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Breast Cancer® UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 8 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Ravdin, Seidman, Budd and Valero on the integration of emerging clinical research data into the management of breast cancer.

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

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TABLE OF CONTENTS

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UPCOMING EDUCATIONAL EVENTS

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

Radiation Therapy Oncology Group Meeting
January 19-22, 2006
Miami Beach, FL
Event website: **www.rtog.org**

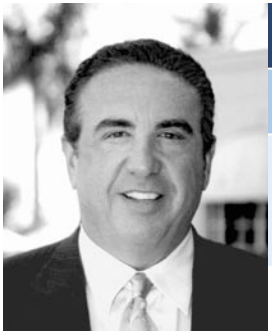
Miami Breast Cancer Conference
February 22-25, 2006
Miami Beach, Florida
Event website: **www.cancerconf.com**

National Comprehensive Cancer Network
11th Annual Conference
March 8-12, 2006
Hollywood, FL
Event website: **www.nccn.org**

Fifth European Breast Cancer Conference
March 21-25, 2006
Nice, France
Event website: **www.fecs.be**

American Association for Cancer Research
97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: **www.aacr.org**

American Society of Clinical Oncology
42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**



EDITOR'S NOTE

Neil Love, MD

Diamond in the rough

DR LOVE: Do you feel that you're compromising the utility of capecitabine as monotherapy in metastatic breast cancer by reducing the dose below the package insert level?

DR VALERO: I personally do not. I believe that by lowering the dose, we are delivering a therapy that has a better therapeutic index, particularly when we remember that this is palliative chemotherapy.

In my opinion, some of our traditional methods to develop drugs in the metastatic setting haven't been optimal, because we increased the dose until the patients were as sick as tolerable to determine the maximum tolerated dose (MTD). If I were a patient and understood that the disease won't be cured, I would want to be able to receive more cycles at a lower dose with less adverse events.

When I began my medical oncology fellowship in 1975, systemic therapy of cancer was mainly utilized as a palliative treatment in the advanced disease setting. It was not until the 80s and 90s that substantial numbers of patients in chemotherapy infusion rooms were receiving adjuvant treatment, first for breast and then for colorectal cancer.

Clinically, the preadjuvant days were profoundly challenging for both patients and oncologists. Antiemetics were suboptimal, and growth factor support was not yet available. Waiting rooms were filled with tragedy, and after a while, I didn't much like coming to work.

In the late 1970s, a brief burst of promise about the potential impact of chemotherapy in the metastatic disease setting arose when Einhorn and others demonstrated the curability of advanced testicular cancer. As we have come to learn though, that experience was isolated, and unfortunately, responses to cytotoxic regimens in most other solid tumors in the metastatic setting remained generally brief, and the risk-benefit equations of these treatments frequently tilt in the wrong direction.

Like all budding cancer docs, I read with enthusiasm the work of laboratory scientists like Skipper and Schnabel, whose mathematical postulates predicted

that with the correct doses and schedules, many tumors would be cured with chemotherapy. This type of preclinical research contributed to Phase I studies attempting to define the MTD.

The eventual outcome of this concept was the high-dose stem cell experiment, which for most tumors was a total bust. However, MTD seemed to live on in the minds of clinical investigators and practitioners, and it does seem intuitive to want to deliver as much therapy as possible in what is often a desperate setting.

Along this desolate path, I encountered a remarkable exception to the "more is better" philosophy that pervaded systemic cancer therapy — an innocuous-looking pill with virtually no side effects that in many patients with breast cancer resulted in objective responses and significant improvement in symptoms. Tamoxifen citrate was a beacon of light that for many oncologists offered hope for a better day. Now, thirty years later, we are fortunate that a variety of targeted, relatively nontoxic agents have entered our armamentarium.

My fellowship was at the University of Miami Comprehensive Cancer Center, whose founding director was Gordon Zubrod, the "father" of cytotoxic chemotherapy. Dr Zubrod was a great man, who championed a treatment that proved to be at best only a very partial answer to this cruel disease. Gordon passed away before the advent of the orally administered fluoropyrimidine prodrug capecitabine, but I wonder what he would say about this other innocuous-looking pill.

Capecitabine first caught my attention at the 2000 San Antonio Breast Cancer Symposium, when Joyce O'Shaughnessy presented data from a Phase III randomized US Oncology trial demonstrating a significant improvement in response rate and overall survival when the drug was combined with docetaxel in the metastatic setting. I immediately started interviewing breast cancer clinical investigators about this "XT" study and observed an interesting response.

While there was considerable enthusiasm for evaluating this combination in the adjuvant and neoadjuvant settings (1.1), there was much less interest in utilizing this therapy off protocol for advanced disease. The thinking of most clinical investigators was that sequential use of the same agents would provide better quality of life and equivalent survival.

However, in my discussions with researchers, I also learned something somewhat unexpected: Most of these sequential monotherapists believed that capecitabine was an excellent single agent and often used it in their practices as their first-line treatment for metastatic disease. It was also clear that the package-insert dose of this agent was considered excessive (2,500 mg/m^2 in two divided daily doses for 14 of 21 days), particularly for women and perhaps even more for patients from North America. (To review a fascinating discussion on this topic, which emerged during our recent colorectal cancer Think Tank, please listen to our current issue of *Colorectal Cancer Update*.)

1.1 **Breast Cancer Clinical Trials Evaluating Capecitabine and "XT" in the Neoadjuvant and Adjuvant Settings**

Study	Projected accrual	Randomization
ID01-580, NCT00050167[1]	930	Paclitaxel qwk x 12 → FEC x 4 → local therapy* (Capecitabine + docetaxel) x 4 → FEC x 4 → local therapy*
US Oncology 01-062[2]	1,810	AC x 4 → docetaxel x 4† AC x 4 → (docetaxel + capecitabine) x 4†
CALGB-49907, NCT00024102[3]	600-1,800	CMF x 6 or AC‡ x 4 Capecitabine x 6

* ER/PR-positive patients will receive endocrine therapy after completion of local therapy
† ER- and/or PR-positive patients receive tamoxifen or anastrozole x 5 years (postmenopausal only)
‡ Patients whose LVEF is not within lower limits of normal must receive CMF, not AC. All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor for five years.

SOURCES: [1] NCI Physician Data Query, October 2005; Livingston R. *Oncology* 2002;16(10 Suppl 12):29-31. **Abstract**; [2] US Oncology Protocol 01-062, June 2002; [3] NCI Physician Data Query, October 2005.

The de facto standard dosing for capecitabine that has evolved in clinical practice is about 20 percent lower than the package-insert dose (1.2). Interestingly, however, some investigators — including Charles Vogel, the fun-loving maverick who roped me into the UM breast cancer division following my fellowship — believe that even this dose is higher than necessary to achieve effective tumor control.

Currently, capecitabine is utilized much more frequently by breast cancer clinical investigators like Chuck than oncologists in general community practice (1.3). Some have postulated that reimbursement and profitability issues explain this discrepancy, but I wonder if there is another explanation, specifically that researchers use lower doses, are perhaps more aggressive about stopping therapy for early toxicity and see fewer resultant side effects, and thus view the drug more favorably. (Say that in one breath!)

1.2 **Dosing of Capecitabine Monotherapy: Survey of 100 Medical Oncologists**

How do you generally dose capecitabine monotherapy when using it in a 2 weeks on/ 1 week off schedule?

2500 mg/m^2 in 2 divided doses (1250 mg/m^2 BID)	21%
2000 mg/m^2 in 2 divided doses (1000 mg/m^2 BID)	71%
1700 mg/m^2 in 2 divided doses (850 mg/m^2 BID)	3%
1650 mg/m^2 in 2 divided doses (825 mg/m^2 BID)	3%
Other	3%

SOURCE: *Colorectal Cancer Update* Patterns of Care 2005;2(2).

1.3

Use of Capecitabine Among Breast Cancer Clinical Investigators and Community Oncologists

Chemotherapy for Asymptomatic Patients with Metastases: No Prior Chemotherapy

- *ER-negative, HER2-negative*
- *No prior systemic therapy*
- *Rising tumor markers, asymptomatic bone mets*

What is your usual first-line treatment for this patient?

	Age 40 (premenopausal)		Age 57		Age 75	
Docetaxel	3%	16%	3%	16%	0%	10%
Paclitaxel	21%	17%	21%	18%	14%	19%
Capecitabine	**42%**	**12%**	**42%**	**14%**	**59%**	**27%**
Other	34%	55%	34%	52%	27%	44%

Chemotherapy for Asymptomatic Patients with Metastases: Prior AC → Paclitaxel

- *ER-negative, HER2-negative*
- ***Adjuvant AC → paclitaxel 2 years ago***
- *Rising tumor markers, asymptomatic bone mets*

What is your usual first-line treatment for this patient?

	Age 40 (premenopausal)		Age 57		Age 75	
Docetaxel	0%	29%	0%	29%	0%	15%
Paclitaxel	3%	8%	3%	8%	3%	6%
Capecitabine	**84%**	**18%**	**88%**	**20%**	**81%**	**36%**
Other	13%	45%	9%	43%	16%	43%

Breast cancer specialists General oncologists

SOURCE: *Breast Cancer Update* Patterns of Care Survey 2005;2(1).

While capecitabine does raise tolerability issues, it does not cause alopecia, myelosuppression or emesis. Many patients who have received capecitabine, oral hormonal therapy and intravenous chemotherapy believe capecitabine is more akin to hormone therapy than it is to its cytotoxic cousins.

Even more impressively, capecitabine not infrequently induces impressive tumor responses. In my travels interviewing docs for our audio programs, I have encountered many cases of patients treated for more than a year or two with impressive stories of prolonged relief of tumor-related symptoms and minimal adverse effects on their quality of life.

Perhaps we need clinical researchers and practitioners to think not only about MTD but also MED (minimally effective dose), and in the case of capecitabine in the metastatic breast cancer setting, I believe that somewhere in between the MED and MTD we may find a dose and schedule that many patients and physicians might view as the second coming of tamoxifen. ■

— Neil Love, MD
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INTERVIEW

Peter M Ravdin, MD, PhD

Dr Ravdin is a Clinical Professor of Medicine at The University of Texas Health Science Center at San Antonio in San Antonio, Texas.

Tracks 1-18

Select Excerpts from the Interview

Track 2

DR LOVE: Your Adjuvant! Online model provides important estimates on the projected benefits of adjuvant therapy. How are you going to include trastuzumab in the model?

DR RAVDIN: There really are three questions that need to be addressed to incorporate this data. The first question is, what are the real efficacy numbers?

What we've seen in the combined analysis of the North American data, as projected for three years of follow-up, is a proportional risk reduction of about 53 percent for relapse and about 33 percent for death for those patients who received trastuzumab (Romond 2005; [2.1]). I believe those numbers are still probably unstable in terms of the fact that they represent the impact of the very earliest relapses.

The second question is, how should we use this information? It potentially will impact how the model is used not only for patients with HER2-positive disease but also those with HER2-negative disease. The estimates in the population with HER2-negative disease will have modestly better risk than if it had included the patients with HER2-positive disease.

The third question addresses the toxicity aspect of trastuzumab therapy, that is, how safe is the therapy over a long period of time? We have three years of data at this point, so whether there's any late cardiac toxicity from the therapy has not been thoroughly addressed. The initial part of the data looks hopeful because most of the toxicity occurs during therapy.

2.1 **Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data**

Parameters	Chemotherapy* (n = 1,679)	Chemotherapy* with trastuzumab (n = 1,672)	Hazard ratio	*p*-value
Disease-free survival				
Three years from randomization	75%	87%		
Four years from randomization	67%	85%	0.48	<0.0001
Overall survival				
Three years from randomization	92%	94%		
Four years from randomization	87%	91%	0.67	0.015

* Chemotherapy plus trastuzumab = AC → paclitaxel; chemotherapy plus trastuzumab = AC → paclitaxel + trastuzumab

SOURCE: Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Track 4

DR LOVE: Do you believe that trastuzumab should now be offered and utilized in the adjuvant setting?

DR RAVDIN: With three trials showing consistent effects, trastuzumab is ready to be used in the adjuvant setting. All of the trials show great consistency. Although the Intergroup and the NSABP trials were combined for analysis (2.1), they were also split out in the presentations so you could see the effects in each one of the trials, and the results were virtually identical (Romond 2005; [2.2]).

The data from the European study — although trastuzumab was administered in a slightly different way — were consistent with trastuzumab having powerful adjuvant effects (Piccart-Gebhart 2005). So I believe we have as good evidence for the early effectiveness of trastuzumab as we have for any other agent right now in breast cancer.

DR LOVE: What about the use of adjuvant trastuzumab in patients with node-negative disease?

DR RAVDIN: The issues for determining when to use trastuzumab are going to be the same as those faced when deciding to use chemotherapy or hormonal therapy. They are going to be a balance between benefit and risk. We have a spectacular early benefit; however, we still need much more information about risks. It's the patients with Stage I node-negative disease for whom it's quite possible that the benefit-to-risk ratio will not actually point favorably in the direction of the use of trastuzumab.

2.2 **Disease-Free Survival for Patients Randomly Assigned to Adjuvant Chemotherapy with or without Trastuzumab**

	NSABP-B-31		NCCTG-N9831	
	AC → T (n = 872)	AC → TH (n = 864)	AC → T (n = 807)	AC → TH (n = 808)
Three years from randomization	74%	87%	78%	87%
Four years from randomization	66%	85%	68%	86%
Hazard ratio	0.45		0.55	
p-value	1×10^{-9}		0.0005	

AC = doxorubicin plus cyclophosphamide; T = paclitaxel; TH = paclitaxel plus trastuzumab

SOURCE: Romond EH et al. **N9831**. Presentation. ASCO 2005a. No abstract available

Track 5

DR LOVE: What information do we now have regarding cardiac function and trastuzumab?

DR RAVDIN: In the analysis of the NSABP-B-31 trial, the cumulative hazard of developing congestive heart failure was four percent at three years of follow-up. Most of that four percent occurred within the year of trastuzumab treatment. There were some that occurred afterwards; however, it didn't appear to be accelerating (Romond 2005; [2.3]).

What we know from anthracycline-based regimens is that they cause an excess incidence of congestive heart failure of somewhere around 0.5 to one percent. I wouldn't be surprised if trastuzumab doubled that to a level of maybe one to two percent.

If that's the case, then there may be some patients for whom that risk will outweigh the potential benefits. Although it is also important to note that in the Intergroup and NSABP trials with over 3,000 patients, there has been only one cardiac death so far, which was in the control arm (Romond 2005b).

2.3

NSABP-B-31: Cumulative Incidence of Cardiac Events Associated with Adjuvant Chemotherapy with or without Trastuzumab

Years after Day 1 of cycle 5	AC → T (n = 811)	AC → TH (n = 846)
0.5	0.3%	2.5%
1.0	0.4%	3.5%
1.5	0.4%	3.9%
2.0	0.4%	4.0%
2.5	0.6%	4.0%
3.0	0.6%	4.0%

AC = doxorubicin plus cyclophosphamide
T = paclitaxel; TH = paclitaxel plus trastuzumab

SOURCE: Romond EH et al. Presentation. ASCO 2005. No abstract available

Track 6

DR LOVE: In your own practice, will you start trastuzumab during the taxane portion of chemotherapy or wait until the chemotherapy is completed?

DR RAVDIN: I will be starting trastuzumab concurrently with paclitaxel. There really are two pieces of information that address this issue, and they're somewhat contradictory. One of them is in the Intergroup study. It had an arm that was not included in the NSABP-B-31 study — a sequential arm — in which all of the chemotherapy was administered before trastuzumab was started (Romond 2005a). In this arm, the proportional risk reduction was a lot less obvious and spectacular than with concurrent treatment.

2.4

HERA Trial: Disease-Free Survival (DFS) for Patients Randomly Assigned to One Year of Trastuzumab or Observation Following Completion of Adjuvant Chemotherapy

	Trastuzumab (n = 1,694)	Observation (n = 1,693)
Two-year DFS	85.8%	77.4%
Hazard ratio (95% CI)	0.54 (0.43-0.67)	
p-value	<0.0001	

CI = confidence interval

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353(16):1659-72. **Abstract**

The European data actually point in a somewhat opposite direction. The patients in the European trial completed their chemotherapy before trastuzumab was started, and those patients seemed to gain more than a 40 percent proportional benefit (Piccart-Gebhart 2005; [2.4]). In that case, administering chemotherapy and trastuzumab sequentially seemed to work quite well.

At any rate, there didn't seem to be any additional risks to administering them concurrently, at least with the safety data we have now. The benefit certainly looked a little bit better — actually, a lot better — in the Intergroup study (Perez 2005). I believe most people will be starting trastuzumab at the same time they're starting paclitaxel.

Track 7

DR LOVE: At this point, all of the trastuzumab data are for a total duration of one year. Is that what you recommend?

DR RAVDIN: Yes, and the Europeans are actually taking a look at the duration question. In the European trial, one arm has no trastuzumab, the second arm has one year of trastuzumab after chemotherapy and the third arm has two years of trastuzumab after chemotherapy (Piccart-Gebhart 2005). Because the data at this point addresses one year of trastuzumab, I believe that's the appropriate length of time.

DR LOVE: Another very common question is the issue of what to do for patients with HER2-positive tumors who were diagnosed six months, one year or three years ago — the impact of delayed implementation of trastuzumab.

DR RAVDIN: In the Intergroup trial, they're supplying trastuzumab to the control group of patients who want to cross over out to one year of follow-up. I believe there are theoretical arguments that one year is somewhat an arbitrary length of follow-up. Actually, the peak in relapses occurs in patients at approximately two to three years. So I could see a rationale for treating even out beyond a year, particularly for high-risk patients with multiple nodes, although that, of course, is going beyond the data that we have at hand and is somewhat speculative. I can't see any reason to treat patients who are many years out and have had a HER2-positive tumor.

Track 8

DR LOVE: How are you planning to approach cardiac monitoring in patients receiving adjuvant trastuzumab?

DR RAVDIN: Both of the North American studies utilized exactly the same cardiac monitoring plan, and it was very thorough. Patients were only eligible if they had a normal left ventricular ejection fraction and no cardiac history. After the first cycles of the AC times four — the anthracycline part of the therapy — they had another left ventricular ejection fraction measured (Romond 2005).

At the end of the anthracycline portion of the regimen, approximately four percent of the patients had left ventricular ejection fractions that had fallen

below the normal limits (Perez 2004), so they did not receive trastuzumab (Perez 2005). Patients who went on to receive trastuzumab were a very carefully selected group.

During treatment with trastuzumab, patients underwent a MUGA scan every three months. During the year of treatment, 20 percent of patients had to stop trastuzumab because of an asymptomatic drop in left ventricular ejection fraction or because of developing symptomatic problems (Romond 2005a).

2.5

NSABP-B-31: Incidence of Trastuzumab-Associated Congestive Heart Failure (TACHF) Correlated with Age and Post-AC LVEF

	TACHF	
Post-AC LVEF (%)[1]	Age <50 years[2] n (%)	Age ≥50 years[2] n (%)
50-54	3/48 (6.3%)	9/47 (19.1%)
55-64	5/229 (2.2%)	10/194 (5.2%)
65+	1/160 (0.6%)	2/159 (1.3%)

[1] LVEF = *p*-value < 0.0001; [2] age = *p*-value = 0.04

SOURCE: Romond EH et al. Presentation. ASCO 2005. No abstract available

The predictors of developing symptomatic problems were age and a relatively low ejection fraction. For patients who were older than 50 years of age and had a left ventricular ejection fraction after the AC times four that was between 50 and 54 percent, their risk of developing congestive heart failure was 20 percent.

Conversely, for the patients who were younger than 50 years of age and had left ventricular ejection fractions of greater than 65 percent after the AC times four, their risk of congestive heart failure during therapy was 0.6 percent.

It's clear that there are at-risk populations that need to be identified and monitored during such treatment (Romond 2005; [2.5]).

Track 10

DR LOVE: Would you comment on the study that was done in Canada to validate the Adjuvant! Online model?

DR RAVDIN: Adjuvant! Online is an evidence-based model, but there are a few studies that have been done to validate it. One of them utilized the excellent population-based database in British Columbia (Olivotto 2005). They have very good records across the province, capturing most of the breast cancer cases and detailed information about them. They sent us the actual patient and tumor descriptions. Based on that information, we generated projections of 10-year survivals for those patients.

We put 4,000 cases into the model. The results of our projections were then sent back to British Columbia, and they matched them with the outcomes. We were very close to the actual numbers, on average, within about one percent (2.6).

2.6 **Observed versus Predicted 10-Year Results**

	Overall survival	Breast cancer-specific survival	Event-free survival
Adjuvant! predicted outcome	71.7%	83.2%	71.0%
Observed outcome	72%	82.5%	70.1%
Predicted minus observed	-0.3%	0.7%	0.9%

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

One of the areas of inaccuracy was in patients less than 35 years of age, where we debated about whether or not, based on the literature and some of our own analyses, to assign those patients a little bit worse prognosis. The British Columbia analysis would suggest that we should have (Olivotto 2005).

Our analysis overall was strongest for breast cancer-specific mortality. Relapse was very strong, but not as strong as mortality. I still feel that mortality is the best endpoint for the model. They felt the model was well validated across all the different subsets and endpoints. It was presented last year at ASCO, and on April 20th, it was published in the *Journal of Clinical Oncology* (Olivotto 2005).

Track 12

DR LOVE: Let's talk about adjuvant endocrine therapy. Do you think there's any justification for utilizing five years of adjuvant tamoxifen at this point in postmenopausal women?

DR RAVDIN: I believe very few people are being started on tamoxifen with the intention of receiving five years of tamoxifen and then switching to an aromatase inhibitor. The problem with initially starting on tamoxifen is that strategies that originally start with an aromatase inhibitor will have lower recurrence rates than those starting with tamoxifen.

For instance, if you start a patient on tamoxifen, you're conceding that she is going to do worse than she would have done on an aromatase inhibitor. Then you have to feel that when you switch her, the curves will then recross.

In other words, the aromatase inhibitor will be so much more effective if delivered later that it will catch up and overtake the group that did not receive the aromatase inhibitor from the beginning. That is possible, theoretically, because tamoxifen and the aromatase inhibitors — since they have somewhat different mechanisms of action — will actually be somewhat noncross resistant.

Therefore, a strategy that employs both agents might provide the most benefit. But that's a theoretical consideration against the very real fact that we know if you start with an aromatase inhibitor, the patients do better.

DR LOVE: Our CME group did a patterns of care study looking at whether physicians switch postmenopausal women to an aromatase inhibitor after two to three years of tamoxifen. A surprising number of community oncologists continue tamoxifen for five years, whereas breast cancer clinical investigators tend to switch to an aromatase inhibitor after two to three years of tamoxifen. Who's right?

DR RAVDIN: At this point, it's not clear who's right, because it's not clear which strategy is really better. My money is on the idea that switching is the right thing to do, because we know that the patients whose therapy is switched at two to three years are doing better than the patients who continue on tamoxifen for five years.

I believe much of the benefit of adjuvant tamoxifen actually occurs in the first two years. There's a little bit of additional benefit for continuing it out to five years. Continuing it beyond that doesn't apparently provide any additional benefit, at least in NSABP-B-14 (Fisher 2001).

So with time, the benefit of tamoxifen attenuates. If you're switching at two to three years, what you're doing is you're switching away from a drug that's beginning to be less and less effective. And it looks like you're obtaining a very effective impact from the aromatase inhibitor administered at that point.

DR LOVE: In the patient who's going to switch from tamoxifen during the first five years of therapy, how long are you going to use the aromatase inhibitor?

DR RAVDIN: The clinical trial data we have right now use two to three years of an aromatase inhibitor after tamoxifen. There are some trials extending aromatase inhibitor therapy out beyond five years of therapy. MA17 is looking to see whether or not there might be additional benefit. My guess is there will be additional benefit because the aromatase inhibitors, I believe, are not agonists-antagonists like tamoxifen.

Tamoxifen can be reinterpreted by cells, after molecular changes, to be a stimulant, whereas I can't see how the absence of estrogen could ever be re-interpreted as a stimulant. I would suspect the aromatase inhibitors would be harder to develop resistance to and therefore might be superior in the adjuvant hormonal therapy of breast cancer.

DR LOVE: What about the patient who's been on tamoxifen for six months, one year or one and a half years? Do you wait until she is at the two-year or three-year point to switch her therapy?

DR RAVDIN: Actually, I wait. At this point I have no patients who have just started tamoxifen. For those patients who have been on tamoxifen for a year, I wait until the two- to three-year point before switching.

Track 14

DR LOVE: What about hormonal therapy in the premenopausal patient with an ER-positive tumor? There are a number of major international trials looking at this (2.7). How do you approach it right now in a clinical setting? The question a lot of people have is in regard to the patient with many positive nodes or the patient with many positive nodes and an ER-positive, HER2-positive tumor.

DR RAVDIN: The data, of course, are insufficient to decide or we wouldn't be conducting these trials. Nonetheless, off study, particularly in patients less than 35 years of age, looking at the trial data, it's apparent that combined hormonal therapy looks like it's better than single-modality hormonal therapy. Specifically, the kind of combined therapy that's been looked at up until this point in that scenario is ovarian suppression with an LHRH analog plus tamoxifen.

I actually like that strategy more than the strategy of using such ovarian suppression plus an aromatase inhibitor. The reason why I like that strategy better is because tamoxifen is blocking the estrogen receptor and you're lowering the estrogen level.

If you're using both ovarian suppression and also the aromatase inhibitor, you're using two things to reduce estrogen, and you're not really attacking two different parts of the chain. Whether that is the right way to think will be, I believe, demonstrated by the ongoing trials, which are comparing the two strategies.

2.7 **Trials of Adjuvant Endocrine Therapy with Ovarian Suppression**

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Tamoxifen x 5y OFS + tamoxifen x 5y OFS + exemestane x 5y
IBCSG-25-02 (TEXT trial)	1,845 (open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + tamoxifen x 5y Triptorelin ± chemotherapy + exemestane x 5y
IBCSG-26-02 (PERCHE trial)	1,750 (open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	OFS + tamoxifen or exemestane x 5y OFS + any chemotherapy + tamoxifen or exemestane x 5y

OFS = ovarian function suppression with triptorelin or surgical oophorectomy or ovarian irradiation

SOURCES: www.ibcsg.org; NCI Physician Data Query, September 2005.

Track 17

DR LOVE: The 2000 overview (EBCTCG 2005) was published recently. Is there anything in this publication that you think is important for clinicians in practice to know about?

DR RAVDIN: Actually, there's nothing in it that I believe is strikingly different from the overview that was published in 1998. I believe what is important about the overview is it shows that we're not delaying recurrence and death, but rather adjuvant therapy seems to be preventing it.

In other words, the relapse-free survival and the overall survival advantages that accrue early in the patients' clinical course actually are maintained out to 15 years (EBCTCG 2005). That is really good news, because there don't appear to be late toxicities eroding those advantages. I believe that's one thing the overview says that's powerfully important.

There are a lot of data in the overview about anthracyclines and some of the anthracycline-based regimens. What made the headlines is if you use a good chemotherapy regimen plus a good hormonal regimen, you reduce your risk of mortality by about 50 percent (2.8). So that's something we all knew, but the publication caused a special notice.

2.8 Estimated Effects of Adjuvant Therapy on 15-Year Breast Cancer Mortality in Women with ER-Positive Disease

Systemic adjuvant treatment and age at diagnosis (years)	Proportional reduction of annual breast cancer mortality rate
Tamoxifen (any age)	31%
Anthracycline + tamoxifen (<50 years)	57%
Anthracycline + tamoxifen (50-69 years)	45%

SOURCE: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2005;365(9472):1687-717. Abstract

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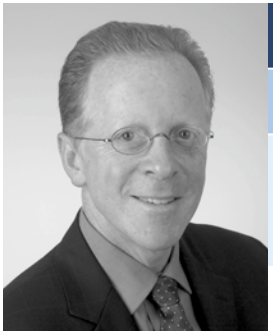


INTERVIEW

Andrew D Seidman, MD

Dr Seidman is an Associate Attending Physician in Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: What are the implications of the ECOG-E2100 trial comparing paclitaxel to paclitaxel plus bevacizumab?

DR SEIDMAN: ECOG-E2100 was a pivotal study. This is the kind of information you take home and interject into your practice the very next week. Here, we're looking at targeted therapy, where one doesn't necessarily need to test for the target. Docs who have been treating patients with metastatic breast cancer already are well aware of using targeted therapy in the form of trastuzumab.

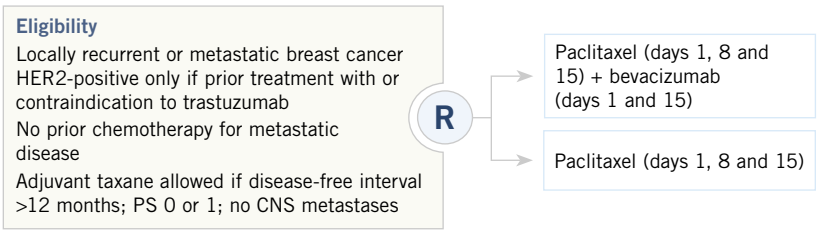
In a sense, we now have a new targeted, better-tolerated, rationally designed biologic therapy that doesn't require testing of the tumor. I believe the design of E2100 (3.1) was an appropriate one, using weekly paclitaxel as the control arm — a regimen very close to my heart on the heels of CALGB-9840 — in which we showed the superiority of weekly paclitaxel in terms of causing a higher response rate and a longer time to progression than conventional paclitaxel (Seidman 2004;[3.2]).

ECOG-E2100 showed us that the addition of bevacizumab to weekly paclitaxel not only improved the response rate (Miller 2005a), as was observed in the prior study with capecitabine (Miller 2005b), but unlike the study with capecitabine, now we had an increase in time to progression of about five months (3.2). The additional costs in terms of toxicity were fairly modest, with some increase in hypertension and proteinuria (Miller 2005a; [3.3]). Also, a slight increase in the risk of Grade III neuropathy was seen with bevacizumab (Miller 2005a; [3.3]).

3.1

ECOG-E2100: Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 715 (Closed)



SOURCE: Miller KD et al. Presentation. ASCO 2005a. No abstract available

3.2

ECOG-E2100 Efficacy Results

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate	28.2%	14.2%	<0.0001
Progression-free survival	10.97 months	6.11 months	<0.001
Overall survival	Hazard ratio = 0.674 (CI 0.495-0.917)		0.01

SOURCE: Miller KD et al. Presentation. ASCO 2005a. No abstract available

Track 3

DR LOVE: What's your take on the clinical implications of ECOG-E2100 in terms of daily practice?

DR SEIDMAN: It has already made an impact on our daily practice at Memorial Sloan-Kettering. I believe the data speak very loudly for themselves. This is the kind of data where one doesn't go back and say, "Well, I'm looking forward to six months from now when the FDA approves this."

This is the kind of information where we feel almost an ethical imperative to come back and integrate it into practice, the benefit being so substantial.

3.3 ECOG-E2100 Safety Results

	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy††		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

* $p < 0.0001$; † $p = 0.0004$; †† $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005a. No abstract available

For me, it's a no-brainer for a patient who would appropriately receive a taxane as monotherapy as first-line treatment of metastatic disease. That woman should also receive bevacizumab, provided she has no serious contraindications — brain metastases, uncontrolled hypertension or significant proteinuria.

DR LOVE: You mentioned using bevacizumab with taxane monotherapy. Does that include docetaxel and nanoparticle albumin-bound (*nab*) paclitaxel?

DR SEIDMAN: The data that exist to date are with paclitaxel. We have a history, though, that tells us, for example, with the integration of trastuzumab, that with few exceptions, what worked with trastuzumab and paclitaxel also worked with trastuzumab and docetaxel.

So do we really need to repeat every single experiment — for example, the use of bevacizumab with weekly docetaxel, since it worked with paclitaxel I think probably not. I would rather not see the reproduction of all of these same Phase III studies over again with docetaxel that were done with paclitaxel. I would ditto the same sentiment for *nab* paclitaxel with bevacizumab.

DR LOVE: Would you want to see some Phase II or safety data with docetaxel or *nab* paclitaxel combined with bevacizumab?

DR SEIDMAN: Yes, I clearly want to see some safety data first. We've learned to expect the unexpected. There certainly could be differences in patterns of toxicity, based simply on the vehicles of those agents and how they might interact with bevacizumab.

At Memorial, we're about to embark on a trial in which we will be comparing every three-week, every two-week and weekly dosing of *nab* paclitaxel with bevacizumab as first-line therapy and also trastuzumab for patients with HER2-positive disease. We're looking at a *nab* paclitaxel schedule question and also the safety of the co-administration of bevacizumab.

Track 5

DR LOVE: Would you continue bevacizumab upon disease progression?

DR SEIDMAN: I hope we don't repeat the same mistake I believe we made in the development of trastuzumab — to not definitively ask the research question: "Is this an agent I should continue beyond the point of disease progression?"

Although it was talked about for many years and it was attempted to determine whether trastuzumab might be valuable to use beyond progression, we simply don't know the answer to that question on a clinical basis. Most of us have developed a bias to continue trastuzumab for all practical purposes.

I believe that with bevacizumab, we have an opportunity to learn from the lessons of the past and to design trials early on that look at the duration of therapy question. If your patient progresses after her first-line taxane/bevacizumab regimen, should you continue bevacizumab for the next course or the course after and combine it with agents such as vinorelbine, gemcitabine and capecitabine? I honestly don't know the answer to that question.

DR LOVE: Are there active discussions right now in the cooperative groups about a trial like that, looking at bevacizumab or not on progression?

DR SEIDMAN: There are discussions, and in thinking about this question, one of the reasons such trials have been thought, perhaps, not to be feasible relates to the half-life of the antibody and the need for a wash-out period. The argument with trastuzumab is that if you randomly assign patients to a do-not-continue-trastuzumab arm, pharmacologically, they're still getting trastuzumab many weeks after the last dose.

There is no really good way around that issue, but I still believe it's a clinically relevant question to ask: Does stopping the antibody, as opposed to continuing it with the next regimen, make a difference? If there is a pharmacologic effect, it may translate early on into no difference at the first follow-up or the first set of scans. But presumably, if continuing the antibody — in this case bevacizumab — makes a difference and it's a big enough difference, you may see that

even regardless of the fact that the antibody will hang around for many weeks after you discontinue it.

Tracks 6-7

DR LOVE: Can you discuss what we know about *nab* paclitaxel?

DR SEIDMAN: *Nab* paclitaxel basically is paclitaxel formulated without Cremophor. It was tested in the clinic in a large randomized trial involving about 450 women (Gradishar 2005), and there does seem to be a differential effect apart from the obvious advantage of not having to use premedications to avoid the hypersensitivity reactions — no need for corticosteroids or antihistamines (3.4).

The administration of 260 mg/m^2 *nab* paclitaxel caused a higher response rate and a longer time to progression than the conventional 175 mg/m^2 three-hour infusion, every three-week regimen of Cremophor-based paclitaxel (Gradishar 2005; [3.4]). In my mind, this represents a real step forward.

There was less Grade III and IV neutropenia with 260 mg/m^2 of *nab* paclitaxel compared to 175 mg/m^2 of paclitaxel (3.4), although this really didn't translate into a difference in febrile neutropenia, which was low in both arms. There was a 10 percent incidence of Grade III neuropathy with *nab* paclitaxel, versus a two percent incidence with Cremophor-based paclitaxel (Gradishar 2005; [3.4]). This may not be all that surprising, given the differences in the doses that were used.

3.4

Phase III Randomized Trial Comparing *Nab* Paclitaxel to Paclitaxel as First-, Second-, Third- or Fourth-Line Therapy in Women with Metastatic Breast Cancer

	Nab paclitaxel (n = 229)	Paclitaxel (n = 225)	*p*-value
Complete response + partial response Investigator assessment Overall First-line therapy	 33% 42%	 19% 27%	 0.001 0.029
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival Overall ≥Second-line therapy	 65 weeks 56.4 weeks	 55.7 weeks 46.7 weeks	 0.374 0.024
Neutropenia (Grade IV)	9%	22%	<0.001
Sensory neuropathy (Grade III)	10%	2%	<0.001
Hypersensitivity (any grade)	<1%	2%	Not reported

SOURCE: Gradhishar WJ et al. *J Clin Oncol* 2005;23:7794-803. **Abstract**

There was an apparent, fairly rapid reversibility of the Grade III neuropathy. The 10 percent of the population who experienced that degree of neuropathy seemed to have a median time to resolution back to baseline of about three weeks (Gradishar 2005), perhaps almost by the next cycle. Reversibility seemed to take longer in the patients randomly assigned to Cremophor-based paclitaxel.

I'm very intrigued by the data from the US Oncology Group Joanne Blum has reported. A weekly regimen of *nab* paclitaxel — administered in a population of patients who are already taxane-exposed to either paclitaxel or docetaxel and many, but not all, of whom have some pre-existing neuropathy — seemed not to cause a lot of severe neuropathy, particularly the 100 mg/m^2 three-weeks-on and one-week-off regimen (Blum 2004).

Track 8

DR LOVE: How would you compare the efficacy of weekly *nab* paclitaxel compared to weekly paclitaxel?

DR SEIDMAN: That's a good question. Right now, it's really hard to do. The US Oncology Group treated nice-sized populations with their weekly regimen. There were about 70 patients at the 100 mg/m^2 dose (Blum 2004), and at the other dose — the 125 mg/m^2 dose — in the range of about 100 patients (O'Shaughnessy 2004). Since that's a nice sample size in terms of Phase II data, what we can say is that weekly *nab* paclitaxel has activity in patients with prior taxane exposure and even with prior recent taxane exposure.

Most of the data supporting the use of weekly Cremophor-based paclitaxel are not in the same population but are in women who haven't had prior taxanes with a well-described activity with that approach from Phase II and the Phase III randomized trial (Seidman 2004).

The randomized Phase II trial with docetaxel, published in the *Annals of Oncology* by Tabernero (Tabernero 2004), is too difficult to compare with these data. My sense, and this is a real "guesstimation," is that I wouldn't expect weekly *nab* paclitaxel to be inferior to docetaxel.

There clearly are no direct comparisons, and I'm not sure I think that the appetite is very strong in the cooperative groups to do these kinds of trials. I believe there are too many other interesting targeted agents that beg asking questions rather than how *nab* paclitaxel weekly stacks up to weekly docetaxel.

Track 10

DR LOVE: Based on the current research data, where do you see the role of *nab* paclitaxel in a clinical setting?

DR SEIDMAN: The ability to deliver drugs more safely offers a real potential benefit. Even if the randomized trial, perhaps, didn't show a higher response rate or a modestly longer time to progression compared to paclitaxel (O'Shaughnessy 2003), simply not having to premedicate and not having to worry about serious allergic reactions, in my mind, would make *nab* paclitaxel the obvious choice.

The issue that comes around with the emergence of any new drug is always cost. There is a cost differential right now, since Cremophor-based paclitaxel is generically available. It's not a trivial differential. Even at Memorial Sloan-Kettering, this is a consideration for the pharmacy budget.

We have guidelines for the use of *nab* paclitaxel, and the guidelines tend to reflect the data. In scenarios that are parallel to those where *nab* paclitaxel's efficacy was shown — in the first-line and second-line setting — when one would use paclitaxel, then I'm very motivated to substitute *nab* paclitaxel.

DR LOVE: Have you utilized *nab* paclitaxel in the adjuvant setting, particularly in patients who may be having problems with Cremophor-based paclitaxel or docetaxel?

DR SEIDMAN: I have used *nab* paclitaxel a handful of times so far in the adjuvant setting. The scenarios are all memorable — patients who have had strong allergic histories to other agents. One scenario involved a woman with bipolar disease who becomes manic with steroid exposure, to the point where I spoke with her psychiatrist about the need to avoid corticosteroids.

With appropriate permission from our Pharmacy and Therapeutics committee, I was granted the approval to use *nab* paclitaxel in the adjuvant setting. This was a nice thing that allowed us to administer appropriate anthracycline and taxane-based adjuvant therapy without having to use corticosteroids.

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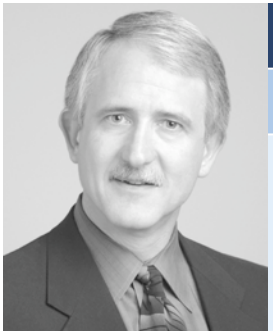
Tabernero J et al. **A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer.** *Ann Oncol* 2004;15(9):1358-65. **Abstract**

Zamora P et al. **Capecitabine (X) as single agent in elderly patients (p) with metastatic breast cancer (MBC).** *Proc ASCO* 2005;**Abstract 843**.



INTERVIEW

G Thomas Budd, MD

Dr Budd is a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University's Cleveland Clinic Foundation in Cleveland, Ohio.

Tracks 1-13

Select Excerpts from the Interview

Track 4

DR LOVE: In the metastatic setting, how would you compare the efficacy of *nab* paclitaxel, docetaxel and paclitaxel in a patient who has never received a taxane?

DR BUDD: I believe paclitaxel is at the bottom, and then we have *nab* paclitaxel and docetaxel. There's really no head-to-head comparison. You can only do indirect comparisons. There was a survival advantage with docetaxel as compared to paclitaxel (Jones 2005). We haven't seen that yet with the *nab* paclitaxel. I believe that's an important difference. It would be of interest to see a direct comparison.

DR LOVE: In the metastatic setting, how would you decide between those three agents in a patient who's never received a taxane?

DR BUDD: I believe it would be a matter of toxicity. I try to put patients on clinical trials, of course, but realistically, it would boil down to *nab* paclitaxel, if you're going to administer paclitaxel, and probably the weekly schedule would be more tolerable, or docetaxel every three weeks.

I believe it would be a matter of discussing it with the patient. In a younger patient, either docetaxel or *nab* paclitaxel. In an older patient, I have tended to use weekly paclitaxel because it's less toxic, but that is also a patient for whom *nab* paclitaxel could be considered.

Track 5

DR LOVE: In the future, do you see people utilizing bevacizumab with the other two taxanes as well, or just with paclitaxel?

DR BUDD: I believe people will probably use it with the other taxanes. It may be that the weekly schedule of paclitaxel is a so-called metronomic regimen and may have some anti-angiogenic effects, as well as direct antitumor effects.

If you believe that's the case, it might be reasonable to use a weekly regimen of one of the other chemotherapeutic agents, particularly one of the other taxanes.

I believe that probably the results will be generalized. In general, I believe it's best to start with a regimen as reported, but if the principle can be found to hold true in one other trial, I believe the results would be generalized to other agents.

Track 6

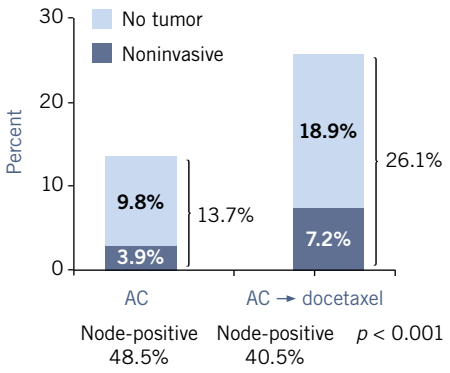
DR LOVE: Can you review the results of the NSABP-B-27 study?

DR BUDD: In NSABP-B-27, there was essentially a doubling of the pathologic complete response (pCR) rate by adding docetaxel to doxorubicin/cyclophosphamide preoperatively (Bear 2003; [4.1]). However, there was no advantage in terms of the primary endpoint, which was disease-free survival.

If you look at relapse-free survival, which is any sort of recurrence but excludes

4.1

NSABP-B-27 Initial Results: Pathologic Response (pCR) in Breast



No difference in rate of breast conservation: 61% versus 63%

SOURCE: Bear H et al. *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

second breast cancers and other second primary malignancies, there is a modest advantage for adding the docetaxel to doxorubicin/cyclophosphamide, particularly preoperatively (Bear 2004). If you're going to use docetaxel in the adjuvant setting, I believe it ought to be TAC.

4.2

NSABP-B-27: 68-Month Update of Study Endpoints (Hazard Ratios Compared to AC)

	AC → T → surgery (n = 803)	AC → surgery → T (n = 799)
Overall survival	0.94 (p = 0.57)	1.07 (p = 0.53)
Disease-free survival with cPR after AC	0.86 (p = 0.10) 0.68 (p = 0.003)	0.91 (p = 0.27) 0.90 (p = 0.40)
Relapse-free survival	0.81 (p = 0.03)	0.91 (p = 0.32)

No significant difference in overall or disease-free survival by treatment but improved relapse-free survival compared to AC for preoperative docetaxel

T = docetaxel; cPR = clinical partial response

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

Track 7

DR LOVE: In our patterns of care study, we looked at adjuvant hormonal therapy in postmenopausal women. We saw a high utilization of the aromatase inhibitors up front (4.3) — specifically anastrozole (4.4). What are your thoughts on that?

DR BUDD: We've seen that the aromatase inhibitors are better than other hormonal agents in every stage of the disease — as a second-line treatment for metastatic disease and as first-line treatment for metastatic disease. It was not much of a leap to believe that they'd be better in the adjuvant setting, and the toxicities, in general, are less.

Patients are very concerned about bone density, as are their physicians. The bottom line — in terms of the proportion of patients complaining about side effects or quitting treatment because of side effects — is there is an advantage for the aromatase inhibitors over tamoxifen.

DR LOVE: Right now, which aromatase inhibitor do you utilize up front?

DR BUDD: I tend to use anastrozole up front, because I tend to follow the clinical trial data (Howell 2005b). The BIG FEMTA trial, looking at letrozole, has been presented but has not yet been published (Thürlimann 2005a, 2005b; [4.5]). So I believe there's a rationale to use letrozole as well.

4.3

Adjuvant Hormonal Therapy in Postmenopausal Patients with Node-Negative Disease: Survey of 50 Medical Oncologists

- *Tumor is 1.2 centimeters, ER-positive, node-negative*
- *Which hormonal therapy, if any, would you most likely recommend?*

	Age 55		Age 75		Age 85	
Anastrozole	63%	72%	68%	72%	57%	73%
Exemestane	—	2%	—	—	—	—
Letrozole	5%	—	2%	—	2%	—
Tamoxifen	32%	26%	28%	28%	25%	28%
Would not recommend endocrine therapy	—	—	2%	—	16%	—

Breast cancer specialists General oncologists

SOURCE: *Breast Cancer Update* Patterns of Care 2005;2(3).

DR LOVE: The other thing that was seen in the BIG FEMTA trial that was interesting was an increase in deaths from myocardial infarction. What are your thoughts about that?

DR BUDD: I thought that was an interesting finding, and there are possibly adverse effects on blood lipids.

4.4

Use of Adjuvant Aromatase Inhibitors

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is generally with each of the following agents?

Anastrozole	85%	84%
Letrozole	12%	14%
Exemestane	3%	2%

Breast cancer specialists General oncologists

SOURCE: *Breast Cancer Update* Patterns of Care 2005;2(1).

It may be, too, that tamoxifen has some beneficial effect in terms of myocardial infarction, which has been noticed in some other studies.

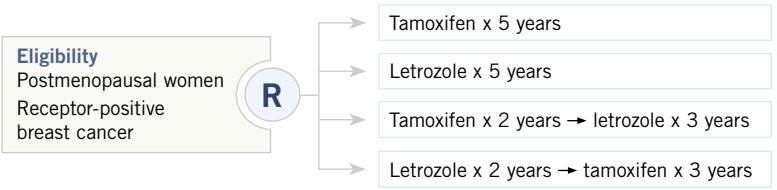
This is a bit paradoxical when you compare this to trials with hormone replacement therapy, in which there actually was an increase in cardiac events. I believe we'll just have to follow this further, to see whether tamoxifen, in fact, might have some beneficial effects in terms of cardiac events.

Track 11

DR LOVE: In our patterns of care study, we saw a lot of heterogeneity in how physicians approach the postmenopausal patient with metastatic disease, particularly the woman who had relapsed on adjuvant tamoxifen. A fair number of physicians are using fulvestrant, while some are using aromatase inhibitors (4.6). How do you approach that decision?

4.5 BIG FEMTA: Phase III Trial Comparing Letrozole and Tamoxifen as Adjuvant Endocrine Therapy

Protocol IDs: IBCSG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, NCT00004205, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98
Accrual: 8,028 (Closed)



SOURCES: BIG 1-98 Collaborative Group. www.ibcsg.org. Abstract; NCI Physician Data Query, October 2005.

4.6 Hormonal Therapy After Progression on Adjuvant Tamoxifen: Asymptomatic Patients

- *ER-positive, HER2-negative*
- *On adjuvant tamoxifen x 4 years*
- *Rising tumor markers, asymptomatic bone mets*

What is your first-line endocrine treatment for this patient, and your second-line endocrine treatment if she had objective progression over several months but was clinically the same?

	Age 57				Age 75			
	1st-line		2nd-line		1st-line		2nd-line	
Anastrozole	14%	46%	0%	9%	14%	45%	0%	8%
Exemestane	0%	7%	24%	30%	0%	6%	24%	28%
Letrozole	73%	37%	3%	7%	70%	39%	7%	6%
Fulvestrant	3%	4%	63%	47%	3%	6%	55%	51%
Other	7%	4%	3%	4%	6%	2%	7%	4%
No endocrine therapy	3%	2%	7%	3%	7%	2%	7%	3%

Breast cancer specialists General oncologists

SOURCE: *Breast Cancer Update* Patterns of Care 2005;2(1).

DR BUDD: I tend to use an aromatase inhibitor first and then use fulvestrant. One could build a rationale for using an alternative sequence, but I believe the data for aromatase inhibitors are really quite strong.

DR LOVE: If you're trying to decide between fulvestrant and an aromatase inhibitor in a postmenopausal woman who's relapsed on adjuvant tamoxifen, what's the advantage of the aromatase inhibitor from your point of view?

DR BUDD: I believe ease of administration and the magnitude of the information. We have trials with each one of these agents that indicate, in one way or another, that the aromatase inhibitors are an optimal treatment. Granted, anastrozole and fulvestrant appear to be equivalent in that situation (Robertson 2003; Howell 2005a; [4.7]). So fulvestrant is also a reasonable choice.

I believe most patients would still rather take a pill than have an intramuscular injection, but not all. Many of these patients are coming back to the clinic on a monthly basis for a bisphosphonate, so some of the practical advantages of a pill may not pertain for all patients.

4.7

Combined Analysis of Two Phase III Multicenter Trials Comparing Fulvestrant to Anastrozole in Postmenopausal Women with Advanced Breast Cancer

	Fulvestrant (n = 428)	Anastrozole (n = 423)	*p*-value
Complete response rate	4.7%	2.6%	—
Partial response rate	14.5%	13.9%	—
Objective response rate	19.2%	16.5%	0.31
Clinical benefit rate*	43.5%	40.9%	0.51
Estimated median time to progression	5.5 months	4.1 months	0.48
Median duration of response in those responding	16.7 months	13.7 months	—
Death rate (median follow-up, n = 27.2 months)	74.5%	76.1%	—
Median time to death	27.4 months	27.7 months	0.81

* Clinical benefit = complete response + partial response + stable disease ≥24 weeks

SOURCES: Robertson JF et al. *Cancer* 2003;98(2):229-38. **Abstract**

Pippen J et al. Poster. San Antonio Breast Cancer Symposium 2003;**Abstract 426**.

DR LOVE: What's been your experience with fulvestrant in terms of tolerability and efficacy?

DR BUDD: I found it to be quite tolerable. I've had some patients complain about injections, but relatively few. I've tended to use it as second-line or even third-line therapy, particularly when it first became available. The results have been what I would expect for an active hormonal agent in that situation. There have been some patients who have had prolonged responses, but there are some patients who are hormone refractory and do not respond to it. I believe it's clearly an active agent, and it's been tolerable to most patients.

DR LOVE: Do you think there's a future for fulvestrant being integrated earlier into neoadjuvant or adjuvant therapy?

DR BUDD: I believe there is a possibility. In the Southwest Oncology Group, we are doing a trial in the metastatic setting (SWOG-S0226) with anastrozole versus the combination of anastrozole and fulvestrant (4.8). If the combination were better, then there would be a rationale to introduce it into the adjuvant setting.

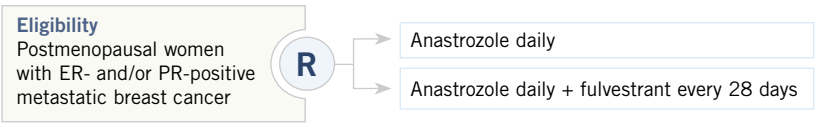
I believe the one lesson we've learned from the aromatase inhibitors is that not all hormonal treatments are the same. Before the aromatase inhibitors, the thought was, "The hormonal agents are all pretty similar in terms of efficacy. We'll just use them in terms of increasing toxicity, so we'll use the least toxic agent first."

With the aromatase inhibitors, we've seen it is actually possible to have a better hormonal agent. I believe that's encouraged us to look at novel combinations and, perhaps, the addition of other biologic agents. I believe there's been a change in viewpoint that's come about with the aromatase inhibitors.

4.8

Phase III Randomized Study of Anastrozole with or without Fulvestrant as First-Line Therapy in Postmenopausal Women with Metastatic Breast Cancer

Protocol ID: SWOG-S0226
Accrual: 690



Study Contact:
Rita Mehta, MD, Study Coordinator
Southwest Oncology Group
Tel: 714-456-5153

SOURCE: NCI Physician Data Query, September 2005.

SELECT PUBLICATIONS

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

Bear HD et al; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. **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

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

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 658**.

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

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials.** *Cancer* 2005a;104(2):236-9. **Abstract**

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

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

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

Jones SE, Pippen J. **Effectiveness and tolerability of fulvestrant in postmenopausal women with hormone receptor-positive breast cancer.** *Clin Breast Cancer* 2005;6(Suppl 1):9-14. **Abstract**

Jones SE et al. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005; 23:5542-51. **Abstract**

Kudachadkar R, O'Regan RM. **Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer.** *CA Cancer J Clin* 2005;55(3):145-63. **Abstract**

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005. No abstract available

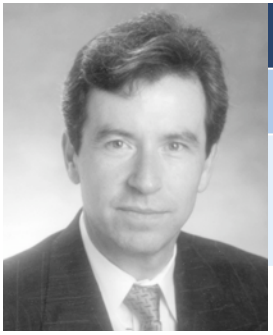
O'Shaughnessy J et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in MBC: A phase III trial.** Presentation. San Antonio Breast Cancer Symposium 2003;**Abstract 44**.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. San Antonio Breast Cancer Symposium 2003;**Abstract 426**.

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**

Thürlimann B. **BIG 1-98: A prospective randomized double-blind double-dummy phase III study to evaluate letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer**. *Breast* 2005a;14(Suppl 1):3;S4.

Thürlimann B et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. ASCO 2005b;**Abstract 511**.



INTERVIEW

Vicente Valero, MD

Dr Valero is a Professor of Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-8

Select Excerpts from the Interview

Track 2

DR LOVE: How do you approach deciding between combination versus single-agent chemotherapy for metastatic disease?

DR VALERO: There are two combination regimens that have been proven to be superior to single-agent taxane therapy. One is gemcitabine plus paclitaxel, which was compared to paclitaxel alone. The data were presented at ASCO last year, showing an improvement in time to progression and preliminary evidence of an increase in overall survival (Albain 2004; [5.2]).

The other study compared docetaxel plus capecitabine to docetaxel alone and also showed a time to progression and overall survival advantage (O'Shaughnessy 2002; [5.1]).

Based on the evidence, both of these combinations are reasonable for first-line chemotherapy of metastatic disease. However, in some patients, sequential chemotherapy is our preference. I tend to use more sequential single-agent chemotherapy, but I believe the role of combination chemotherapy in some instances is well documented by the two studies I just mentioned.

DR LOVE: Which situations, specifically?

DR VALERO: For women who have symptomatic breast cancer with visceral involvement, it is essential to have a response to alleviate the symptoms and improve their quality of life. In those patients, in spite of the enhancement of the adverse events, I strongly consider combination chemotherapy.

5.1

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

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

SOURCE: O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-2823. **Abstract**

5.2

Phase III Trial of Gemcitabine/Paclitaxel versus Paclitaxel as First-Line Treatment in Patients with Anthracycline-Pretreated Metastatic Breast Cancer

Accrual: 529 (Closed)

Eligibility
Locally recurrent or metastatic breast cancer

Prior adjuvant anthracycline treatment

No prior therapy for metastatic disease

R

→ Gemcitabine 1250 mg/m^2 + paclitaxel 175 mg/m^2 q3wk

→ Paclitaxel 175 mg/m^2 q3wk

Endpoint	GT (n = 267)	T (n = 262)	*p*-value
Response rate (95% CI)	40.8%, (34.9, 46.7)	22.1%, (17.2, 27.2)	<0.0001
Median TTP (95% CI)	5.2 mo, (4.2, 8.6)	2.9 mo, (2.6, 3.7)	<0.0001
Median overall survival (95% CI)	18.5 mo, (16.5, 21.2)	15.8 mo, (14.4, 17.4)	0.018

GT = gemcitabine + paclitaxel; T = paclitaxel; TTP = time to progression; CI = confidence interval

SOURCE: Albain KS et al. Presentation. ASCO 2004;**Abstract 510**.

Track 3

DR LOVE: When you utilize capecitabine, what dose do you use?

DR VALERO: In patients with a good performance status who are not heavily pretreated, I use 2,000 mg/m^2 daily in two divided doses for 14 of 21 days. After two cycles of therapy, I will consider escalating the dose if the patient has no toxicity. For patients with a poor performance status, in whom you're going to consider capecitabine as a second- or third-line therapy — patients who are fragile — I may use 1,750 mg/m^2 daily.

We recently published in the *Annals of Oncology* about our experience at MD Anderson with different doses of capecitabine (Hennessy 2005; [5.3]). We believe that a lower dose is preferable, even though the FDA-approved dose is 2,500 mg/m^2.

I believe this publication really confirms what we do in the clinic. When you have a Phase II study in several locations, but you select people out and monitor them very closely, capecitabine can be administered at a higher dose. I could deliver capecitabine at 2,500 mg/m^2 daily, but it needs close monitoring with a patient who is able to follow very closely with her oncologist. In the clinical trials, as soon as the patients start to develop early signs of mucositis, diarrhea or hand-foot syndrome, capecitabine is stopped immediately (5.4).

Then the patient reports to the oncologist or the research nurse for instructions. Then you restart the capecitabine, and you may restart it at a lower dose. So it needs some very close monitoring. In general, most patients at the end of the day receive an average dose of around 2,000 mg/m^2 daily as a single agent. In some patients, I also use even lower doses — 1,500 mg/m^2 daily.

The bottom line is — the evidence that a lower dose is efficacious is just not there. Our study is one of the first that provides information (Hennessy 2005; [5.3]), but it was not a prospective study to assess response and time to progression in a well-designed Phase II fashion.

DR LOVE: Even though we don't have definitive evidence right now, do you feel that you're compromising efficacy by reducing the dose?

DR VALERO: I personally don't. We have to remember that we are giving palliative chemotherapy. I believe some of our traditional ways to develop drugs in the metastatic setting haven't been, in my opinion, optimal because we escalate the dose until we make patients as sick as possible and then we determine that's the maximum tolerated dose (MTD).

Remember that MTD is based on administration of one cycle. Ideally, you would like to develop a therapy in which you're going to determine an MTD for patients who receive at least four cycles, which is what you're using in the adjuvant setting. Most patients will receive a median of four cycles in the metastatic setting.

5.3 MD Anderson Retrospective Analysis: Patients with Breast Cancer Treated with Capecitabine

	Starting dose level of capecitabine		
	A 2500 ± 5% mg/m²/day (n = 49)	B 2250 ± 5% mg/m²/day (n = 15)	C ≤2000 + 5% mg/m²/day (n = 41)
Response			
Improved disease	18%	20%	24%
Stable disease	35%	47%	37%
Progressive disease	47%	33%	39%
Median time to progression	2.8 months	4.6 months	3.5 months
Adverse events (Grade III/IV)			
Hand-foot syndrome	33%	63%	20%
Diarrhea	13%	12%	3%
Stomatitis	8%	0	3%
Nausea/vomiting	4%	6%	5%
Neutropenia	3%	0%	9%
Thrombocytopenia	3%	6%	0
Anemia	12%	0	3%

SOURCE: Hennessy BT et al. *Ann Oncol* 2005;16(8):1289-96. **Abstract**

5.4 Adjustment of Capecitabine Therapy Due to Side Effects

What percentage of your patients on capecitabine or capecitabine-containing regimens develop hand-foot syndrome that requires dose reduction or delay?

Mean	34%

Which of the following best describes how you instruct your patients taking capecitabine to contact your office if they experience the following hand-foot related symptoms?

	Redness	Pain	Redness and pain	Blisters
Contact office	66%	61%	34%	26%
Discontinue and contact office	11%	34%	61%	68%
No action	18%	—	—	—

Which of the following best describes how you instruct your patients taking capecitabine to contact your office if they experience the following gastrointestinal symptoms?

	Loose stools	Abdominal cramping	Diarrhea
Contact office	66%	61%	58%
Discontinue and contact office	11%	16%	32%
No action	18%	18%	5%

SOURCE: *Colorectal Cancer Update* Patterns of Care Survey 2005;2(2).

Tracks 4-5

DR LOVE: Can you overview what we know about fulvestrant, how you utilize it in your practice, and how you dose it?

DR VALERO: I believe fulvestrant has been a major step in hormonal therapy for women with estrogen or progesterone receptor-positive breast cancer. It provides patients with an agent with a different mechanism of action. I have been using it in many of my patients with hormone-sensitive breast cancer.

DR LOVE: What is your approach in the postmenopausal patient who's had prior adjuvant tamoxifen?

DR VALERO: Our approach in the institution is to use an aromatase inhibitor up front and then fulvestrant as second-line therapy. Fulvestrant is approved for patients who have failed tamoxifen, so you can use one agent or the other. In the palliative setting, I believe you can use it either way. Fulvestrant has been shown to be as effective as anastrozole (Howell 2005, Robertson 2003) and tamoxifen (Howell 2004; [5.5]). I use them in sequence. I don't believe there is any information that one sequence is better than the other. I use an aromatase inhibitor, and then I use fulvestrant as a second-line therapy.

5.5 **Objective Tumor Response in a Randomized Study Comparing Fulvestrant to Tamoxifen as First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer**

	All patients		Patients with ER- and/or PR-positive tumors	
Response	Fulvestrant (n = 313)	Tamoxifen (n = 274)	Fulvestrant (n = 247)	Tamoxifen (n = 212)
Complete response	9.6%	6.9%	8.9%	5.7%
Partial response	22.0%	27.0%	24.3%	25.5%
Stable disease ≥ 24 weeks	22.7%	28.1%	23.9%	31.6%
Objective response rate[1]	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate[2]	54.3%	62.0%	57.1%	62.7%

[1]Objective response indicates a complete or partial response
[2]Clinical benefit indicates a complete or partial response of stable disease >24 weeks

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

DR LOVE: How do you dose and schedule fulvestrant?

DR VALERO: At MD Anderson, we use a loading dose. We administer 500 mg on day one and 250 mg on day 15 and day 29, and then monthly. Many of the key investigators in the early development of the drug believe it is impor-

tant to attain steady state. As you know, there is no randomized data for the loading approach.

Currently, it is FDA approved at 250 mg monthly and is reimbursed by Medicare at that dose. With all of those caveats, I believe — and I don't know if this is my bias — the loading approach is reasonable.

While we think that may be the best dosing schedule, we won't know unless we do a pharmacokinetic study and also, importantly, a very large study to show that the doses are equally effective. I'm not sure if we're going to be seeing a dosing study large enough to determine efficacy. You can look at the pharmacokinetics in a smaller study, but I don't know if we're going to see efficacy differences.

DR LOVE: Another potential strategy, which is being tested in the SoFEA study (5.6), is combining an aromatase inhibitor with fulvestrant. Many oncologists ask me about the patient who relapses on an aromatase inhibitor. Why not keep her on the aromatase inhibitor and then add in fulvestrant? Is that something you ever do or you think makes sense?

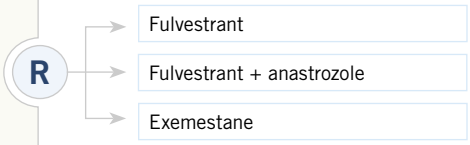
DR VALERO: You're right on target. That is a huge controversy right now about whether or not to maintain lower estrogen levels in a postmenopausal patient and try a different hormonal manipulation. But we have to be cautious. We learned from the ATAC study that lowering the estrogen levels and bringing in something that competes for the ligand — in that case tamoxifen — didn't result in a benefit. If you look at most of the data with combined hormonal therapy throughout a couple of decades, there really hasn't been clear evidence that two hormonal therapies are superior to one.

5.6

Phase III Trial of Fulvestrant with or without Concomitant Anastrozole versus Exemestane Following Progression on Nonsteroidal Aromatase Inhibitors

Protocol ID: ISRCTN44195747, SoFEA
Accrual: 750

Eligibility
Postmenopausal women with ER- and/or PR-positive metastatic breast cancer that has progressed during endocrine therapy with a nonsteroidal aromatase inhibitor (NSAI)



Study Contact:
Stephen Johnston, MD, Principal Investigator
Tel: 0208 722 4062
ICR - Clinical Trials & Statistics Unit

SOURCE: National Cancer Research Network Trials Portfolio. Available at http://controlled-trials.com/isrctn/trial/%7c/o/44195747.html October 1, 2005.

On the other hand, there is preclinical data generated by different laboratories — including Kent Osborne's lab — where lowering the ligand (in this case estrogen) and using fulvestrant had a synergistic effect. This is the basis of the randomized study of anastrozole plus or minus fulvestrant (SWOG-S0226; [4.8]).

DR LOVE: How do you approach hormonal therapy in a premenopausal patient with metastatic disease? If the patient is on ovarian suppression, would you consider fulvestrant or an aromatase inhibitor in that woman?

DR VALERO: We participated in the multicenter trial headed by Robert Carlson from Stanford. In fact, we enrolled the majority of the patients on that trial, which currently has 27 patients. It's a Phase II study looking at hormonal levels and the efficacy of goserelin and anastrozole (Carlson 2004; [5.7]). I'm the principal investigator from MD Anderson.

With this minimal number of patients, we have been very impressed with the combination, and the clinical benefit rate currently is 72 percent. I believe that hormonal therapy in these women, which is the first biological therapy, makes a lot of sense. Believe it or not, this is the only study that is currently available to obtain preliminary efficacy data. The trial is still ongoing.

5.7

Phase II Trial of Goserelin Plus Anastrozole for the Treatment of Premenopausal Women (n = 18) with Hormone Receptor-Positive Recurrent/Metastatic Breast Cancer

Complete response (CR)	6%
Partial response (PR)	22%
Stable disease (SD) ≥6 months	44%
Clinical benefit (CR + PR + SD)	72%

SOURCE: Carlson RW et al. *Proc SABCS* 2004;**Abstract 6052**.

What is the standard of care in patients who have failed tamoxifen and are coming in for hormonal therapy? The standard of care is to use ovarian ablation — medical or surgical. If the patient has had surgical ovarian ablation, an aromatase inhibitor makes sense. Right now, I know that a lot of people are using goserelin and an aromatase inhibitor.

Fulvestrant has not been studied a lot in patients who are premenopausal, because there are not many premenopausal patients with ER-positive disease who are coming in for a second hormonal therapy. But I believe that is changing.

We're using less cyclophosphamide, so fewer women are becoming menopausal after receiving chemotherapy. More women who relapse may have ER-positive disease and be premenopausal, and the pool may increase. ■

SELECT PUBLICATIONS

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

Carlson RW et al. **Goserelin plus anastrozole for the treatment of premenopausal women with hormone receptor positive, recurrent/metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004. **Abstract 6052**.

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

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7. **Abstract**

Hennessy BT et al. **Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: Retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature.** *Ann Oncol* 2005;16(8):1289-96. **Abstract**

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials.** *Cancer* 2005;104(2):236-9. **Abstract**

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004; 22(9): 1605-13. **Abstract**

Jones SE, Pippen J. **Effectiveness and tolerability of fulvestrant in postmenopausal women with hormone receptor-positive breast cancer.** *Clin Breast Cancer* 2005;6(Suppl 1):9-14. **Abstract**

Kudachadkar R, O'Regan RM. **Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer.** *CA Cancer J Clin* 2005;55(3):145-63. **Abstract**

Leonard R et al. **Optimizing the management of HER2-negative metastatic breast cancer with capecitabine (Xeloda).** *Semin Oncol* 2004;31(5 Suppl 10):21-8. **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**

O'Shaughnessy J. **A retrospective evaluation of the impact of dose reduction in patients treated with Xeloda (capecitabine)**. *Proc ASCO* 2000;**Abstract 400**.

Pierga JY et al. **Efficacy and safety of single agent capecitabine in pretreated metastatic breast cancer patients from the French compassionate use program.** *Breast Cancer Res Treat* 2004;88(2):117-29. **Abstract**

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. San Antonio Breast Cancer Symposium 2003. **Abstract**

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

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**

Walko CM, Lindley C. **Capecitabine: A review.** *Clin Ther* 2005;27(1):23-44. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the combined analysis of two adjuvant trastuzumab trials (NSABP-B-31 and NCCTG-N9831), a significant proportional risk reduction in _____ was reported in the patients receiving adjuvant trastuzumab.**
   a. Relapse rate
   b. Death
   c. Both a and b
   d. None of the above
2. **In NSABP-B-31, cardiac events mainly occurred during the year of therapy with adjuvant trastuzumab and not afterwards.**
   a. True
   b. False
3. **Clinical trials have evaluated adjuvant trastuzumab administered _____ with chemotherapy.**
   a. Concurrently
   b. Sequentially
   c. Both a and b
   d. None of the above
4. **Which of the following are predictors of developing congestive heart failure with trastuzumab?**
   a. Age
   b. Left ventricular ejection fraction
   c. Both a and b
   d. None of the above
5. **The most recent ASCO Technology Assessment does not endorse the use of adjuvant aromatase inhibitors in postmenopausal women with hormone receptor-positive breast cancer.**
   a. True
   b. False
6. **According to the recent publication of the breast cancer overview, adjuvant chemotherapy with hormonal therapy reduces the risk of mortality by about 50 percent.**
   a. True
   b. False
7. **In patients with locally recurrent or metastatic breast cancer, ECOG-E2100 demonstrated that the addition of bevacizumab to weekly paclitaxel prolonged progression-free survival by approximately _____.**
   a. One month
   b. Five months
   c. Twelve months
   d. Twenty-four months
8. **In ECOG-E2100, the incidence of which of the following adverse events was increased in the patients receiving bevacizumab and paclitaxel?**
   a. Hypertension
   b. Proteinuria
   c. Neuropathy
   d. All of the above
   e. None of the above
9. **In patients with metastatic breast cancer, several Phase III clinical trials have evaluated the safety and efficacy of bevacizumab in combination with docetaxel and *nab* paclitaxel.**
   a. True
   b. False
10. **In a Phase III randomized trial, *nab* paclitaxel was found to increase the _____ compared to paclitaxel.**
    a. Response rate
    b. Time to progression
    c. Incidence of Grade III neuropathy
    d. All of the above
    e. None of the above
11. **According to a recent patterns of care study, research leaders specializing in breast cancer tend to use capecitabine more frequently than community-based oncologists as first-line chemotherapy in patients with ER-negative, HER2-negative metastatic breast cancer who have received adjuvant AC followed by paclitaxel.**
    a. True
    b. False

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

EVALUATION FORM

Breast Cancer Update — Issue 8, 2005

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion 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	N/A = Not applicable to this issue of *BCU*

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single agent chemotherapy. . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Andrew D Seidman, 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
Vicente Valero, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

EVALUATION FORM

Breast Cancer Update — Issue 8, 2005

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

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

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

Degree:

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

FOLLOW-UP

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

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

☐ No, I am not willing to participate in a follow-up survey.

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

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UPDATE

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