therapy, even with visceral disease. She's asymptomatic, has a tumor that is strongly ER-positive and her disease is easy to follow with a simple chest x-ray. It would be reasonable to give this woman additional hormonal therapy with an aromatase inhibitor and repeat her chest x-ray in two or three months to evaluate response. At this stage, hormonal therapy would be more beneficial than chemotherapy in terms of quality of life, and I don't think it would alter her survival.

I've used fairly equal amounts of anastrozole and letrozole in cases like this. I don't know of any data directly comparing them in practice, and their side effects are similar. We have first-line trials with both agents comparing them to tamoxifen that show — depending on the endpoint — that they are equivalent or superior. As for the adjuvant setting, we don't yet have any data on letrozole.

Breast reconstruction in patients with metastatic disease

This was the first time I sent a patient with metastatic disease for reconstruction. The plastic surgeon called and asked, "What are you doing here? She has metastatic disease, so what's the difference?" And I responded, "She has been asking me for this for quite a while now, and she's still in complete clinical remission. I don't know how long this is going to last, but it seems like it's going to be a while. And when it stops working, we're going to switch to another hormone." Reconstruction — even with metastatic disease — seemed reasonable, because I hoped she still had several years ahead of her. She fully recovered from the reconstructive surgery and was absolutely delighted to be rid of her prosthesis. She was a large-breasted woman and the inequity in size and stress on her neck and back was difficult for her, so she also had contralateral breast reduction.

Quality of life: Chemotherapy versus hormonal therapy

Quality of life is significantly better for patients on hormonal therapy than on chemotherapy. While this patient tolerated chemotherapy quite well, she still felt pretty weak for several days after each treatment. She experienced some fatigue and nausea, but she was able to maintain her weight. She developed significant neuropathy with the paclitaxel, which was beginning to interfere with her activities at about the time her disease was progressing.

She was having difficulty manipulating buttons and holding a pen — certainly not things that we would consider life-threatening toxicities, but certainly life-altering. She had been active with her church and volunteer activities prior to treatment. Although she remained functional on chemotherapy, it was to a lesser degree. She had to discontinue all of her volunteer activities and didn't do much other than attend church. After she switched to hormonal therapy, she was able to return to all of her previous activities.

Hormonal therapy after progression on anastrozole

If fulvestrant had been available, I certainly would have considered it. I am not aware of much data evaluating the response to fulvestrant after aromatase inhibitors, but knowing the data after tamoxifen, I expect there are patients who will respond. While the actual response rates for patients progressing on tamoxifen were similar, fulvestrant improved the duration of response by a couple of months compared to anastrozole. That can be very important to a patient.

In the absence of data as to which treatment is going to give the best or longest-lasting response, issues like convenience and compliance become even more important and need to be discussed with the patient. This patient was already being seen every four weeks for her bisphosphonate infusion, so treatment with fulvestrant would not have required extra trips to the clinic.

Some patients prefer receiving one injection a month, versus having to remember to take a pill every day. I recently saw one patient who admitted that she probably took only 10 percent of her adjuvant tamoxifen because she just doesn't like taking pills and she forgets. When she was suspected of having metastatic disease, she claims she "got religion" about her tamoxifen, but still only managed to take it about 75 percent of the time.

Efficacy of fulvestrant compared to anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy

	Combined Analysis*		European Trial (0020)		North American Trial (0021)	
	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	19.6%	17.3%	20.7%	15.7%	17.5%	17.5%
Clinical Benefit (CR + PR + SD ≥ 24 wks)	43.7%	41.1%	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

*** "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."**

DERIVED FROM:

*Parker LM et al. *Proc ASCO* 2002;Abstract 160.
Howell A et al. *J Clin Oncol* 2002;20:3396-403.
Osborne CK et al. *J Clin Oncol* 2002;20:3386-95.

Chemotherapy after progression in the asymptomatic patient

After progressing on hormones for adjuvant therapy and metastatic disease, single-agent capecitabine, paclitaxel or vinorelbine are all reasonable choices for chemotherapy in this patient. The single-agent response rates are similar,

but they have different toxicities and different modes of administration. Docetaxel and anthracyclines are very active single agents, but overall their toxicities are more difficult.

Capecitabine is a perfectly valid first-line option for an asymptomatic patient who's been on hormonal therapy for two or three years, is used to taking pills and is not concerned about hair loss. It eases patients from hormonal therapy into chemotherapy psychologically and in terms of side effects.

Switching patients from pills to intravenous therapy can trigger thoughts that they must be really sick and nearing the end. On the other hand, some patients think pills are less effective, which is not true, but we have to work with our patients' perceptions.

Comorbidities are also a factor in selecting an agent. A diabetic patient with peripheral neuropathy should avoid taxanes or vinorelbine because of potential neuropathic toxicities. Paclitaxel and docetaxel can be problematic for diabetics because of the need for premedication with steroids. Vinorelbine may not be a good choice for women with long histories of constipation.

Switching to a therapy that requires a vascular access device, like a Hickman, is a much bigger step for the patient than for the oncologist. Many patients see it as an end-stage measure, although after they have it in, they are generally delighted with it. But it's a big step that many patients are not emotionally ready to take, and you won't be able to administer vinorelbine for more than a few weeks without an access device.

Chemotherapy after progression in the symptomatic patient

In the symptomatic patient with rapidly progressing metastatic disease, treatment is aimed at getting the disease under control in order to improve and prolong the patient's quality of life. In this situation, we need to shrink the cancer as quickly as possible, with the hopes of then switching to either a less toxic chemotherapy agent or dosing schedule, or to a hormonal therapy.

We have typically used a combination of an anthracycline and a taxane, but the docetaxel/capecitabine combination is equally reasonable. It's difficult to compare the two combinations. We know there's a survival advantage with the docetaxel/capecitabine combination, and there's no survival advantage with an anthracycline/taxane combination.

But that's a bit of comparing apples and oranges because many of the anthracycline/taxane combinations — including the largest ECOG-1193 trial — included a crossover, and the docetaxel/capecitabine trial didn't. Had they done the study using the ECOG-1193 model — combination versus each single agent by itself with a crossover in the two single-agent groups — I think they would have seen the same results as ECOG-1193: slightly higher response rates with the combination, a minimal increase in time to progression and no difference in overall survival or quality of life.

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	19.1 months	22.5 months	22.4 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):2812-2823. 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):588-592. Abstract

Phase II/III Randomized Trial of DOX vs TAX vs 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 60 mg/m² ➜ paclitaxel 175 mg/m²/24 hr upon progression
ARM 2	Paclitaxel 175 mg/m²/24 hr ➜ doxorubicin 60 mg/m² upon progression
ARM 3	Doxorubicin 50 mg/m² + paclitaxel 150 mg/m²/24 hr + G-CSF

SOURCE: NCI Physician Data Query, February 2003.

The future of targeted therapies

We are moving towards more targeted treatments, but I'm a little less optimistic about how quickly we will get there than I was a few years ago. We hope one day to simply obtain a small sample of the patient's tumor, grind it up and put it on a microarray, that will spit out 10,000 genes and tell us, "This patient has breast cancer Type 15, which you treat with therapy X, which has a 98 percent survival rate." In order to reach that point, we need a large volume of a wide variety of tumors from patients who were treated in standard fashions, and then we need to know what happened to them. Then we can start to identify patterns of exquisite sensitivity or incredible resistance to a particular agent. However, our ability to collect tumor samples

is a problem because so many of the patients are not at university centers, where research on genomics and proteomics is being conducted.

Looking back at this case, we could not have predicted in advance that this patient would have minimal response to doxorubicin and paclitaxel and an excellent response to both anastrozole and capecitabine. It would have been helpful to have known this information at the onset.

If I had put her on anastrozole initially and switched her to capecitabine when she progressed, she would have died of her stroke without ever having had alopecia, nausea, myelosuppression or any other associated toxicities.

CASE 2
49-year-old school teacher with chest wall recurrence after mastectomy, regional radiation and adjuvant chemotherapy

Initial diagnosis: 3-cm, ER-negative, HER2-negative breast cancer with two positive nodes. Treated with modified radical mastectomy, adjuvant anthracycline/taxane regimen and chest wall radiation.

Nine months later: Chest wall recurrence, no evidence of distant metastases. Enrolled on single-agent capecitabine arm in a trial randomizing patients to capecitabine with or without bevacizumab. Complete response of tumor after two cycles of capecitabine (see page 5).

Seven months later: Second primary breast cancer in contralateral breast, treated with mastectomy. Capecitabine continued.

Four and a half months later: Bilateral chest wall progression. Vinorelbine administered with good response.

Some months later: Disease progression. Since that time, the patient has been treated in several Phase II trials, single-agent gemcitabine and doxorubicin HCL liposome injection with minimal response.

Phase III trial of capecitabine with or without bevacizumab in patients with previously treated metastatic breast cancer

This trial looked at a very refractory group of patients, all of whom had received an anthracycline and a taxane. This patient was in the subset of women who had received these drugs as adjuvant therapy and had not received any therapy for metastatic disease.

We considered designing the trial with a crossover to the bevacizumab arm but didn't for pragmatic reasons. The trial was designed with progression-free survival as its primary endpoint, but overall survival was a secondary endpoint.

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
Total evaluable patients: 462

Eligibility	Prior anthracycline and taxane treatment, 1 or 2 prior chemo regimens for metastatic breast cancer OR relapse within 12 months of completing anthracycline- and taxane-containing adjuvant therapy.

ARM 1	Capecitabine 1,250 mg/m² po bid (days 1-14)
ARM 2	Capecitabine 1,250 mg/m² po bid (days 1-14) + bevacizumab 15 mg/kg IV

Treatment repeats in both arms every 3 wks for up to 35 courses in the absence of disease progression or unacceptable toxicity.

SOURCES: Kathy Miller, Presentation, 2002 San Antonio Breast Cancer Symposium; NCI Physician Data Query, March 2003.

Efficacy of capecitabine with and without bevacizumab

The efficacy data confirmed the activity of bevacizumab reported in the Phase II trial with a similar patient population. There was a near doubling of response rates in patients receiving the combination of bevacizumab and capecitabine versus capecitabine alone.

The trial enrolled 462 patients and responses were assessed by an independent review facility, as well as by investigators. There is generally a discrepancy between these two groups. Some describe the independent review facility as more objective, while others say it is more cynical.

In this study, the independent review facility reported a lower response rate than the treating physicians. Although the combination therapy increased the response rate, most of the additional responses were short-lived. Therefore, the proportion of long-term responders and the progression-free survival was the same in both groups.

Tolerability and side-effect profile of capecitabine/bevacizumab

The toxicity data were reassuring. The capecitabine toxicities were similar to what was already reported in the literature, and the bevacizumab toxicities were as expected based on the Phase II results. About 20 percent of patients experienced hypertension requiring intervention. Ten to 20 percent of patients experienced proteinuria, although rarely severe, and no Grade IV events were reported.

Grades I and II bleeding were slightly increased, but Grade III bleeding was extremely uncommon and not increased by the addition of the antiangiogenic agent. There was a slight increase in thrombosis, predominantly deep vein thrombosis and line-associated thrombosis, but no increase in serious thrombotic events or pulmonary embolism with the combination.

Efficacy and toxicity of capecitabine + bevacizumab versus capecitabine alone

	Capecitabine (n=230)	Capecitabine + bevacizumab (n=232)
Objective response rate INV (IRF)	19.1% (9.1%)	30.2% (19.8%)
Duration of response INV (IRF)	6.7 (7.56) months	4.96 (4.96) months
Progression-free survival	4.2 months	4.9 months
	n=215	n=229
Hypertension (grade 3)	0.5%	17.9%
Thromboembolic PE DVT	5.6% 1.4% 2.3%	7.4% 1.3% 6.1%
Bleeding Grade ≥ 3	11.2% 1.4%	28.8% 0.4%
Proteinuria	7.4%	22.3%
Cardiac (Grade 3 or 4)	0.9%	3.1%

INV = Investigator Assessment
IRF = Independent Review Facility

DERIVED FROM: Kathy Miller, Presentation, 2002 San Antonio Breast Cancer Symposium

ECOG-E2100 trial: Phase III trial of paclitaxel with or without bevacizumab in patients with previously untreated metastatic breast cancer

This study takes bevacizumab to the next step. It moves the use of this agent to newly diagnosed, locally recurrent or metastatic patients and combines it with paclitaxel — a combination for which we have a lot of preclinical synergy data.

Bevacizumab is a targeted therapy, yet we currently treat patients based on the history of their disease rather than molecular factors. We need to determine how to select the patients most likely to respond to this type of therapy, but we don't know which factors are going to be predictive.

This study is prospectively collecting primary tumor tissue, serum and urine samples for investigation of potential surrogates of response to VEGF-targeted therapies. We hope VEGF is predictive, but it's technically difficult to measure and be certain that what you're measuring reflects the tumor, and not the white blood cells, macrophages and platelets.

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
Projected 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

Treatment repeats in both arms every 4 wks for 18 courses in the absence of disease progression or unacceptable toxicity.

Study Contacts:
Kathy Miller, MD, Protocol Chair, Tel: 317-274-0920, Eastern Cooperative Oncology Group

Edith A Perez, MD, Protocol Chair, Tel: 507-284-2111, North Central Cancer Treatment Group

Tamara Shenkier, MD, Protocol Chair, Tel: 604-877-6000, NCIC-Clinical Trials Group

Melody A Cobleigh, MD, Protocol Chair, Tel: 312-942-3240, National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, March 2003.

Single-agent capecitabine for metastatic breast cancer

When discussing the trial, I told this patient that capecitabine was one of the best therapies for her disease and that if she was randomized to the capecitabine-alone arm, she would receive exactly what I would have given her if the trial was not a possibility or didn't exist. She was disappointed when she first learned she was not randomized to the investigational arm, but she has a wonderful, supportive spouse who reminded her that they knew when they agreed to enter the trial that this might happen, and she was still receiving the best I had to offer. That quickly turned her around and she was willing to continue with the study.

It would have been reasonable to consider other single agents, such as vinorelbine or gemcitabine, but even off-study I believed that capecitabine was the best choice for her. She did not want to miss teaching days, so oral therapy was a real advantage and she didn't have alopecia. She tolerated the treatment very well. She had a dose reduction for Grade II hand-foot syndrome after her first cycle of therapy, and she did not require any other dose modifications.

After two cycles of capecitabine, she had a complete response with all visible and palpable evidence of her disease completely gone. Her chest wall discomfort disappeared as well, and she was completely symptom-free. It was an amazing response — minimal toxicity, symptoms gone, she felt well and she was able to continue teaching.

Summary of efficacy: Single-agent capecitabine versus standard chemotherapy in patients with anthracycline-resistant metastatic breast cancer

Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF) as first-line therapy		
	Capecitabine	CMF
Response rate (95% CI)	30% (19-43)	16% (5-33)
Complete response	5%	0%
Median time to disease progression (95% CI)	4.1 months (3.2-6.5)	3.0 months (2.4-4.8)
Median survival	19.6 months	17.2 months
Capecitabine versus paclitaxel as second-line therapy		
	Capecitabine	Paclitaxel
Response rate (95% CI)	36% (17-59)	26% (9-51)
Complete response	14%	0%
Median duration of response	9.4 months	9.4 months
Median time to progression (95% CI)	3.0 months (1.4-6.6)	3.1 months (2.5-6.5)

CI = confidence interval

DERIVED FROM: Biganzoli L et al. **Moving forward with capecitabine: A glimpse of the future.** *The Oncologist* 2002;7(suppl 6):29-35. **Abstract**

Selecting a taxane schedule for progression following adjuvant taxane therapy

Phase II data in patients with metastatic disease who received an adjuvant taxane show that you can switch to another taxane or use the same taxane on a different schedule and still obtain some additional response. I have certainly done that, but when considering the alternatives, it's not my first choice. Not because there's data that says it wouldn't work — it just doesn't feel right. It's an agent the patient already tried, it didn't produce the desired results and I have a number of other options. Typically, I will discuss it with patients and tell them that at some point we're likely to come back to the taxanes, but I prefer to try other therapies first.

Discrepancies between the findings of investigators and an independent review facility

The capecitabine with or without bevacizumab trial included a detailed process for reporting findings to an independent review facility. Chest, abdominal and pelvic CTs were taken at every assessment point and sent to the reviewers, regardless of the patient's status. All sites had the same type of Polaroid cameras to take photos of skin lesions with rulers in the image. And all of the physicians' clinical notes were sent after they were censored to ensure they did not indicate to which treatment group the patient was assigned.

Still, as we've seen in other trials, the independent review facility rated responses eight to ten percent lower than the investigators. Part of that is

probably realistic — some of the patients we say are responding probably don't quite meet the strict criteria set forth by the study — but part of that is the difficulty of assessing a patient whom you cannot examine.

This patient was one for whom there was significant discrepancy between the independent reviewers' and the investigators' assessments. When this patient had a complete response following capecitabine, the independent review facility reported her as stable. I would have done the same if I had been part of the independent review facility. While they have my physical exam notes telling them the chest wall is no longer indurated and the nodules are gone, they have no way to independently verify that. They use the clinical data to document progression, but regression on physical exam can't be verified, so the best they can do is call it stable disease.

In addition, they have to rely on photos that may not document skin changes well, particularly in darker-skinned women. This Hispanic patient had an intense hyperpigmentation following radiation. When her disease progressed, the skin lesions covered the radiation field and extended beyond it. Even though those lesions disappeared following two cycles of capecitabine, the hyperpigmentation from radiation was still visible. So, the independent review facility could only look at those photos and say, "This is not normal," and label her disease as stable while we reported a complete response.

Treatment of a second primary and progression in advanced breast cancer

This patient had a very interesting course. She continued on capecitabine but came off study for progression, which was actually a second primary breast cancer without recurrence of the previous extensive chest wall disease. We repeated all of her systemic staging, and there was absolutely nothing. She had a modified radical mastectomy and continued the capecitabine.

Four and a half months later; her cancer recurred with bilateral chest wall involvement that was actually worse on the side that was not radiated. Whether it was recurrence of two primary tumors, I don't know, but it was a curious pattern. She was treated with single-agent vinorelbine and had an excellent response.

Palliation of persistent, localized breast cancer

I've had a couple of patients with persistent, localized breast cancer, which can be intensely painful and socially isolating. It's difficult to put on normal clothes when there's a weeping, sometimes bleeding, often super-infected wound wrapping around one's chest. I've had several patients who don't want to be around people because they're self-conscious about the offensive odor.

Pain control is also very difficult. This patient didn't like the grogginess she experienced with narcotics, and the drugs we use for neuropathic discomfort didn't help much. We tried some topical anesthetics, but as the disease

became more extensive, there was a problem with systemic absorption, so we're not able to use those anymore. Women with this type of localized disease tend not to have a lot of visceral disease. It's certainly not the quality of survival for which we strive.

Quality of life and continued treatment for advanced disease

This is a truly amazing woman and I'm honored to care for her. She knows of my reservations regarding further treatment because we've discussed it several times. Yet, when I last saw her two weeks ago, the question utmost in her mind was, "How can you get me back to the classroom, because I need to finish out the year?" All she ever wanted to do was teach. She's taught me an incredible amount, and she's still a teacher whether she's in a classroom or not.

She is a very strong-willed woman who would probably rate her quality of life higher than I would at this point. She typically refuses to take analgesics and I've had to adjust how I ask her about pain because she usually says, "It's okay." Now I go one step further and ask, "Would other people say the pain medication is working well enough?" And then she'll admit that maybe it could be better. So, we continue adjusting doses and schedules of her treatments so that she can to be in the classroom as much as possible, because that's what's most important to her.

This is a difficult situation. I can certainly come up with agents that she's not received, but we're likely to have diminishing returns with increasing toxicity, and I'm concerned that I've made her feel worse, not better. I've tried very hard to get her to think about not having additional chemotherapy, but she is not quite ready to make that transition. In this situation, I think her opinion still trumps mine.

Select Publications

Publications discussed by Dr Miller

Gennari A et al. **Weekly docetaxel/paclitaxel in pretreated metastatic breast cancer.** *Clin Breast Cancer* 2002;3(5):346-52. **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**

Perez EA et al. **Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer.** *J Clin Oncol* 2001;19(22):4216-23. **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**

Stemmler HJ et al. **Weekly docetaxel (Taxotere) in patients with metastatic breast cancer.** *Ann Oncol* 2001;12(10):1393-8. **Abstract**

Estrogen receptor downregulator, fulvestrant

Bundred NJ et al. **Fulvestrant, an estrogen receptor downregulator, reduces cell turnover index more effectively than tamoxifen.** *Anticancer Res* 2002;22(4):2317-9. **Abstract**

Bundred N, Howell A. **Fulvestrant (Faslodex): Current status in the therapy of breast cancer.** *Expert Rev Anticancer Ther* 2002;2(2):151-60. **Abstract**

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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Dowsett M et al. **Effect of HER2 amplification status on the antiproliferative response of ER+ primary breast cancer to fulvestrant (Faslodex).** *Breast Cancer Res Treat* 2002; **Abstract 365.**

Elkak AE, Mokbel K. **Pure antiestrogens and breast cancer.** *Curr Med Res Opin* 2001;17(4):282-9. **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**

Howell A. **Future use of selective estrogen receptor modulators and aromatase inhibitors.** *Clin Cancer Res* 2001;7(12 Suppl):4402s-4410s;discussion 4411s-4412s. **Abstract**

Howell A. **Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies.** *Breast Cancer Res Treat* 2002; **Abstract 251.**

Howell A. **Preliminary experience with pure antiestrogens.** *Clin Cancer Res* 2001;7(12 Suppl):4369s-4375s;discussion 4411s-4412s. **Abstract**

Johnston SR. **Endocrine manipulation in advanced breast cancer: Recent advances with SERM therapies.** *Clin Cancer Res* 2001;7(12 Suppl):4376s-4387s;discussion 4411s-4412s. **Abstract**

Jones SE. **A new estrogen receptor antagonist--An overview of available data.** *Breast Cancer Res Treat.* 2002;75 Suppl 1:S19-21;discussion S33-5. **Abstract**

Massarweh S et al. **The estrogen receptor antagonist fulvestrant, but not the partial antagonist tamoxifen, is an effective endocrine treatment in a xenograft model of HER2 overexpressing breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 247.**

Morris C, Wakeling A. **Fulvestrant ('Faslodex')—A new treatment option for patients progressing on prior endocrine therapy.** *Endocr Relat Cancer* 2002;9(4):267-76. **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**

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Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24 Suppl C:C43-57. **Abstract**

Perey L et al. **Fulvestrant ('Faslodex') as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing phase II SAKK trial.** *San Antonio Breast Cancer Symposium* 2002:**Poster 249.**

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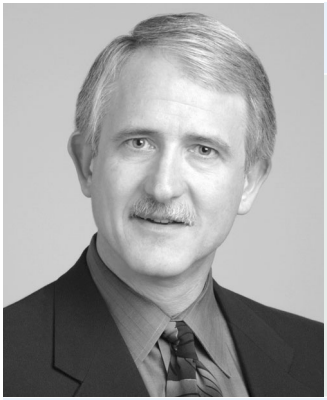

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Edited comments by Dr Budd

SWOG-S0221: A new Phase III adjuvant Intergroup trial evaluating chemotherapy schedules

In SWOG-S0221, the combination dose-dense arm of CALGB-9741 was selected for the initial randomization instead of the sequential arm. Our rationale was to shorten the duration of treatment and to make it more comparable to the AC regimen in the experimental arm.

In the second randomization, we were originally going to compare docetaxel alone to docetaxel plus capecitabine. There were a couple of reasons we decided to compare paclitaxel every two weeks to paclitaxel every week. First, the docetaxel/capecitabine combination is being investigated in several other multicenter adjuvant trials.

Second, it was felt that we should preserve the control arm from CALGB-9741, which administered paclitaxel every two weeks. At the end of SWOG-S0221, we hope we will know the optimal way to administer paclitaxel in the adjuvant setting.

CALGB Trial 9741

2x2 Factorial Design	Q 2 wk + filgrastim	Q 3 wk
Sequential A ➜ T ➜ C	24 weeks of therapy	36 weeks of therapy
Concurrent AC ➜ T	16 weeks of therapy	24 weeks of therapy

DERIVED FROM: Presentation, M Citron, San Antonio Breast Cancer Symposium 2002.

Phase III Trial of Continuous Schedule AC + G Versus Q 2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer Open Protocol

Protocol ID: SWOG-S0221
Accrual: 5,700 patients

Eligibility	Stage I - III invasive breast cancer, node positive or high-risk node negative, with no prior cytotoxic chemotherapy or radiation therapy.

ARM 1	AC q2w + PEG-G x 6 cycles ➜ T q2w + PEG-G x 6
ARM 2	Continuous AC + G x 15 weeks ➜ T q2w + PEG-G x 6
ARM 3	AC q2w + PEG-G x 6 cycles ➜ T qw x 12
ARM 4	Continuous AC + G x 15 weeks ➜ T qw x 12

A = doxorubicin; C = cyclophosphamide; G = filgrastim; T = paclitaxel; PEG-G = pegfilgrastim
Continuous AC = weekly doxorubicin + daily, oral cyclophosphamide

SOURCE: SWOG-S0221 Protocol, Version Date February 4, 2003.

SWOG-SO221: Rationale for daily oral cyclophosphamide

Daily oral cyclophosphamide seems to be superior. In the metastatic setting, an EORTC trial comparing intravenous CMF to a regimen with oral cyclophosphamide found the oral cyclophosphamide regimen — the so-called "classical" regimen — to be superior. Furthermore, in the adjuvant trials comparing CAF and CMF regimens, only when cyclophosphamide is given in the same way — either both arms receive intravenous or oral cyclophosphamide — is there a difference seen with the addition of the anthracycline.

Why does the oral method of administration seem to be superior? One reason could be dose density — you deliver more milligrams in per unit time. By giving cyclophosphamide orally and doxorubicin weekly, the dose density in terms of mg/m^2 per week compared to the accelerated regimen, at least for doxorubicin, is not necessarily superior but is denser. Bob Livingston sometimes calls this the "dense and denser" protocol, because we are giving what we believe to be an effective dose of an anthracycline on a more frequent schedule.

Metronomic chemotherapy

The third way of looking at this is the concept of metronomic chemotherapy, which suggests that more frequent drug administration at lower doses — sometimes even very low doses — might actually be superior to higher doses given less frequently. It appears that this advantage is based upon the antiangiogenic effects of the chemotherapy. Giving a low dose of chemotherapy frequently appears to optimize its antiangiogenic effects.

A number of preclinical models have evaluated this concept. When cyclophosphamide-resistant cell lines are put into animals and the animals are given cyclophosphamide on an infrequent bolus schedule, responses are rarely seen. However, if cyclophosphamide is given frequently (every six days) at a lower dose, responses may occur. In these animal models, the results appear to be due to the antiangiogenic effects. This metronomic schedule seems to be optimal for the addition of other antiangiogenic factors.

Some clinical studies also support the concept of metronomic chemotherapy. If you look back at the old Cooper regimen (CMFVP), maybe that was the secret to its efficacy. In Europe, there was a very interesting trial involving patients with refractory advanced breast cancer who were treated with very low doses of cyclophosphamide and very low doses of weekly methotrexate, and some responses were observed. These clinical studies offer evidence suggesting that there might be something to this concept.

It could be argued that another mechanism of action for these regimens is that daily oral cyclophosphamide is more likely to induce ovarian dysfunction. I think, however, that chemotherapy has cytotoxic effects in and of itself. Part of the effect of chemotherapy in premenopausal women may be related to its effects on ovarian function, but it's certainly not the whole story.

SWOG-S0221: Use of growth factor support

Pegfilgrastim is used in the dose-dense arm of the new SWOG-S0221 trial because it certainly makes the regimen more acceptable to patients. Looking at the time course to recovery of neutropenia, it appears that administration every 14 days is possible. There are anecdotal results indicating this is quite tolerable.

Initially, filgrastim will be used in the experimental arm of weekly doxorubicin and daily oral cyclophosphamide. At the University of Washington, pilot studies are being performed to evaluate pegfilgrastim with this regimen. If those studies show that this combination is safe, as expected, then we hope to amend the protocol and use pegfilgrastim in both arms of the study.

Results of CALGB-9741 trial

CALGB-9741 is a very interesting and provocative study, particularly the 31 percent relative reduction in mortality. However, the results are preliminary because it is very early in follow-up. At least in the first few years, the results should be stable. Dr Piccart's accompanying editorial was intriguing and laid the groundwork for the trial we are launching.

Also, it was of interest that in CALGB-9741, there was no clear difference between patients with ER-positive and ER-negative disease. I feel comfortable offering this every-two-week regimen to patients with ER-positive or ER-negative disease.

It is also interesting that these were not new agents being studied in CALGB-9741. There is a lot to be learned using currently available agents, and we can continue to take incremental steps in treating breast cancer.

Impact of CALGB-9741 on clinical practice and ongoing trials

On the practice level, physicians have been quite willing to adopt dose-dense regimens, partly because there is no increase in toxicity. In fact, in terms of neutropenic fever or documented myelosuppression, the every-two-week regimen is less toxic. More transfusions are required, but this is something we can deal with if we monitor counts and start replacement therapy with erythropoietic agents.

In terms of ongoing Phase III studies, the trials that I see in need of modification are N9831 and other trastuzumab trials. If a patient was randomized to the standard arm of doxorubicin/cyclophosphamide given every three weeks and followed by a taxane, there would be a nagging concern that the patient was not receiving optimal therapy. I think there has to be strong consideration made to amend those trials.

Managing patients with node-positive breast cancer

In the nonprotocol setting, I feel obligated to discuss the results from CALGB-9741 with patients who have positive nodes. After discussing the fact that these were very early results but perhaps relevant to a particular patient's care, I have treated some patients at high risk with this dose-dense regimen.

I also discuss standard treatment options, including the combination of doxorubicin and cyclophosphamide followed by a taxane, although I also discuss CAF-type regimens

Case discussion: Dose-dense chemotherapy for locally advanced disease

This is a very intelligent woman in her late 40s, in whom locally advanced breast cancer developed over a period of time. She was quite panicked and very anxious to begin therapy, but at the same time quite fearful of starting treatment. She was on vacation when she first noticed the tumor, so there was a delay in seeking medical care, and naturally she was quite concerned about the possible result of this delay.

On physical examination, she had a breast mass on the left side that was about 8-cm. There was some erythema over the tumor, although it was not a true inflammatory breast cancer. There was palpable adenopathy, which was not fixed. I think it was a relatively rapidly growing tumor, but perhaps not the most aggressive that I've seen. The hormone receptor and the HER2 status are currently pending.

I wanted to start her on treatment, but the locally advanced study at our institution was not open. I discussed a variety of treatment options with her. In my mind, the standard treatment is an anthracycline-containing regimen, and I believe a taxane should generally be used.

I presented the every-two-week doxorubicin/cyclophosphamide regimen as an option, believing we could generalize the results from CALGB-9741 to her situation. We reached a mutual decision to embark on that regimen and, as part of that, she is receiving pegfilgrastim.

A week after starting treatment, her tumor already seems to be responding and surgery is planned. I had discussed giving her doxorubicin/cyclophosphamide for four cycles followed by a taxane, which can be given preoperatively or postoperatively. If an extensive reconstruction (i.e., a TRAM reconstruction) is planned, there may be advantages to giving the taxane prior to surgery, so there's no delay in administering the taxane.

Implications of the ATAC trial for clinical practice

The ATAC trial is very important. It rejuvenates interest in hormonal therapy. Many of us were educated believing that "a hormone is a hormone." In postmenopausal women, it appears that the aromatase inhibitors are superior to tamoxifen. I believe that treatment with an aromatase inhibitor ought to be presented to those patients as an option in the adjuvant setting, and I only utilize anastrozole because that's the drug for which we have data. I tell patients that it appears that anastrozole may be superior to tamoxifen, but with tamoxifen we have a much longer track record. Then, I describe the differences in the toxicity profiles.

In premenopausal women, there is a rejuvenation of interest in ovarian ablation in combination with tamoxifen. Is ovarian ablation in addition to tamoxifen or in combination with an aromatase inhibitor superior to tamoxifen alone in a premenopausal woman? Right now that is the $64-million question that is being addressed in the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT).

Planned or ongoing trials of adjuvant endocrine therapy in premenopausal patients

Study	Entry	Intervention	Target Accrual	Status
ABCSG AU12	Stage I, II	Tamoxifen + Goserelin ± Zoledronate Anastrozole + Goserelin ± Zoledronate	1,250	600 patients ongoing
IBCSG TEXT	T1-T3, pN0-N2	Ovarian suppression + Exemestane Ovarian suppression + Tamoxifen	2,025	Planned
IBCSG SOFT	T1-T3, pN0-N2	Tamoxifen Ovarian suppression + Tamoxifen Ovarian suppression + Exemestane	2,700	Planned

DERIVED FROM: ASCO Technology Assessment: Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.

Sequential single-agent versus combination chemotherapy in metastatic disease

The trial recently published by George Sledge, comparing doxorubicin and paclitaxel given sequentially to the combination, is quite interesting. It indicates that, in the long run, sequential single-agent chemotherapy may be just as effective as combination chemotherapy in terms of survival.

This harkens back to studies done in the 1970s. Dr Chlebowski compared sequential single agents to combination chemotherapy. He found that sequential single agents provided an equivalent survival, but seemed to be inferior in patients with liver metastases.

That trial was done at a time when liver metastases referred to patients with bulky liver metastases who had a very poor prognosis; if they did not respond to frontline therapy, they would likely expire from their disease. In the majority of patients, I think single-agent chemotherapy is quite acceptable.

On the other hand, we have the trial comparing docetaxel with or without capecitabine. However, the majority of the patients who received docetaxel did not receive capecitabine as second-line treatment.

In terms of decision-making for metastatic disease, combination chemotherapy is optimal in a patient who needs a response in order to have a good outcome. In patients for whom you have the luxury of waiting to see if there is a response to treatment, then sequential single agents are quite acceptable.

Selecting the order of single-agent chemotherapy

In hormone-refractory disease, patients will be on chemotherapy indefinitely. We have to consider their lifestyle, figure out what's important to them and be able to accommodate their needs, consistent with good medical practice. Patients must consider the schedule, how frequently they need to come to the clinic and the toxicities of the particular agents.

It's hard to say that any individual single agent is the gold standard. We have the taxanes and the anthracyclines, but the newer agents, such as capecitabine, are also perfectly reasonable to use as frontline agents. In some patients, I would see no problem in doing that. I'm not sure that the sequence in which you use agents makes a difference; therefore, we tend to use the agent with the least toxicity or the toxicity profile most consistent with the patient's needs.

Use of fulvestrant in patients with ER-positive metastatic disease

In postmenopausal women, I tend to use fulvestrant following an aromatase inhibitor. That is generally my practice, although we really are lacking data in that situation.

There are some Phase II studies and anecdotal reports; however, I believe that there are Phase III trials that are being launched comparing fulvestrant to a steroidal aromatase inhibitor.

In my mind, aromatase inhibitors are the treatment of choice as frontline therapy, based on the bulk of evidence in the majority of postmenopausal women who have received adjuvant tamoxifen. Fulvestrant is certainly an alternative because it was shown to be at least equivalent to anastrozole. From a practical point of view, I tend to use the oral agents initially and then go to fulvestrant as a second-line treatment.

In my experience, fulvestrant is well tolerated. Many of these patients receive a bisphosphonate on a monthly basis anyway, so it really doesn't involve an additional trip to the clinic. The injections tend to be well tolerated, and most patients have not complained about hot flashes. I have seen results that are consistent with what I would expect for an active hormonal agent in that patient population.

Ongoing Phase II, multicenter noncomparative study evaluating fulvestrant as hormonal treatment in postmenopausal patients with advanced breast cancer who have progressed after treatment with tamoxifen and nonsteroidal aromatase inhibitors.

Patient Characteristics	Stratum A: AI-responsive patients* (n=30)		Stratum B: AI-resistant patients** (n=6)	
Prior hormonal therapy other than AI: Number of patients (%)				
Adjuvant	15 (50)		1 (17)	
Metastatic	19 (63)		5 (83)	
Prior hormonal therapy with AI: Number of patients (%)				
Adjuvant	—		—	
Metastatic	28 (93)		—	
Overall response rate (n=32)	Clinical Benefit***	PR	SD ≥ 24 wks	Disease progression
Number of patients (%)	11 (34)	2 (6)	9 (28)	21 (66)

* Patients who progressed while on AI treatment (anastrozole, letrozole, aminoglutethimide, exemestane or formestane) for advanced breast cancer after OR disease stabilization of ≥ 24 weeks).
** Patients who did not respond to AI treatment for advanced breast cancer or showed disease stabilization of < 24 weeks).
*** PR or SD for ≥ 24 weeks.
Abbreviations: AI = aromatase inhibitor; PR = partial response; SD = stable disease

SOURCE: Perey L et al. **Fulvestrant ('Faslodex') as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing phase II SAKK trial.** *San Antonio Breast Cancer Symposium* 2002:Poster 249.

First-line therapy for patients with HER2-positive metastatic disease

There is a survival advantage with the use of trastuzumab up front in a woman with HER2-positive metastatic disease, and giving an anthracycline may inhibit the ability to receive trastuzumab in the future. I think it's inexplicable to use an anthracycline as first-line therapy in this situation.

If I were a patient, I would certainly prefer to receive a trastuzumab-containing regimen. With trastuzumab and chemotherapy as first-line therapy, there is the option of giving the combination for a period of time, then stopping the chemotherapy and maintaining the remission with trastuzumab.

Phase II trial of liposomal doxorubicin and trastuzumab

We currently have a clinical trial looking at liposomal doxorubicin and trastuzumab as frontline therapy. Some preclinical studies suggest that this combination might be synergistic, and liposomal doxorubicin seems to have less cardiac toxicity than the parent anthracycline.

It is very early in the development of this combination. Thus far, we have not seen any cardiac toxicity, and it's quite active. I certainly would not recommend it outside of a clinical trial in which the patient is given appropriate informed consent. In the statistical design, we are looking for either cardiac events or lack of efficacy to stop the trial early. We are looking at efficacy and safety, so that we will get a response rate and some notion of the cardiac toxicity.

Trastuzumab monotherapy

I use trastuzumab monotherapy in some situations; however, I tend to use it in combination with chemotherapy because the combination offers a survival advantage compared to chemotherapy alone. Certainly there are patients who do not wish to take chemotherapy, have disease that might not warrant chemotherapy or in whom a single-agent regimen would certainly be reasonable.

Select publications

Publications discussed by Dr Budd

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Bhardwaj S et al. **An intensive sequenced adjuvant chemotherapy regimen for breast cancer.** *Cancer Invest* 1993;11(1):6-9. **Abstract**

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Hutchins L et al. **CMF versus CAF with and without tamoxifen in high-risk node-negative breast cancer patients and a natural history follow-up study in low-risk node-negative patients: First results of Intergroup trial INT 0102.** *Proc ASCO* 1998. **Abstract**

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Metronomic chemotherapy

Bocci G et al. **Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs.** *Cancer Res* 2002;62(23):6938-43. **Abstract**

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Edited comments by Dr Robert

US Oncology Phase III study of trastuzumab/paclitaxel with or without carboplatin

The study in advanced breast cancer was spawned by the results of the pivotal trial by Slamon and colleagues, in which the combination of paclitaxel/trastuzumab improved the response rate to the 40 percent range and the time to progression to 6.9 months compared to paclitaxel alone.

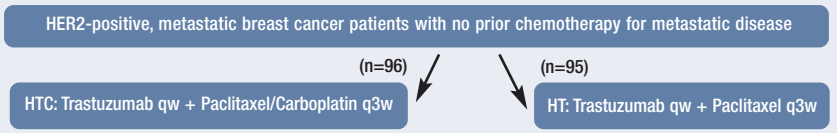
We couldn't add doxorubicin to the paclitaxel/trastuzumab combination because in the pivotal trial, 28 percent of patients in the group given doxorubicin, cyclophosphamide and trastuzumab had cardiotoxicity. We knew of preclinical synergy between the taxanes and carboplatin, as well as three first-line therapy trials showing response rates between 52 percent and 62 percent produced by the combination of paclitaxel and carboplatin. Therefore, adding carboplatin seemed an obvious next step in evaluating the paclitaxel/trastuzumab combination.

Eligibility and protocol

We recruited 196 patients with Stage IV, HER2-positive breast cancer, of whom 191 were eligible and 186 were evaluable for response. As in the trial by Slamon and colleagues, we accepted IHC 2+ and 3+ patients, but as the data became available, we found that only 30 percent of the IHC 2+ patients were FISH positive. Therefore, we changed our eligibility requirements so that patients who were IHC 2+ also had to be FISH-positive. Patients had to have measurable disease and a normal left ventricular ejection fraction. They were ineligible if they received adjuvant taxanes or more than 360 mg/m^2 of doxorubicin.

Patients were randomized to receive trastuzumab/paclitaxel, the successful arm of the pivotal trial, or the combination plus carboplatin. Paclitaxel was administered at 175 mg/m^2 over three hours every 21 days, trastuzumab was administered at a standard loading dose of 4 mg/kg followed by weekly 2 mg/kg, and carboplatin was administered at an AUC of six every 21 days. As in the pivotal trial, physicians had to give six cycles of chemotherapy, but could discontinue chemotherapy and continue the trastuzumab after that.

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%	34/74 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	$P = 0.205$

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

SOURCE: Robert N. Presentation, 2002 San Antonio Breast Cancer Symposium

Trial results

The addition of carboplatin improved both the response rate and time to progression. The primary endpoint was the response rate, which improved from 36 percent with the two-drug regimen to 52 percent with the addition of carboplatin, with a *P* value of 0.04. We stratified IHC 2+ and 3+ patients, and the response rate in the 3+ patients jumped to 37 percent with the two-drug regimen and to 57 percent with the addition of carboplatin, with a *P* value of 0.03. FISH data was collected retrospectively and, although the comparison is not powered for significance, we saw a similar trend as in the IHC 3+ patients — response rates of 39 percent and 59 percent with the two- and three-drug regimens, respectively.

Time to progression was a secondary endpoint in the trial. The time to progression in the trastuzumab/paclitaxel control arm was similar to what was seen in the pivotal trial by Slamon and colleagues. The addition of carboplatin increased the time to progression from 6.9 months to 11.2 months. Looking only at the IHC 3+ patients, we saw a similar improvement (7.2 months increased to 13.5 months); similar results were seen in the FISH-positive patients as well.

We looked at survival, although it was early to do so as over 120 patients are still alive. The preliminary analysis shows a trend for improvement with the three-drug regimen. In the IHC 3+ patients, we saw an improvement in survival, with a *P* value of 0.06, approaching 0.05, and the FISH-positive population showed a similar trend. It will be important to see if the survival advantage persists.

Tolerability and safety data

The trastuzumab/paclitaxel/carboplatin regimen was well tolerated. The only significant difference in toxicity was increased myelosuppression, which we expected to see from adding carboplatin. However, there were no significant differences in terms of serious complications, such as infectious complications, significant neutropenia or fever. Other toxicities, such as neuropathy, allergic responses, nausea and arthralgias, were comparable in both arms.

It is important to note that we did not use prophylactic growth factors or attempt a dose-dense trial. We utilized dose reduction or dose delay when needed. In responding patients, only about 25 percent continued treatment beyond six cycles, so, there are a number of important caveats in administering this regimen in order to get the benefits and avoid unacceptable toxicities.

Implications for research

One of the questions our trial evoked was: Could we achieve the same results by treating patients with paclitaxel/trastuzumab and switching to carboplatin and trastuzumab when they progress? Historically, carboplatin is not a very effective agent when given outside the first-line setting, with response rates in the range of 10 percent; but, it's possible that in combination with trastuzumab it's a different drug. A small study from UCLA using cisplatin in heavily pretreated patients showed about a 24 percent response rate. This may be a strategy to consider in future clinical trials.

Edith Perez and the North Central Cancer Treatment Group, in anticipation of positive results from our study, are looking at giving paclitaxel and carboplatin weekly versus every three weeks. The Breast Cancer International Research Group, in BCIRG-007, is comparing trastuzumab and docetaxel with or without carboplatin in FISH-positive patients. They hope to recruit over 500 patients and have about 70 to date. We won't be able to compare the different taxanes with these two studies, but we will be able to evaluate the impact of carboplatin on the trastuzumab/taxane regimen.

We also know that the combination of trastuzumab and vinorelbine has activity. Currently there's a randomized Phase II trial in Boston, comparing that combination to trastuzumab and a taxane. It will be interesting to compare the efficacy and toxicity of this two-drug regimen (trastuzumab/vinorelbine) with the three-drug regimen (docetaxel/trastuzumab/carboplatin).

Phase III Randomized Study of Docetaxel and Trastuzumab (Herceptin) with or without Carboplatin in Women with HER2-Positive Stage IIIb or IV Breast Cancer Open Protocol

Protocol ID: UCLA-0109024, BCIRG-007, ROCHE-UCLA-0109024, GENENTECH-UCLA-0109024, NCI-G02-2116
Projected Accrual: 444 patients (222 per treatment arm)

Eligibility	Stage IIIB or IV, HER2-positive breast cancer

ARM 1	T+C q3w + H qw x 8, then H q3w
ARM 2	T q3w + H qw x 8, then H q3w

T = docetaxel; C = carboplatin; H = trastuzumab

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SOURCE: NCI Physician Data Query, February 2003.

Trastuzumab as first-line therapy for metastatic breast cancer

I am not aware of any evidence supporting sequencing a non-trastuzumab combination followed by a trastuzumab combination in chemotherapy-naïve patients with HER2-positive metastatic disease. Rather, the pivotal trial comparing chemotherapy plus or minus trastuzumab showed improvement in response rate, time to progression and survival when trastuzumab was added. In addition, over 50 percent of the patients who did not receive trastuzumab initially, received it subsequently, and did not get the same survival benefit.

In patients with HER2-positive, ER-negative metastatic disease, single-agent trastuzumab is a reasonable first step. Both Chuck Vogel in the first-line setting, and Melody Cobleigh in second- and third-line settings, have experience with single-agent trastuzumab in patients with indolent ER-negative disease.

In a trial of single-agent trastuzumab, the Sarah Cannon Cancer Center investigators saw a greater than 50 percent clinical benefit. Patients who crossed over to adding carboplatin and paclitaxel exhibited an increased response rate, but there is probably a subset of patients who could be treated with trastuzumab alone for a while to see how they do.

Single-agent trastuzumab versus trastuzumab with chemotherapy

The decision to use trastuzumab sequentially versus concomitantly with chemotherapy is based on issues such as extent of metastatic disease and the time between diagnosis and progression. In a younger, relatively asymptomatic patient with bone metastases and a good performance status, I don't think there is compelling evidence to use both chemotherapy and trastuzumab initially. There is no randomized trial comparing sequential versus concomitant therapy

in such a patient, but in other settings comparing sequential versus concomitant therapy with chemotherapy, concomitant therapy doesn't do any better in terms of survival.

Certainly there are patients with metastatic disease in whom you feel chemotherapy is indicated, such as patients with significant visceral or life-threatening disease. Given the positive results of the trials where trastuzumab was added to chemotherapy — improved response rate, time to progression and survival — my approach has been to give trastuzumab with the chemotherapy. Given our recent Phase III trial results, I would use the carboplatin/paclitaxel regimen.

BCIRG-006: Adjuvant trastuzumab trial

I am excited about the novel approach of BCIRG-006 for HER2-positive patients in the adjuvant setting. In this trial, patients in the control arm receive doxorubicin/cyclophosphamide followed by docetaxel. The second arm is the same doxorubicin/cyclophosphamide regimen, followed by docetaxel plus trastuzumab, continuing trastuzumab weekly for one year. The third arm is quite innovative in that it includes a taxane rather than an anthracycline. Patients receive trastuzumab, docetaxel and carboplatin or cisplatin for six cycles, followed by weekly trastuzumab for one year from the beginning of therapy.

This trial has an accrual goal of 3,000 patients and over 1,000 patients are already enrolled. It requires patients to be FISH-positive, which is probably the best predictor of interaction between trastuzumab and chemotherapy. I think the results will be quite meaningful to the future management of HER2-positive patients in the adjuvant setting.

Implications of the ATAC trial results for clinical practice

When I heard the ATAC trial data last year, I was impressed. It's a large trial of more than 9,000 patients, and the disease-free survival benefit with anastrozole was credible. It was interesting that the combination didn't work, but anastrozole certainly appeared superior to tamoxifen.

The results of the 47-month update show continued improvement in disease-free survival with actual improvement in the hazard rate with time, which provides even more support for the use of anastrozole in the adjuvant setting.

Currently, I uniformly recommend anastrozole to my patients at high risk for recurrence. I also use anastrozole in patients who are experiencing problems with tamoxifen — severe hot flashes, weight gain or issues related to their uterine status. Occasionally, I have had patients on anastrozole who switched to tamoxifen because of arthralgias. Tamoxifen is still a reasonable choice in an older patient with a low risk of recurrence.

I have not switched a patient who was doing well on tamoxifen to anastrozole. I also have not used the other aromatase inhibitors outside of a clinical trial, because the data is with anastrozole.

Adjuvant trial of capecitabine/docetaxel

Under the leadership of Joyce O'Shaughnessy, we are conducting an adjuvant trial aimed at taking advantage of the biochemical interaction between taxanes and capecitabine. Doxorubicin/cyclophosphamide followed by docetaxel, the control arm, will be compared to the capecitabine/docetaxel combination. This trial is based on the US Oncology study that evaluated this combination in the metastatic setting and showed improved outcome, including survival, in the capecitabine/docetaxel arm.

The tolerability of the regimen is a real concern in the adjuvant setting, so we lowered both the capecitabine and docetaxel doses in the investigational arm of the adjuvant trial. Accrual has been good to date and we have some early toxicity data.

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
Projected 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.

"It is expected that treatment with AC followed by XT provides an improvement in the five-year disease-free survival rate from 65% with AC→T to 71.5% with AC→XT in patients at substantial risk for systemic recurrence. This corresponds to a 22% reduction in the risk of disease recurrence (i.e., the hazard ratio of AC→XT versus AC→T is 0.78) in patients at substantial risk for systemic recurrence."

SOURCE: Protocol 01-062 synopsis, June 2002.

CALGB-9741: Dose-dense versus conventional adjuvant chemotherapy

The results of the dose-dense trial are exciting. We've looked at dose for a long time and the strategies studied — increasing cyclophosphamide from 600 mg/m^2 to 2,400 mg/m^2, increasing doxorubicin from 60 mg/m^2 to 90 mg/m^2 and giving high-dose chemotherapy in the adjuvant setting — were not successful.

However, dose density — giving the drugs every two weeks versus every three weeks — has translated into a disease-free survival advantage and, at this point, a survival advantage. I'm waiting to see more data, but I will present the results from the dose-dense trial to my patients, letting them know these are early results and there is some tradeoff.

Treatment algorithm for patients with metastatic breast cancer

Choosing a chemotherapy regimen for patients with metastatic breast cancer depends on the pace of the disease. If someone with indolent disease progresses on endocrine agents, switching them to another oral agent such as capecitabine is a very attractive option.

Capecitabine is generally well tolerated, especially now that we have improved dosing. We now begin with 1,000 milligrams per meter squared BID, rounding down as needed for 14 out of 21 or 28 days (two weeks on, one to two weeks off). In my experience, this regimen is both well tolerated and efficacious.

Combination chemotherapy is a consideration in patients with more aggressive disease. In a patient who's had prior anthracyclines, a taxane or taxane combination (such as taxane/carboplatin), especially with the weekly schedule, is a well-tolerated and efficacious approach.

Use of fulvestrant in patients with ER-positive metastatic disease

I've used a fair amount of fulvestrant, and I find that it's well tolerated. Patients don't have any problem coming in once a month for their intramuscular injections. In terms of efficacy, we've had patients experience stabilization of disease for six months. What is nice about fulvestrant is that it offers another option, especially for the patient who may be experiencing difficulty tolerating their current endocrine therapy.

Targeting angiogenesis in the treatment of breast cancer

Although it was disappointing that the response rates in the bevacizumab trial did not translate into time to progression, I would not get too discouraged. It reminds us that we need to know the target in order to target therapy. Chemotherapy covers a number of different tumor cells, and we don't need to be as specific with therapy. But, imagine if we had done the trastuzumab trials without knowing to target HER2, IHC 2+ and 3+ patients — we would not have seen the benefits of the therapy. Tamoxifen is another good example of a targeted therapy; it works in ER-positive tumors, but it took us a long time to figure that out.

In order to target angiogenesis, we need to identify tumors in which angiogenesis is important, and we probably need to use a multiagent approach to hit multiple targets. Our increased understanding of the molecular biology of breast cancer has given us better insight, and we need to step up to the challenge of developing targeted strategies to take advantage of that biology.

EGFR inhibitors in the management of ER-negative breast cancer

We know from the NSABP P-1 study that in the high-risk population, tamoxifen reduces only ER-positive breast cancer incidence. Dr Craig Allred, in analyzing NSABP B-24, found that patients with ER-negative DCIS received no benefit from tamoxifen. What are the strategies available to treat ER-negative breast cancer?

The role of EGFR inhibitors in the management of patients with ER-negative breast cancer was discussed at the San Antonio meeting. First, one has to be certain that the immunohistochemistry is properly interpreted and the patient is truly ER-negative. Tamoxifen doesn't work in that group, but could an EGFR inhibitor — like gefitinib — potentially work? Manipulating the EGF receptor tyrosine kinases is a potential approach, but additional research needs to be done in this area.

Participation of the elderly in clinical trials

I have a lot of respect for CALGB-49907 for both the trial design and the idea of recruiting the elderly for clinical trials. It will be interesting to see the results comparing capecitabine to standard regimens. US Oncology also has a trial for the elderly, comparing intravenous CMF versus weekly docetaxel.

When you look at previous trials, patients over 70 are underrepresented. The accrual in both of these trials is slow, which may just be the nature of treating an older population with other medical illnesses. Maybe their ability to tolerate chemotherapy is less, although there are studies that suggest that isn't the case.

The number of eligible patients is probably smaller, and their ability to come in for treatment may be a barrier. While both of these trials are reasonable, the challenge is getting them done.

Underrepresentation of elderly women in recent CALGB adjuvant trials

Trial # Regimens	Total Accrued	Age 70 and older
CLB-8541 CAF in three different doses	1572	150 (10%)
CLB-9344 AC ± T	3170	182 (6%)
CLB-9741 A→T→C vs AC→T in a q2 vs q3 wk schedule	2005	162 (8%)

C = cyclophosphamide; A = doxorubicin; F = fluorouracil; T = paclitaxel

SOURCE: CALGB-49907 Protocol, July 2002.

Development of a nonalopecia-causing breast cancer regimen

The US Oncology breast committee is seeking to develop a regimen that does not cause alopecia. While 20 years ago we had only a handful of drugs to work with, we now have a number of drugs that are not associated with alopecia — capecitabine, vinorelbine, gemcitabine, doxorubicin HCL liposome injection — and a number of combinations can be studied. It is worth noting that we don't do a good job of recording alopecia in clinical trials, and we need better documentation.

It will take some time to find a successful nonalopecia-causing regimen in the adjuvant setting — we certainly won't compromise survival to save hair. This is also important in the metastatic setting. Breast cancer is a very private matter, and alopecia makes it difficult to hide. Eliminating this side effect of therapy would make breast cancer treatment easier for patients.

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Post-test: Breast Cancer Update, Issue 3, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. A Phase III trial compared the efficacy of fulvestrant and anastrozole in women who failed therapy with _____.
a. Exemestane
b. Letrozole
c. Tamoxifen
d. Megestrol acetate

2. The efficacy of fulvestrant in women whose breast cancers progress while on an aromatase inhibitor has been documented in a large multicenter trial.
a. True
b. False

3. Which of the following was not one of the randomization arms in ECOG-1193?
a. Doxorubicin
b. Paclitaxel
c. Capecitabine
d. Doxorubicin plus paclitaxel

4. Which of the following should be considered first-line therapy for a woman with HER-2 positive metastatic breast cancer who has not received any prior chemotherapy?
a. Doxorubicin
b. Paclitaxel
c. Trastuzumab plus a taxane
d. Trastuzumab monotherapy
e. c or d

5. The dose-dense chemotherapy regimens evaluated in CALGB-9741 were effective in women with both ER-positive and ER-negative breast cancer.
a. True
b. False

6. In women with metastatic breast cancer, sequential single-agent chemotherapy is more effective than combination chemotherapy in terms of survival.
a. True
b. False

7. Which of the following statements is true about the results from the trial comparing trastuzumab plus paclitaxel with or without carboplatin?
a. There was an improvement in response rate for trastuzumab plus paclitaxel plus carboplatin.
b. There was no difference in response rate for trastuzumab plus paclitaxel plus carboplatin compared to trastuzumab plus paclitaxel.
c. There was an improvement in time to progression for trastuzumab plus paclitaxel plus carboplatin.
d. b and c
e. a and c

8. One of the advantages associated with the regimen of capecitabine plus vinorelbine, which has been studied in Phase II trials, is that it does not usually cause alopecia.
a. True
b. False

9. The Phase III trial of capecitabine with or without bevacizumab, reported a significant survival advantage to the combination over capecitabine alone.
a. True
b. False

10. In the SWOG-S0221 trial, pegfilgrastim is used in the dose-dense chemotherapy arm.
a. True
b. False

11. The pivotal trial by Slamon et al comparing chemotherapy plus or minus trastuzumab showed improvement in response rate, time to progression and survival when trastuzumab was added.
a. True
b. False

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

Evaluation Form: Breast Cancer Update, Issue 3, 2003

NL Communications 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 only 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 HER2-positive breast cancer patients. 5 4 3 2 1
- Develop and explain a management strategy for women with ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1
- Develop and explain a management strategy for women with ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1
- Counsel ER-positive postmenopausal patients about the risks and benefits of aromatase inhibitors in the adjuvant setting. 5 4 3 2 1
- Evaluate the relevance of emerging data on dose-dense chemotherapy to patients. . . . 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 3

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

- Formulate a treatment plan for a postmenopausal woman with ER-positive breast cancer who develops asymptomatic metastatic disease while receiving adjuvant tamoxifen. 5 4 3 2 1
- Choose a first-line chemotherapeutic regimen for a woman with hormone refractory ER-positive metastatic breast cancer. 5 4 3 2 1
- Design a treatment plan for a woman with HER-2 positive metastatic breast cancer who has not received any prior chemotherapy. 5 4 3 2 1
- Discuss the impact of dose-dense adjuvant chemotherapy on patient care. 5 4 3 2 1
- Assess the results of the clinical trial comparing trastuzumab plus paclitaxel with or without carboplatin. 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Kathy Miller, MD	5 4 3 2 1	5 4 3 2 1
G Thomas Budd, MD	5 4 3 2 1	5 4 3 2 1
Nicholas J Robert, 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 3, 2003

Please Print Clearly

Name: _____

Specialty: _____ ME#: _____ SS#: _____

Street Address: _____ Box/Suite: _____

City: _____ State: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____Email: _____

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

Signature: _____

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

___Yes ___No

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

_____

_____

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

_____

_____

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

_____

_____

Degree:

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

To obtain a certificate of completion and receive credit for this activity, please complete the exam, fill out the evaluation form and mail or fax both to: NL Communications, Inc., 400 S. E. Second Avenue, Suite 401, Miami, FL 33131-2117, FAX (305) 377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.