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Breast Cancer® UPDATE

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

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CME Certified

Breast Cancer Update
A Continuing Medical Education Audio Series

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 preventative, neoadjuvant, adjuvant and metastatic 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, nonanthracycline-based regimens 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 the risks and benefits, selection and sequencing of endocrine therapy, single-agent and combination chemotherapy regimens.
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- Describe the computerized risk models and genetic markers that provide prognostic and predictive information on the quantitative risk of breast cancer relapse and/or treatment response, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 6 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Burstein, Gradishar, O'Shaughnessy, Schwartzberg and Sledge on the integration of emerging clinical research data into the management of breast cancer.

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EDITOR'S NOTE

Neil Love, MD

Peto's curse

Sir Richard Peto presenting at Research To Practice Meet The Professors session, San Antonio, December 2004

"If you're looking only for big advances, then the only things that will contribute towards your aim are exaggerated claims, over-optimistic claims, claims by people who actually are not being realistic about what they can achieve. Now this is a pity, and it's particularly a pity in the context of breast cancer because in breast cancer, moderate improvements in prognosis are really worthwhile. They can be humanly worthwhile. They're not large percentages, but they're large numbers of human beings.

Every year in the United States, there are 400,000 cancer deaths roughly. Of these, about 40,000 involve breast cancer. Now, realistically, the kinds of change that you're going to hear described today, the kinds of trials that you're going to hear described, might, if we're lucky, involve avoidance about say of 4,000 of those 40,000 deaths. Now avoidance of 4,000 deaths is humanly worthwhile. I mean there's nowhere near 4,000 people in this auditorium, and avoidance of the instant deaths of all of us would certainly be worthwhile.

So, 4,000 deaths is worth knowing about, but it's a small percentage, and it's very difficult to pick out those kinds of small percentages. And, so, you've really got to have very accurate and very sensitive, large randomized trials."

Sir Richard Peto
NIH Consensus Conference on Early Breast Cancer
First presentation of the International Trials' Overview of Breast Cancer
September 9, 1985

"For the first time in recorded history, annual cancer deaths in the United States have fallen."

Graphic from NIH website noting progress in cancer control as demonstrated by the decrease in US deaths from 557,271 in 2002 to 556,902 in 2003

When Richard Peto, the boy-genius statistician from Oxford, took the stage in a dusty auditorium in Bethesda more than 20 years ago, he had the Cheshire-like visage of the kid in your class who had the answer no one could figure out — and the cool thing was that it looked so simple.

Prior to this historic first presentation of the International Breast Cancer Overview, a series of smallish clinical trials had evaluated the role of tamoxifen as adjuvant therapy mostly for women with ER-positive, node-positive tumors. Only one or two of these studies demonstrated a statistically significant improvement in survival.

Peto, who worked closely with fellow Brit Richard Doll (both would be knighted by Queen Elizabeth II) fully understood several important aspects of research methodology that very few investigators appreciated at that time, including two key issues related to Phase III randomized clinical trials:

1. The importance of primary study endpoints in clinical trial design

For example, in adjuvant trials, overall survival occupies center stage, but Peto pointed out that it takes longer to see deaths, and there are fewer deaths than recurrences. Today, overall survival surrogates like two- to three-year disease-free survival yield quicker answers, and these in turn lead to the next generation of trials.

2. Interpretation of "negative" clinical trials

Peto noted that if a trial does not demonstrate a difference in measured primary endpoints, there are two very different potential explanations: either the therapy does not have an effect on that endpoint, or it does but there are not enough events to be able to detect it.

These observations were profoundly simple and Peto drove his points home in vivid black and white. Like many academicians of that era, he loved transparencies.

Presenting a mind-boggling panorama of graphics utilizing methods that were new to oncologists (eg, Forest plots as in Figure 1), Peto stunned the meeting attendees by demonstrating that when individual trials (and events) were combined, all kinds of interesting effects could be seen.

Peto was also obsessed with the idea of publication bias and as such badgered, pleaded and cajoled every researcher in the world he could identify who had completed a randomized breast cancer trial — positive or negative — to turn over to him the raw data. He and his team then "cleaned up" this information individually on a case-by-case basis to, in effect, create one large clinical trial.

This first meta-analysis instantly validated a major impact of tamoxifen on survival in the adjuvant setting. Within weeks, the NCI released a consensus statement suddenly supporting adjuvant tamoxifen, and as a result, tens of thousands of women received a potentially curative therapy that had previously been considered a "kinder, gentler" way to delay disease progression.

Unfortunately, we needed one more overview to really drive home the events issue. Specifically, when this first tamoxifen overview was broken down by nodal and menopausal status, the benefits observed were statistically significant only in postmenopausal women with positive nodes, prompting the NCI consensus statement to support treatment only in this subset.

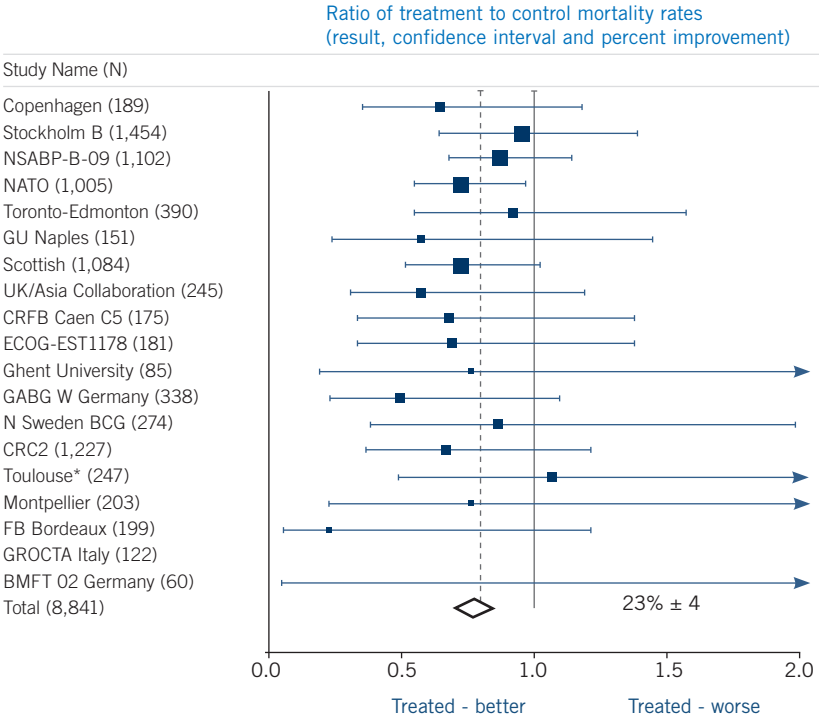
In the five years that led up to the next overview in 1990, I interviewed Michael Baum on several occasions, one of Peto's original overview accomplices (along with Craig Henderson, Bill Wood and others). Mike would routinely become apoplectic when I raised this tamoxifen subset issue, which in retrospect we now see was all about events. Five years later, with more recurrences in both the node-negative and premenopausal subsets, it was clear that tamoxifen worked pretty much the same in all women with ER-positive disease.

So here we are, 22 years later, with a finely honed clinical research machine that produces increasingly gigantic trials, vividly demonstrated by the ATAC and BIG 1-98 trials, which included more than 17,000 patients compared to 16,513 women in 28 trials of tamoxifen in the original 1985 overview.

We now frequently learn at plenary presentations at ASCO and other meetings that new and oftentimes costly novel agents improve progression-free survival

1

1985 EBCTCG Overview Analysis of Adjuvant Tamoxifen Trials in Early Breast Cancer for Women 50 Years of Age or Older Who Received Tamoxifen for Two or More Years



* Significant imbalance in initial nodal status

SOURCE: EBCTCG. *N Engl J Med* 1988;319(26):1681-92. **Abstract**

in the metastatic setting by a few weeks, and treatment standards quickly adapt as clinical investigators dutifully extol these benefits and CME vehicles like this one get the word out.

The relative failure of this step-by-step approach to cancer research is evident considering that in 1985, as noted by Sir Richard, there were approximately 400,000 people dying of cancer in the United States every year. Twenty-two years later, the NCI is pleased to report our current annual mortality of more than 550,000 has dropped by one tenth of one percent. With all due respect to the aging of our population, these numbers are going in the wrong direction fast.

I am not here to disparage the meaningful advances we have made, nor our plan for rational molecular targeted therapy. Adjuvant trastuzumab has been a stand-up triple, if not a home run, and I love the imatinib story in CML and GIST as much as anyone. Hopefully, targeted molecular therapy won't be a dream gone sour like cytotoxic chemotherapy, which is unfortunately a lot less effective in breast cancer and other common tumors than it is for testicular cancer. However, it seems logical that, for this enormous public health problem, there should also be room for a spectrum of interventions, including some with creativity.

Peto's brilliant observation and his charismatic leadership helped to form the basis of an oncology research strategy where huge trials move the field slowly forward. This approach can and must continue, but at the same time, with apologies to the numbers knight, we also need to be a lot less satisfied with incremental gains and find the resources to investigate new ideas that shoot for the stars.

So what would this new "swing for the fences" approach look like? Well, if I were the "Cancer Czar" empowered with a blank check and a directive to find quicker answers in this endless war, the first step would be to bring together the best minds in the business and start brainstorming. Think of it as cancer's version of the Manhattan Project, but our objective would be to salvage lives instead of obliterating them.

As a team, we would look at historical examples like ulcer disease, where the *Helicobacter* model replaced arcane theories such as the "ulcer personality." We would then start discussing and debating our own ideas. Who knows where this might lead, but off the top of my head I can think of a couple of dozen clinical investigators, including those featured on this issue of *Breast Cancer Update*, who perhaps could be putting more of their impressive brainpower toward emptying the very clinics they spend so much time running and staffing.

My second major objective would be to develop a "living laboratory" to study this disease that we seem to know so little about. We would launch a massive effort to expand the current tumor registry concept to a level previously unknown.

The goal would be to enlist hundreds of thousands of patients with all tumor types to participate in a huge prospective data-gathering effort. This initiative would include a translational bank of tumor blocks and sera that would be linked to a clinical database comprising electronic medical records and information provided by patients themselves, as discussed on this program by Lee Schwartzberg from The West Clinic in Memphis.

Lee and his extraordinary network of about 500 community-based oncologists gather all types of valuable information from their patients utilizing a simple hand-held, touch-screen computer tablet, and using the same device, they are also able to deliver back educational activities and videos.

My vision would be to employ this innovative technology across the country, in hundreds of oncology offices and cancer centers, to gather data on what patients are eating, how they are exercising, whether they are using supplements and alternative nutraceuticals and to cross-reference these and other data with tumor endpoints and outcomes. Then I would invite my brainy bunch in "Los Alamos" to masticate this outpouring of information and come up with testable hypotheses as to how to intervene in cancer progression.

These are just a few possibilities off the top of my overcrowded head. Undoubtedly there are people way smarter than me who can add to this list if we just let go of the Peto-nian notion that major advances in oncology aren't possible. ■

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
October 29, 2007

Select Contributions of Richard Peto and the Early Breast Cancer Trialists' Collaborative Group

Darby SC, McGale P, Taylor CW, Peto R. **Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries.** *Lancet Oncol* 2005;6(8):557-65. **Abstract**

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005a;365(9472):1687-717. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and on 15-year survival: An overview of the randomised trials.** *Lancet* 2005b;366(9503):2087-106. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials.** *Lancet* 2000;355(9217):1757-70. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Polychemotherapy for early breast cancer: An overview of the randomised trials.** *Lancet* 1998a;352(9132):930-42. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomised trials**. *Lancet* 1998b;351(9114):1451-67. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation in early breast cancer: Overview of the randomised trials.** *Lancet* 1996;348(9036):1189-96. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Effects of radiotherapy and surgery in early breast cancer: An overview of the randomized trials.** *N Engl J Med* 1995;333(22):1444-55. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women.** *Lancet* 1992;339(8785):1-15, 71-85. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women.** *N Engl J Med* 1988;319(26):1681-92. **Abstract**

INTERVIEW

George W Sledge Jr, MD

Dr Sledge is Ballve-Lantero Professor of Oncology and Professor of Medicine and Pathology at the Melvin and Bren Simon Indiana University Cancer Center in Indianapolis, Indiana.

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Tracks 3, 7

DR LOVE: What's your take on the issue of the optimal chemotherapy regimen to combine with trastuzumab?

DR SLEDGE: With the recent three-year update from the BCIRG 006 trial, we have evidence that TCH appears to be roughly similar to AC → TH in terms of clinical outcome for risk of recurrence, although we still have relatively early follow-up (Slamon 2006).

It's possible that the curves might diverge somewhat, but it's reassuring to have a nonanthracycline-containing approach to treating patients. The major controversy raging right now is whether we should be using anthracyclines for anyone who has HER2-positive early breast cancer.

DR LOVE: What are you doing right now in your own practice outside of a protocol setting?

DR SLEDGE: A year ago, based on the data we had at that time with what appeared to be a somewhat premature analysis of BCIRG 006, I routinely recommended AC → TH to patients because I thought the curves did not yet support the idea that TCH was equivalent (Slamon 2005).

With maturation of the data and what looks like at least approximate equivalence (Slamon 2006), I now routinely talk to patients about TCH as an alternative.

My experience with disease-free survival curves is that once you're out two or three years — certainly for a disease like HER2-positive early-stage breast cancer — you have a fair number of events and those curves begin to appear mature.

DR LOVE: What's your take on the cardiac safety of TCH?

DR SLEDGE: Occasional cases of congestive heart failure occurred in the population of patients who received TCH. Having said that, it's a low risk — maybe 0.5 percent (1.1).

Tracks 6-7

DR LOVE: What's the natural history of smaller, node-negative, HER2-positive tumors, and do you treat those patients with trastuzumab?

DR SLEDGE: This is what I call the "how low do you go" issue. If we evaluate the clinical trials that we have available in the adjuvant setting, we see that the HERA trial routinely allowed patients with lymph node-negative disease, which represents approximately a third of their population (Piccart-Gebhart 2005; [1.2]).

The NSABP trial did not allow patients with lymph node-negative disease, and the North Central trial only allowed those patients toward the end of

the study recruitment. Approximately 10 to 12 percent of the North Central population and five to six percent of the joint analysis (NSABP-B-31 and NCCTG 9831) had lymph node-negative breast cancer (Romond 2005).

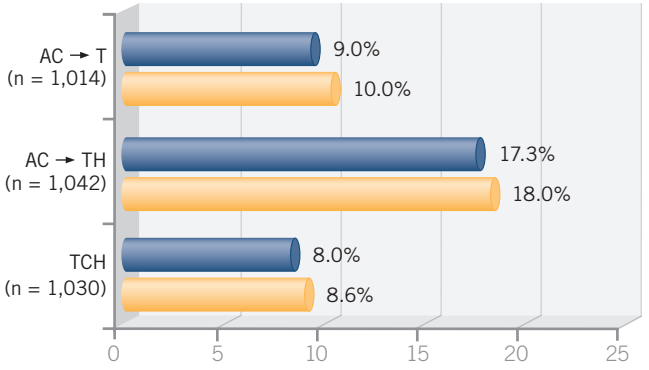
That's too few patients for a valid subset analysis, but it's reasonable to ask whether biology would be less important than nodal status in these patients. My bias is that HER2-positive, node-negative breast cancer can kill you and can metastasize just as well as HER2-positive, node-positive cancer.

The issue is further complicated when these tumors are in the subcentimeter size range, for which we have vanishing few data in the clinic. To be honest, many of our "guesstimates" about risk of recurrence are just that.

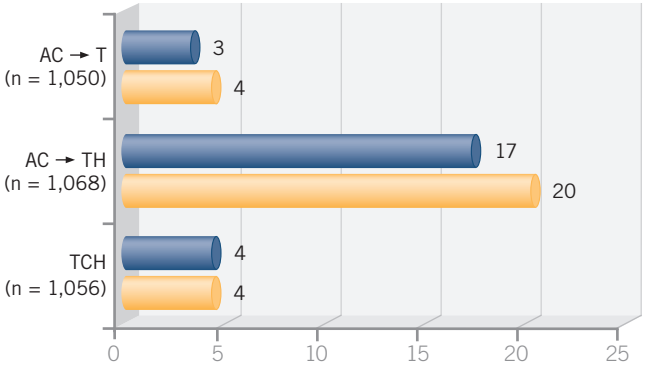
1.1

Cardiac Events in BCIRG 006

Percent of Patients with >10% Relative LVEF Decline



Left Ventricular Function Grade III/IV (Congestive Heart Failure) Events



First interim analysis Second interim analysis

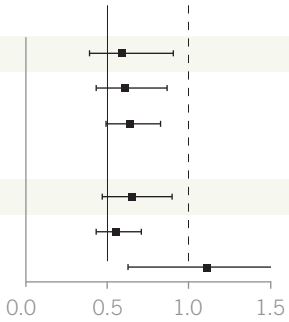
(n values from second interim analysis)

SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

1.2

Exploratory Disease-Free Survival Subgroup Analysis for One Year of Trastuzumab versus Observation: Two-Year Update of the HERA Trial

Subgroup (N)	Hazard ratio (HR)	No. of events: Trastuzumab vs observation	HR (95% CI)
Nodal status			
Node-negative (1,099)		34 vs 58	0.59 (0.39-0.91)
1-3 positive nodes (976)		50 vs 80	0.61 (0.43-0.87)
≥4 positive nodes (953)		95 vs 132	0.64 (0.49-0.83)
Pathological tumor size			
0-2 cm (1,351)		61 vs 95	0.65 (0.47-0.90)
>2-5 cm (1,482)		97 vs 150	0.55 (0.43-0.71)
>5 cm (171)		20 vs 25	1.14 (0.63-2.06)



"Our exploratory subgroup analysis suggests that all subgroups of women seem to benefit from trastuzumab. In particular, there is so far no significant difference in efficacy between women with node-positive and node-negative disease..."

SOURCE: Derived from Smith I et al. *Lancet* 2007;369(9555):29-36. **Abstract**

The databases we have for small, node-negative, HER2-positive tumors are limited, in part because HER2-positive tumors are more likely to be larger. Therefore, it will be difficult to generate a data set that might allow us to examine this issue.

DR LOVE: What would you say to a patient who has a 3- to 5-mm node-negative tumor who might be considering TCH in terms of the risk of clinically significant heart problems that wouldn't otherwise be a factor?

DR SLEDGE: In the ballpark of one half of a percent. This question has actually come up in my clinic for patients with subcentimeter tumors. For instance, I remember distinctly sharing data with a relatively young woman who had subcentimeter, HER2-positive, lymph node-negative breast cancer.

The most compelling issue for her was that her father died of congestive heart failure as a "cardiac cripple" in bed for several years. So this will be the type of negotiation between patient and physician that we've dealt with in other adjuvant settings.

Track 8

DR LOVE: Do you think physicians are less confident now in the activity of hormonal therapy when the patient has hormone receptor-positive, HER2-positive disease?

DR SLEDGE: If you believe the disease-free survival data in the adjuvant trastuzumab trials, then the primary driver of the biology of these breast cancer types is HER2.

More important, the other data that have influenced me are from the TAnDEM trial for patients with ER-positive, HER2-positive, metastatic breast cancer receiving front-line hormonal therapy with an aromatase inhibitor, our current best hormonal therapy (Mackey 2006). The median progression-free survival was 2.4 months for the overall population, so hormonal therapy alone does not work well in these patients.

DR LOVE: Does that push the bar lower in terms of using adjuvant trastuzumab?

DR SLEDGE: Yes, that tends to reinforce the importance of HER2 and anti-HER2 therapy, even in ER-positive tumors.

Tracks 9-10

DR LOVE: Can you discuss the ALTTO adjuvant trial for patients with HER2-positive early breast cancer?

DR SLEDGE: ALTTO is an 8,000-patient, four-arm trial in which patients receive chemotherapy followed by paclitaxel with trastuzumab, lapatinib, the combination or the sequence (1.3). This is a large enough undertaking that it was thought to require two continents' worth of breast cancer patients to complete.

DR LOVE: One of the key controversies about this study is that some patients will not receive trastuzumab. Will physicians enroll patients with lower-risk disease but be nervous about patients with high-risk breast cancer?

DR SLEDGE: I'm completely comfortable with a nontrastuzumab arm, but many of my colleagues are not. The initial study with lapatinib was for patients whose disease had progressed on trastuzumab, and in that setting lapatinib was clearly beneficial (Geyer 2006).

A second issue, albeit with smaller trials, is that lapatinib monotherapy produces response rates in the metastatic setting that are equivalent to trastuzumab monotherapy (Vogel 2002).

Third, we now have data that were presented at the last ASCO meeting that reflect one of those fascinating natural biologic experiments. This was a population of patients who received paclitaxel or paclitaxel with lapatinib and whose disease was said to be either HER2-negative or HER2-unknown when they entered the trial (Di Leo 2007).

Based on where the trial was conducted, HER2 testing was not routine, and it turned out that a substantial proportion of patients entering this trial in fact had HER2-positive tumors when central testing was performed.

So an experiment was conducted inside this larger "HER2-negative trial" that allowed us to see what happened with paclitaxel and lapatinib versus paclitaxel

for patients with HER2-positive disease, and the results are strikingly positive for the combination in terms of progression-free survival. The results are similar to those of the larger, pivotal trastuzumab trial (Slamon 2001).

Track 13

DR LOVE: Another strategy in HER2-positive disease that might have promise is adding bevacizumab to chemotherapy/trastuzumab, an investigational approach that the NSABP and BCIRG have been discussing (1.4). What are your thoughts about that study?

DR SLEDGE: That trial has been designed to evaluate a chemotherapy backbone with trastuzumab, and my understanding at present is that it will be TCH with or without bevacizumab.

1.3 Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial

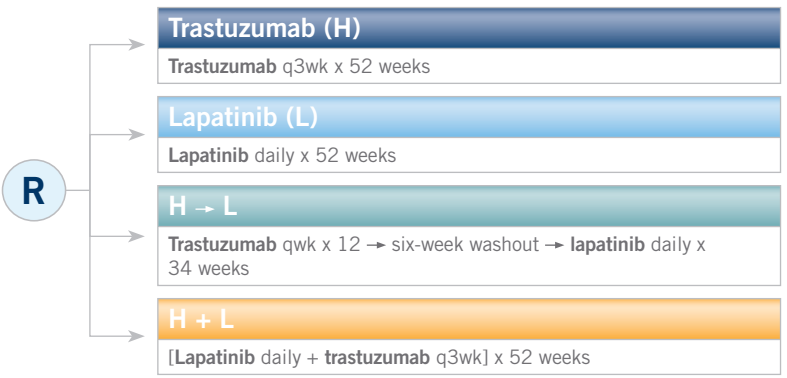
Protocol IDs: BIG 2-06, NCCTG-N063D, IBCSG 36-07
Target Accrual: 8,000

Eligibility

- HER2-positive breast cancer
- Prior treatment with at least four cycles of an approved anthracycline-based chemotherapy regimen

In STRATA 1, patients will receive weekly paclitaxel together with the anti-HER2 targeted therapy following anthracycline-based (neo)adjuvant chemotherapy

STRATA 2 will comprise patients who complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy



Study Contacts

Martine J Piccart-Gebhart, MD, PhD
Edith A Perez, MD

SOURCES: *Breast International Group Newsletter* Spring 2007;9(1); **www.ibcsg.org**; NCI Physician Data Query, September 2007.

DR LOVE: What do we know about angiogenesis and HER2-positive tumors?

DR SLEDGE: We know that HER2 is an upstream regulator of VEGF production. That has been shown definitively both in cell lines and in the clinic. A woman who has HER2-positive breast cancer simply has more VEGF in her tumor.

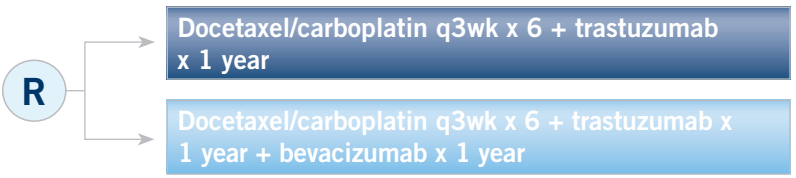
In some lovely preclinical modeling that was presented in *Nature* a few years ago, the HER2-positive tumors were considerably more vascular than the HER2-negative tumors (Izumi 2002).

From a clinical standpoint, these tumors have a higher microvessel density. More importantly, VEGF expression is a clear regulator of outcome. In a study conducted by Gottfried Konecny at UCLA analyzing a German database, the tumors with the worst performance were the ones that were both HER2-positive and VEGF-positive (Konecny 2004), so that combination of HER2 positivity and VEGF overexpression appears to be clinically important.

1.4

BETH: Proposed NSABP/CIRG Trial of Adjuvant Monoclonal Therapy in Patients with HER2-Positive Early Breast Cancer

Target Accrual: 2,875



Eligibility

- Node-positive or high-risk node-negative early breast cancer
- HER2-positive by central testing

Stratification

- Number of positive nodes
- Hormone receptor status

SOURCE: Slamon D. The Art of Oncology Satellite Symposium at ECCO-14, Barcelona, Spain. September 26, 2007.

Track 17

DR LOVE: Could you review the data you presented at ASCO with capecitabine and bevacizumab as first-line therapy in metastatic disease (Sledge 2007)?

DR SLEDGE: Several years ago, Kathy Miller presented the ECOG-E2119 trial, which randomly assigned patients with anthracycline- and taxane-refractory metastatic breast cancer to receive either capecitabine or capecitabine with bevacizumab (Miller 2005a). That trial showed a statistically significant

improvement in response rate but no improvement in the primary endpoint of progression-free survival. So Kathy appropriately called that a negative trial when she presented it.

The question that came up for me was, is this a case of "nice drugs getting beaten up in bad neighborhoods"? Or was it possible that capecitabine/bevacizumab was simply not a good combination for whatever reason, or perhaps more appropriately, is a taxane with bevacizumab a better or more synergistic combination?

To examine this issue, we launched a multicenter study, XCaliBr, with patients who in essence were similar to the patients who went into ECOG-E2100, which evaluated paclitaxel and bevacizumab (Miller 2005b). They had HER2-negative breast cancer and were receiving their first chemotherapy for metastatic disease.

These patients were treated in a Phase II, single-arm setting, and all received the combination of bevacizumab and capecitabine until progression. At the time of progression, they crossed over and continued to receive bevacizumab with either a taxane — paclitaxel — or vinorelbine.

We have data from the first portion of that trial, and the median progression-free survival for patients receiving bevacizumab and capecitabine was 5.7 months (1.5), which is a disappointing result compared to the 11 months that we saw with the combination of paclitaxel/bevacizumab in E2100.

DR LOVE: Did these patients have worse disease than those in E2100?

DR SLEDGE: They were slightly different, with a higher proportion that had received prior adjuvant therapy and a higher rate of estrogen receptor (ER) negativity than those who entered E2100.

One always has to be excruciatingly careful about making too much of an unplanned retrospective subset analysis on small, Phase II trials, but a fascinating observation was that the population with ER-negative disease did extremely poorly. They had a progression-free survival of less than four months and a median overall survival of 7.5 months.

However, the patients with ER-positive disease fared considerably better, with a median progression-free survival in excess of eight months and overall survival in excess of 16 months (1.5), although the median survival has not yet been reached.

Track 22

DR LOVE: Can you discuss the upcoming ECOG trial that will be evaluating bevacizumab in the adjuvant setting for HER2-negative disease?

DR SLEDGE: ECOG-E5103 will be a trial within the Intergroup and will accrue approximately 5,000 patients with node-positive or high-risk node-negative, HER2-negative disease (1.6). We have incorporated the Onco*type* DX assay into the definition of low risk and high risk for patients with hormone receptor-positive, node-negative disease.

This is a three-arm trial that uses AC followed by *weekly* paclitaxel as a backbone. The second arm uses the same chemotherapy but adds bevacizumab only during the course of the chemotherapy, beginning with the anthracycline. The third arm uses bevacizumab during chemotherapy and out to a total of one year.

So first we are asking the proof-of-concept question, does bevacizumab add benefit above and beyond adjuvant chemotherapy? And for the second question, is duration of bevacizumab important?

One possibility is that if bevacizumab works, most of its benefit may come as a modifier or a chemopotentiator against endothelial cells. The second biologic possibility is that continued suppression of VEGF is required to prevent microscopic metastases developing into gross metastases.

1.5

XCaliBr: Efficacy of Capecitabine with Bevacizumab as First-Line Therapy in Metastatic Breast Cancer

Capecitabine + bevacizumab

Capecitabine (1,000 mg/m^2 BID days 1-14 q21d) + **bevacizumab** (15 mg/kg day 1 q21d)

↓

Disease progression

↓

Second-line chemotherapy + bevacizumab

Paclitaxel (80 mg/m^2 days 1, 8 and 15) or **vinorelbine** (25 mg/m^2 qwk x 4) + **bevacizumab** (10 mg/kg q2wk)

Eligibility

- Metastatic breast cancer previously untreated with chemotherapy except in the neoadjuvant/adjuvant setting
- HER2-negative
- No prior anti-angiogenic or oral fluoropyrimidine
- No clinically significant peripheral vascular disease, evidence of bleeding or diathesis or coagulopathy

Efficacy (median follow-up = 12.9 months)

Parameter	ITT (n = 106)	ER-negative (n = 49)	ER-positive (n = 57)
Median TTP (95% CI)	5.7 mos (4.9-8.4)	4.0 mos (3.0-4.9)	8.9 mos (7.5-13.6)
Median OS (95% CI)	16.0+ mos (12.9-*)	7.5 mos (5.6-16)	16.6+ mos (15.1-*)
ORR (CR + PR)	38%	27%	47%

* Not yet reached

ER-positive versus ER-negative, $p < 0.001$ for all endpoints

SOURCE: Sledge G et al. *Proc ASCO* 2007;**Abstract 1013**.

It's worth pointing out that we have already conducted an adjuvant pilot trial, ECOG-E2104, which evaluated the combination of bevacizumab with AC followed by paclitaxel, with a particular interest in cardiotoxicity.

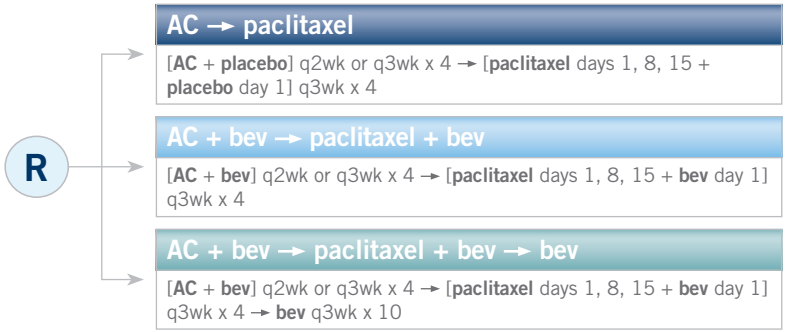
Patients were subject to fairly significant cardiac monitoring to explore whether any cardiac signal is emitted by bevacizumab in combination with the anthracycline.

We are still analyzing those data, and we have recorded some cases of congestive heart failure in patients receiving AC with bevacizumab. We have not yet seen enough events to cross our boundary for concern in terms of using the combination in ECOG-E5103, but we are following the data carefully. ■

1.6

Phase III Randomized Study of Adjuvant AC → Paclitaxel with or without Bevacizumab (Bev)

Protocol IDs: ECOG-E5103, NCT00433511
Accrual: 4,950 (Approved — not yet active)



Eligibility

- Pre- or postmenopausal
- ER and PR status known, HER2-negative
- Node-positive or high-risk, node-negative
- Patients enrolled on ECOG-PACCT-1 (TAILORx)

Study Contacts

Eastern Cooperative Oncology Group
Kathy Miller, MD, Protocol Chair
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Cancer and Leukemia Group B
Chau Dang, MD, Protocol Co-Chair
Tel: 800-525-2225

SOURCE: NCI Physician Data Query, September 2007.

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Di Leo A et al. **Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A phase III randomized, double-blind study of 580 patients.** *Proc ASCO* 2007;**Abstract 1011**.

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Gomez HL et al. **Updated biomarker results from a phase II randomized study of lapatinib as first-line treatment for patients with ErbB2-amplified advanced or metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 1090**.

Izumi Y et al. **Tumour biology: Herceptin acts as an anti-angiogenic cocktail.** *Nature* 2002;416(6878):279-80. **Abstract**

Konecny GE et al. **Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients.** *Clin Cancer Res* 2004;10(5):1706-16. **Abstract**

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

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).** San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. No abstract available

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer — Combined analysis of NSABP-B31/NCCTG-N9831.** Presentation. ASCO 2005. No abstract available

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

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

Sledge G et al. **Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer.** *Proc ASCO* 2007;**Abstract 1013**.

Smith I et al. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

Stewart HJ et al. **Scottish adjuvant tamoxifen trial: A randomized study updated to 15 years.** *J Natl Cancer Inst* 2001;93(6):456-62. **Abstract**

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

INTERVIEW

William J Gradishar, MD

Dr Gradishar is Director of Breast Medical Oncology and Professor of Medicine at the Robert H Lurie Comprehensive Cancer Center at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

Tracks 1-20

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the background of your recently reported study of *nab* paclitaxel versus docetaxel?

DR GRADISHAR: *Nab* paclitaxel was developed to take advantage of the significant antitumor activity of the taxanes but also to avoid some of their side effects. Solvents typically used with drugs such as docetaxel or Cremophor®-based paclitaxel are absent, and instead the paclitaxel is administered in an

albumin delivery system to increase the amount of drug that reaches the tumor tissue. That's the underlying rationale.

What's been shown to date, both through some of the early Phase I/II trials and ultimately the Phase III trial, is that when administered every three weeks, *nab* paclitaxel was superior to solvent-based paclitaxel administered every three weeks (Gradishar 2005).

Despite more of the paclitaxel being administered in the *nab* preparation than with the every three-week solvent-based paclitaxel, less neutropenia occurred. A different kind of neuropathy appeared to be present that resolved more quickly. A greater antitumor effect was also observed in terms of response rate and improved progression-free survival.

In an era when we're increasingly using weekly therapy and when many perceive docetaxel to be the most active single-agent anticancer therapy for breast cancer, what most people want to know is, how does *nab* paclitaxel compare to a weekly taxane schedule? How does it compare to docetaxel?

We conducted a randomized Phase II trial, which we reported in San Antonio last December (Gradishar 2006b) and updated at ASCO this year (Gradishar 2007).

Patients with metastatic breast cancer were randomly assigned to first-line treatment with a dose of 300 mg/m^2 of *nab* paclitaxel every three weeks, 100 mg/m^2 of docetaxel every three weeks or *nab* paclitaxel administered weekly three out of four weeks at a dose of either 100 or 150 mg/m^2 (2.1).

In December, we reported that the weekly *nab* paclitaxel schedules were more active from the standpoint of antitumor activity than either every three-week docetaxel or every three-week *nab* paclitaxel (Gradishar 2006b).

The weekly treatment arms were not only active but also well tolerated, particularly the 100 mg/m^2 dose, which appeared at the time to be the optimal schedule.

The weekly schedule with 150 mg/m^2 had a slightly higher response rate, but it also is associated with slightly more toxicity. We did not see much of a difference in terms of progression-free survival between these two arms.

Track 2

DR LOVE: Could you comment on the difference in the efficacy findings you reported at ASCO 2007 compared to San Antonio in 2006?

DR GRADISHAR: In December we found that the weekly treatment arms were associated with response rates in the 60-plus percent range, markedly higher than the every three-week treatment arms of either *nab* paclitaxel or docetaxel (Gradishar 2006b).

Part of the more recent ASCO presentation was the response rate findings from the independent radiology review (2.2). As expected, there was a drop-

off in response rates among all four treatment arms. However, consistent with the original investigator-reported findings, response rates for both weekly *nab* schedules remained numerically superior to every three-week docetaxel or every three-week *nab* paclitaxel.

When you include an independent radiology review, you'll often find that the response rates are less than what the clinicians report. Part of that is because the radiologists are blinded and not directly involved in the trial, so they don't know what the index lesions are, for instance.

DR LOVE: What was seen with progression-free survival?

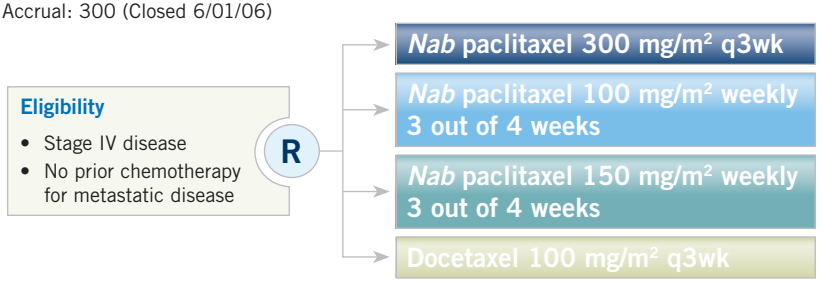
DR GRADISHAR: Last December we would have said that the progression-free survival is not different across the *nab* paclitaxel treatment arms, but all are superior to docetaxel administered every three weeks.

What's emerging now is that both the every three-week *nab* paclitaxel and the weekly schedule of 150 mg/m^2 *nab* paclitaxel arms appear to be the superior treatments. But, from the standpoint of efficacy and tolerability, the 150 mg/m^2 schedule appears to be the treatment arm to be pursued in a pivotal Phase III trial.

2.1

Randomized Phase II Study of Weekly or Every Three-Week *Nab* Paclitaxel versus Every Three-Week Docetaxel as First-Line Therapy for Patients with Metastatic Breast Cancer

Accrual: 300 (Closed 6/01/06)



	Nab paclitaxel 300 mg/m^2 q3wk	*Nab* paclitaxel 100 mg/m^2 weekly 3 out of 4 weeks	*Nab* paclitaxel 150 mg/m^2 weekly 3 out of 4 weeks	Docetaxel 100 mg/m^2 q3wk
Objective response rate	33%	58%*	62%†	36%
Grade III/IV neutropenia	37%	19%	35%	95%
Grade III/IV peripheral neuropathy	14%	7%	12%	5%
Grade III/IV fatigue	4%	0%	3%	15%

* p-value = 0.004 versus docetaxel arm; † p-value = 0.016 versus docetaxel arm

SOURCE: Gradishar W et al. Presentation. San Antonio Breast Cancer Symposium 2006b; **Abstract 46**.

I believe one of the things that will come out of the upcoming randomized trial is whether the added antitumor efficacy that's presumed to be associated with the weekly schedule will offset what might be slightly more toxicity than we see with lower-dose weekly schedules of *nab* paclitaxel.

2.2

Weekly or Every Three-Week *Nab* Paclitaxel versus Every Three-Week Docetaxel: Response Rate by Investigator Assessment versus Independent Radiology Review

	Nab paclitaxel 300 mg/m^2 q3wk	*Nab* paclitaxel 100 mg/m^2 weekly 3 out of 4 weeks	*Nab* paclitaxel 150 mg/m^2 weekly 3 out of 4 weeks	Docetaxel 100 mg/m^2 q3wk
Investigator	43%	62%*	70%†	38%
IRR	35%	45%	47%	28%

* *p*-value = 0.002 versus docetaxel arm; † *p*-value = 0.003 versus docetaxel arm

IRR = independent radiology review

SOURCE: Gradishar W et al. *Proc ASCO* 2007;**Abstract 1032**.

Track 4

DR LOVE: Were there differences in tolerability between the docetaxel and *nab* paclitaxel arms in your study?

DR GRADISHAR: One of the interesting observations made across all the reported *nab* paclitaxel trials is the notion that the neuropathy might be different. One of the first things people would have considered is that with this agent, when you eliminate the Cremophor, no neuropathy should occur.

But what has been observed in every trial — even in the Phase I trials — is that with high doses, you see neuropathy even in the absence of Cremophor. This might be attributable to the chemotherapy drug itself. So neuropathy occurs with *nab* paclitaxel — that seems to be a consistent finding.

The numbers are not huge, but there appears to be resolution of the neuropathy to the point at which you can readminister the chemotherapy drug within about three weeks.

In other words, you get a decrease in the severity of the neuropathy to the point at which you feel comfortable readministering the drug. That's in contrast to what we typically see when patients develop Grade III neuropathy with solvent-based paclitaxel, with which the duration of the neuropathy is much longer.

In terms of other side effects, the degree and frequency of significant neutropenia are decreased with the *nab* paclitaxel every three-week and weekly schedules, relative to the three-weekly docetaxel, and minimal febrile neutropenia is associated with *nab* paclitaxel at the doses evaluated.

Additionally, in contrast to docetaxel, in our study the incidence of stomatitis is clearly less frequent whether you're using every three-week or weekly schedules of *nab* paclitaxel.

Tracks 6-7

DR LOVE: Can you describe the *nab* paclitaxel Phase III trials currently in development?

DR GRADISHAR: One randomized trial will evaluate patients with metastatic breast cancer receiving therapy with either docetaxel at 100 mg/m^2 every three weeks or *nab* paclitaxel with a 150-mg/m^2 weekly schedule.

A third arm is building on data Linda Vahdat presented on ixabepilone, which is not a taxane per se but an epothilone (Vahdat 2007). All three arms will evaluate weekly schedules of something that works at the microtubular level.

A separate CALGB study will address the question of weekly schedules of solvent-based paclitaxel compared to *nab* paclitaxel.

DR LOVE: Is this trial going to include bevacizumab?

DR GRADISHAR: It's not going to include bevacizumab to my knowledge, but some small trials have combined *nab* paclitaxel with bevacizumab.

I believe at this point it's feasible. There have not been any unexpected side effects. More interest will be seen in evaluating that combination moving forward.

DR LOVE: What about the use of *nab* paclitaxel/bevacizumab in a clinical setting, off protocol?

DR GRADISHAR: We have combined *nab* paclitaxel with bevacizumab. As we see patients with newly diagnosed metastatic breast cancer and try to identify the optimal treatment approach, we are acutely aware of ECOG-E2100, which examined weekly solvent-based paclitaxel with or without bevacizumab (Miller 2005).

In ECOG-E2100, the addition of bevacizumab was associated with an enhanced response rate and better progression-free survival. It naturally leads to the question of whether there would be an advantage to using *nab* paclitaxel, as opposed to solvent-based paclitaxel, in that combination. I believe the simple answer is yes.

There is the sense that *nab* paclitaxel would be better tolerated than solvent-based paclitaxel over time, with the added benefit that you don't have to administer steroids, with their associated side effects.

We have administered *nab* paclitaxel with bevacizumab to patients. I believe an economic issue exists with that, but it's a reasonable consideration. The drugs are active, and they're well tolerated.

Track 10

DR LOVE: Some pilot studies evaluated dose-dense AC → *nab* paclitaxel. Can you talk about what those have shown and also where you see *nab* paclitaxel heading in terms of adjuvant therapy?

DR GRADISHAR: Reports of adjuvant AC → *nab* paclitaxel demonstrate that you can administer this regimen in a dose-dense fashion. You can administer the every three-week dose on a two-week schedule. So feasibility has been demonstrated (Burstein 2007).

What we don't know is how it compares directly to other regularly used regimens, such as TAC or dose-dense AC → solvent-based paclitaxel. I don't believe you'll find some huge surprise substituting *nab* paclitaxel for any position that a standard taxane holds in the adjuvant setting.

In fact, it is possible that by being able to administer *nab* paclitaxel at a higher dose safely — in essence, being able to administer more of the taxane safely — you would have greater efficacy.

The only way of addressing that is an enormous randomized trial with thousands of patients. I'm not sure anyone will have the willpower or the resources to do a trial that requires that many patients for that kind of question. So it's a dilemma.

Another question could be, would you consider using *nab* paclitaxel in the adjuvant setting as a substitute for a solvent-based paclitaxel? The answer is yes.

We have done it for some patients, generally the rare patients who are either sensitive to the effects of steroids or have experienced some sort of hypersensitivity reaction.

From what we know in the metastatic disease setting, I have absolutely no reason to think *nab* paclitaxel would not be a good substitute for paclitaxel in the adjuvant setting.

Track 15

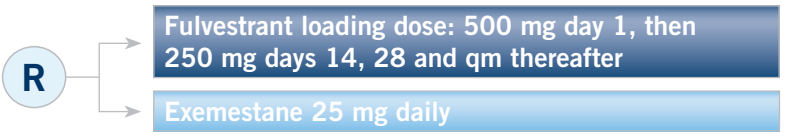
DR LOVE: Can you talk about the EFECT study you headed, which evaluated fulvestrant versus exemestane in advanced disease?

DR GRADISHAR: EFECT was an effort to address the issue of what to do for patients who receive nonsteroidal aromatase inhibitors as treatment in the adjuvant or metastatic setting and then develop progressive disease (Gradishar 2006c). This topic has received no shortage of discussion.

Is there an optimal sequence with endocrine therapy? With smaller pilot experiences, we know that you could treat with a different subclass of aromatase inhibitor — in other words, go from a nonsteroidal to a steroidal — and that some fraction of patients respond.

2.3 **EFECT: Evaluation of Fulvestrant versus Exemestane Clinical Trial**

Protocol IDs: EFECT, NCT00065325, 9238IL/0048
Accrual: 693 (Closed)



Eligibility
Postmenopausal, hormone receptor-positive, progression on a nonsteroidal aromatase inhibitor

Efficacy results

	Fulvestrant	Exemestane	*p*-value
OR	7.4%	6.7%	0.7364
CB	32.2%	31.5%	0.8534
TTP	3.7 months	3.7 months	0.6531
DOR	13.5 months	9.8 months	NR
DCB	9.3 months	8.3 months	NR

OR = objective response; CB = clinical benefit; TTP = median time to progression; DOR = median duration of response; NR = not reported; DCB = median duration of clinical benefit

SOURCE: Gradishar W et al. San Antonio Breast Cancer Symposium 2006c;**Abstract 12**.

Other pilot studies suggested that you could go from a nonsteroidal to fulvestrant, a selective estrogen receptor regulator, and obtain a clinical response. EFECT attempted to rigorously address the issues of which agent to employ in this setting and whether using a loading dose of fulvestrant might lead to a more rapid achievement of steady-state drug levels.

Preclinical experiments long ago suggested that the FDA-approved dose of fulvestrant was probably on the threshold of obtaining antitumor activity. The question was, could you feasibly administer more volume intramuscularly and reach steady-state levels more quickly?

Patients received 500 milligrams on day one — basically a shot in each buttock — and then 250 milligrams on days 14 and 28 and monthly thereafter. Modeling experiments suggested that if you use a higher dose early, you reach the steady state quicker.

A corollary of that is that if you don't get there through routine dosing, perhaps you might be taking patients off the agent prematurely because they're simply not experiencing the effect of the drug rapidly enough. Pharmacokinetic analysis from this trial did demonstrate that clinical use of the loading dose mirrors what the modeling predicted.

Regarding efficacy, just about every endpoint was superimposable. Whether

you compare response rate, time to disease progression, or even tolerability and adverse events, patients who received either fulvestrant or exemestane had identical outcomes in all of those categories (Gradishar 2006c; [2.3]).

The conclusion is that one could legitimately approach a patient who has experienced progression on a nonsteroidal aromatase inhibitor with either one of these agents. It's not absolutely clear whether there is a superior sequence you must follow.

Moving forward, we see continued interest in exploring the dose used with fulvestrant. Trials are underway to evaluate continuing 500 milligrams beyond the first dose and to examine the effect of using somewhat higher doses within that early time period.

We also see interest in combining endocrine agents to induce a total estrogen blockade. One approach is to combine an aromatase inhibitor — to eliminate the estrogen or drive it down — with fulvestrant, which in a sense eliminates the receptor. Also, in some trials patients whose disease progresses on anastrozole continue the anastrozole, and fulvestrant is added. ■

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Gradishar W et al. **Randomized comparison of weekly or every-3-week (q3w) *nab*-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1032**.

Gradishar WJ. **Albumin-bound paclitaxel: A next-generation taxane.** *Expert Opin Pharmacother* 2006a;7(8):1041-53. **Abstract**

Gradishar W et al. **A randomized phase 2 trial of qw or q3w ABI-007 (ABX) vs q3W solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC).** Presentation. San Antonio Breast Cancer Symposium 2006b;**Abstract 46**.

Gradishar W et al. **Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: First results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer.** San Antonio Breast Cancer Symposium 2006c;**Abstract 12**.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Henderson IC, Bhatia V. ***Nab*-paclitaxel for breast cancer: A new formulation with an improved safety profile and greater efficacy.** *Expert Rev Anticancer Ther* 2007;7(7):919-43. **Abstract**

Ibrahim NK et al. **Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.** *J Clin Oncol* 2005;23(25):6019-26. **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).** San Antonio Breast Cancer Symposium 2005;**Abstract 3**.

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INTERVIEW

Lee S Schwartzberg, MD

Dr Schwartzberg is Medical Director at The West Clinic and Clinical Professor of Medicine at the University of Tennessee School of Medicine in Memphis, Tennessee.

Tracks 1-16

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you describe the novel electronic tool your community research network has been routinely using to collect patient symptom data?

DR SCHWARTZBERG: We developed the Patient Care Monitor (PCM), a tablet-based computerized questionnaire with a series of symptom scales that patients complete, via a touch screen, every time they come into the office. It generally takes a patient 10 minutes to finish the survey, whereas it once took a nurse 60 to 90 minutes to glean all of this information.

A printout is then handed to the clinician that shows, on a scale of zero to 10,

the patient's new responses, his or her baseline data and the last two determinations. This information shapes the interview because I can instantly identify the real issues. I've been using the PCM for approximately seven years, and I find it indispensable. It has been validated and has been tested with the elderly, and we also have a Spanish version.

DR LOVE: How does a physician acquire this system?

DR SCHWARTZBERG: The current model is available at no cost to the physician. We supply them through data-reporting projects and currently have 100 practices and 500 doctors around the country using it. Physicians can also correlate PCM data across their practice and we can extract that information to conduct retrospective symptom-assessment studies, which have become powerful because we have this huge database.

Track 4

DR LOVE: In a recent Patterns of Care survey we conducted, we learned that 30 percent of physicians in the US who prescribe *nab* paclitaxel use steroid premedications with it, which surprised us because one of the advantages of this agent is that this prophylaxis is not required. What patient-reported impact do you see from corticosteroids used as premedications?

DR SCHWARTZBERG: We see profound effects from corticosteroids on patient symptoms and behavior, including acute symptoms of insomnia and jitteriness, anxiety, agitation of diabetes and the attendant problems with that. We also see an increase in infections and swelling.

DR LOVE: What are your thoughts about the fact that some physicians are still using steroid premedications with this agent?

DR SCHWARTZBERG: It's sobering. I believe it reflects a lack of information getting through and the fact that oncologists today wear many hats and are barraged with information. Through efforts such as yours, it's become easy for practitioners to receive the information, but the problem is filtering and making sense of all the new data while they are busy taking care of patients.

We have no good reason to routinely premedicate patients who are treated with *nab* paclitaxel, and your finding may be due to the inertia of having used corticosteroids with other taxanes.

DR LOVE: In the clinical trials with *nab* paclitaxel, were the patients premedicated?

DR SCHWARTZBERG: No, they were not.

DR LOVE: Is there a rationale for it with regard to nausea and vomiting?

DR SCHWARTZBERG: I don't believe so. In my experience, the incidence of nausea and vomiting associated with *nab* paclitaxel is low, and I believe that according to the NCCN and ASCO guidelines, no reason exists to routinely premedicate these patients. Occasionally we see a patient who has a hypersen-

sitivity reaction or experiences nausea and vomiting, and the lowest level of first-line antiemetic prophylaxis would be steroids alone or a 5-HT3 receptor antagonist alone.

Track 10

DR LOVE: Can you tell me about your Phase II trial of *nab* paclitaxel and capecitabine as first-line therapy for metastatic breast cancer?

DR SCHWARTZBERG: This trial evaluated *nab* paclitaxel at 125 mg/m^2 administered on days one and eight with capecitabine administered at 825 mg/m^2 BID on days one through 14 of a 21-day cycle. We reported on it at San Antonio in 2006 and ASCO in 2007, and now we're writing it up for publication (Schwartzberg 2006; Somer 2007).

The results are highly favorable for this regimen. We reported a 60.9 percent overall response rate, which was the primary endpoint, and the tolerability was good (3.1). Patients were eligible to continue monotherapy with either drug beyond the initial six months of treatment, and a few patients actually remained on the study up to 12 months after initiation of therapy.

DR LOVE: When Joyce O'Shaughnessy reported on docetaxel/capecitabine, some excitement emerged but people were concerned about the toxicity (O'Shaughnessy 2002). Then Bill Gradishar reported on one study and Joanne Blum on another that evaluated paclitaxel and capecitabine, which seemed less toxic but similar in efficacy (Gradishar 2004; Blum 2006).

So a study combining *nab* paclitaxel and capecitabine seems to make sense. Has this combination been studied before?

DR SCHWARTZBERG: I'm not aware that this particular regimen has been studied previously. A great debate has been waging over the last few years in breast cancer. We have spent a lot of energy — in my opinion undue energy — debating singlet versus doublet therapy.

In my opinion, it doesn't matter whether therapy is a singlet or a doublet — what matters is the toxicity. If a comparison of drug A versus drug B showed B had the same toxicity as A yet doubled the progression-free survival, we'd pick B every time. If B happened to be two agents, what difference would it make?

I'm still a believer that doublet therapy is reasonable for a subset of patients, such as those who have visceral disease that is rapidly progressing, in whom we want the best response as soon as possible. That's not every patient with metastatic breast cancer, but patients come into my clinic every day who I believe can benefit from the most effective therapy as defined by response rate.

Track 11

DR LOVE: What is your algorithm for treating patients with triple-negative metastatic disease?

DR SCHWARTZBERG: We are currently conducting a large Phase II trial that is evaluating docetaxel and bevacizumab (with trastuzumab if HER2-positive), so that study would be my first-line approach for a patient with triple-negative breast cancer.

Outside of a clinical trial, if a patient has triple-negative breast cancer with visceral disease and/or is symptomatic, I generally use a taxane and bevacizumab, based on the ECOG-E2100 data (Miller 2005).

To some extent it depends on what the patient received as adjuvant therapy. In my practice the adjuvant treatment of choice has been dose-dense AC/paclitaxel, so if a patient relapses within 24 months, off protocol I use docetaxel and bevacizumab.

DR LOVE: Have you considered using a combination of either paclitaxel or *nab* paclitaxel with capecitabine and bevacizumab?

DR SCHWARTZBERG: For our next Phase II trial, we are considering using our *nab* paclitaxel and capecitabine regimen, which was well tolerated, and adding bevacizumab.

3.1

Phase II Trial of *Nab* Paclitaxel with Capecitabine

Accrual: 50 (Closed)

Eligibility

- Measurable metastatic breast cancer by RECIST
- More than six months since adjuvant fluoropyrimidine and/or paclitaxel
- No prior capecitabine
- No prior chemotherapy for metastatic disease

Protocol → ***Nab* paclitaxel + capecitabine**

(***Nab* paclitaxel** 125 mg/m^2 days 1, 8 with no premedications + **capecitabine** 825 mg/m^2 BID days 1-14) q3wk

Efficacy data (n = 46)	
Overall response rate	60.9%
Complete response rate	4.3%
Partial response rate	56.5%
Stable disease	21.5%
Progressive disease	17.4%

Conclusions

- Capecitabine and *nab* paclitaxel is a highly active combination regimen in first-line metastatic breast cancer with an overall response rate of 61 percent.
- *Nab* paclitaxel on days one and eight at 125 mg/m^2 with capecitabine at 825 mg/m^2 BID on days one to 14 every three weeks is well tolerated, and common AEs did not differ from those expected with single-agent *nab* paclitaxel or capecitabine.

SOURCE: Somer et al. *Proc ASCO* 2007;**Abstract 1053**.

Tracks 13, 16

DR LOVE: What is the rationale behind your new trial combining fulvestrant and capecitabine for patients with hormone receptor-positive advanced breast cancer?

DR SCHWARTZBERG: We're just launching that study now, but I considered it approximately 18 months ago when I reviewed the literature and found that no work had been done on combining chemotherapy and hormonal therapy on a clinical level for at least 20 years. The work that was conducted previously suggesting some signals of antagonism was with tamoxifen — a less effective hormonal therapy if you will — and often CMF or CMF-like chemotherapy. In addition, study designs used 20 to 25 years ago are different from what we would use today. I believe that it's worth exploring again.

Today most patients with hormone receptor-positive disease receive an aromatase inhibitor in the adjuvant setting. However, we have few data on how well patients fare whose disease recurs or progresses after they receive an adjuvant aromatase inhibitor. If you extrapolate and examine some of the data, including Bill Gradishar's EFECT study (Gradishar 2006; [2.3, page 25]), you see that the time to progression for these patients is short. In fact, 50 percent of them have failed by four months.

Our paradigm for decades has been to begin a patient on hormonal therapy to buy as much time as possible before starting chemotherapy. However, if half of the patients are experiencing only four months of progression-free survival, we're not providing benefit to the majority.

Fulvestrant by itself may be more effective, but we don't anticipate that because the patients in our study will be somewhat hormone resistant to an aromatase inhibitor. The downregulation of the receptor alone may help to some degree, particularly in certain groups such as patients with HER2-positive breast cancer, but we don't know that.

The question is, is it beneficial to administer chemotherapy and hormonal therapy? It harkens back to the argument about whether to use a doublet versus a singlet. I believe it comes down to a toxicity issue. If you can administer an oral drug that is well tolerated, doesn't bring a lot of toxicity and prolongs the time until the patient receives IV chemotherapy, then you might see some benefit.

DR LOVE: How is the capecitabine administered in this trial?

DR SCHWARTZBERG: The capecitabine dosing is novel because it's metronomic in the sense that it's a fixed, relatively low dose of 1,500 milligrams per day administered continuously with the fulvestrant. Even though this study was designed before we saw the XCaliBr data, I was encouraged by the fact that capecitabine, at least in combination with bevacizumab, seemed to benefit patients with estrogen receptor-positive breast cancer much more than receptor-negative disease (Sledge 2007).

DR LOVE: In this protocol, do you use a loading dose of fulvestrant?

DR SCHWARTZBERG: Yes. The loading-dose strategy we use is to administer 500 milligrams on day one, 250 milligrams on days 14 and 28 and then 250 milligrams monthly. That's based on pharmacokinetic data that show that the label dose, 250 milligrams every 28 days, takes several months to reach a steady state (Robertson 2007). In that case, we may not achieve target concentrations of the drug for three or four months and many patients' disease may have progressed by that time. This loading-dose strategy has become the standard in my practice.

DR LOVE: Have you encountered any problems in terms of reimbursement for the loading-dose strategy?

DR SCHWARTZBERG: No, we haven't had any problems with that. ■

SELECT PUBLICATIONS

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FACULTY TUMOR PANEL

Harold J Burstein, MD, PhD and Joyce O'Shaughnessy, MD

Tracks 1-18

Track 1 Case discussion: A woman in her midforties, status postneo-adjuvant dose-dense AC → T for locally advanced triple-negative breast cancer who presents with significant residual tumor at the time of surgery

Track 2 Adjuvant therapy in the setting of an incomplete pathologic response

Track 3 Correlation between ethnicity and triple-negative breast cancer

Track 4 Treatment alternatives for triple-negative disease

Track 5 Combining chemotherapy with bevacizumab

Track 6 Phase II trial of irinotecan/carboplatin with or without cetuximab

Track 7 Clinical trials of DNA-damaging agents

Track 8 Mastectomy for local control in patients with documented metastatic spread

Track 9 Case discussion: A woman with a history of lobular breast cancer treated two years prior with definitive surgery, adjuvant AC → T and continuous anastrozole who presents with an isolated colon metastasis identified via routine colonoscopy

Track 10 Assessment of rising tumor markers in patients progressing on adjuvant therapy

Track 11 Clinical experience with Halotestin® for progressive, hormone-responsive breast cancer

Track 12 Hormone therapy for lobular breast cancer

Track 13 Case discussion: A premenopausal woman with a large hormone receptor-positive, HER2-negative breast tumor and de novo bone metastases

Track 14 Fulvestrant dosing strategies

Track 15 The unique natural history of hormone receptor-positive breast cancer

Track 16 A place for fulvestrant in the adjuvant setting

Track 17 Case discussion: A young woman with strongly serum HER2-positive, progressive bone and visceral metastases after treatment for HER2 FISH-negative, Grade III breast cancer

Track 18 Serum conversion of HER2 status

Select Excerpts from the Discussion

Tracks 1, 4-5

Case Discussion 1 (Patient of Dr Burstein)

A woman in her midforties who presented with ER-negative, PR-negative, HER2-negative, locally advanced breast cancer with palpable lymphadenopathy and underwent neoadjuvant dose-dense AC → paclitaxel followed by lumpectomy, which revealed a 1-cm residual tumor.

DR LOVE: Joyce, how would you approach patients with significant residual disease at surgery after neoadjuvant chemotherapy?

DR O'SHAUGHNESSY: For a patient like this, with triple-negative breast cancer and a fair amount of tumor burden, I order a PET scan up front. It is particularly useful in highly proliferative tumors with a lot of axillary adenopathy, where we sometimes observe lymphadenopathy in the intramammary chain, in the low cervical nodes and even in the mediastinum. If the disease is chemotherapy sensitive and you have a chance for a decent prognosis, then you can include those nodal beds in the radiation port.

Second, if we can document metastatic disease, we may have the opportunity to use bevacizumab outside of a clinical trial if the patient does not show a complete pathologic response to neoadjuvant therapy.

DR BURSTEIN: This patient received a baseline PET scan that suggested disease in the breast and ipsilateral axilla in addition to equivocal findings in some of the other regional lymph nodes, including the contralateral axilla. In this case, the PET scan muddied matters more than clarifying them, and she had been treated with curative intent.

DR LOVE: How do you usually treat patients like this outside of a clinical trial?

DR O'SHAUGHNESSY: I generally use noncross-resistant chemotherapy agents in cases like this. In the absence of any other data, I turn to agents with either a proven track record in the adjuvant setting or for which there is evidence of some preoperative activity.

I would probably choose capecitabine combined with a platinum agent and bevacizumab. Capecitabine is a noncross-resistant drug, and work from Farber and others suggests it has some activity in triple-negative disease. I would try to give the patient the best chance for cytoreduction and disruption of any micrometastatic niche she might have.

DR LOVE: Hal, did this patient receive any further treatment after surgery?

DR BURSTEIN: She received radiation therapy to the breast and regional lymph nodes after her chemotherapy, but she did not receive further systemic therapy after surgery. She was followed expectantly and within three or four months developed changes in the ipsilateral breast. She had a red rash, which was thought to be a cellulitis, and she received a course of antibiotics.

A skin biopsy confirmed recurrence and a repeat staging PET and CT scan showed changes in the left breast, the left supraclavicular lymph node chain, the right axilla, some mediastinal nodes, a "hot" pericardiac node and perhaps a bone lesion.

She received two cycles of docetaxel at 75 milligrams and carboplatin at an AUC of six. She developed febrile neutropenia with the first cycle, so with the second cycle she received growth factor support. She had a partial clinical response in that the erythema decreased and some of the lymph node burden improved clinically. She then saw me as a second opinion in the case.

DR LOVE: What did you recommend at that point?

DR BURSTEIN: She seemed to be having a minor response to this regimen, so we suggested a third cycle. It wasn't clear how much benefit she was receiving from the chemotherapy by itself, so we began discussing other ways we might treat this particular variant of breast cancer, including clinical trials.

We discussed introducing bevacizumab, despite the fact that the data on its use in heavily refractory breast cancer are not so compelling. Kathy Miller's original study of anthracycline- and taxane-treated patients who received capecitabine with or without bevacizumab did not show a major clinical advantage to adding bevacizumab (Miller 2005).

However, many of us believe that targeting the angiogenesis pathway may offer something different, particularly for patients like this. We've all had many patients similar to this one, for whom it seems unlikely chemotherapy itself will turn the tide, and the temptation arises to consider agents like bevacizumab.

Also, we are increasingly developing and participating in specific clinical trials for this type of breast cancer. At our institute, we have several Phase II trials specifically focusing on triple-negative tumors, offering either novel therapies or combinations of therapies.

DR LOVE: Assuming this patient is not eligible for or not interested in participating in a clinical trial, what's your next step if her disease progresses on the chemotherapy?

DR BURSTEIN: She is currently receiving platinum-based therapy, which has been discussed considerably, particularly for triple-negative tumors, but at this time the literature doesn't tell us whether these patients will routinely fare better with such a regimen. We have a long list of agents that have been studied in advanced breast cancer, including many familiar options such as capecitabine, vinorelbine and gemcitabine. If her disease progresses, we will start reaching for those.

DR LOVE: Would you consider bevacizumab?

DR BURSTEIN: I would probably try bevacizumab at some point, although the magnitude of benefit for a case like this is not clear. I would consider offering it with capecitabine, based on the safety data with that combination. George Sledge's Phase II, first-line trial, the XCaliBr study, demonstrated a reasonable response rate with bevacizumab and capecitabine and confirmed the safety experience previously reported (Sledge 2007; Miller 2006).

Track 9

Case Discussion 2 (Patient of Dr O'Shaughnessy)

A woman in her mid- to late fifties with a history of lobular breast cancer treated two years prior with surgery, adjuvant AC → taxane followed by anastrozole who presents with an isolated colon metastasis identified via routine colonoscopy.

DR O'SHAUGHNESSY: The lobular invasive cancer in the gastrointestinal (GI) tract was discovered on routine colonoscopy. The patient was asymptomatic, but when we checked her CA27.29, it was more than 1,000 U/mL.

We performed an extensive evaluation with every imaging study known to mankind, including bilateral marrow biopsies, but found nothing. I was surprised, considering that she had 10 positive nodes at baseline. Yet every time we checked her CA27.29, it was clearly rising in the face of adjuvant anastrozole.

DR LOVE: Hal, what is the association between invasive lobular cancer and the GI tract?

DR BURSTEIN: A clinical association has been well documented. Lobular tumors seem to have slightly different tissue predilections than ductal carcinomas when it comes to the initial site of metastasis. They are almost always ER-positive and almost always HER2-negative. In metastatic disease, they spread to visceral sites less frequently, as initial manifestations, and will more likely metastasize to bone or cirrhosal surfaces, such as the pleura or intra-abdominal cavity.

DR LOVE: Joyce, how did the patient fare on anastrozole?

DR O'SHAUGHNESSY: She was feeling great, so we continued the anastrozole. A year later, her GI tract was rescoped and nothing was found. She received anastrozole for another two or three years, and when we checked her CA27.29 every two or three months, it continued to rise another 500 points each time, but still we found nothing.

I was concerned about the abdominal cavity because it's a common site for metastases, and I watched for early evidence of hydronephrosis. One particular abdominal CT scan revealed perinephric stranding, so I took that as a sign of trouble and switched her to exemestane.

Her tumor marker did not come down, and she began losing a little weight. I then switched her to megestrol acetate, and she responded. For the first time, her marker began going down, and she gained a few pounds, which was good.

However, after six to nine months her disease began to progress — she became a little anemic and began losing weight again. Considering the documented disease in her colon and the perinephric findings, I was thinking "gut" and placed her on fluoxymesterone.

DR LOVE: How did this patient respond to the fluoxymesterone?

DR O'SHAUGHNESSY: She had a fantastic response to fluoxymesterone. I increased the dose to 10 milligrams QID, and month after month her marker went down. It's currently around 1,200 to 1,500, but it had been as high as 5,000 or 6,000 U/mL.

DR LOVE: Has she had any problems on fluoxymesterone?

DR O'SHAUGHNESSY: She told me she noticed more hair on her legs, but nothing major. I use fluoxymesterone because approximately 80 to 90 percent of ER-positive breast cancer cases have the androgen receptors. It's one of my

"go-to" drugs with lobular breast cancer, and I've been impressed with it.

Lobular cancer is common in the metastatic setting. Even though it accounts for only 15 percent of adjuvant cases because it is not particularly responsive to chemotherapy or endocrine therapy, it accounts for one third of my metastatic practice.

DR BURSTEIN: This is an interesting case, but I'm not sure the literature supports the idea that lobular cases are more resistant to the standard hormone therapies. Historically it's been said that size for size, node for node, lobular and ductal breast cancer fare comparably if they are ER-positive.

Well, Chuck Vogel used to say that he had a dozen different kinds of endocrine therapy, and I give Joyce kudos for thinking outside of the box and reaching for some older drugs. I don't believe our fellows have ever seen Halotestin used.

It's hard to say exactly what's going on in this case. It's unusual in that the markers have been so markedly elevated without more measurable disease. The case has many interesting parts, and I'm glad the patient is doing well.

Tracks 13-16

Case Discussion 3 (Patient of Dr Burstein)

A premenopausal woman with a large hormone receptor-positive, HER2-negative breast tumor and de novo bone metastases.

DR BURSTEIN: We started this patient on bisphosphonate therapy for her bone lesions, in addition to combined endocrine therapy consisting of ovarian suppression and tamoxifen. She experienced an excellent period of tumor control, and at some point she underwent an oophorectomy and continued on tamoxifen.

Eventually she experienced progression in the bone, so we switched her to an aromatase inhibitor, which she received for eight or nine months. She began having more bone symptoms, and her bone scan suggested possible evolution of her disease. We restaged the cancer but did not find significant visceral disease.

Then the questions arose as to whether we should continue the endocrine therapy or whether we should try chemotherapy, which she hadn't received.

My colleague at Mass General, Paul Goss, holds this interesting concept involving withdrawal of the aromatase inhibitor, and he has a trial for that. This patient is a bit of an eccentric character, and although she didn't want to participate in the study, she did want to take a break from all therapy.

We stopped her aromatase inhibitor, and astonishingly she's doing fine. It's only been approximately four months, but her disease appears to be stable. Every time she comes into the clinic, I tell her I want to do something, but she's content to do nothing.

DR LOVE: If she agreed to further therapy, what would you use at this point?

DR BURSTEIN: She had been receiving a nonsteroidal aromatase inhibitor, and I believe the choice would be either to switch her to a steroidal aromatase inhibitor, such as exemestane, or to try fulvestrant. We could also consider chemotherapy, but she really does not want chemotherapy.

DR LOVE: Bill Gradishar reported on the EFECT study at the San Antonio Breast Cancer Symposium in 2006, which compared fulvestrant to exemestane after progression on nonsteroidal aromatase inhibitor therapy for patients with advanced breast cancer. That pretty well describes this patient's options. Joyce, what did you think of the EFECT data?

DR O'SHAUGHNESSY: That trial reassured me because it was a large, well-executed, prospective study and it showed that we have some choices for patients like this (Gradishar 2006). She can receive either exemestane or fulvestrant, and each therapy has an approximately 30 to 33 percent clinical benefit rate (2.3, page 25).

DR LOVE: In the study, how long did the tumor need to be stable for the endpoint of clinical benefit?

DR BURSTEIN: It varies from trial to trial. In fact, some studies report clinical benefit simply if no progression is evident at the first staging, so you have to read the fine print.

DR O'SHAUGHNESSY: In EFECT, they used six months, and a third of the patients went six months without progression.

DR LOVE: Hal, do you believe there might be a place for fulvestrant or a combination of fulvestrant with an aromatase inhibitor in the adjuvant setting?

DR BURSTEIN: In the ATAC trial, combining tamoxifen with an aromatase inhibitor did not improve the prognosis. Therefore, I believe combining fulvestrant and an aromatase inhibitor must be studied to determine whether it confers any benefit.

However, the people who conduct a lot of scientific work with fulvestrant maintain that because it leads to substantial downregulation of estrogen receptor and degradation of the receptor, an advantage may exist in combining it with an aromatase inhibitor.

We have sufficient rationale for conducting trials comparing an aromatase inhibitor with or without fulvestrant in either the metastatic setting or the adjuvant setting.

Similarly, interest exists in using fulvestrant as an extended adjuvant treatment, although getting patients to come in monthly for an injection as opposed to taking a pill daily might be a challenge, so we need to see some compelling data before pursuing such a trial.

Tracks 17-18

Case Discussion 4 (Patient of Dr O'Shaughnessy)

A woman in her late twenties diagnosed with ER-positive, PR-negative, HER2-negative (via FISH) Grade III breast cancer was treated with AC → taxane and tamoxifen, and recurred a couple of years later with extensive bony metastases.

She was treated with oophorectomy/aromatase inhibitor followed by multiple lines of combination chemotherapy, including bevacizumab, but developed rapidly progressive bone and hepatic metastases. After obtaining a strongly positive serum HER2, the patient was started on carboplatin/gemcitabine with trastuzumab and experienced a major clinical response.

DR O'SHAUGHNESSY: This patient's original adjuvant therapy at the time of diagnosis consisted of AC followed by paclitaxel and subsequent tamoxifen. However, after a disease-free interval of three to four years, she experienced bone recurrence. She had already undergone an oophorectomy and received an aromatase inhibitor, in addition to a trial of another endocrine agent, when I saw her in consultation, and her cancer progressed with extensive bone disease.

She was treated with docetaxel and capecitabine and did benefit from that regimen. However, this time it wasn't one of those unbelievable, multiyear responses that we sometimes see with this particular luminal B biology. When the disease progressed, this time it was in the liver, as is so often the case with luminal B disease. First it metastasizes to the bone, then to the bone and liver.

She then received bevacizumab with vinorelbine and she responded. However, when the disease progressed, her cancer picked up speed, particularly in the liver, and I was becoming nervous. She had already received most of the major agents we have to offer at that point, so in desperation I drew a serum HER2.

This patient originally had HER2-negative disease as determined by FISH. I had seen negative results on a couple of determinations, but her serum sample was strongly HER2-positive.

I have tested the serum for conversion in six to 10 cases over the last few years, and I've always been somewhat disappointed. I've seen results like 14, 15, maybe 20 at the most, but nothing impressive. However, this patient's serum HER2 was 75, so I started treating her with gemcitabine, carboplatin and trastuzumab, and she's showing a major response.

DR LOVE: What happened to her tumor markers?

DR O'SHAUGHNESSY: Before this regimen, they were skyrocketing. They kept doubling, and they reached the 3,000 range. However, after she began treatment with this combination, they were halving every time I tested. They are now down to around 1,200 and her liver function tests are normalizing, and she's only received two cycles so far.

DR LOVE: Did she have symptoms from the tumor?

DR O'SHAUGHNESSY: Yes, she was experiencing significant bone pain and severe fatigue, and these symptoms have improved as well. Also, she has been experiencing some depression. She's on an SSRI and was sleeping a lot. She's usually lying down when I see her in the exam room, but the other day she was sitting up.

I've seen a couple of elevated serum HER2 levels after progression on bevacizumab. My partner has a similar patient who was also heavily pretreated, but she too responded when she received chemotherapy and trastuzumab.

DR LOVE: Joyce, what do we know about serum HER2, particularly in patients who have tumors that have been labeled HER2-negative?

DR O'SHAUGHNESSY: In a paper published in *Cancer* a year or two ago, Allan Lipton documented that approximately a third of patients with negative serum HER2 at study initiation who had received first-line tamoxifen or letrozole for metastatic or locally advanced breast cancer had a significant elevation of their serum HER2 upon disease progression (Lipton 2005; [4.1]). This was seen in both arms of the study but particularly in the letrozole arm.

DR LOVE: Did you think your patient's disease had transformed?

DR O'SHAUGHNESSY: Yes. A second paper, by Jonathan Uhr at UT Southwestern, showed clearly in initially HER2-negative disease that approximately 30 percent of the circulating tumor cells were HER2-positive (Meng 2004).

DR LOVE: Did you consider a liver biopsy for this patient to document the change in HER2 status?

DR O'SHAUGHNESSY: She had recently finished bevacizumab, so I wasn't too anxious to biopsy her liver, but if she hadn't been on it, I might have considered it. However, the serum is different, and one hypothesis is that when a patient experiences progression on bevacizumab, HER2 may be a mechanism of resistance. That hypothesis should be studied.

4.1

Serum HER2 Conversion to Positive at the Time of Disease Progression in Breast Cancer Patients Treated with Endocrine Therapy

"The objective of this study was to determine whether patients with metastatic or locally advanced breast carcinoma who have negative serum HER-2/neu status at the initiation of first-line hormone therapy with letrozole or tamoxifen convert to positive serum HER-2/neu status at the time of disease progression and to determine whether serum HER-2/neu conversion to positive status is associated with response to therapy and overall survival....

Conversion to positive serum HER-2/neu status occurred in approximately 25% of patients who received first-line hormone therapy. Conversion to serum HER-2/neu-positive status occurred with equal frequency in antiestrogen and aromatase-inhibitor therapy. The current results showed that serum conversion to HER-2/neu-positive status was an independent risk factor for decreased survival in patients with breast carcinoma."

SOURCE: Lipton A et al. *Cancer* 2005;104(2):257-63. **Abstract**

DR LOVE: Hal, what do you think about this case?

DR BURSTEIN: I see several different issues here. This case underscores the fact that we're treating advanced breast cancer based on the biology of the disease. Just as we discussed in the first case the need for new agents to treat triple-negative breast cancer, obviously we have several effective agents in the treatment of HER2-positive breast cancer and we need to tailor our therapies for the patient based on that.

In question is the nature of this tumor, and several possibilities exist. One is that the initial test results were wrong. We know variations occur in testing quality and reproducibility. A second possibility is that a shift has occurred and a tumor that began life as HER2-negative breast cancer is now emerging as HER2-driven breast cancer. ■

SELECT PUBLICATIONS

Carey LA et al. **The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes.** *Clin Cancer Res* 2007;13(8):2329-34. **Abstract**

Esteva FJ et al. **Clinical utility of serum HER2/neu in monitoring and prediction of progression-free survival in metastatic breast cancer patients treated with trastuzumab-based therapies.** *Breast Cancer Res* 2005;7(4):R436-43. **Abstract**

Fehm T et al. **Changes of serum HER2 status during clinical course of metastatic breast cancer patients.** *Anticancer Res* 2004;24(6):4205-10. **Abstract**

Fornier MN et al. **Serum HER2 extracellular domain in metastatic breast cancer patients treated with weekly trastuzumab and paclitaxel: Association with HER2 status by immunohistochemistry and fluorescence in situ hybridization and with response rate.** *Ann Oncol* 2005;16(2):234-9. **Abstract**

Gradishar W et al. **Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: First results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

Kong SY et al. **Serum HER-2 concentration in patients with primary breast cancer.** *J Clin Pathol* 2006;59(4):373-6. **Abstract**

Lipton A et al. **Serum HER-2/neu conversion to positive at the time of disease progression in patients with breast carcinoma on hormone therapy.** *Cancer* 2005;104(2):257-63. **Abstract**

Mayer EL et al. **Clinical trial update: Implications and management of residual disease after neoadjuvant therapy for breast cancer.** *Breast Cancer Res* 2007;9(5):110. **Abstract**

Meng S et al. **HER-2 gene amplification can be acquired as breast cancer progresses.** *Proc Natl Acad Sci USA* 2004;101(25):9393-8. **Abstract**

Miller K et al. **Capecitabine plus bevacizumab in first line metastatic breast cancer: An interim safety and efficacy report of the first phase of Xeloda plus Avastin 1st line metastatic breast cancer trial.** San Antonio Breast Cancer Symposium 2006;**Abstract 2068**.

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* 2005;23(4):792-9. **Abstract**

Park H et al. **Effects of tetramethoxystilbene on hormone-resistant breast cancer cells: Biological and biochemical mechanisms of action.** *Cancer Res* 2007;67(12):5717-26. **Abstract**

Sledge G et al. **Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer.** *Proc ASCO* 2007;**Abstract 1013**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **ECOG trial E5103 will evaluate bevacizumab in combination with _____ for patients with node-positive or high-risk node-negative, HER2-negative breast cancer.**
   a. AC alone
   b. AC → paclitaxel
   c. AC → docetaxel
   d. TCH

2. **In the XCaliBr study, capecitabine with bevacizumab as first-line therapy resulted in a significantly better _____ for patients with ER-positive compared to ER-negative disease.**
   a. Time to progression
   b. Overall survival
   c. Overall response rate
   d. All of the above

3. **In the updated analysis of the Phase II trial of weekly or every three-week *nab* paclitaxel versus every three-week docetaxel, the *nab* paclitaxel schedule with the greatest antitumor activity appears to be _____.**
   a. 300 mg/m^2 every three weeks
   b. 100 mg/m^2 weekly three out of four weeks
   c. 150 mg/m^2 weekly three out of four weeks

4. **Which of the following is *not* being evaluated with chemotherapy in the ALTTO trial?**
   a. Trastuzumab alone
   b. Lapatinib alone
   c. Trastuzumab followed by lapatinib
   d. Trastuzumab and lapatinib
   e. Lapatinib followed by trastuzumab

5. **In an analysis of NSABP-B-31, which of the following were significant predictors for congestive heart failure in the multivariate risk model for cardiotoxicity after AC → paclitaxel/trastuzumab?**
   a. Age greater than 50 years old
   b. Baseline LVEF of 50 to 54 percent
   c. Treatment for hypertension
   d. All of the above

6. **In ECOG-E2100, paclitaxel and bevacizumab significantly prolonged disease-free survival compared to _____ as initial chemotherapy for patients with metastatic breast cancer.**
   a. Paclitaxel alone
   b. Paclitaxel and capecitabine
   c. *Nab* paclitaxel and bevacizumab

7. **Compared to the standard formulation of paclitaxel, *nab* paclitaxel requires _____.**
   a No premedication with steroids
   b. Shorter infusion time
   c. Both a and b

8. **In the second interim analysis of BCIRG 006, no statistically significant difference appeared in disease-free survival between AC → TH and TCH in the overall population or in the population with amplification of TOPO II.**
   a. True
   b. False

9. **In the EFECT study of women with metastatic breast cancer who were previously treated with a nonsteroidal aromatase inhibitor, the fulvestrant loading dose regimen resulted in achievement of steady-state levels by week four.**
   a. True
   b. False

10. **In the TAnDEM study, the progression-free survival with anastrozole among postmenopausal patients with hormone receptor-positive, HER2-positive metastatic breast cancer was _____.**
    a. 2.4 months
    b. 5.4 months
    c. 8.4 months

11. **Approximately what percent of patients with negative serum HER2 status treated with first-line hormonal therapy converted to serum HER2-positive?**
    a. Five percent
    b. 12 percent
    c. 25 percent
    d. 50 percent

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

EVALUATION FORM

Breast Cancer Update — Issue 6, 2007

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 will be issued upon receipt of your completed Post-test and 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 preventative, neoadjuvant, adjuvant and metastatic 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, nonanthracycline-based regimens 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 the risks and benefits, selection and sequencing of endocrine therapy, single-agent and combination chemotherapy regimens. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers that provide prognostic and predictive information on the quantitative risk of breast cancer relapse and/or treatment response, 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
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
William J Gradishar, MD	5 4 3 2 1	5 4 3 2 1
Joyce O'Shaughnessy, MD	5 4 3 2 1	5 4 3 2 1
Lee S Schwartzberg, MD	5 4 3 2 1	5 4 3 2 1
George W Sledge Jr, 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

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EVALUATION FORM

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

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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:

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BCU607

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