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Breast Cancer® UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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Special feature: Rounds with Dr Charles Vogel and six of his patients

CME Certified

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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 switching to or 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 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 appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations.
- 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 4 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Jones, Miller and Vogel on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

12th Annual Perspectives in Breast Cancer
October 6-7, 2006
Boston, Massachusetts
Event website: **imedex.com/calendars/oncology.asp**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

The Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow
November 8-11, 2006
New York, New York
Event website: **mssm.edu/tcf**

29th Annual San Antonio Breast Cancer Symposium
December 14-17, 2006
San Antonio, Texas
Event website: **sabcs.org**

Miami Breast Cancer Conference
February 22-25, 2007
Miami Beach, Florida
Event website: **cancerconf.com**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

EDITOR'S NOTE

Neil Love, MD

The bond that heals

On this program we launch another experiment in oncology education as I visit the practice of clinical investigator Dr Charles Vogel, my former mentor at the University of Miami. For more than three decades, Chuck has been a fervent advocate of a meticulous and intensive — yet gentler — management of metastatic breast cancer. To demonstrate how this treatment philosophy translates to practice, he introduced me to six of his patients.

Over the course of this fascinating day, listening to Dr Vogel and these courageous women, it became clear that triumphing even temporarily over the intimidating specter of metastatic breast cancer requires special magic on both sides of the stethoscope. The bond between an attentive, dedicated physician and a patient who gathers fortitude from both internal and external resources can result in miracles, and Chuck's patients are living examples.

The following are sound bites from this program along with a related email from a loyal listener. As with all our programs, we greatly welcome your thoughts and comments on this slightly out-of-the-box initiative. ■

— Neil Love, MD
NLove@ResearchToPractice.net
June 10, 2006

Metastatic breast cancer, for the vast majority of patients, has turned into a chronic disease. It's rare in our practice to see a superaggressive type of presentation. Maybe three or four percent of my patients have disease that you just cannot get into remission. They mostly fall into the new classification of basaloid tumors — the triple negative tumors — and no matter how you treat those patients, they progress right through it.

But for the average patient with metastatic breast cancer, we can get them into remission very easily with either hormonal therapy or chemotherapy, and patients often live many, many years. We all have women in our practices who are now out 10, 12, 14 years or more with metastatic disease that is controlled and living reasonably normal lives most of the time. Many of these patients have never been hospitalized, even for complications of therapy.

— Charles Vogel, MD

(Received by email on May 15, 2006)

I think your CDs on breast, lung and colon cancer are terrific, but I would offer one comment about what I hear being said more and more (and not just on your CDs) in terms of changing cancer into a chronic disease.

I am not sure what anyone's definition of a chronic disease is, but to the lay person (and to most nononcologists) a chronic disease is one you live with for many years (ie, decades, such as with diabetes or COPD), with perhaps even a normal life expectancy or a somewhat shortened life, though you are always dealing with issues from the disease.

That is clearly not what we are achieving when, for example, we control liver metastases from colon cancer for three or four years. And it is especially not a chronic disease when we tell a 38-year-old woman with metastatic breast cancer that we will make her disease a chronic one because she won't die from it until she is at least 45 or possibly even 50.

I have a concern that we are misleading our patients (plus families and other healthcare professionals, including other oncologists) when we say we have converted metastatic breast cancer to a chronic disease.

While we have made substantial strides in recent years in treating a variety of metastatic cancers, we really should not be promoting this rather utopian concept of cancer as a chronic disease, at least not until more profound and dramatic improvements in disease control are achieved. Once again, however, many thanks for providing to us a terrific forum on critical issues involving our most common cancers.

— *Tony Coscia, MD*
Norwalk, Connecticut

I have an excellent quality of life interspersed by periods of sheer terror that I try to keep very short and very far between. Obviously you appreciate life a lot more in this situation.

Each day is very precious, and you are very happy to be out and about and able to do things you never thought you were going to be able to do again. The scary times usually last for several days, generally triggered by checkups and body scans, which for sure are harrowing experiences.

— 60-year-old woman with metastatic breast cancer to the liver on high-dose estrogen therapy

I love life. I get out. I'm alive and I do things. I feel good. I've got energy. This situation has completely changed my life. Before this, I just kind of lived. Now, I live for a reason: To do better things and have more compassion for people. I want to help more.

I'm very involved with the Lord, and His will is my will. If tomorrow it's time for me to go, I have no problem with that, and I'm very aware that that can happen to me. God brought Dr Vogel to me, and he's just been wonderful. I know I'm in the best hands, and when it's time to go, I'm ready.

I never cried over this. I never felt sorry for myself. I just thanked God it wasn't one of my children. I'm very lucky. I'm very blessed.

— 72-year-old woman with soft-tissue metastases on capecitabine

You can't explain this to someone who hasn't gone through it. My family has watched me live with this for eight years. Do they really understand? No. And I don't expect them to because you have to live it to understand it.

It's maybe not a great saying, but I live like I'm on my way out and not on my way in. A girlfriend of mine who just passed away used to say, "These are my senior years now." She was 40 years old. She's right. These are my senior years now also, and I am on my way out. Anything can happen at any given time. I'm lucky. The treatment is working. Is it going to work forever? Probably not. But it's working now, so I enjoy everything now.

If I could bottle what I have learned and teach it to other people, this world would be a better place.

— 44-year-old woman who has been treated with trastuzumab for metastatic breast cancer since 1998

SELECT PUBLICATIONS

Bang SM et al. **Changes in quality of life during palliative chemotherapy for solid cancer.** *Support Care Cancer* 2005;13(7):515-21. **Abstract**

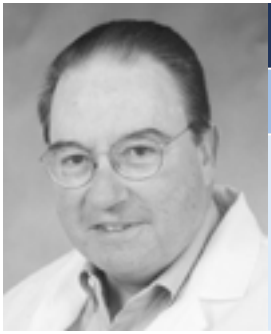
Ershler WB. **Capecitabine monotherapy: Safe and effective treatment for metastatic breast cancer.** *Oncologist* 2006;11(4):325-35. **Abstract**

Gralow JR. **Optimizing the treatment of metastatic breast cancer.** *Breast Cancer Res Treat* 2005;89(Suppl 1):9-15. **Abstract**

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

Hussain SA et al. **Endocrine therapy and other targeted therapies for metastatic breast cancer.** *Expert Rev Anticancer Ther* 2004;4(6):1179-95. **Abstract**

Stevanovic A et al. **Metastatic breast cancer.** *Aust Fam Physician* 2006;35(5):309-12. **Abstract**



INTERVIEW

Stephen E Jones, MD

Dr Jones is Director of Breast Cancer Research at the Charles A Sammons Cancer Center at Baylor University Medical Center in Dallas, Texas, Chair of US Oncology Breast Cancer Research and Medical Director of US Oncology Research in Houston, Texas.

Tracks 1-21

Select Excerpts from the Interview

Tracks 4, 5, 7

DR LOVE: Can you discuss the US Oncology trial evaluating TC versus AC as adjuvant therapy that you reported at the 2005 San Antonio Breast Cancer Symposium?

DR JONES: We reported an adjuvant study in which we compared four cycles

of standard-dose AC to four cycles of standard-dose TC (docetaxel and cyclophosphamide). Chemotherapy was administered before radiation therapy or tamoxifen, and we included patients with node-positive and higher-risk node-negative disease (Jones 2005a; [1.1]).

When we started this trial in 1997, everyone was interested in combining doxorubicin with the taxanes, but we felt that we didn't have enough data to combine docetaxel with doxorubicin. Consequently, we pursued this alternative route, which stands alone because it is one of the only nonanthracycline-containing regimens out there.

We now have mature results based on more than 170 events, with a median follow-up of 5.5 years. We have seen significantly fewer recurrences and events on the TC arm compared to the AC arm. I emphasized at San Antonio that the endpoint for this trial was disease-free survival, not overall survival. Overall survival was the secondary endpoint (Jones 2005a).

At five years, the disease-free survival was 86 percent for TC versus 80 percent for AC — a six percent absolute difference. The reduction in risk was roughly one third, and it was highly significant, with a *p*-value of 0.015. Also, a strong trend was favoring TC for overall survival — a three percent absolute difference at five years, with approximately a 24 percent reduction in the odds of dying from breast cancer (Jones 2005a; [1.2]).

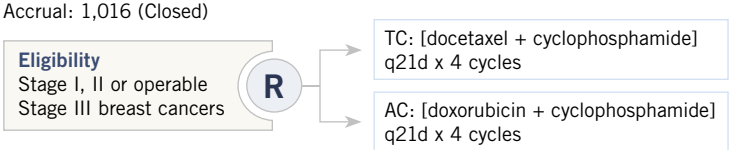
In general, TC was better tolerated. Some low-grade docetaxel-type side effects do occur, such as myalgias, arthralgias and edema, but they are fairly transient. The fever and neutropenia rates are also slightly higher; the numbers were 5.5 percent on the TC regimen and 2.5 percent on the AC regimen (Jones 2005a; [1.3]). We didn't use any prophylactic growth factors, but prophylactic antibiotics were used and encouraged.

The rate of CHF with AC was probably lower than would be expected. The usual figure that's quoted is 0.5 to 1.0 percent; fortunately we haven't seen that kind of rate. We have no reason to believe that TC would cause cardiac toxicity.

AC brought significantly more Grade III/IV nausea and vomiting, despite antiemetics (Jones 2005a; [1.3]). That's an unpleasant side effect we didn't see with TC. I was amazed at how much better tolerated TC was than AC.

1.1

Phase III Adjuvant Trial Comparing TC to AC in Women with Early-Stage Breast Cancer



SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005a;**Abstract 40**.

1.2

Phase III Adjuvant Trial Comparing TC to AC in Women with Early-Stage Breast Cancer: Efficacy

	TC (n = 506)	AC (n = 510)	Hazard ratio	*p*-value
Five-year disease-free survival	86%	80%	0.67	0.015
Five-year overall survival	90%	87%	0.76	0.131

TC = docetaxel/cyclophosphamide; AC = doxorubicin/cyclophosphamide

SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005a;**Abstract 40**.

1.3

Phase III Adjuvant Trial Comparing TC to AC in Women with Early-Stage Breast Cancer: Toxicities with Significant Differences

	TC (n = 506)	AC (n = 510)
Neutropenic fever (Grade III/IV)*	6%	3%
Nausea (Grade III/IV)†	2%	7%
Vomiting (Grade III/IV)†	<1%	5%
Edema (Grade I-IV)†	35%	2%
Myalgia (Grade I-IV)†	33%	17%
Arthralgia (Grade I-IV)†	24%	15%

* $p = 0.03$, † $p < 0.01$

TC = docetaxel/cyclophosphamide; AC = doxorubicin/cyclophosphamide

SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005a;**Abstract 40**.

Track 9

DR LOVE: What are your thoughts on the controversy about whether dose-dense AC/paclitaxel is as effective as TAC in patients with ER-positive disease?

DR JONES: We are seeing some data that seem to break out on the basis of ER status. If I present a patient with HER2-positive disease, it's a no-brainer that she needs trastuzumab. However, physicians haven't generally been thinking about patients with ER-positive disease requiring a different kind of chemotherapy.

At the 2005 San Antonio Breast Cancer Conference, Cliff Hudis updated the dose-dense data and presented an unplanned exploratory analysis of the impact of ER status. Cliff's description of the results would be that there was less evidence of benefit among patients with ER-positive disease. My description would be that I didn't see any evidence of benefit among patients with ER-positive disease.

Both of these viewpoints are probably a little extreme. However, almost all the

treatment effect in their first study adding paclitaxel to AC (Henderson 2003) or in the update of the dose-dense trial (Hudis 2005) appears to be in the population with ER-negative disease. Yet now we have data that both TAC and TC appear to be equally effective in patients with ER-positive disease.

Another presentation at the 2005 San Antonio Breast Cancer Symposium, which followed mine, was the results from GEICAM 9906 by Professor Martin. The trial compared four cycles of FEC-90 followed by eight doses of weekly paclitaxel to six cycles of FEC-90; the paclitaxel arm received a slightly longer duration of therapy.

They saw an improvement in disease-free survival with the addition of weekly paclitaxel and a trend in overall survival. It appeared to be equally effective in patients with ER-positive versus ER-negative disease (Martin 2005). So we are seeing differences among some of these regimens.

Track 10

DR LOVE: Which chemotherapy regimens are you usually using off-study in a patient with node-positive disease?

DR JONES: We've actually just completed enrollment in our third US Oncology adjuvant study, which compared AC followed by docetaxel every three weeks to AC followed by capecitabine/docetaxel — the XT regimen. Joyce O'Shaughnessy is the principal investigator of this trial, which tests XT as part of an adjuvant regimen. We'll have to see how that pans out.

In the context of practice, if you present to a patient the standard treatment as AC followed by docetaxel, and she decides not to enter a clinical trial, it's hard to recommend something that you haven't discussed with her. So many of us use AC followed by docetaxel.

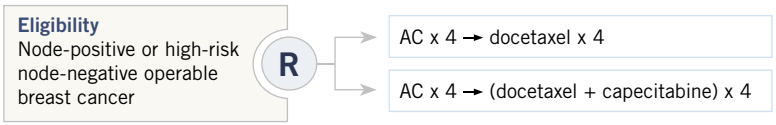
DR LOVE: Is that what you're doing now that the study accrual is completed?

DR JONES: We see many regimens used within US Oncology. Dose-dense therapy is used for many patients. Some people are starting to use TC more.

1.4

Phase III Trial Comparing AC Followed by Either Docetaxel or Capecitabine Plus Docetaxel

Protocol ID: US Oncology 01-062
Accrual: 1,810 (Open)



TC = docetaxel/cyclophosphamide; AC = doxorubicin/cyclophosphamide

SOURCE: Protocol 01-062 synopsis, June 2002.

We have a 30-year history with AC. It's hard to say one day you should abandon it. I've heard people say that, but I've also heard the other extreme that they would only use TC in a patient with cardiac disease, in whom you wouldn't want to take a chance with doxorubicin.

Track 11

DR LOVE: Can you discuss the ECOG-E2197 trial, reported by Lori Goldstein, which compared AT to AC? Do you think those results are relevant to use of the TC regimen?

DR JONES: I believe they are relevant. In the manuscript we recently submitted, it's the one study I selected to compare because it was a larger study with 3,000 women. Two thirds of the patients had node-negative disease and one third had node-positive disease (Goldstein 2005).

If we had the data when we started our trial in 1997, I believe we would have liked to combine doxorubicin and docetaxel, which is what they did, and compare it to AC. We weren't comfortable enough to do that, so we used TC.

Their trial showed absolutely no difference in outcome, with about an 87 percent disease-free survival at four years in both arms. The curves were absolutely superimposable (Goldstein 2005). It's hard to explain why TC was better than AC (Jones 2005a) but AT was not (Goldstein 2005).

Part of the difference in the data sets could be that we used a higher dose of docetaxel — 75 mg/m^2 (Jones 2005a). In ECOG-E2197, they used docetaxel at 60 mg/m^2 and doxorubicin at 60 mg/m^2 (Goldstein 2005).

In metastatic breast cancer, a dose-response relationship exists with docetaxel, and Mouridsen will publish a paper evaluating different doses of docetaxel in metastatic disease. The numbers of patients aren't huge, but clearly the lower dose of 60 mg/m^2 is not quite as effective as 75 mg/m^2, which isn't quite as good as 100 mg/m^2. Some of those differences aren't statistically significant, but the trend is there (Mouridsen 2002).

Track 15

DR LOVE: Can you comment on the rates of neutropenic fever associated with docetaxel?

DR JONES: We keep seeing a 16 to 17 percent rate of fever and neutropenia with docetaxel as a single agent. Chuck Vogel conducted a study of docetaxel with or without pegfilgrastim, and he showed a 17 percent rate of fever and neutropenia for docetaxel alone versus one percent for docetaxel with pegfilgrastim (Vogel 2005). I would probably use pegfilgrastim if I were going to use docetaxel for many patients.

In our AC versus TC study, we saw a higher rate of fever and neutropenia with TC. The actual numbers were 5.5 percent with TC, which is a far cry

from 16 or 17 percent, and 2.5 percent with AC (Jones 2005a; [1.3]). I see no justification for prophylactic white blood cell growth factors for regimens with a 2.5 to 3 percent incidence of fever and neutropenia. You might consider it for older patients or patients who have had severe, profound neutropenia even without fever during the first course.

DR LOVE: When you use AC followed by docetaxel, do you use preemptive growth factors?

DR JONES: Generally I don't, but I'm starting to consider it. With the older patients who have comorbidities, I believe we are close to having justification for using growth factors.

Track 16

DR LOVE: What's the next US Oncology adjuvant trial?

DR JONES: We have piloted a trial of dose-dense AC followed by dose-dense nanoparticle albumin-bound *(nab)* paclitaxel. Dose-dense *nab* paclitaxel is interesting because you only need growth factors about one third of the time. Nick Robert reported that in a pilot trial of about 30 patients (Robert 2005). That would probably be our next study, but we have not come to a final decision.

We're in the process of rethinking this at the moment. The world has changed with the introduction of bevacizumab. Suddenly, everyone wants to put bevacizumab into the adjuvant setting with the hope that it will be the next trastuzumab for patients with HER2-negative disease, which is 80 percent of the patients with breast cancer.

We're also thinking about doing something further with the TC regimen. Up to this point, it stands alone. There are no other studies with TC, and no one is using it. The idea that immediately comes to mind is to combine TC with trastuzumab for patients with HER2-positive disease.

In BCIRG 006, docetaxel/carboplatin with trastuzumab wasn't quite as good as an anthracycline-based regimen with trastuzumab. However, there was a separation of the disease-free survival curves, and Dr Slamon has been careful to point out that there was only a 20-event difference between the treatment groups (Slamon 2005).

Still, you wouldn't rush to pick docetaxel/carboplatin/trastuzumab as your front-line regimen if it's not quite as good. Dr Slamon has put forward the topoisomerase II (TOPO II) hypothesis to explain this, and it may be correct (Press 2005). We may end up with one treatment for the patients with nonamplified TOPO II and another treatment for those with amplified TOPO II.

For HER2-negative tumors, we now have a regimen up front — TC — that offers a significant improvement in disease-free survival compared to AC (Jones 2005a; [1.2]), and we've not had that before. We also don't have cardiac issues with TC, so you could think about combining it with trastuzumab, either concurrently or immediately after chemotherapy. We can't go back and do a

trial of TC with or without trastuzumab — that is no longer ethical — but we could look at concurrent or sequential therapy to obtain some toxicity data.

Track 19

DR LOVE: What are your thoughts on the E2100 bevacizumab data, from both the point of view of future clinical research and that of daily patient care?

DR JONES: The bevacizumab story is interesting because, although I focus on breast cancer, it seems to work in almost every tumor type in which it has been studied. It is clearly active in breast cancer. If the study Kathy Miller reported had been negative, I believe bevacizumab would have disappeared in breast cancer, but it wasn't negative (Miller 2005a, 2005b). It shows the same order of benefit that we saw combining trastuzumab with chemotherapy in metastatic disease, and suddenly everyone's excited about moving bevacizumab into the adjuvant setting.

Studies are under way evaluating single agents — gemcitabine, docetaxel, doxorubicin, capecitabine and *nab* paclitaxel — with or without bevacizumab to prove efficacy. These are randomized studies; I believe it's a 2:1 randomization favoring bevacizumab.

If the patient isn't randomly assigned to receive bevacizumab, she can receive it at the time of progression. The idea is to try to obtain the same kind of data for the other active agents in breast cancer.

Track 20

DR LOVE: What's your impression of the side-effect profile of docetaxel compared to paclitaxel?

DR JONES: I was the first author on the TAX-311 trial that was reported in *JCO* in August 2005. In this study, we directly compared paclitaxel to docetaxel at their FDA-approved doses and schedules — on an every three-week basis. Docetaxel clearly showed more hematologic toxicity than paclitaxel, but it showed a better response rate, time to tumor progression and overall survival (Jones 2005b; [1.5]).

In the last 12 years or so, however, weekly paclitaxel has been introduced. It probably falls somewhere in between, with less toxicity other than some neurotoxicity. I believe weekly paclitaxel has stepped up, and we see it in the adjuvant setting these days.

Track 21

DR LOVE: What are your thoughts about *nab* paclitaxel?

DR JONES: We've done a good deal of Phase II work with *nab* paclitaxel in

1.5

TAX-311: Docetaxel versus Paclitaxel

"This is the first clinical trial to compare directly the taxanes, docetaxel and paclitaxel, as monotherapy for patients with advanced breast cancer. Using US Food and Drug Administration–approved doses and schedules for each agent, this phase III study has demonstrated that docetaxel is superior to paclitaxel in TTP (5.7 v 3.6 months; $P < .0001$), response duration (7.5 v 4.6 months; $P = .01$), and OS (15.4 v 12.7 months; $P = .03$). The overall response rate was also greater with docetaxel (32% v 25%; $P = .10$). The survival advantage for docetaxel was observed despite the increased incidence of toxicities leading to dose reductions and treatment withdrawal, and the slightly greater use of salvage treatment in patients randomly assigned to paclitaxel."

SOURCE: Jones SE et al. *J Clin Oncol* 2005b;23(24):5542-51. **Abstract**

metastatic breast cancer using the weekly schedules. Joanne Blum has been the principal investigator for US Oncology on those trials (Blum 2004, 2003). It's an active regimen.

It does have some neurotoxicity, but it's well tolerated. Also, you can administer it in a short time. The novel formulation is what makes it really intriguing — the way the drug is delivered. Other drugs could potentially be administered this way also.

The lack of premedication is a big advantage. Some patients don't do very well with steroid premedication, and they can't sleep. That's an issue for both paclitaxel and docetaxel. The lower amount of chair time with *nab* paclitaxel — depending on how busy you are — and the lack of need for special tubing can also be advantages.

DR LOVE: Are you using *nab* paclitaxel in the clinical setting?

DR JONES: We use it for selected patients — patients who may not have had prior paclitaxel. The oncologists at US Oncology are probably more likely to use it on our Phase II weekly schedule, which is very well tolerated.

DR LOVE: How would you compare the neurotoxicity associated with *nab* paclitaxel to that associated with paclitaxel, particularly when using weekly regimens for both?

DR JONES: Neurotoxicity is definitely associated with *nab* paclitaxel, but it comes and goes very quickly. You do see neurotoxicity, but in two or three weeks it resolves. In Nick Robert's pilot study of dose-dense *nab* paclitaxel (Robert 2005), some neurotoxicity required dose reductions, but it went away pretty quickly. That is my clinical impression also. ■

SELECT PUBLICATIONS

Blum JL et al. **Long term disease control in taxane-refractory metastatic breast cancer treated with *nab* paclitaxel.** ASCO 2004;**Abstract 543**.

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** *Proc ASCO* 2003;**Abstract 64**.

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005a;23(16):3676-85. **Abstract**

Buzdar AU et al. **Prospective data of additional patients treated with neoadjuvant therapy with paclitaxel followed by FEC chemotherapy with trastuzumab in HER-2 positive operable breast cancer, and an update of initial study population.** San Antonio Breast Cancer Symposium 2005b;**Abstract 5049**.

Chlebowski RT et al. **Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS).** Presentation. ASCO 2005;**Abstract 10**.

Goldstein L et al. **E2197: Phase III AT (doxorubicin/docetaxel) vs AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer.** *Proc ASCO* 2005;**Abstract 512**.

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

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;**Abstract 41**.

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005a;**Abstract 40**.

Jones SE et al. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005b;23(24):5542-51. **Abstract**

Martin M et al. **Multicenter, randomized phase III study of adjuvant chemotherapy for node positive breast cancer comparing 6 cycles of $FE_{90}C$ versus 4 cycles of $FE_{90}C$ followed by 8 weekly paclitaxel administrations: Interim efficacy analysis of GEICAM 9906 Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 39**.

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 2005a. No abstract available

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Mouridsen H et al. **Phase III study of docetaxel 100 versus 75 vs 60 mg/m² as second line chemotherapy in advanced breast cancer.** San Antonio Breast Cancer Symposium 2002;32. No Abstract Available

Robert N et al. **Pilot study of dose dense doxorubicin + cyclophosphamide followed by ABI-007 in patients with early stage breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 2073**.

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

INTERVIEW

Kathy D Miller, MD

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

Tracks 1-30

Track 1 Introduction

Track 2 Role of VEGF in normal and tumor cell function

Track 3 Mechanism of action of bevacizumab

Track 4 Role of bevacizumab in decreasing interstitial tumor pressure and increasing vascular permeability

Track 5 Clinical trial of neoadjuvant bevacizumab in patients with inflammatory breast cancer

Track 6 Anti-angiogenic effects of chemotherapeutic agents

Track 7 Utility of basic science to understand clinical observations

Track 8 Biologic rationale for side effects associated with bevacizumab

Track 9 Dosing of bevacizumab in different tumor types

Track 10 Potential role of small molecule tyrosine kinase inhibitors (SMTKIs) in breast cancer

Track 11 Case discussion: Woman with ER/PR/HER2-negative metastatic disease treated with a SMTKI

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Track 14 Interpretation of results from the Phase III trial with capecitabine/bevacizumab

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Track 17 Rationale for lack of crossover in ECOG-E2100

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Track 22 Phase II trial evaluating bevacizumab in combination with trastuzumab

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Track 25 Background and design of adjuvant bevacizumab trial

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Track 28 Integration of bevacizumab into clinical practice

Track 29 Utilization of bevacizumab with other chemotherapeutic agents

Track 30 Societal and economic costs associated with cancer therapy

Select Excerpts from the Interview

Track 5

DR LOVE: Can you talk about Sandy Swain's study of bevacizumab for patients with inflammatory breast cancer?

DR MILLER: The patients were treated with a single dose of bevacizumab and then with docetaxel and doxorubicin added to bevacizumab for the rest of their neoadjuvant therapy.

The investigators didn't directly measure the tumor interstitial pressure, but they did use dynamic contrast-enhanced MRI to measure the perfusion and permeability of the vessels after an initial dose of bevacizumab and after a couple of doses of the combination therapy. They also measured the clinical response, and they collected blood and serum samples for several other circulating correlative studies (Wedam 2006; [2.1]).

What was perhaps most interesting was that they saw improvements in the appearance of the tumors of some of those patients with inflammatory breast cancer after their first dose of bevacizumab, before they'd even received chemotherapy. If you think about the intense vasculature and leakiness of those structures and the skin edema in inflammatory breast cancer, it's not surprising to see improvement just with an anti-angiogenic agent, at least in the short term.

2.1

Bevacizumab in Patients with Inflammatory and Locally Advanced Breast Cancer

"We have demonstrated a significant decrease in VEGFR2 activation in tumor cells and increase in tumor apoptosis after one cycle of bevacizumab alone...However, this is the first clinical study to demonstrate that bevacizumab has a direct inhibitory effect on angiogenic parameters in tumor cells, possibly as a result of the disruption of both autocrine and paracrine functions of VEGF. Interestingly, endothelial proliferation was decreased in five of five cases after bevacizumab, which also suggests an inhibitory effect on endothelium."

SOURCE: Wedam SB et al. *J Clin Oncol* 2006;24(5):769-77. **Abstract**

Track 9

DR LOVE: Can you comment on the different doses of bevacizumab used for different tumors?

DR MILLER: The breast cancer program did not have any randomized dose-finding studies. We conducted a sequential cohort study, initially planned to evaluate two different dose levels — 3 mg/kg or 10 mg/kg every two weeks (Cobleigh 2003). The 3-mg/kg dose was chosen because it was the dose from the Phase I study that eliminated circulating VEGF, and the 10-mg/kg dose was one of the highest doses that had been studied in the Phase I trial (Gordon 2001).

We thought 10 mg/kg showed greater activity than the 3-mg/kg dose. So the study was amended to evaluate an even higher dose of 20 mg/kg every two weeks. We didn't see any increase in activity at 20 mg/kg, but we saw migraines, which was the dose-limiting toxicity that had not yet been identified (Cobleigh 2003).

The lung and colon programs proceeded a little differently in that they each did a randomized Phase II study. The colon trial compared 5 mg/kg to 10 mg/kg every two weeks (Kabbinavar 2003). The lung trial administered bevacizumab every three weeks but at doses equivalent to either 5 mg/kg or 2.5 mg/kg per week. In the lung cancer trial, the higher dose appeared to be superior (Johnson 2004), and in the colon cancer trial, the lower dose appeared to be superior (Kabbinavar 2003). So they used those doses going forward.

I believe this teaches us to be cautious with randomized Phase II studies, because they're small and not designed to provide a direct comparison. Those results could easily have been spurious rather than teaching us anything true about doses. I don't know that the dose we picked for the breast cancer trials is the right dose because it came from a fairly small, sequential Phase II study (Cobleigh 2003). So a randomized Phase III study is planned to evaluate two different doses of bevacizumab in breast cancer.

Tracks 13-15

DR LOVE: Would you discuss the clinical trials that have been conducted with bevacizumab in breast cancer?

DR MILLER: The first one was the monotherapy Phase II trial that sequentially enrolled 75 patients in three different dose cohorts. Overall, the objective response rate was about nine percent, and about 17 percent of the patients had disease that was responding or stable at five months, which is an unconventional time point but one of the time points the protocol required to evaluate the disease (Cobleigh 2003). So we know it's a solid endpoint. Four of those 75 patients were treated for at least a year without progression.

Those results led to a randomized Phase III trial for patients with refractory disease evaluating capecitabine alone or in combination with bevacizumab. This trial required patients to have received previous therapy with an anthracycline and a taxane; they could have received up to two previous chemotherapy regimens for metastatic disease. So they were a pretty advanced group (Miller 2005a).

The trial enrolled 462 patients and found essentially a doubling in the response rate by adding bevacizumab. The response rate went from nine percent to 19 percent in the eyes of the independent review facility and from about 19 percent to 30 percent in the eyes of the investigators. Those low response rates, however, did not budge the median progression-free survival, which was the primary endpoint, and it did not alter the overall survival (Miller 2005a; [2.2, 2.3]).

2.2 **Phase III Randomized Trial of Capecitabine with or without Bevacizumab in Patients with Previously Treated Metastatic Breast Cancer: Efficacy**

	Bevacizumab + capecitabine (n = 232)	Capecitabine (n = 230)	*p*-value
Objective response rate			
Investigator	30.2%	19.1%	0.006
IRF	19.8%	9.1%	0.001
Median PFS			
IRF	4.86 months	4.17 months	0.857
Median duration of response			
IRF	5.0 months	7.6 months	—
Median overall survival	15.1 months	14.5 months	—

IRF = independent review facility; PFS = progression-free survival

SOURCE: Miller KD et al. *J Clin Oncol* 2005a;23(4):792-9. **Abstract**

2.3 **Phase III Randomized Trial of Capecitabine with or without Bevacizumab in Patients with Previously Treated Metastatic Breast Cancer: Conclusions**

"The addition of bevacizumab to capecitabine clearly increased response rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen. Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups."

SOURCE: Miller KD et al. *J Clin Oncol* 2005a;23(4):792-9. **Abstract**

I reported it as a negative trial, although I was more encouraged than discouraged by the results. It was a difficult trial to report because the primary endpoint was progression-free survival. It had to be reported as a negative trial because it didn't meet that endpoint. However, we learned a lot from that trial, and it brought more good news than bad news.

If you consider the correlative pathology studies showing that as breast cancers progress, the number of pro-angiogenic factors expressed increases, it's hard to imagine how inhibiting one factor very late in the game would provide a demonstrable clinical effect or an effect that would last very long. However, inhibiting that same factor much earlier, when the system includes less redundancy, might provide a much greater effect.

That was the idea behind ECOG-E2100, which had a similar design but used paclitaxel instead of capecitabine, primarily because we were looking at patients with earlier-stage disease. Most of the patients had not received a taxane as part of their adjuvant therapy, although about 18 percent of them had, and they had not received previous chemotherapy for recurrent disease. They were all randomly assigned to paclitaxel with or without bevacizumab (Miller 2005b; [2.4]).

ECOG-E2100 enrolled 680 eligible patients. In some ways, the results mirrored the earlier trial. It was essentially a doubling of response rates, although the baseline response rates were a bit higher than in the more refractory population. In this setting, that translated into a very striking improvement in progression-free survival of more than five months — from 6.1 months among the patients receiving paclitaxel alone to 11.4 months among the patients receiving the combination (Miller 2005b; [2.4]).

2.4

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

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

Eligibility
Locally recurrent or metastatic breast cancer
HER2-positive only if prior treatment with or contraindication to trastuzumab
No prior chemotherapy for metastatic disease
Adjuvant taxane allowed if disease-free interval > 12 months; PS 0 or 1; no CNS metastases

R

- Paclitaxel (days 1, 8 and 15) + bevacizumab 10 mg/kg (days 1 and 15)
- Paclitaxel (days 1, 8 and 15)

	Paclitaxel + bevacizumab (n = 341)	Paclitaxel alone (n = 339)	Hazard ratio (95% CI)	*p*-value
Response rate				
All patients	29.9%	13.8%	—	<0.0001
Measurable disease	37.7%	16.0%	—	<0.0001
Progression-free survival	11.4 months	6.1 months	0.51 (0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months	0.84 (0.64-1.05)	0.12

CI = confidence interval

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Tracks 17-19

DR LOVE: We've been sensitized to the issue of treatment crossover because of the combination chemotherapy trials. Can you review how ECOG-E2100 was structured in terms of crossover?

DR MILLER: ECOG-E2100 did not include a crossover. We made no provisions for patients who were assigned to paclitaxel alone to receive bevacizumab at the time of progression. For at least part of the duration of the trial, bevacizumab was approved and commercially available for colon cancer. It's possible that a few of our patients might have had access to the drug for a crossover at that point.

However, because bevacizumab was approved only for colon cancer and the costs are prohibitive for most patients, I believe the likelihood of crossover contaminating our study is minimal.

We talked about whether we should have a crossover in ECOG-E2100, and we decided not to for a couple of pragmatic reasons. One was that it would have made the trial a lot more complicated and expensive. Also, our primary endpoint was progression-free survival, so having a crossover would not have contributed to our primary endpoint.

At the time ECOG-E2100 was designed, we didn't have the results from the bevacizumab/capecitabine trial (Miller 2005a), but we had those results within the first year of ECOG-E2100 being open for accrual.

Those patients who have progressed on their first chemotherapy regimen are the largest group of patients who enrolled in the bevacizumab/capecitabine trial, which found improvements in response rate but not in progression-free survival (Miller 2005a; [2.2]).

It was hard at that point to justify going back and amending ECOG-E2100 to include a crossover based on the results of a negative trial in that patient population.

Those who point to this as a criticism of the design and wonder if the survival data would be different if we had allowed for a crossover have a legitimate criticism. The data with more advanced disease suggest that it's not likely to influence our results. Without a trial that includes a crossover, however, I don't have data that will prove it.

DR LOVE: Many look at the ECOG-E2100 results as a signal that has biologic implications and, hopefully, implications for the adjuvant setting.

DR MILLER: We believe the results will be even greater in the adjuvant setting because first-line chemotherapy for metastatic disease is used fairly late in the natural history of breast cancer. Although our patients hadn't received chemotherapy for metastatic disease, two thirds of them had received adjuvant chemotherapy, and 18 percent had received a taxane (Miller 2005b).

These were not chemotherapy-naïve patients. They were much more advanced than the patients enrolled a decade ago in trials of first-line chemotherapy for metastatic disease. We expect much greater activity in the adjuvant setting, and recent laboratory data suggest that we're likely to see it.

DR LOVE: You mentioned the patients in ECOG-E2100 who had received prior adjuvant taxanes. Can you talk about that?

DR MILLER: In the design of ECOG-E2100, we allowed patients who had received a taxane-containing adjuvant regimen to enroll as long as their disease-free interval was at least 12 months. We did that for pragmatic reasons because the taxanes were being used more frequently in the adjuvant setting. We thought it would be reasonable to consider re-treating those patients if their disease-free interval was at least a year.

Approximately 18 percent of our patients had received a taxane-containing regimen. Their hazard ratio was 0.38 (Miller 2005b; [2.5]), which was the best hazard ratio of all of the clinically based subsets. For those patients, that translated into an improvement not from six to 11 months but from four to just more than 12 months in median progression-free survival (Miller 2005b).

2.5 **ECOG-E2100: Progression-Free Survival**

Subgroup	Hazard ratio (95% confidence interval)
No adjuvant chemotherapy (n = 178)	0.60 (0.44-0.82)
Nontaxane-containing adjuvant chemotherapy (n = 234)	0.51 (0.39-0.67)
Taxane-containing adjuvant chemotherapy (n = 86)	0.38 (0.25-0.59)

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Track 21

DR LOVE: Let's talk about some of the ongoing clinical trials that may affect clinical decision-making in the next couple of years.

DR MILLER: One of the trials that we activated shortly after we had the results from ECOG-E2100 was a Phase II trial known as XCaliBr, which uses the capecitabine/bevacizumab combination from the earlier Phase III trial (Miller 2005a; [2.6]) but as first-line therapy for patients with metastatic disease.

It's essentially the ECOG-E2100 patient population using the regimen from the capecitabine/bevacizumab trial (Miller 2005a). We thought that was a reasonable trial because we had ample safety data with the combination, and we knew that adding bevacizumab to capecitabine improved the response rates.

It potentially will provide patients in that first-line chemotherapy setting another option and one that would be oral and wouldn't cause alopecia, if we see similar response rates and progression-free survival in a decent-sized Phase II study.

DR LOVE: In colon cancer, bevacizumab adds to 5-FU, so you would expect it to work.

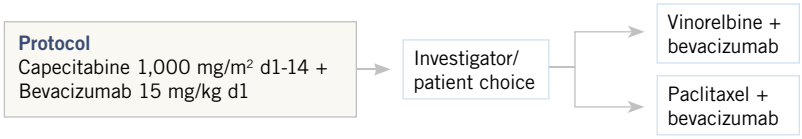
DR MILLER: You certainly would expect so. Our trial with refractory patients found a doubling of response rates (Miller 2005a). We have data that strongly suggest this would be active. What we don't know is whether we'll have the same response rate and progression-free survival as with the paclitaxel-based regimen. I believe that would be an important piece of data clinically to allow people greater flexibility in their first-line regimen of chemotherapy with bevacizumab.

2.6

Phase II Study of Capecitabine/Bevacizumab Followed by Bevacizumab Continuation with Chemotherapy after Disease Progression

Protocol ID: XCaliBr
Target Accrual: 92 (Open)

Eligibility: Newly diagnosed metastatic breast cancer



SOURCE: Miller KD. Presentation. Research To Practice *Breast Cancer Update* CME Forum, Los Angeles, California, 2005.

Tracks 22-23

DR LOVE: What other important trials of bevacizumab are being conducted in the metastatic breast cancer setting?

DR MILLER: Mark Pegram and his group at UCLA are running a trial (UCLA-0109030-03) combining bevacizumab with trastuzumab for patients with HER2-positive disease (2.7). That's a patient group for whom we currently don't have many clinical data with bevacizumab. They were excluded from ECOG-E2100 or were required to have received trastuzumab previously, but those patients are more likely to have increased VEGF expression.

That is certainly a population in which, based on the biology of their tumors, you would want to block both of those two signaling pathways. Dr Pegram's Phase II trial will then be expanded, we hope, into a Phase III trial that has been proposed within ECOG and is currently being reviewed by the National Cancer Institute (NCI), which will evaluate a taxane/trastuzumab regimen with or without bevacizumab as first-line therapy for those patients.

DR LOVE: Is that regimen eventually going to be evaluated in the adjuvant setting?

DR MILLER: Discussions are ongoing within BCIRG about moving it into the adjuvant setting in their next trial for patients with HER2-positive disease.

I would also like more information about the patients with ER-positive disease who don't yet need chemotherapy. The patients in ECOG-E2100 were receiving first-line chemotherapy for metastatic disease, but many of them had metastatic disease for several years and were treated sequentially with hormonal agents before enrolling in E2100. Estrogen increases VEGF expression, so a biologic rationale exists for combining bevacizumab with hormone-based therapies.

2.7

Phase II Study of Bevacizumab and Trastuzumab in Women with Relapsed or Metastatic HER2–Positive Breast Cancer

Protocol IDs: UCLA-0109030-03, TORI-B-03, NCT00093535
Target Accrual: 37-50 (Open)

Eligibility
Relapsed (surgically unresectable) or metastatic breast cancer
HER2 positive (FISH)
No prior trastuzumab or bevacizumab
No chemotherapy for metastatic disease

→ Trastuzumab weekly + bevacizumab every 2 weeks (beginning day 8)

Study Contact:
Jonsson Comprehensive Cancer Center at UCLA
Mark Pegram, MD
Tel: 888-798-0719

SOURCE: NCI Physician Data Query, May 2006.

DR LOVE: Are any trials evaluating that combination?

DR MILLER: A safety trial is ongoing with letrozole (UCSF-037518). It's a trial that I hope people will not look at in the wrong way and become disappointed. I've already heard some people say they weren't very impressed with the response rates in the early reports.

This trial was designed purely to look at safety. So it allowed patients who had been on an aromatase inhibitor for any period of time for metastatic disease, but whose disease was not actively progressing, to enroll and have bevacizumab added. Most of the patients reported so far had been on an aromatase inhibitor for quite some time before bevacizumab was added (Traina 2005).

I wouldn't expect to see these patients, who had prolonged stable disease and didn't have easily measurable disease, to suddenly show an easily identified objective response just by adding bevacizumab. It is definitely going to take a much larger study, with bevacizumab added at the time of the initial hormonal therapy, to really see the benefits.

However, this was a first step in investigating whether any unique safety issues arose from combining bevacizumab with hormone therapy. They certainly found no safety signals that would limit you from moving forward (Traina 2005).

Track 24

DR LOVE: What about evaluating bevacizumab in the neoadjuvant setting?

DR MILLER: Some studies are evaluating bevacizumab in the neoadjuvant setting. The one complicating factor is whether it will interfere with wound

healing at the time of surgery. In Sandy Swain's very small experience, five patients had either wound dehiscence or significant seromas that seemed out of proportion to what had been seen before, in both severity and chronicity of those problems (Wedam 2006).

This could be purely bad luck. These were all folks with very locally advanced disease. It's a select population that makes its way to the NCI Clinical Center, but five out of 21 patients is a significant fraction, and that raises this as a concern in the neoadjuvant setting. We don't know nearly enough to say that it's prohibitive, and there's certainly a lot that could be learned about biology in the neoadjuvant setting.

Track 25

DR LOVE: Where are we with the adjuvant bevacizumab trials?

DR MILLER: The pilot adjuvant trial (ECOG-E2104; [2.8]) is enrolling patients. That trial is critically important to us because it will evaluate adding bevacizumab to an anthracycline-based treatment regimen. To date, approximately 100 patients in all have ever been treated with an anthracycline and bevacizumab combined. All of those studies have raised some question of increased cardiac toxicity.

DR LOVE: What's the exact regimen in the pilot adjuvant trial?

DR MILLER: The chemotherapy regimen in the pilot adjuvant trial is dose-dense AC followed by paclitaxel, as used in CALGB-9741. ECOG-E2104 is observing two different cohorts. The first cohort receives bevacizumab with the anthracycline and throughout therapy. The second cohort receives bevacizumab only with paclitaxel, and this is our backup if we do see cardiac toxicity issues with the combined administration (2.8). Hence, we'll have safety data with both strategies. The pilot adjuvant trial will enroll a total of 212 patients.

The full adjuvant trial will use a slightly different chemotherapy backbone that won't require growth factors. We will be using AC on an every three-week basis followed by weekly paclitaxel. I wanted to use a weekly taxane regimen because the biggest support for moving this into the adjuvant setting is the data from ECOG-E2100, which used a weekly taxane schedule (Miller 2005b).

I don't have direct data to say we wouldn't have obtained the same improvements with an every three-week or every two-week taxane schedule, but the data we have are with a weekly schedule.

The full adjuvant trial has three arms, on which everybody receives the same chemotherapy. Patients in arm A receive no bevacizumab. Those in arm B receive six months of bevacizumab, concurrently with chemotherapy, and those in arm C receive 12 months of bevacizumab, six months with chemotherapy and an additional six months of maintenance.

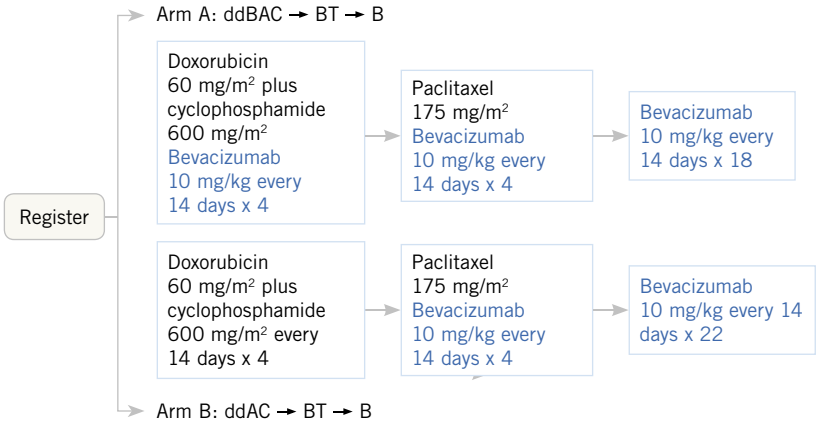
The first six months of therapy are blinded and placebo controlled. At the end of the chemotherapy treatment, patients and their physicians will be told to which arm they have been assigned and whether they're continuing bevacizumab for an additional six months.

2.8

Phase II Study of Adjuvant Bevacizumab and Dose-Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel in Patients with Resected Lymph Node-Positive Breast Cancer

Protocol IDs: ECOG-E2104, NCT00119262
Target Accrual: 212 (Open)

Eligibility: Node-positive, non-HER2-positive early breast cancer



dd = dose dense

Patients who require radiation therapy (postlumpectomy) or who plan radiation therapy at the discretion of the investigator (postmastectomy) undergo radiation therapy beginning within six weeks after the completion of chemotherapy.

Premenopausal patients with ER-positive and/or PR-positive disease receive oral tamoxifen once daily for five years beginning at the time of radiation therapy or within six weeks after the completion of chemotherapy. Postmenopausal patients with ER-positive and/or PR-positive disease receive an aromatase inhibitor (eg, anastrozole, letrozole or exemestane) or tamoxifen followed by an aromatase inhibitor once daily for up to 10 years.

Trial Lead Organizations:
Eastern Cooperative Oncology Group
Kathy Miller, MD, protocol chair — Tel: 317-274-1690; 888-600-4822
Robin Zon, MD, protocol co-chair — Tel: 574-234-5123

North Central Cancer Treatment Group
Edith Perez, MD, protocol chair — Tel: 904-953-7283

SOURCES: Miller KD. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 3**; NCI Physician Data Query, June 2006.

Track 26

DR LOVE: What do we know about the arterial events associated with bevacizumab?

DR MILLER: Adding bevacizumab increases the risk of arterial thrombotic events, although to a very modest degree. We know a little about the risk factors in that the risk seems to be preferentially borne out in patients who are older than age 65 or those who have had previous arterial thrombotic events, particularly MI, TIA or stroke.

This is not surprising. If you're older or you've had one before, you're at a greater risk of having such an event.

No reports associate cardiomyopathy or congestive heart failure with bevacizumab in any of the trials that either did not use concurrent anthracyclines or were in patient populations who would not have been previously treated with anthracyclines. So this is an issue specific to patients with breast cancer, sarcoma or leukemia, for which anthracyclines are used.

In the randomized bevacizumab/capecitabine trial, two patients had congestive heart failure or cardiomyopathy in the capecitabine-alone group compared to seven in the capecitabine with bevacizumab group (Miller 2005a). That sounds like an increase, but the overall event rate was so low that, statistically, those numbers were not different.

In ECOG-E2100, we didn't see any sign of congestive heart failure when comparing the two groups (Miller 2005b). In Sandy Swain's 21-patient experience, which is the only breast cancer trial that has used an anthracycline and bevacizumab concurrently, none of the patients had clinical congestive heart failure, but two of them showed a decrease in their ejection fraction to less than 40 percent (Wedam 2006).

Track 28

DR LOVE: Putting aside the issues of FDA approval, reimbursement and cost, what do you think the results of ECOG-E2100 mean in terms of clinical decision-making?

DR MILLER: Aside from issues of cost and access to the drug, for patients who would have been eligible for ECOG-E2100 — those receiving first-line chemotherapy for metastatic disease who have not received an adjuvant taxane within the last 12 months — I would strongly recommend treating them with the E2100 regimen of weekly paclitaxel with bevacizumab.

No regimen has been shown to have the same improvements in progression-free survival with the lack of toxicity. Many patients are still being treated on ECOG-E2100 who are now out more than two years without progression. So I find those data compelling and hard to ignore.

The other thing that makes me say that so strongly is that we have data using bevacizumab for more refractory disease, and those patients don't derive the same benefit. So, you can't say, "We're going to hold this in reserve. We'll try something else first, and if this doesn't work, then I'll add bevacizumab." That makes no more sense than saying the same thing about trastuzumab.

Yes, you can derive some benefit by using it later but not nearly the same amount as using it with first-line therapy.

DR LOVE: What about the patients for whom you don't want to use a taxane because they may have diabetes or neuropathy?

DR MILLER: If someone otherwise meets the ECOG-E2100 criteria but has some specific contraindication to a taxane, I would feel comfortable using one of the regimens for which we have some safety and efficacy data. They include the bevacizumab/capecitabine data from our previous randomized trial (Miller 2005a) and data with bevacizumab/vinorelbine from a Phase II trial conducted at Dana-Farber (Burstein 2002). ■

SELECT PUBLICATIONS

Burstein HJ et al. **Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer.** San Antonio Breast Cancer Symposium 2002;446. No abstract available

Cobleigh MA et al. **A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):117-24. **Abstract**

D'Adamo DR et al. **Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas.** *J Clin Oncol* 2005;23(28):7135-42. **Abstract**

Gordon MS et al. **Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer.** *J Clin Oncol* 2001;19(3):843-50. **Abstract**

Jain RK et al. **Lessons from phase III clinical trials on anti-VEGF therapy for cancer.** *Nat Clin Pract Oncol* 2006;3(1):24-40. **Abstract**

Johnson DH et al. **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol* 2004;22(11):2184-91. **Abstract**

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Karp JE et al. **Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: Therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab.** *Clin Cancer Res* 2004;10(11):3577-85. **Abstract**

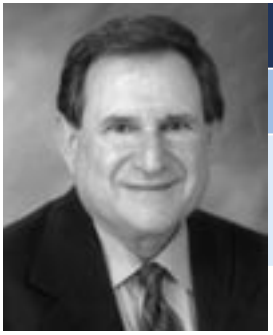
Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005a;23(4):792-9. **Abstract**

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Ramaswamy B, Shapiro CL. **Phase II trial of bevacizumab in combination with docetaxel in women with advanced breast cancer.** *Clin Breast Cancer* 2003;4(4):292-4. No abstract available

Traina TA et al. **A feasibility study of an aromatase inhibitor (AI), letrozole (L) and the antibody to vascular endothelial growth factor (VEGF), bevacizumab (B), in patients (pts) with hormone receptor-positive metastatic breast cancer (MBC).** *Proc ASCO* 2005;**Abstract 796**.

Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *J Clin Oncol* 2006;24(5):769-77. **Abstract**



INTERVIEW

Charles L Vogel, MD

Dr Vogel is Medical Director of Cancer Research Network Inc in Plantation, Florida.

Tracks 1-23

Select Excerpts from the Interview with Dr Vogel and His Patients

Track 2: Case 1

DR VOGEL: Ms C is a practicing attorney who was originally diagnosed in

March 2001 at the age of 55. She presented with a 12-cm mass, which was found to be an ER-positive, PR-positive, HER2-negative, invasive lobular carcinoma. She underwent a mastectomy, and six out of 20 nodes were positive.

She received four cycles of AC and four cycles of docetaxel followed by radiation therapy to the chest wall and draining lymphatics, and then she began tamoxifen. She did well, but only for about a year, when she was diagnosed with a new primary in the contralateral breast. Tamoxifen was discontinued, and she underwent a left mastectomy.

Again it was an ER-positive, PR-positive, HER2-negative, infiltrating lobular carcinoma, but this time the nodes were negative. She did not receive radiation or chemotherapy.

She began an aromatase inhibitor, but she was unable to tolerate either anastrozole or letrozole because of unbearable arthralgias. She took exemestane for two years, but disease progression was found in the liver in November 2004.

She then received fulvestrant and did not respond. Then she was treated with high-dose estrogen in March 2005. We used estradiol at 30 mg/day, which is supplied as 2-mg tablets, so she took five tablets three times a day.

Much to everyone's delight, she experienced very little toxicity and a complete response in the biopsy-proven liver metastases. She continues on estradiol and has now been on it for a year.

DR LOVE: That's an unusual choice of therapy.

DR VOGEL: Well, it's not an unusual choice of therapy for me or for many of the "hormonalists."

As you recall, in the past, diethylstilbestrol, which is now off the market, was the only available hormonal preparation until tamoxifen became available. We participated in the original tamoxifen trials in the early 1970s. At that time, one of the original trials compared DES to tamoxifen (Ingle 1981; [3.1]).

As a little history, the estrogens did every bit as well as tamoxifen, but some people

Comment from the patient

PATIENT: *I have an excellent quality of life. I try to travel about every six weeks for four or five days. I have eliminated as much stress as possible from my life, because I believe stress can trigger cancer. I try not to get aggravated in my work. It just isn't worth it.*

Of course, you have a whole different life perspective after all this. Each day is wonderful, and you don't sweat the small stuff. I practice family law, and often my clients call frantically. Whereas I used to get really upset, I don't now. What seemed to be major crises are no longer crises. I tell my clients, "This will pass. A year from now, you won't remember any of this." I recommend counseling to everybody.

I use complementary medicine, and I do meditation, hypnosis — whatever it takes. I read spiritual books and try to stay out of the fear in my mental framework. You have to stay out of the fear. The anxiety and fear can be overwhelming, and that's no way to live.

couldn't tolerate estrogens. One of the problems was nausea and vomiting, and some had intractable nausea and vomiting. Some developed menstrual-like cramps, which can be troubling. Some of the women we treated with high-dose estrogen mentioned an increase in libido, which they found to be a positive side effect.

This case illustrates that we almost never run out of hormone options. For a woman with a hormone-sensitive cancer, you can always rechallenge with tamoxifen or other aromatase inhibitors at some point in the very protracted course that many of these women experience.

Metastatic breast cancer can be a chronic disease, and therefore the use of high-dose estrogen shouldn't be forgotten as a therapeutic maneuver.

3.1

Clinical Trial Comparing DES and Tamoxifen for Women with Advanced Breast Cancer

"Before the introduction of tamoxifen, diethylstilbestrol (DES) was widely considered to be the hormonal treatment of choice in postmenopausal women with advanced breast cancer. We performed a randomized clinical trial of these two agents to determine their relative efficacy and toxicity. ...The regression rates (complete plus partial) were higher in patients receiving DES (41 percent) than in those receiving tamoxifen (33 percent), but not significantly so (P = 0.37). ... Analysis of the time until treatment failure for the two treatment groups showed no significant difference (medians: DES, 142 days; tamoxifen, 171 days). Toxicity was greater in patients receiving DES; nine of 74 patients (12 percent) discontinued therapy solely because of adverse reactions."

SOURCE: Ingle JN et al. *N Engl J Med* 1981;304(1):16-21. **Abstract**

Track 4: Case 2

DR VOGEL: The next three cases relate to the use of capecitabine in metastatic disease. Along the way, we adopted a blanket policy in my practice of treating patients with a total dose (not mg/m^2) of 2 g/day of capecitabine 14 days on, seven off.

In an occasional overweight individual, we might go up to 2,500 mg as a starting total dose. Even at these doses, very frequently we're forced to cut back. However, the beautiful responses you can see with relatively modest doses of capecitabine like these are incredible.

The first patient was diagnosed in 1994, at the age of 67, with a four-centimeter, ER-positive, PR-positive, node-negative invasive lobular carcinoma. She was treated at another institution with a right partial mastectomy and sentinel node dissection, followed by radiation therapy and tamoxifen.

Tamoxifen was stopped after four months because of elevated liver function test results. At that time, not many other hormones were available, so she was just followed. She did really well until seven years later, when she developed a new primary tumor in the ipsilateral breast, which proved to be an infiltrating ductal carcinoma.

Shortly thereafter she developed local skin lesions that were surgically excised and treated with radiation therapy. No additional therapy was administered. In 2002, she had another skin recurrence and began taking letrozole. She had a good response that lasted about 1.5 years. Then fulvestrant was initiated, but it was stopped after three months because of disease progression.

Comment from the patient

DR LOVE: *What's your life like nowadays?*

PATIENT: *Boring! I meet friends for lunch sometimes, or sit at home. I love music. I'm a singer. I sing opera, or I did. I would love to sing again, but I don't know where to throw my voice.*

DR LOVE: *What's this experience been like overall for the last 12 years?*

PATIENT: *I've handled it extremely well. I have a positive attitude, and that helps. I never really worry. I'm not even worried now after having it come back five times. What will be will be, and lately I've been saying that this should be the worst thing that happens because I feel fine, I really do. I feel very good.*

By this time, she had a couple hundred small erythematous nodules on the right chest wall. At another institution, she was treated with reduced doses of capecitabine, but the dose was not as low as we generally use. I venture to say that she received something like 3 gm/day.

It certainly was not wrong to dose capecitabine this way, given common practice, but it backfired on her. She ended up in the hospital with severe stomatitis, diarrhea and horrible hand-foot syndrome. Because of that experience, she sought another opinion and was adamantly opposed to the reintroduction of capecitabine.

We treated her with high-dose estrogen. However, unlike the first patient, the tumors continued to progress unabated. I finally convinced her in December 2004 to resume capecitabine but at a total dose of 2 g/day, two weeks on and one week off. Interestingly enough, this patient — with these 200 lesions on the chest wall — had a complete response, and she continues on capecitabine to this day.

DR LOVE: Has she had any side effects or toxicity?

DR VOGEL: Very little. She complains of some fatigue, but she's an active woman and has done beautifully.

Track 6: Case 3

DR VOGEL: This woman was diagnosed with an infiltrating lobular carcinoma in 1995 at the age of 61. She had five positive nodes, and her tumor was ER-positive, PR-positive and HER2-negative. She underwent a left mastectomy, adjuvant AC followed by radiation therapy to the chest wall and supraclavicular area, and five years of tamoxifen.

In 2003 she had a regional recurrence in the previously irradiated left supraclavicular area and started to develop a brachial plexopathy. She was in a lot of pain, and we entered her into a local clinical trial studying the combination of

docetaxel and capecitabine. It started out as a Phase II study, and it turned into a reverse Phase I study as we kept reducing the dose in subsequent cohorts of patients.

We started docetaxel at 36 mg/m^2 on days one and eight and capecitabine at 1,500 mg twice a day, which is a relatively typical dose but lower than the package insert dose. She experienced a lot of side effects — stomatitis, hand-foot syndrome and diarrhea — so the dose was reduced, and she did very well. Her neuropathy improved, her brachial plexopathy cleared and within a few months she had no palpable supraclavicular adenopathy. She had a beautiful response to the reduced doses of docetaxel and capecitabine.

In July 2003, she took a chemotherapy break and began letrozole. She stayed on that for approximately 1.5 years, when she discontinued the drug on her own. Why she did that remains a matter of conjecture. Within two months, her disease recurred and letrozole was restarted. She stayed on it for about six months, and by that time she had developed a new lesion in a very strange place — a painful 2.5-cm mass within the left biceps. She was also experiencing recurrent symptoms of her brachial plexopathy.

Comment from the patient

PATIENT: *My arm was hurting very badly when I started the Xeloda®, but the pain went away and the lump disappeared. I returned to my usual activities. I'm very busy in my church. I have a musical I am working on. I don't have time to really think about myself, and I don't want to. I have so much energy and I am so thankful. I have four grandc hildren and three daughters, and we're always doing something together.*

DR LOVE: *How has it been receiving capecitabine compared to the other chemotherapy?*

PATIENT: *It's better. I'm not losing my hair, my nails or anything. When you're getting intravenous chemotherapy, it makes you sick. I was sick all the time with it, but taking the pills — I take two in the morning and two in the evening for a two-week period — is easy. It's not making me sick, and my energy level is very high. I feel healthy.*

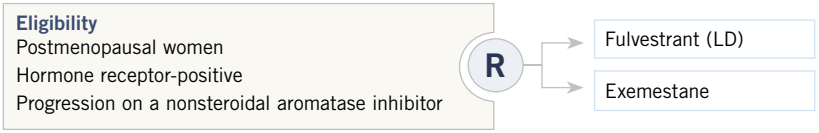
She was entered into the EFECT trial, which randomly assigned patients to receive either fulvestrant or exemestane (3.2). She experienced progression on whichever medication she was assigned, and we started her on capecitabine at our standard total dose of 2 g/day. At the same time, we referred her to a surgeon to see if he could remove this mass, which had now grown to about four centimeters. He didn't want to attempt it, so we referred her for radiation therapy.

When she came back to see me, I commented that the radiation was doing great, and she replied, "I never went for radiation because the tumor started to shrink and nothing was left."

She continues to receive capecitabine, with complete relief of all symptoms and complete disappearance of the mass. She had a dramatic response within a month and remains on capecitabine eight months later with continued response.

3.2 **EFECT Trial: Phase III Study Comparing Fulvestrant and Exemestane**

Protocol IDs: 9238IL/0048, NCT00065325, EFECT
Target Accrual: 660 (Closed)



LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study Contact: AstraZeneca Pharmaceuticals LP, AstraZeneca Cancer Support Network
Tel: 866-992-9276

SOURCES: NCI Physician Data Query, June 2006; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9. **Abstract**

Track 10: Case 4

DR VOGEL: The next patient was 29 years old when she was first diagnosed in 1994, and she received adjuvant CMF. She later presented with a local regional recurrence; it was during the era of high-dose chemotherapy and stem cell transplant. She was a proactive person, and although I was never a proponent of this approach, she fell into the category of patients — Stage IV, NED — for which, at the time, I felt if any group of patients might benefit from that approach, we should try it.

She received high-dose chemotherapy and a stem cell transplant on a Duke University protocol. She also received thalidomide on protocol, and then maintenance tamoxifen. In June 2002 she developed a mass in the right side of her neck, and her CEA increased into the many hundreds. She tried different hormonal therapies, including letrozole and fulvestrant.

Then she was treated on the local clinical trial studying docetaxel and capecitabine. She received tolerable doses of these medications — docetaxel at 30 mg/m^2

Comment from the patient

DR LOVE: *How would you compare your quality of life on Xeloda versus some of the other chemotherapies you've received?*

PATIENT: *It's a breeze — there is no comparison. Xeloda means staying home, taking your own medicine orally versus sitting in a chair for hours, being pricked with needles, and getting that nauseous feeling during which you have to keep eating to get that taste out of your mouth and eliminate the nausea.*

I think the main thing, as a woman, is not losing my hair. I know it sounds weird, but if I had hair going through chemotherapy, I could have dealt with it better. Not having any hair made going through chemotherapy harder.

When you see someone and they don't have hair, you know they're sick. When you see someone with hair, you don't make that connection. My kids were young when I went through chemotherapy, and they knew I was sick when I had no hair. When I had hair on capecitabine, I was still sick, but they were less aware of it.

and capecitabine at 1 gm twice a day for 14 days — and didn't have much of a problem. Her supraclavicular nodes disappeared, and her CEA decreased from 272 ng/mL to 82 ng/mL.

However, in October 2004 she developed right cervical and mediastinal adenopathy. We tried radiation therapy to eradicate those foci of disease, but then she developed another metastasis in the left posterior neck — a very strange presentation. It was actually a subcutaneous lesion that measured about two centimeters. It was surgically removed, and she was treated with capecitabine.

Now in a Stage IV, NED situation, her tumor markers have continued to regress on capecitabine at 2 g/day as the total dose. She has been receiving this for about eight months while leading a normal life with no manifestations of recurrent disease.

Tracks 14-15: Case 5

DR VOGEL: The next two patients have HER2-positive disease. The first woman was diagnosed at the age of 39 with infiltrating lobular carcinoma of the breast. She is a very outgoing, bouncy, outspoken and assertive woman. When she was diagnosed in 1998, she had no question in her mind that both breasts were going to be removed. She underwent bilateral mastectomy, and the main mass was 3.8 centimeters.

Fifteen out of 19 nodes were positive, and the tumor was reported to be ER-negative and PR-negative, which is an interesting point I'll discuss later. The tumor was also HER2-positive, and this was prior to the commercial availability of trastuzumab.

She was treated with doxorubicin and cyclophosphamide almost immediately after surgery. A metastatic workup was done at another institution, and she was found to have tumor in the wall of the surgical defect and bone metastases. For whatever reason, and I can't reconstruct it because she was not my patient at that time, she was taken off doxorubicin and cyclophosphamide and switched to paclitaxel.

She then heard about the compassionate use of trastuzumab and entered the lottery. As you recall, prior to the commercial availability of trastuzumab, a lottery was held, and she was selected to receive it. We elected to treat her with induction chemotherapy with a rather heretical regimen at that time, which was capecitabine and trastuzumab.

DR LOVE: What was your reason for selecting capecitabine?

DR VOGEL: It was felt that the patient's disease had progressed on paclitaxel, doxorubicin and cyclophosphamide, and capecitabine was approved for that particular subpopulation of patients.

Convention at that time indicated, based on Mark Pegram's in vitro data, that 5-fluorouracil and capecitabine were not synergistic with trastuzumab, unlike many other agents, which were felt to be synergistic or additive. However, we elected to "fly in the face of convention" and treated her with our standard

capecitabine dose of 2 g/day and standard doses of trastuzumab. She responded beautifully.

The disease was largely in the bone, so it was difficult to follow. The lesions in the bone stabilized. Being an assertive and sometimes aggressive patient, she elected to stay on capecitabine for a year and a half. I probably would have taken her off capecitabine at about six months and tried to maintain her on trastuzumab alone.

She's now been on single-agent trastuzumab for more than six years. She has intercurrent problems with lymphedema, but otherwise she has been leading a normal life. She comes in for zoledronic acid and trastuzumab. We've offered her every two-week and every three-week dosing, but for the most part she comes in weekly.

As an aside in this case, one day we were discussing with the patient the problem of quality control with the testing for HER2, ER and PR. She said, "You know, I was estrogen and progesterone receptor-negative."

Comment from the patient

PATIENT: *Herceptin® is easy to tolerate. It has very few side effects. I look at it as what I have to do to stay alive, and I was willing to do anything to stay alive. So I consider the weekly visit to the doctor as my job. It's what I do every week.*

DR LOVE: *What was your experience with capecitabine?*

PATIENT: *I rarely had any side effects on capecitabine. It was a pill, and I took a couple in the morning and a couple at night, two weeks on and one week off. I had a little reddening of my hands and feet but no real side effects from capecitabine.*

DR LOVE: *What's it been like to go through this experience?*

PATIENT: *You look at things differently. When people say, "Don't sweat the small stuff, and everything is small," they mean it. I remember the first time going into an MRI. I thought, "Ugh, I can't breathe." Now it's not a big deal to me. When people complain, "Oh, I have to go into this tube," I say, "You've got to be kidding! The only time I get any rest is when I'm lying in the tube."*

When people say, "You have your health, you have everything," they're right. So I enjoy every day. I do what I want. I try to have fun in everything I do. I really don't sweat the small stuff because when somebody tells you that you have cancer, your whole life changes in a second.

I told her we had our own series running with Craig Allred, who found that 30 percent of our 30 tumor specimens originally reported as ER-negative and PR-negative were positive.

Even though we didn't intend to do anything with the information, she insisted that we send off her tumor blocks. Indeed, her tumor was found to be ER-positive and PR-positive.

Fortunately, at this juncture, we haven't had to use that information. Her disease continues to be controlled by trastuzumab, and she doesn't want to stop this agent. I also see no reason to add the additional toxicities from an aromatase inhibitor.

DR LOVE: I find the percentage of false negatives in ER testing to be very disturbing.

DR VOGEL: It really is, and the American College of Pathologists needs to do something about it. They're the only body that can do anything. I know the NCCN and ASCO are both starting to exert major pressure in this area. I participated in a guidelines development meeting for NCCN recently at which the issue of quality control for HER2 monitoring was discussed. I'm sure a guideline will be forthcoming shortly.

DR LOVE: Do you see a light at the end of the tunnel for HER2 and ER testing?

DR VOGEL: I don't see a light at the end of the tunnel. I'm rather pessimistic, unless the American College of Pathologists pulls together all of its resources. They were able to do that once before, when Jim Wittliff sent powders to labs to test for estrogen and progesterone receptors using dextran-coated charcoal.

That converted a major quality control issue into a minor quality control issue back in the 1970s and early 1980s. We as medical oncologists face, on a daily basis, the problem of sending out tissues to referee pathologists just because we can't trust our laboratories.

Track 21: Case 6

DR VOGEL: This 42-year-old woman was diagnosed in 1995, at the age of 31, with an infiltrating ductal carcinoma. She had bilateral mastectomies with reconstruction. Within a year, she was diagnosed with bone metastases, and her tumor was 3+ positive for HER2. She was eligible for and joined the pivotal trastuzumab clinical trial. Because she had received doxorubicin in the adjuvant setting, she was randomly assigned to paclitaxel and trastuzumab (Slamon 2001; [3.3]).

After a period of time, she received single-agent trastuzumab for approximately a year, and then she developed progression in the bone. She went on the extension trial, on which we were allowed

Comment from the patient

PATIENT: *My reaction to breast cancer was that I had to fight, and I cannot give up. The theme in our house is "never give up." No matter how mad or how sad we are, we never give up. I was able to overcome the year I had with the chemotherapy with three little girls. I had to fight for them. I love my husband and my kids, but my girls are my main focus in continuing my life.*

It has been like a roller coaster with ups and downs, but I thank God a lot. We're very strong believers in our house, but it's not easy. I'm the one who is always telling everybody to have faith and be strong, but sometimes I need that too. This time around has not been easy for the whole family. The girls are older, and it is more difficult for them to accept that Mom is sick. It's hard for them to help me because they always have had all the help in the house.

It has not been easy for my husband, either. Sometimes I want to always be the strong one in the house. If I'm not strong, then they get hesitant or aggravated or sad because they don't see the strong woman that they're used to seeing. But sometimes it's not easy.

to continue trastuzumab and added cisplatin. In spite of that, her disease progressed rapidly in the bone. Then she had a good response to trastuzumab and vinorelbine; however, after a year, she experienced progression. The big problem was a skull metastasis.

In January 1998 her ovaries were removed as a therapeutic maneuver and trastuzumab was continued. In spite of that, the skull metastasis continued to increase in size, and we radiated her skull. We then added toremifene, and she remained on toremifene and trastuzumab for 6.5 years.

In February 2005 she developed further progression in the bone and was changed to letrozole with trastuzumab for a year. She then developed a new lesion in the left femur and was put on fulvestrant with trastuzumab. She also underwent radiation to the left femur, which is her only symptomatic lesion.

This young woman, the mother of three young girls, never dreamed she would be able to see her little one driving a car. Her firstborn is now 17 years old, driving a car, and doing beautifully in school. The patient has been on trastuzumab now for a total of 10 years. ■

3.3

Clinical Benefit, Duration of Response and Cardiotoxicity of Chemotherapy versus Chemotherapy with Trastuzumab

	AC (n = 138)	AC + H (n = 143)	Paclitaxel (n = 96)	Paclitaxel + H (n = 92)	Chemo (total) (n = 234)	Chemo (total) + H (n = 235)
Median time to progression (months)	6.1	7.8	3.0	6.9	4.6	7.4
Median duration of response (months)	6.7	9.1	4.5	10.5	6.1	9.1
Median survival (months)	21.4	26.8	18.4	22.1	20.3	25.1
Complete + partial response	58/138 42%	80/143 56%	16/96 17%	38/92 41%	74/234 32%	118/235 50%
Any cardiac dysfunction	8%	27%	1%	13%	5%	22%
Severe cardiac dysfunction	3%	16%	1%	2%	2%	10%

A = anthracycline; C = cyclophosphamide; H = trastuzumab

DERIVED FROM: Slamon DJ et al. *N Engl J Med* 2001;344(11):783-92. **Abstract**

SELECT PUBLICATIONS

Ingle JN et al. **Randomized clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer.** *N Engl J Med* 1981;304(1):16-21. **Abstract**

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a randomized Phase III trial, adjuvant docetaxel/cyclophosphamide (TC) significantly reduced the risk of recurrence compared to _____.**
   a. AC
   b. CMF
   c. TAC
   d. Dose-dense AC/paclitaxel
   e. All of the above
2. **In the Vogel study, the rate of neutropenic fever associated with docetaxel was reduced from 17 percent to _____ percent with the use of pegfilgrastim.**
   a. One
   b. Five
   c. 10
   d. 15
3. **Which of the following is an advantage of *nab* paclitaxel?**
   a. Shorter infusion time
   b. Premedications not required
   c. Both of the above
   d. None of the above
4. **Among patients with breast cancer, bevacizumab as monotherapy yielded an objective response rate of about _____.**
   a. 10 percent
   b. 30 percent
   c. 50 percent
   d. 70 percent
5. **In ECOG-E2100, patients who had previously received a taxane-containing adjuvant regimen had the best hazard ratio of all the subsets.**
   a. True
   b. False
6. **Among patients with taxane- and anthracycline-refractory metastatic breast cancer, the addition of bevacizumab to _____ approximately doubled the response rate but did not change progression-free or overall survival.**
   a. Paclitaxel
   b. Docetaxel
   c. Capecitabine
   d. Epirubicin
   e. Doxorubicin
7. **The same doses of bevacizumab were used in the breast, colon and lung cancer Phase III trials.**
   a. True
   b. False
8. **Among patients with previously untreated metastatic breast cancer, the addition of bevacizumab to _____ improved the response rate and progression-free survival.**
   a. Paclitaxel
   b. Docetaxel
   c. Capecitabine
   d. Epirubicin
   e. Doxorubicin
9. **The XCaliBr trial will evaluate bevacizumab in combination with _____ as initial first-line therapy for patients with metastatic breast cancer.**
   a. Paclitaxel
   b. Docetaxel
   c. Capecitabine
   d. Epirubicin
   e. Doxorubicin
10. **The EFECT trial will compare fulvestrant to _____.**
    a. Anastrozole
    b. Letrozole
    c. Exemestane
    d. All of the above
11. **A randomized Phase III trial evaluating capecitabine with or without bevacizumab in patients with previously treated metastatic breast cancer demonstrated an increase in overall response rate with the combination of agents.**
    a. True
    b. False
12. **Which of the following side effects are associated with capecitabine treatment?**
    a. Stomatitis
    b. Hand-foot syndrome
    c. Diarrhea
    d. All of the above
    e. None of the above

Post-test answer key: 1a, 2a, 3c, 4a, 5a, 6c, 7b, 8a, 9c, 10c, 11a, 12d

EVALUATION FORM

Breast Cancer Update — Issue 4, 2006

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 switching to or 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 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 appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations. . . . . 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
Stephen E Jones, MD	5 4 3 2 1	5 4 3 2 1
Kathy D Miller, MD	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, 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

Which of the following audio formats of this program did you use?
☐ Audio CDs ☐ Audio tapes ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 4, 2006

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

Degree:

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

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

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City, State, Zip: .....

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Research To Practice designates this educational activity for a maximum of 4.25 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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:

.....

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 BreastCancerUpdate.com/CME.

BCU406

Breast Cancer® UPDATE

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