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Breast Cancer® UPDATE

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

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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 adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations.
- 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 to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

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

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UPCOMING EDUCATIONAL EVENTS

Colorectal Cancer Clinical Investigator Think Tank: A Live CME Event Featuring Computer-Based Audience Participation
January 20, 2007
Orlando, Florida
Event website: **ColorectalCancerUpdate.com/LiveThinkTank**

NCCN 12th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care
March 14-18, 2007
Hollywood, Florida
Event website: **nccn.org**

Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions
March 26-27, 2007
Bethesda, Maryland
Event website: **ctep.cancer.gov/bcmeeting**

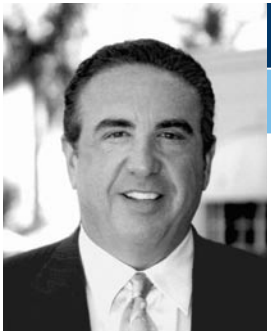
American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **aacr.org**

NCCTG Semi-Annual Meeting
April 16-19, 2007
Rochester, Minnesota
Event website: **ncctg.mayo.edu**

NSABP Semi-Annual Meeting
April 27-30, 2007
Jacksonville, Florida
Event website: **nsabp.org**

SWOG Semi-Annual Meeting
May 2-6, 2007
Chicago, Illinois
Event website: **swog.org**

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



EDITOR'S NOTE

Neil Love, MD

Heart of Oncology

For an audiophile like me, the internet is truly a wonderful thing. Now, with a few clicks of a mouse, you can sign up for a Podcast and have interesting content delivered right to your iPod on a regular basis. Even better, you can also quickly, easily and inexpensively distribute audio programs to hundreds, dare I say thousands, of people around the world. To take advantage of the benefits of this powerful technology, our CME group has begun to offer all of our audio series for internet downloading and as Podcasts, but even more importantly, we have also started to produce unique programs available only through the web.

Our first attempt in this interesting endeavor is called Heart of Oncology (**HeartofOncology.com**) and it will include a compilation of some of the most compelling human moments from our interviews and meetings. What makes this program unique is that it does not focus so much on management issues or treatment choices but rather on the most fundamental aspect of our profession: the personal side of cancer caring.

Below, you will find a few comments from the first posting of The Heart of Oncology. This particular interlude occurred during a recent "Meet The Professors" (MTP) recording session held in Manhattan with 12 local oncologists and faculty members Drs Hy Muss and Sandra Swain.

Dr Jeff Vacirca had just presented the case of a 32-year-old woman diagnosed with metastatic breast cancer while she was 26 weeks pregnant. The patient received chemotherapy, but at 31 weeks, the disease was progressing rapidly and she was having significant tumor-related symptoms.

Hours before the MTP meeting, an apparently healthy daughter entered the world by emergency cesarean section, causing Jeff to arrive at the event seeking suggestions regarding therapy for the new mom. After reviewing a number of palliative treatment options, the discussion turned to the deeply human side of this case, including the toll treating these types of patients can take on oncology professionals.

Please let us know what you think.

— Neil Love, MD
NLove@ResearchToPractice.net
December 15, 2006

DR MUSS: As an oncologist, I don't think you ever get used to being in this type of situation, and perhaps if you do, you need to be doing something else. I call these "two-scotch nights," and I have had a fair amount of them. It helps to have good colleagues and friends reassure you that you've done your best and to empathize with you, but I don't think you ever quite get used to it.

I also think oncologists are a preselected group — including all of us around the table. If you get into your fellowship and you see these patients and you really can't handle it, you get out. In my career, I've had fellows come in and, six or eight months later, leave the program. It's rarely ever academic ability. It's just dealing with these kinds of patients.

So I think that we are preselected, that we probably like high-impact medicine and that we might not be very happy in the acne clinic. We get a lot of sharing and help from our friends, but we never get used to it. And the hardest thing is, you'd think with all the tools we have, we'd be doing better, but I'm not so certain how much more we're helping people with metastatic breast cancer.

DR SWAIN: Over the years, I have really felt that it was important to develop a relationship with patients and find out what's important to them. So I try, even on the first visit, to find out what is important to them. Is it their grandchild, or their husband, and what do they need?

I then follow them throughout their whole course. I've seen, as many of you have, some physicians who can't deal with that, and they basically abandon their patients. I feel that one of my strengths is that I don't do that. I really can help them at the end, help them to try to cope. The way I put it to a lot of patients in the beginning is that, in a way, it's a gift because it's a gift of time. If you go into the street and get hit by a bus, you don't have any time. You don't prepare. This way, you have time — you


Hyman B Muss, MD


Sandra M Swain, MD


Alan B Astrow, MD


Samuel N Bobrow, MD


Charles M Farber, MD, PhD


Jeffrey L Vacirca, MD


Stanley E Waintraub, MD

can make the best of your time. So I try to work with a patient on that. But I agree — it is very hard.

DR ALAN ASTROW: A few years ago I organized a series of interfaith dialogues about spiritual issues and medical care, and we had one about sadness, in which we had a dialogue between a Franciscan friar — a well-known scholar by the name of Richard Rohr — and a rabbi from UCLA, named Chaim Seidler-Feller.

I think about it a lot because what Rohr talked about was how important it is to get out of "the fixing mode." How I translate that into common-sense advice is that, often, doctors and nurses faced with a difficult situation jump into reassuring the patient too soon. What Rohr said, and other physicians and psychiatrists have said this, is that you don't want to try to fix initially. The first step is to allow the person to express his or her emotions and to empathize.

What the rabbi said was also interesting. He said that in the Hasidic tradition, there is this view that you're commanded to be joyful. So what I got out of that is that you follow the patient into their sadness, you get out of that fixing mode, but then you remember that you're actually commanded to get that patient out of their sadness. You're commanded to be joyful and to try to find some way to get the patient out of their sadness. I find that a useful way to think about it.

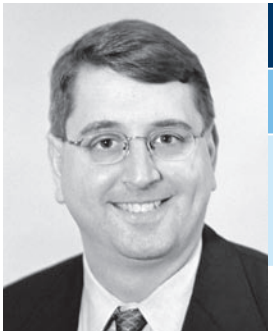
DR LOVE: Where does humor fit in, if at all?

DR CHARLES FARBER: I'm in a relatively large oncology group. There are nine other physicians, and we use a lot of black humor — things that are totally inappropriate, that you'd never want anyone to hear. It's a way we deal with it, and a lot of times we laugh so we don't cry. We just look at the absurdity of many of the situations, and it helps me get through the day.

DR SAMUEL N BOBROW: One way I deal with patients is to help them focus on the here and now. You can't deal with metastatic breast cancer wondering whether you're going to live two years, three years or four years, but you can focus on now and feeling well and doing what you want to do — travel, enjoy whatever you like to do. The future will come.

DR STANLEY WAINTRAUB: I always look at who comes in with the patient. Most of the young women I take care of — and we all have a lot of young women with metastatic breast cancer — don't come in with their husbands. They come with their friends. I always say to them, "Who's your support system?"

If they come alone, that's very bad. If they don't come with their husband, there's something wrong. We also have psychiatric social workers in the office, and I want them to talk to the husband. I want to know where the husband is. Is he in denial? Is he angry? We all forget about the spouse. I'm very interested in who comes with the patient. When I give you bad news, I want to know who's going to hold your hand. ■



INTERVIEW

Harold J Burstein, MD, PhD

Dr Burstein is Assistant Professor of Medicine at Dana-Farber Cancer Institute's Breast Oncology Center at Harvard Medical School in Boston, Massachusetts.

CD 1, Tracks 1-14

Select Excerpts from the Interview

CD 1, Tracks 2-3

DR BURSTEIN: More and more, we are splintering breast cancer into several different diseases, so most of the clinical trials moving forward are focusing on biologically defined subsets of patients with breast cancer. We will see specific studies for hormone receptor-positive disease, for HER2-overexpressing disease and for triple-negative or basal-like disease. I believe this is reasonable because the questions of most interest are probably different in each of those patient populations.

DR LOVE: You wrote a number of articles — prior to the publication of the adjuvant trastuzumab trials — that said that in addition to the likelihood that the trastuzumab data were going to be positive, the data would most likely affect how we treat patients with HER2-negative disease and the trials that those patients enter.

DR BURSTEIN: That's right, and that's even truer at this time. What we thought we knew about treating with adjuvant chemotherapy, for instance, was all derived from trials that included patients with all different types of breast cancer.

If you carefully review the role of anthracyclines, you see that a lot of retrospective data (Paik 1998, 2000) suggest that most of the benefit of anthracycline therapy is in HER2-overexpressing breast cancer (1.1). Once you take those patients with HER2-positive disease out of the general mix, it's not as clear that anthracyclines are critically important.

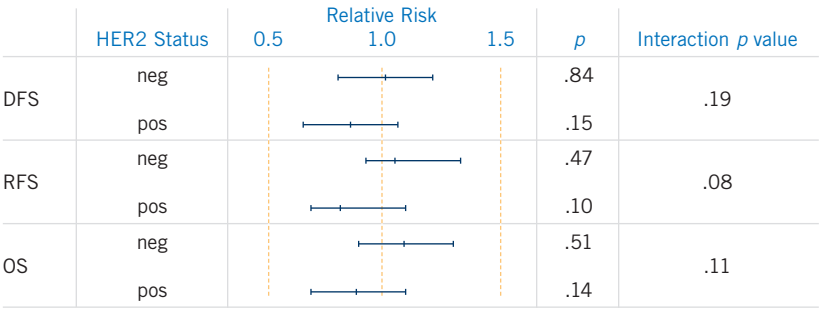
Similarly, a lot of retrospective work now suggests that the benefits associated with the major tweaks of chemotherapy are mostly observed in hormone receptor-negative breast cancer. For hormone receptor-positive breast cancer, it is not as clear that those are major advances (Berry 2006), so the idea of separating breast cancer into different subsets makes sense, but it does present challenges.

The first is that the creation of subsets dilutes the patient population base, so instead of rapid accrual to studies that require thousands of patients to enroll, we will need more carefully selected patients.

Second, the identification of subsets puts a high priority on the quality of testing tumors. Obviously, if you're going to make clinical decisions based on anything such as hormone receptor status, HER2 status, or Onco*type* DX™ and genomic assays, you must know the reproducibility of the testing and the quality control. That will be a challenge for community oncologists in the United States.

1.1

Efficacy of Treatment with AC Relative to Efficacy of Treatment with CMF According to HER Status Among Patients from NSABP-B-15



Relative Risk of Failure < 1.0 favors AC versus CMF

AC = doxorubicin and cyclophosphamide
CMF = cyclophosphamide, methotrexate and 5-fluorouracil

SOURCE: Paik S et al. **HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15.** *J Natl Cancer Inst* 2000;92(24):1991-8, by permission of Oxford University Press. **Abstract**

No fewer than three expert panels are currently convened to discuss HER2 testing. ASCO, the National Comprehensive Cancer Network and the College of American Pathology are all issuing guidelines for HER2 testing. My understanding, although of course the details may change, is that most of these panels will make the same recommendation, namely, that either well-conducted immunohistochemical testing or well-conducted FISH testing is acceptable.

But the key questions are, how good is the specific tester, and what quality control measures does the pathologist use? The panels will demand that pathologists prove they can conduct high-quality testing, or they will be asked to stop HER2 testing. That's a big change.

If you're a practicing oncologist who is about to treat a patient for HER2-overexpressing disease based on the results of a certain pathology lab and you don't know the performance characteristics of that lab, you can't make a good decision about whether or not HER2 is overexpressed.

DR LOVE: A lot of concern has arisen about HER2 testing because of the excitement about adjuvant trastuzumab, but some observers think that ER testing is in even worse shape.

DR BURSTEIN: When it was appreciated five or six years ago that HER2 testing was in many ways mediocre, a lot of educational campaigns and quality initiatives were put forward to address those concerns. It has been shown that you can train people to do a better job, but that same educational process has not happened in ER testing for decades, and that is a significant issue.

Regarding the Genomic Health and the Onco*type* DX experience, when they start taking sensitive quantitative RNA measurements for genes, including ER and PR, my understanding is that a small fraction — probably five or 10 percent — of cases that are thought to be ER-positive will be ER-negative.

So here is the real lesson, and it is not unique to breast cancer: As soon as you ask the pathology service to tell you more than whether a tumor is present, how big it is and whether nodes are involved, you introduce a level of expertise that not every pathology group will have.

We will need high-quality, high-volume pathology testing for all these new molecular markers that are coming along in all the different tumor types. That will be a challenge for the pathologists. The good ones will rise to that challenge by instituting appropriate quality assurance plans. They will also realize that they can't do every test well, so they will collaborate with people who may do certain tests better than they do.

CD 1, Track 5

DR LOVE: What are some of the strategies — specifically focusing on ER-positive disease — you think might reduce recurrence rates and mortality in the future?

DR BURSTEIN: Work is being done in several important areas. One involves the question about treatment with aromatase inhibitors in the early-stage setting: When and for how long? Well-orchestrated trials are tackling those questions, and there will be chances to update those experiences annually for many years to come.

Another big question is to figure out, within the group of patients with ER-positive early-stage breast cancer, which women need chemotherapy. A lot of attention has focused on the Onco*type* DX (Paik 2004) experience with the NSABP and Soon Paik. I like that general approach. I believe it exemplifies where most of us believe the field should be going.

DR LOVE: Are you using Onco*type* in your practice?

DR BURSTEIN: I use it in my practice, and I find it is very helpful. Patients understand it, and it resonates with other measures in breast cancer pathology. It gives you a quantitative readout. Patients readily understand that this is an extra piece of information that can help us stratify risk and therefore allow them to make a better-informed choice about chemotherapy.

I believe this will remarkably change the playing field for ER-positive breast cancer. Many of these women will no longer be receiving chemotherapy. They simply won't need it, based on their prognosis. However, we need to refine that.

The Onco*type* DX test was developed with tamoxifen-treated patients who received what many would consider old-fashioned chemotherapy. I believe the principles will be the same, but we want to see studies in the adjuvant setting using aromatase inhibitors, and we want to see studies that use different chemotherapy programs, and so on.

DR LOVE: What about patients with node-positive disease?

DR BURSTEIN: This approach will be extended to node-positive disease. These ideas are being worked on. Again, the general question is, how can we use genomic-type information and the analysis of multiple gene expression patterns to refine our prognosis and treatment selection? That general strategy is appearing across cancer medicine and specifically in breast cancer, and this choice of which patients with ER-positive disease need chemotherapy is the place where it has been most readily and successfully exploited so far.

CD 1, Track 10

DR LOVE: What are some of the most frequently asked questions you receive from community-based oncologists?

DR BURSTEIN: The biggest question I hear at tumor boards right now is how to approach patients who have small HER2-positive tumors such as the patient with the 7-mm, ER-negative, HER2-positive tumor or the 1.2-cm, ER-positive, HER2-positive tumor.

We don't have great data on the outcomes for these women. Our group has

proposed, and I believe we'll put forward, a multicenter trial evaluating trastuzumab with paclitaxel as a treatment regimen for patients at low risk.

We will treat approximately 300–400 patients in what will essentially be a feasibility study to show that if you carefully select the patients at low risk and administer a paclitaxel/trastuzumab combination that should be well tolerated, you have a low risk of recurrence.

We would love to see a huge randomized trial for these women, but that is impractical given the resources and the generally low risk for patients with node-negative disease.

CD 1, Track 11

DR LOVE: Can you discuss the treatment of patients with triple-negative tumors?

DR BURSTEIN: We don't have a targeted agent for these tumors, so the work in this area has been focusing on optimizing chemotherapy. Some trials are evaluating adding products like capecitabine, and some are evaluating platinum-based chemotherapy.

Additionally, there is interest in other biological approaches, and probably the one that is furthest along has been to add bevacizumab to the treatment of these patients.

ECOG-E2100 (1.2) indicated that the ER-negative, HER2-negative patients did handsomely with paclitaxel and bevacizumab. So that is a reasonable patient population in which to try optimizing chemotherapy and other biological approaches.

DR LOVE: In general, how do you approach therapy for a woman with visceral metastatic disease that is extensive, symptomatic, associated with poor performance status, triple-negative and chemotherapy naïve?

DR BURSTEIN: Obviously, we will administer chemotherapy. Most frequently, I use paclitaxel with bevacizumab for patients like that. I find the data from ECOG-E2100 compelling. We can do better than using chemotherapy alone by adding bevacizumab treatment. I like the idea of using a relatively exciting biological therapy. The other point is that few women who walk in the door are chemotherapy naïve at that point.

CD 1, Track 14

DR LOVE: Can you provide an update on trials looking at bevacizumab in the adjuvant setting?

DR BURSTEIN: Bevacizumab is moving to the adjuvant setting. The Intergroup will be running a trial (1.3) with a design of AC followed by paclitaxel with or without bevacizumab.

1.2

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

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 680 (Closed)

Eligibility

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

R

BT

Paclitaxel (days 1, 8 and 15) + **bevacizumab** 10 mg/kg (days 1 and 15) q4wk

T

Paclitaxel (days 1, 8 and 15) q4wk

Subgroup	Hazard ratio (95% confidence interval)
ER+, PR+ (n = 200)	0.39 (0.29-0.53)
ER+, PR- (n = 80)	0.86 (0.52-1.43)
ER-, PR- (n = 184)	0.47 (0.35-0.63)

HER2-positive disease was observed in only four percent of the paclitaxel group and five percent of the paclitaxel plus bevacizumab group.

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

What makes this exciting is that bevacizumab is an encouraging drug. If you believe the anti-angiogenesis model and the hypothesis that targeting the blood supply will inhibit the growth of tumors, the best setting in which to observe that will be the adjuvant setting because you have micrometastatic disease. It does not have a fully established blood supply already.

If you agree with the Judah Folkman hypothesis, this setting is where you want to evaluate these types of drugs. These clinical trials have the potential to be tremendously beneficial and important.

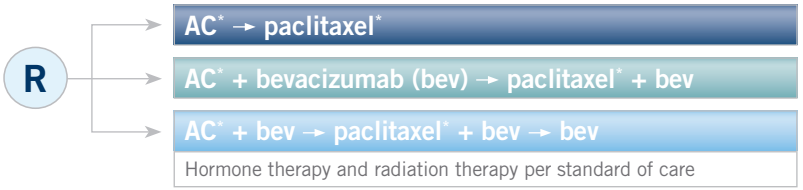
One needs to conduct the studies, of course, but there is a reasonable chance that the benefits will be even better in the adjuvant setting than in the metastatic setting.

DR LOVE: How do you think the safety and tolerability profile will play out in the adjuvant setting?

DR BURSTEIN: I believe it will be feasible to administer the drug. The median time to progression with paclitaxel and bevacizumab in ECOG-E2100 was 11 months, so we know that you can feasibly administer the drug for a long period, but we don't know about the late side effects. ■

1.3 ECOG-E5103: A Phase III Adjuvant Study of Chemotherapy and Bevacizumab in Patients with HER2-Negative, Node-Positive or High-Risk Node-Negative Early Breast Cancer

Protocol ID: ECOG-E5103 (Pending)



* Investigator's choice of classic or dose-dense chemotherapy

SOURCE: George W Sledge, MD. Personal communication, September 2006.

SELECT PUBLICATIONS

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Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER 2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

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INTERVIEW

Peter M Ravdin, MD, PhD

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

CD 1, Tracks 15-22 — CD 2, Track 1

CD 1

Track 15 Introduction

Track 16 Overview of the Oxford trialists' meta-analysis of randomized trials in breast cancer

Track 17 Benefit of adjuvant taxanes in the Oxford Overview analysis

Track 18 Overview data on the impact of estrogen receptor status

Track 19 Oxford Overview analysis of adjuvant hormonal therapy

Track 20 Estrogen receptor status and time course of recurrence

Track 21 Incorporation of HER2 status and trastuzumab into the Adjuvant! Online computer model

Track 22 Development of biologic predictors of response to chemotherapy

CD 2

Track 1 Evaluation of long-term anthracycline-associated cardiotoxicity

Select Excerpts from the Interview

CD 1, Track 17

DR LOVE: You just returned from Oxford and the latest trialists meeting. What will the new Oxford Overview analysis tell us about adjuvant chemotherapy?

DR RAVDIN: The questions include: How much do taxanes add and what about subsets of patients receiving taxanes? Individual trials have suggested taxanes may be more effective in patients with a few positive nodes than those with many positive nodes. Other trials, notably the analysis of CALGB data by Don Berry and colleagues, have suggested that these agents work well in patients with ER-negative disease but don't add much for those with ER-positive tumors (Berry 2006; [2.1]). In the Oxford Overview, we were not surprised to see that taxanes improve recurrence-free and overall survival. In a subset analysis of pooled data, both patients with node-negative and node-positive disease appeared to be benefiting.

DR LOVE: Roughly speaking, what was the relative reduction of risk of recurrence and death for taxanes versus nontaxanes?

DR RAVDIN: Roughly 20 percent. The Oxford Overview analysis includes trials with an arm containing a taxane versus one that does not, but it includes a mix of trials. Sometimes the two regimens are identical except for the addition of a taxane. For example, CALGB trial 9344 is AC versus AC with paclitaxel (Henderson 1998). Other trials evaluated a taxane versus some other regimen. The BCIRG 001 trial evaluated TAC versus FAC (Martin 2005).

Estrogen receptor status did not seem to strongly modulate the benefit of taxanes. This isn't a big surprise because if individual trials don't find a correlation with ER status, they don't emphasize it. For instance, the TAC/FAC trial didn't show a large difference in benefit by ER status (Martin 2005). When all the trials were assessed together, ER itself did not appear to be a predictor of particular benefit from taxanes.

2.1

Chemotherapy Outcomes by Estrogen Receptor Status for Patients with Node-Positive Breast Cancer

	ER-negative	ER-positive
Relative risk reduction		
Recurrence	55%	26%
Death	55%	23%
Absolute difference at 5 years		
Disease-free survival	22.8%	7.0%
Overall survival	16.7%	4.0%

SOURCE: Berry DA et al. *JAMA* 2006;295:1658-67. **Abstract**

CD 1, Tracks 18, 20

DR LOVE: In the overall Oxford Overview chemotherapy data, what was the correlation between estrogen receptor status and outcome?

DR RAVDIN: This was hotly debated and complicated by the fact that age has to be taken into account in evaluating the first-generation trials, because if you are comparing chemotherapy to nothing in young patients, you are seeing not only cytotoxic effects but also the effects due to ovarian ablation or suppression. Young patients with ER-positive disease may be a little less responsive to the cytotoxic effects of chemotherapy, but the adjuvant endocrine effects they are also receiving brings up their response. Overall, ER status did not appear to make a difference in these patients.

That being said, this analysis describes the benefit of chemotherapy versus nothing. The regimens that included taxanes were never compared to nothing. They were compared to regimens that had already resulted in ovarian ablation in many patients who would have experienced it. In those patients, the effects of the taxanes appeared equal between older and younger women, irrespective of ER status. That was a surprise because I would have expected patients with ER-negative disease to be more chemosensitive than those with ER-positive

disease. In fact, the taxanes appeared to be somewhat more effective with ER-positive disease, irrespective of age or ER status.

DR LOVE: Would it be fair to conclude that this finding contradicts the analysis by Berry and colleagues (Berry 2006)?

DR RAVDIN: In a way it does. I've heard people say, "Patients with ER-positive disease don't benefit from chemotherapy, particularly if they're older, and these patients shouldn't be treated with chemotherapy." I believe this is an inaccuracy and an oversimplification.

Patients with ER-positive disease benefit, although they benefit less than those with ER-negative tumors. In fact, with first-generation regimens, patients with ER-positive disease benefit dramatically less than those with ER-negative disease, but with second-generation regimens, the difference begins to be obscured by the addition of agents that are effective in both patient groups.

DR LOVE: Were there any data presented on the time course of recurrence in ER-positive versus ER-negative disease?

DR RAVDIN: In the first-generation trials, chemotherapy was equally beneficial in ER-positive and ER-negative disease during the early years, when chemotherapy is most effective against recurrence. The same was observed in the middle time period. During the late time period, the data start to become noisy, and the effectiveness of those regimens against late relapse seemed to decrease to about the same level in all patients.

One could argue, "For those first-generation regimens, patients with ER-positive and ER-negative disease should have benefited equally." But that's not true. Patients with ER-negative disease tend to experience early relapses, when therapy is most effective against relapses. In contrast, ER-positive disease tends to have later relapses, say after three years. Therefore, when you look cumulatively at the impact of therapy after 10 years, you see a difference.

We already see there are some important differences between ER-negative and ER-positive patients. What we haven't really seen before is that the effectiveness in given time intervals between ER-positive and ER-negative looks rather similar, which is a surprise to me. It emphasizes that the time course of recurrence is important and that it differs between ER-positive and ER-negative disease. In looking at early versus late relapse, I believe we will gain some interesting insights.

DR LOVE: Is there a rule for calculating the late risk of relapse? I know you have that in your Adjuvant! Online computer program.

DR RAVDIN: Adjuvant! (**adjuvantonline.com**) considers the time course of relapse for patients with node-positive versus node-negative disease and whether to give hormonal therapy (Ravdin 2001).

Late relapse rates are higher among patients with node-positive than node-negative disease, but they are not as dramatically different as they are during

the early period. On average, the late relapse rate was about four percent per year for node-positive and two percent per year for node-negative disease.

CD 1, Track 19

DR LOVE: What else was presented at the Oxford meeting that you believe is important for clinicians to know?

DR RAVDIN: With regard to hormonal therapy, we are all looking forward to data from the big trials of five versus 10 years of tamoxifen. The ATLAS (Adjuvant Tamoxifen — Longer Against Shorter) and ATTOM (Adjuvant Tamoxifen Treatment Offers More) trials are still blinded and ongoing. As we've seen with endocrine therapies and aromatase inhibitors, trials with particularly positive results or survival benefits are stopped early. I believe we can infer that the ATLAS and ATTOM trials are not strikingly positive, which is reassuring to American oncologists.

DR LOVE: What about the aromatase inhibitors?

DR RAVDIN: The aromatase inhibitors are interesting. Looking at all the trials, including the "switching" studies, the proportional benefit for an aromatase inhibitor over tamoxifen was about 20 percent for recurrence and 10 percent for survival.

The aromatase inhibitor trials demonstrate the limitations of an overview analysis. To statisticians, all aromatase inhibitor trials look alike, whereas to clinicians, all aromatase inhibitor trials look different. A number of us, including myself, had a crisis of confidence in the overview process knowing that all of these trials would be lumped together.

It's not necessarily a good thing to apply the overview analysis to a group of trials in a general sense. In fact, it can obscure important differences.

Moreover, I don't believe that a meta-analysis can address the question that a lot of us want answered: Should I be using an aromatase inhibitor up front, or should I be administering two or three years of tamoxifen and then using an aromatase inhibitor?

CD 1, Track 21

DR LOVE: Where are you in terms of integrating trastuzumab data into the Adjuvant! Online program?

DR RAVDIN: Now that the trastuzumab trials have been formally published, we are able to evaluate and include the data. Currently, the program doesn't make projections for trastuzumab outcomes at 10 years because we have data with follow-up of only two to three years.

Many of the patients with ER-positive disease will experience recurrence later. If we don't know that part of the story, we could give wildly inaccurate estimates.

Version 9 of the breast cancer program is about to be released. For the first time, it includes HER2 status as one of the program parameters. The 9.0 program provides a separate output for trastuzumab, projecting benefit at five years, which is reasonable to talk about. Some patients have been followed for five years in the trastuzumab trials. The program also provides information about some of the toxicities and uncertainties about toxicity.

DR LOVE: Understanding the caveat of not having the longer follow-up that the other modalities have, what's the number you're going to put in there in terms of relative reduction of recurrence and mortality for trastuzumab?

DR RAVDIN: The literature-based estimates are about one third for mortality and 50 percent for recurrence. Those are the numbers that the program will use.

DR LOVE: HER2 will be a completely separate variable? ER status, et cetera, won't matter, and trastuzumab will cut the recurrence rate in half?

DR RAVDIN: Correct, but remember that all the trials thus far have not evaluated the one question that a lot of us would like to know: What would be the impact of trastuzumab alone? A lot of people may not be enthusiastic about chemotherapy, but the limitation of the data limits the program.

We don't have any results on the impact of trastuzumab alone. We only have randomized trial results of the impact of trastuzumab when added to adjuvant chemotherapy. ■

SELECT PUBLICATIONS

Baum M, Ravdin P. **Decision-making in early breast cancer: Guidelines and decision tools.** *Eur J Cancer* 2002;38(6):745-9. **Abstract**

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295:1658-67. **Abstract**

Goldhirsch A et al. **Meeting highlights: International expert consensus on the primary therapy of early breast cancer 2005.** *Ann Oncol* 2005;16(10):1569-83. **Abstract**

Henderson IC et al. **Improved disease-free and overall survival from the addition of sequential paclitaxel but not from the escalation of doxorubicin dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer.** *Proc ASCO* 1998;**Abstract 390**.

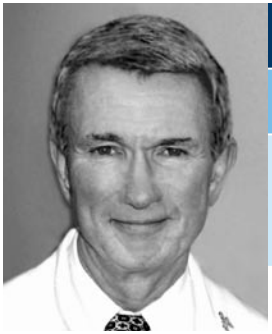
Martin M et al. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Olivotto IA et al. **Population-based validation of the prognostic model ADJUVANT! for early breast cancer.** *J Clin Oncol* 2005;23(12):2716-25. **Abstract**

Peele PB et al. **Decreased use of adjuvant breast cancer therapy in a randomized controlled trial of a decision aid with individualized risk information.** *Med Decis Making* 2005;25(3):301-7. **Abstract**

Piccart-Gebhart MJ. **Treatment guidelines for systemic adjuvant therapy of breast cancer: Strengths and weaknesses.** San Antonio Breast Cancer Symposium 2005;**Abstract P1**.

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. **Abstract**



INTERVIEW

Robert Livingston, MD

Dr Livingston is Professor of Medicine and Oncology at Arizona Cancer Center in Tucson, Arizona.

CD 2, Tracks 2-15

Select Excerpts from the Interview

CD 2, Track 3

DR LOVE: Could you describe the SWOG neoadjuvant trial presented at ASCO 2006?

DR LIVINGSTON: SWOG-S0012 was designed for women with locally advanced and inflammatory breast cancer and randomized patients to AC followed by weekly paclitaxel (T) versus weekly doxorubicin and daily oral cyclophosphamide with G-CSF followed by T. The eligibility criteria were fairly standard. Most typically, patients with locally advanced breast cancer had a tumor measuring five centimeters or greater, but they could also be enrolled if they had Stage III disease by other criteria. For patients with inflammatory

disease, the diagnosis was made on a clinical basis with pathologic confirmation. Standard treatment for these patients in the community has been anthracycline-based neoadjuvant chemotherapy.

Our primary endpoint in the study was pathologic complete response, and the only variable studied was the method of administration of AC because the paclitaxel was given in the same way to all patients.

The MD Anderson group and others have shown that pathologic complete response (pCR) is a very good predictor of long-term outcome for these patients. It is defined as the disappearance of all evidence of invasive disease under the microscope when the pathologist examines the specimen after completion of chemotherapy.

At ASCO 2006, my colleague Dr Georgiana Ellis presented the data for the first 265 out of 398 patients entered (Ellis 2006). The pCR was 31 percent for the continuous arm — the experimental arm — versus 19 percent for the standard arm (3.1), which was statistically significant.

As you might expect, the toxicity data indicated less myelosuppression for the experimental arm, and that's because those patients received prophylactic G-CSF. In terms of other toxicities, more stomatitis and hand-foot syndrome occurred with the experimental regimen. More nausea, vomiting and myelosuppression occurred on the standard arm. Both regimens were well tolerated, and more than 95 percent of the patients entered on the study were able to go to surgery.

We will be conducting another analysis, but it seems likely that the continuous administration of AC is better than the every three-week administration. That furnishes, of course, a strong rationale for trying to finish SWOG-S0221, the current adjuvant trial for patients with node-positive disease, in which the randomization basically involves every two-week or dose-dense therapy.

CD 2, Track 5

DR LOVE: In SWOG-S0012, was there any correlation between the ER-status or HER2-status and outcome?

DR LIVINGSTON: Patients were eligible regardless of their ER and HER2 status. This trial preceded the release of information about the value of adjuvant trastuzumab, so none of the patients received trastuzumab.

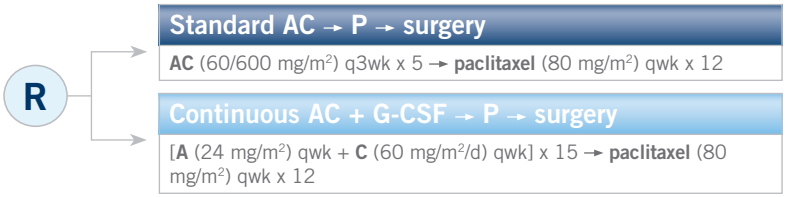
When we did subgroup analyses, we saw that the pathologic complete response rate for patients with hormone receptor-negative disease — ER-negative and PR-negative — was strikingly higher for those patients in the experimental versus the standard arm, 43 versus 26 percent (3.1). Although a trend favors the experimental therapy for patients with hormone receptor-positive disease, the pathologic complete response rate in the experimental arm is only 14 percent versus nine percent in the standard arm.

These results are in line with what most other investigators have reported: The benefit in terms of the pathologic complete response rate with anthracycline-based chemotherapy, with or without a taxane, appears to be much more striking among the patients with hormone receptor–negative disease (3.1).

When we examined data from the patients with HER2-positive disease, which was 28 percent of those entered on the trial, interestingly, we saw no evidence of an advantage for the continuous arm versus the standard arm. Both arms had a pathologic complete response rate of approximately 25 percent. The other group of patients who appeared to show a striking benefit were those with inflammatory breast cancer, which was a third of the patients entered on the study.

3.1 **Standard AC Followed by Weekly Paclitaxel versus Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Locally Advanced or Inflammatory Breast Cancer**

Protocol ID: SWOG-0012
Accrual: 372 (265 evaluable for primary outcome)



Pathologic complete response by disease type and ER status

Treatment arm	All	ER-positive	ER-negative	LABC	Inflammatory
Standard AC → P (n = 132)	19%	9%	26%	20%	12%
Continuous AC + G → P (n = 133)	31%	14%	43%	25%	32%

Unadjusted $p = 0.03$; adjusted for disease type, ER, $p = 0.02$; G = G-CSF

SOURCE: Ellis GK et al. *Proc ASCO* 2006;**Abstract LBA537**.

CD 2, Track 7

DR LOVE: What is your opinion regarding the clinical use of nanoparticle albumin-bound (*nab*) paclitaxel? Do you feel we need trials to demonstrate that it's equivalent to or better than paclitaxel, given the advantage of the infusion time and the lack of premedication in all clinical situations?

DR LIVINGSTON: We have a fair amount of data, both from preclinical systems and from clinical trials, to suggest that the drug is superior to paclitaxel, independent of its ability to prevent allergic reactions.

A reputable randomized study published in the *Journal of Clinical Oncology* compared *nab* paclitaxel to paclitaxel on an every three-week schedule for women with metastatic breast cancer (Gradishar 2005; [3.2]). That study shows a magnitude of improvement in terms of response rate and time to progression, which is fairly similar to the magnitude of difference that was demonstrated in ECOG-E2100 between paclitaxel alone and paclitaxel with bevacizumab (Miller 2005).

However, the paclitaxel with bevacizumab trial was accepted with great enthusiasm — legitimately — and presented in a fairly frenzied special oral session at ASCO, while the trial involving *nab* paclitaxel versus paclitaxel was basically disregarded.

In my own practice, I'm prescribing patients paclitaxel because of the cost differential. If cost were not an issue, I would stop administering paclitaxel today and substitute it with *nab* paclitaxel.

3.2

Pivotal Phase III Trial of *Nab* Paclitaxel versus Paclitaxel: Efficacy Data

Parameter	*Nab* paclitaxel* (n = 229)	Paclitaxel† (n = 225)	*p*-value
Complete and partial response			
All patients	33%	19%	0.001
First-line therapy	42%	27%	0.029
Second-line or greater therapy	27%	13%	0.006
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
All patients	65.0 weeks	55.7 weeks	0.374
Second-line or greater therapy	56.4 weeks	46.7 weeks	0.024

* *Nab* paclitaxel 260 mg/m^2 every three weeks without premedication
† Paclitaxel 175 mg/m^2 every three weeks with premedication

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

CD 2, Track 8

DR LOVE: Can you discuss more about what we know in terms of clinical research with neoadjuvant bevacizumab and comment on the study reported by Sandy Swain's group at the NCI (Wedam 2006)?

DR LIVINGSTON: The interesting part of that study, of course, has to do with the run-in phase, during which the patients receive bevacizumab alone. Investigators performed serial tumor sampling and were able to demonstrate down-modulation of appropriate targets for angiogenesis. It was a nice in vivo demonstration that the drug does have an effect on the expected target, the VEGF receptor.

The other observation from the Swain trial, which she has perhaps downplayed a little bit, was the difficulty with postoperative complications in patients who had received bevacizumab up until a few weeks prior to surgery. Certainly that provided a take-home message, together with the colorectal experience, to the rest of us that this drug does stick around for several weeks.

CD 2, Track 12

DR LOVE: What are your thoughts about TOPO II and response to systemic therapy? Do you think it's ready for prime time?

DR LIVINGSTON: I believe we need more data, but the data will be coming very soon. A completed Southwest Oncology Group trial (9313) is in press in the *Journal of Clinical Oncology*.

Importantly, all the patients in that study received AC. In that study, Larry Norton's single-agent sequenced A → C was compared to concurrent AC, and no difference appeared between the two, which is rather "ho-hum."

However, we have tumor material from all those patients who received an anthracycline and have long-term follow-up available. I suspect that data will be presented soon on the correlation between the presence or absence of TOPO II amplification and benefit from an anthracycline-based regimen.

We should see no difference between the two arms, but we would expect to see a tremendously better result in patients with TOPO II amplification who are receiving an anthracycline than in patients without TOPO II amplification.

DR LOVE: What about that issue for the patient with HER2-positive disease?

DR LIVINGSTON: Certainly the data from BCIRG 006 that Dennis Slamon presented in December of last year at San Antonio suggest that an anthracycline-based regimen is superior for women with HER2-positive disease if they have TOPO II amplification and is not superior if TOPO II is not amplified (Press 2005; Slamon 2005). Thirty-five percent of the patients have TOPO II amplification.

Remember that although those curves looked impressive, the follow-up and number of events are not yet sufficient for the *p*-value to be statistically significant. We need more information.

CD 2, Track 13

DR LOVE: What chemotherapy would you consider for patients with triple-negative, node-positive disease?

DR LIVINGSTON: Patients with triple-negative, node-positive disease are perhaps the single greatest therapeutic challenge right now. In terms of management off study, I am offering those patients aggressive treatment. I'm offering them our metronomic version of AC with growth factor support followed by weekly paclitaxel. Having said that, I don't believe this is enough.

This is a patient population that cries out for well-designed therapeutic trials. We know, for example, that those patients with triple-negative disease appear to have a fairly high incidence of overexpression of the EGF receptor by immunohistochemistry.

Does that mean that they might benefit from the administration of targeted therapy, such as either a monoclonal antibody or a small molecule directed at the EGF receptor? We simply don't know the answer.

The second issue that is hinted at, especially by work out of the University of Chicago group, is that even women with the "sporadic" triple-negative cancers, setting aside the BCRA1 mutations, appear to have a fairly high incidence of down-regulation of BRCA1 function, meaning that their cancer cells are relatively sensitive to agents that produce DNA injury and require DNA repair. Remember, BRCA1 is a DNA repair-causing gene.

From data that were presented in San Antonio, in cell lines derived from such patients, the platinums appear to be quite active (Nanda 2005). It may be that triple-negative patients with high-risk disease should receive a platinum. It may be that those patients should receive an EGF receptor-targeted drug. But would I give them either one of these outside of a study right now? No, we will have to conduct studies to find out.

CD 2, Tracks 14-15

DR LOVE: In general, how would you approach the choice of chemotherapy and the question of bevacizumab for a patient with moderately symptomatic, triple-negative metastatic disease?

DR LIVINGSTON: We do not have hard evidence that one chemotherapy regimen is better than another chemotherapy regimen for the patient you just described.

I believe most of us would be inclined to use anthracycline-based therapy if the patient hadn't received it previously or if it had been more than a year since completion of her adjuvant treatment.

Many of us would be inclined to use a combination rather than a single agent, and I'm one of those because these patients have particularly aggressive disease and tend to experience short times to progression. The delay in time to progression that one sees with combinations may be important for patients with this type of disease.

At both my earlier institutional affiliation in Seattle and in the Southwest Oncology Group, we have been exploring antitubulin combinations, investigating combinations of vinorelbine and a taxane, either docetaxel or paclitaxel.

Most recently, I've been involved in a trial with *nab* paclitaxel and vinorelbine. Those combinations are active. What I can honestly tell you is they're probably not more active than somebody else's choice of docetaxel and capecitabine or gemcitabine-based therapy.

DR LOVE: What about bevacizumab?

DR LIVINGSTON: The only patient right now, outside of a study, for whom I would probably urge the use of bevacizumab is this individual you've just described, because we do have evidence that the taxanes are as active, if not more active, than any other drugs. We do have evidence that weekly paclitaxel, which is the best way to administer the drug, is potentiated by the use of bevacizumab.

And we do have, in the triple-negatives, a group of patients for whom, right now, no targeted therapy is available, except bevacizumab, that we can justify on the basis of a randomized trial. So if I were seeing such a patient in the clinic today, I would talk to her about a taxane-based treatment program, in all likelihood, and I would recommend that she also receive bevacizumab. ■

SELECT PUBLICATIONS

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

Ellis GK et al. **SWOG 0012, a randomized phase III comparison of standard doxorubicin (A) and cyclophosphamide (C) followed by weekly paclitaxel (T) versus weekly doxorubicin and daily oral cyclophosphamide plus G-CSF (G) followed by weekly paclitaxel as neoadjuvant therapy for inflammatory and locally advanced breast cancer.** *Proc ASCO* 2006;**Abstract LBA537**.

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**

Lyons JA et al. **Toxicity results and early outcome data on a randomized phase II study of docetaxel ± bevacizumab for locally advanced, unresectable breast cancer.** *Proc ASCO* 2006;**Abstract 3049**.

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**.

Nanda R et al. **BRCA1 promoter methylation confers sensitivity to cisplatin in vitro.** San Antonio Breast Cancer Symposium 2005;**Abstract 4055**.

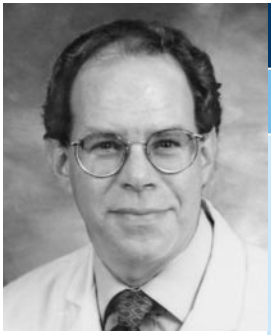
Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (Herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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

Walshe JM et al. **Effect of bevacizumab (BV) and chemotherapy (CT) on serum levels of vascular endothelial growth factor receptor-2 (sVEGFR-2) in patients with inflammatory and locally advanced breast cancer.** *Proc ASCO* 2006;**Abstract 13003**.

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

Yang SX et al. **Response in gene expression profile to bevacizumab treatment in patients with inflammatory and locally advanced breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 2028**.



INTERVIEW

Harry D Bear, MD, PhD

Dr Bear is Chairman of the Division of Surgical Oncology, Professor of Surgery and Microbiology and Immunology and Walter Lawrence Jr Distinguished Professor in Oncology at Massey Cancer Center at the Virginia Commonwealth University School of Medicine in Richmond, Virginia.

CD 2, Tracks 16-29 — CD 3, Tracks 1-5

CD 2

Track 16 Introduction

Track 17 Background and results of NSABP neoadjuvant trial B-27

Track 18 NSABP-B-27 post-hoc analysis: Benefit from docetaxel based on response to AC

Track 19 Pathologic complete response as an endpoint in NSABP-B-27

Track 20 Selection of a neoadjuvant chemotherapeutic regimen

Track 21 Postoperative treatment for patients with residual disease after neoadjuvant chemotherapy

Track 22 NSABP-B-40 neoadjuvant trial: Docetaxel alone or with capecitabine or gemcitabine before AC with or without bevacizumab

Track 23 NSABP-B-40 correlative science program

Track 24 Potential antitumor effects of bevacizumab

Track 25 Comparison of paclitaxel and docetaxel

Track 26 Sentinel lymph node biopsy for patients undergoing neoadjuvant therapy

Track 27 Proposed NSABP neoadjuvant trial evaluating AC followed by weekly paclitaxel with trastuzumab, lapatinib or the combination

Track 28 Development of the Onco*type* DX multigene assay

Track 29 Clinical utility of the Onco*type* DX assay

CD 3

Track 1 Adjuvant hormonal therapy for postmenopausal patients with hormone receptor-positive disease

Track 2 Side effects and tolerability of adjuvant aromatase inhibitors versus tamoxifen

Track 3 Study of Tamoxifen and Raloxifene (STAR) for postmenopausal women at high risk for breast cancer

Track 4 Clinical trials of aromatase inhibitors for prevention or treatment of DCIS

Track 5 Historical development of trastuzumab for HER2-positive disease

Select Excerpts from the Interview

CD 2, Tracks 17-18

DR LOVE: Can you review the design and key findings from NSABP-B-27?

DR BEAR: NSABP-B-27 was the successor to NSABP-B-18, which was a randomized trial of four cycles of preoperative versus postoperative AC (Wolmark 2001). In NSABP-B-27 the objective was to determine whether adding four cycles of either preoperative or postoperative docetaxel to four cycles of preoperative AC would improve patient outcomes (Bear 2006; [4.1]).

We also wanted to correlate the addition of preoperative docetaxel with improvements in response, particularly pathologic response in the breast, which we had shown in NSABP-B-18 to be the most powerful predictor of patient outcomes (Wolmark 2001). We found that preoperative docetaxel almost doubled the pathologic complete response rate in the breast (Bear 2003; [4.1]).

It is surprising that we did not see a statistically significant improvement in either disease-free or overall survival with the addition of preoperative or postoperative docetaxel (Bear 2006). I believe there are a number of potential reasons. Some have attributed it to the concurrent use of tamoxifen, but I am not sure that is entirely correct. Concurrent tamoxifen may have somewhat degraded the chemotherapy's effects, but we saw no interaction between hormone receptor status and the effect of docetaxel (Bear 2006).

DR LOVE: The issue of responsiveness to chemotherapy based on ER status is a hot topic. Where do you think the NSABP-B-27 data fit in?

DR BEAR: The NSABP-B-27 data are a little problematic because we don't have the hormone receptor status on all patients. From those patients for whom we had the pretreatment hormone receptor status, our data were like the TAC trial. The patients with either ER-negative or ER-positive disease had a significantly higher pathologic complete response rate with docetaxel and AC than with AC alone (Bear 2003).

In a subset analysis of NSABP-B-27, we also analyzed the benefit of docetaxel according to whether the patients responded clinically to AC. We found that patients who did not respond to AC did not benefit from docetaxel, indicating that those were probably patients with chemoresistant disease and that the addition of another chemotherapy drug probably didn't help much (Bear 2006).

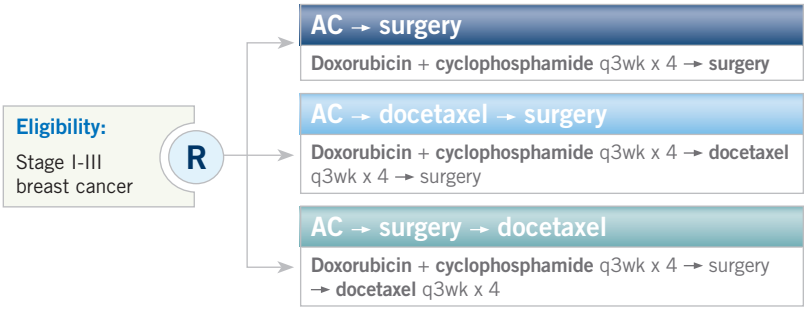
Among patients who had a clinical complete response to AC, we also did not see much benefit from docetaxel, indicating that those are probably patients with good-prognosis chemoresponsive disease. The group of patients who had a clinical partial response to AC was the most interesting. Those patients showed a significant improvement in disease-free survival with the addition of preoperative docetaxel (Bear 2006).

One might ask why those patients who had a clinical partial response to AC didn't benefit from postoperative docetaxel (Bear 2006). I suspect it's because of the delay in the administration of the second chemotherapy regimen. The delay between completing AC and starting docetaxel may have negated the benefit by allowing the regrowth of metastatic clones.

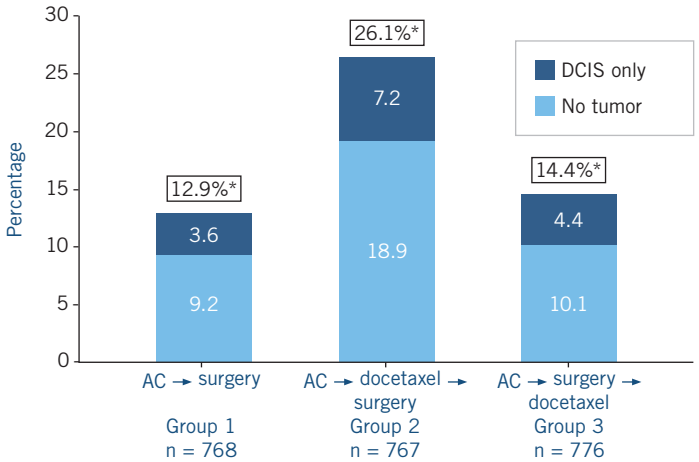
4.1

NSABP-B-27: Sequential Preoperative or Postoperative Docetaxel Added to Preoperative Doxorubicin and Cyclophosphamide for Operable Breast Cancer

Protocol ID: NSABP-B-27
Accrual: 2,411 (Closed)



Pathologic Tumor Response at the Time of Surgery



*$p < 0.0001$ for testing percentage of patients with pathologic complete response in group 2 (after doxorubicin and cyclophosphamide [AC] plus docetaxel) versus group 1 and 3 combined (after AC), adjusted for age, clinical tumor size, and clinical nodal status.

SOURCE: Bear HD et al. *J Clin Oncol* 2006;24(13):2019-2027. **Abstract**

CD 2, Track 20

DR LOVE: What is a reasonable approach to neoadjuvant chemotherapy outside of a study?

DR BEAR: For a patient who has been chosen for neoadjuvant treatment because of a large tumor, I would use an anthracycline-with-taxane-based

regimen. Some people use TAC in this situation, although we have no data with neoadjuvant TAC. I would choose a sequential regimen, such as AC followed by docetaxel, FAC followed by weekly paclitaxel or weekly paclitaxel followed by FAC.

I believe waiting to administer the additional treatment postoperatively offers no advantage and potentially carries a disadvantage. For most of the patients who really need neoadjuvant chemotherapy, I believe there is nothing wrong with committing them to an aggressive treatment course, as we would a patient with node-positive disease.

CD 2, Track 22

DR LOVE: Can you talk about the new NSABP-B-40 neoadjuvant trial?

DR BEAR: NSABP-B-40 (4.2) has evolved over a long period of time. We were hampered by not knowing the results of NSABP-B-27, but we wound up using AC followed by docetaxel as the control regimen.

From the very beginning we wanted to evaluate the effect of adding a biologic response modifier. We observed many agents over the period of years this trial has been developed, and each one did not pan out to have the activity that we thought indicated it would be useful. Bevacizumab has come along recently as a promising drug not only in the metastatic setting (Miller 2005) but also in the locally advanced neoadjuvant setting.

We are now poised to take a number of actions with NSABP-B-40 (4.2). One is to examine docetaxel combined with capecitabine or gemcitabine as a potential way to increase the response rate and improve patient outcomes. Another is to add bevacizumab to chemotherapy for half of the patients in the three different chemotherapy groups.

We will administer docetaxel or docetaxel doublets first, which is different from our previous design and is mainly being done to take advantage of the documented synergy between a taxane and bevacizumab. It will also allow us to stop bevacizumab two months or so before surgery so we don't run into surgical complications as a result of angiogenesis inhibition.

NSABP-B-40 will involve docetaxel, docetaxel with capecitabine, or docetaxel with gemcitabine administered every three weeks for four cycles followed by AC for four cycles. Bevacizumab will be used during the first six cycles of chemotherapy, and then those patients who are randomly assigned to preoperative bevacizumab will also receive 10 cycles of postoperative bevacizumab.

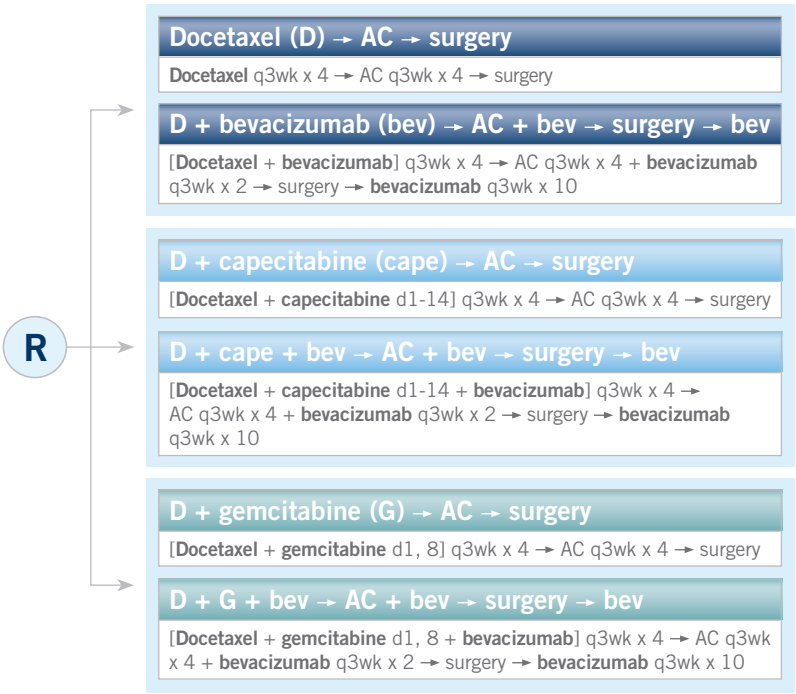
One of the exciting things about this study is the attempt to further understand the mechanism of action of bevacizumab. We have evidence that macroscopic tumor shrinkage may be synergistic between bevacizumab and chemotherapy, and the NCI showed nicely that cancer cells express VEGF receptor and the phosphorylation of that receptor is dramatically downregulated in

patients who respond to bevacizumab, so there may be a significant effect on the tumor cells directly and on the tumor's blood supply.

4.2

Phase III Randomized Trial of Six Neoadjuvant Regimens in Patients with Palpable and Operable HER2-Negative Breast Cancer

Protocol IDs: NSABP-B-40
Target Accrual: 1,200



Eligibility:

- Tumor ≥ 2 cm
- HER2-negative breast cancer

Patients with ER-positive and/or PR-positive disease receive a minimum of five years of hormonal therapy.

SOURCE: NCI Physician Data Query, December 2006.

CD 2, Track 28

DR LOVE: Another area of research in the NSABP that I wanted to ask you about was the Onco*type* DX assay.

DR BEAR: The Onco*type* DX assay was developed through a joint effort of Genomic Health and NSABP. It required a number of steps, one of which was to figure out how to measure gene expression in paraffin-fixed tissue.

Once that was worked out, the next step was to determine whether we could find a limited number of genes that when combined could be used as a prognostic indicator for patient outcomes (Paik 2004).

To do that, we went back to NSABP-B-14, a trial in which patients were randomly allocated to receive either tamoxifen alone or no treatment. All the patients in NSABP-B-14 had ER-positive, node-negative disease. Then the assay was validated in another group of patients who were treated with tamoxifen. It has also been validated in a separate group of patients not in the trial.

In practical terms, for a patient with a hormone-responsive, small to moderate-size tumor faced with the decision about taking hormonal therapy alone or in combination with chemotherapy, we have a way to measure their residual risk and the likelihood they will derive a benefit from chemotherapy (Paik 2004, 2006).

In our working group, we are talking about applying this kind of profiling to patients with node-positive disease. It's not clear that just because a patient has node-positive disease she will necessarily have a bad outcome or benefit from chemotherapy. We're talking about our next generation of what we used to call "node-positive trials."

We are approaching the time when we will consider trials for patients with high-risk disease. Those trials would include patients with negative nodes and a high recurrence score, and they may exclude patients with positive nodes and a low recurrence score. I believe Soon Paik is in the process of evaluating some of our trials for patients with node-positive disease to determine whether we can in fact identify those with node-positive disease who have a low risk.

DR LOVE Gary Lyman, with others, examined the economics of the Onco*type* DX and found it to be cost effective. For patients at low risk, you can avoid the cost of chemotherapy and, conversely, for patients at high risk who choose chemotherapy, you can significantly reduce the risk of recurrence and the subsequent cost of treatment.

DR BEAR: Chemotherapy can cost $20,000 to $30,000, whereas the assay is $3,500. It requires a careful analysis of how many patients forego chemotherapy as a result of the assay and the money you save to offset the cost of performing the tests in patients who do receive chemotherapy. From a noneconomist's perspective, that is, someone who is not an expert in cost effectiveness, it does seem logical that it would be cost effective, but it takes a more careful analysis to prove it.

CD 3, Tracks 1-2

DR LOVE: What has been your usual approach in terms of adjuvant hormonal therapy for postmenopausal patients?

DR BEAR: By and large, postmenopausal patients who do not already have osteoporosis are receiving aromatase inhibitors up front. The ATAC results are

difficult to dispute. With patients who have been on tamoxifen for a year, I haven't jumped to switching them to an aromatase inhibitor.

I will probably follow the paradigm of some of the other trials and leave them on tamoxifen for two or three years, then I'll switch them over. I believe they will obtain some bone-density benefit by staying on tamoxifen for a while and start out at a better baseline when we switch them over to an aromatase inhibitor.

NSABP-B-42 will address the question of duration of hormonal therapy. It will examine the group of patients who have received five years of either a combination of tamoxifen and an aromatase inhibitor or an aromatase inhibitor alone. The trial will determine whether those patients should receive an aromatase inhibitor for another five years. It's a five- versus 10-year question, reminiscent of the NSABP-B-14 rerandomization.

DR LOVE: What is your opinion about the safety and tolerability of the aromatase inhibitors compared to tamoxifen?

DR BEAR: The aromatase inhibitors bring some advantages compared to tamoxifen in terms of the risk of uterine cancer, which is not an issue if a woman has had a hysterectomy. The concerns about osteopenia and osteoporosis are probably the biggest downsides to the aromatase inhibitors. Monitoring or treatment with bisphosphonates is required to limit the morbidity. The aromatase inhibitors have other side effects. I have had a number of patients who cannot tolerate them because of the muscle aches, et cetera. We can always go back to tamoxifen, if they are willing. The aromatase inhibitors may cause fewer or less severe hot flashes, although they still cause them. ■

SELECT PUBLICATIONS

Bear HD et al. **Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2006;24(13):2019-27. **Abstract**

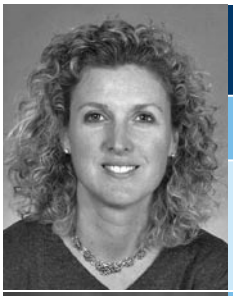
Bear HD et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

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 conducted by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 3**.

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Wolmark N et al. **Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18.** *J Natl Cancer Inst Monogr* 2001;(30):96-102. **Abstract**



ROUNDTABLE DISCUSSION: MOLECULAR BIOLOGY 101

Lisa Carey, MD

Dr Carey is Associate Professor in the Hematology and Oncology Clinical Research Program at UNC Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Jenny C Chang, MD

Dr Chang is Associate Professor at the Breast Center at Baylor College of Medicine in Houston, Texas.

CD 3, Tracks 6-24

Track 6 Introduction

Track 7 A molecular taxonomy of breast cancer

Track 8 Changes in molecular tumor classification over time

Track 9 Development of the intrinsic list of genes comprising the molecular portraits of breast cancer

Track 10 Biological and clinical characteristics of the five tumor subtypes

Track 11 Distribution of tumor subtypes in breast cancer

Track 12 Molecular profiles as prognostic and predictive factors

Track 13 Molecular profiles as predictors of general chemotherapy resistance or sensitivity

Track 14 Development of molecular signatures predictive of response to specific chemotherapeutic agents

Track 15 Biologic distinctions among HER2-positive tumors

Track 16 cMYC as a predictor of response to trastuzumab

Track 17 TOPO II as a predictor of response to anthracyclines

Track 18 Receptor cross talk and potential changes in ER or HER2 phenotype

Track 19 Clinical trial strategies with neoadjuvant hormonal therapy

Track 20 NSABP-B-40 neoadjuvant trial: Docetaxel alone or with capecitabine or gemcitabine before AC with or without bevacizumab

Track 21 Proposed neoadjuvant trial of paclitaxel with trastuzumab, lapatinib or the combination

Track 22 Potential synergy between trastuzumab and lapatinib

Track 23 Proposed CALGB neoadjuvant trial for patients with triple-negative disease

Track 24 Future efforts to identify patients who will or will not benefit from chemotherapy

CD 3, Tracks 7-9

DR LOVE: Lisa, can you review the landmark work by your colleague Charles Perou and others on the molecular classification of breast cancer?

DR CAREY: It turns out that molecular portraits of breast cancer differ from one type to another. At least five subtypes, and probably more, exist.

The seminal paper on this topic was coauthored by Chuck Perou and Therese Sørlie. It was called "Molecular Portraits of Human Breast Tumours." They asked simple questions: Can you identify a subset of genes in a gene expression array that seem to be more altered in one group than another group of breast cancers? Is breast cancer a range of different diseases, or are clusters identifiable (Perou 2000)?

They performed cluster analysis to identify whether groups of breast cancer existed. They started with a relatively small dataset of fewer than 100 samples (Perou 2000). They asked: Which genes are the most altered between cancers but not altered within cancers?

Within that dataset, a group of breast cancer samples were collected before and after neoadjuvant chemotherapy. They said, "We want to eliminate genes that may have changed in the same woman, before and after doxorubicin, and keep the genes that are the most different between cancers" (Perou 2000).

They ended up with about 500 genes that met those criteria. About a fourfold difference was identified between one cancer and another, and they tended to stay the same within a cancer. That's where the 496 genes — what's called the intrinsic list — came from (Perou 2000).

The five subtypes we talk about most commonly include the two luminal subtypes — luminal A and luminal B, the basal-like subtype (Perou 2000; Sørlie 2001), the HER2 subtype, which is what we now call the HER2-positive/ER-negative subtype, and then the unclassifiable group that's called the normal-like type, probably because there was too much stroma involved to categorize them effectively (Perou 2000; Sørlie 2001).

These profiles have been replicated in multiple independent data sets. They exist regardless of treatment and outcome, which is not to say they don't have prognostic implications. They do, and that's also been shown in multiple independent datasets.

If there were no prognostic relevance of these subtypes, it wouldn't change their value. I don't believe they're the best way to prognosticate, and they weren't developed for prognostication. Their value is in their ability to biologically define the different diseases under the umbrella of breast cancer.

DR CHANG: I believe that's absolutely true — the molecular classification just tells you the different subtypes of breast cancer. For me, what would be interesting to determine is whether all these subtypes come from the same cell of origin.

In terms of what we know, there are five broad categories, and maybe more, perhaps, in the triple-negative groups. There may be more than the

basal type, and there may be different types within that.

CD 3, Track 10

DR LOVE: Can you review the subtypes in terms of HER2, ER and other biological and clinical characteristics?

DR CAREY: Luminal A and luminal B are the two ER-positive subtypes. The luminal As tend to have a higher expression of the ER and ER-regulated genes compared to the luminal Bs, which tend to have a lower expression of ER and related genes (Sørlie 2001).

The HER2-positive, ER-positive subtypes tend to fall into the luminal B category, which tends to have a higher expression of the proliferative gene clusters.

DR LOVE: Why are they called "luminal"?

DR CAREY: The gene expression pattern they most resemble from the normal epithelial component is the luminal epithelial cells. The basal-like subtypes, similarly, have a crude resemblance to the expression patterns of the basal epithelial cells of the breast (Perou 2000).

The basal-like subtype we call the triple-negatives in the clinical scenario because they're usually low in ER and its related genes and low in HER2. When we conduct clinical assays, most ER-negative, PR-negative, HER2-negative breast cancers are basal-like. The proliferative gene cluster is usually high in this subtype. The HER2 subtype is high in the genes that are related to HER2 expression and usually low in the ER-related genes (Perou 2000).

DR CHANG: Work that Craig Allred has been doing indicates that the same classification holds true for DCIS. Considering the natural evolution of the disease, DCIS has the same five subgroups, and the fact that DCIS has a similar molecular profile as invasive cancer is extremely interesting.

CD 3, Track 12

DR LOVE: Can you review what we know about the mechanism of action of chemotherapy?

DR CHANG: Essentially, chemotherapy affects dividing cells as well as the apoptotic pathway. A cancer cell proliferates, grows and divides because it can beat the apoptotic death signals. Chemotherapy targets cells that divide quickly and, therefore, there will be an increase in apoptosis affecting primarily dividing cells.

The apoptotic pathway, primarily, is the PI3 kinase AKT pathway. There are several upstream receptors and ligands that feed into this pathway. By and large, chemotherapy has a shotgun approach in affecting this pathway, and the apoptotic death signals will affect most dividing cells. That is why you have nonspecific toxicities associated with chemotherapy, including alopecia, GI toxicity, et cetera.

The trick now is whether we can find specific portraits that would distinguish different tumors so that they can receive specific therapeutic agents.

We have completed a study involving approximately 120 patients who have been randomly assigned to receive either a taxane or an anthracycline. The data are not published, but the

portraits are very different. We have a nice, robust signature now for taxanes, as well as for anthracyclines, and they're different.

CD 3, Track 15

DR LOVE: Can you provide an update on HER2-positive breast cancer, focusing on the pathways involved, the interaction with the ER pathway and how trastuzumab and lapatinib affect the cells?

DR CAREY: I consider HER2-driven breast cancer, in a biologic sense, as being at least two different groups. The HER2-positive, hormone receptor-negative group is different from the HER2-positive, hormone receptor-positive group. They both benefit from HER2-targeted treatments, but they are different.

In terms of how HER2 functions, we're obtaining a lot of information from the emerging studies of trastuzumab resistance and the pathways that are important in trastuzumab resistance. The first issue — and I believe lapatinib speaks to this — is whether HER1 is important in acquired HER2 resistance.

The fact that lapatinib shows efficacy in patients with acquired trastuzumab resistance (Geyer 2006; [5.1]), I believe, provides a strong suggestion that the HER1 pathway may be implicated in getting around HER2 signaling. Tumor cells are smart, and they figure out ways to go around our therapeutic interventions.

DR CHANG: A large component of our work is evaluating the crosstalk between the estrogen receptor and HER2. Increasing evidence shows that if you block the HER2 pathway, you can actually upregulate ER, and vice versa. There is crosstalk between the two, and this may be another escape mechanism for trastuzumab resistance.

CD 3, Tracks 16-17

DR LOVE: Jenny, can you discuss cMYC and TOPO II?

DR CHANG: Soon Paik presented his data on cMYC. The bottom-line, take-home message was: If you have HER2-positive and cMYC-positive

5.1

Phase III Randomized Trial of Capecitabine with or without Lapatinib in Women with Previously Treated, HER2-Positive Metastatic Breast Cancer

	Lapatinib + capecitabine (n = 160)	Capecitabine (n = 161)	Hazard ratio (95% CI)	*p*-value*
Median time to progression	36.9 wks	19.7 wks	0.51 (0.35-0.74)	0.00016*
Median progression-free survival	36.9 wks	17.9 wks	0.48 (0.33-0.70)	0.000045*
Overall response rate	22.5%	14.3%	—	0.113†

* Log-rank, one sided; † Fisher exact, two sided

SOURCE: Geyer CE et al. Presentation. *Proc ASCO* 2006. No abstract available

disease, you do well with trastuzumab-based therapies (Kim 2005). This is not the result we expected. cMYC is an oncogene — it basically feeds into the survival pathway. It was expected that if you had cMYC-positive disease, you would do very badly.

In the adjuvant trastuzumab study, however, patients with cMYC-positive disease who received trastuzumab did extremely well. Their chance of relapsing was very low, less than 10 percent (Kim 2005). This was counterintuitive, probably because trastuzumab works through the PI3 kinase AKT survival pathway and, somehow, cMYC is synergistic because it affects the same pathway. That was an unexpected result of the study.

TOPO II is a slightly different story. It is the target for anthracyclines. We know trastuzumab in combination with anthracyclines adversely affects cardiac function and increases cardiotoxicity. Therefore, they wanted to determine whether there were subpopulations of patients receiving trastuzumab who could be spared therapy with anthracyclines.

As presented at the 2005 San Antonio Breast Cancer Symposium, the study demonstrated that, across the board, the nonanthracycline-containing trastuzumab-based regimen was not superior to anthracycline-containing trastuzumab-based therapy. The subset of patients with TOPO II nonamplified disease who received a nonanthracycline-containing regimen, however, did as well as those who received anthracyclines (Slamon 2005; [5.2]).

Whether there is a "smart" population of patients with TOPO II-positive disease who would benefit from anthracyclines and a TOPO II-negative population that could benefit from the absence of anthracyclines is something that needs to be studied.

CD 3, Track 21

DR LOVE: Lisa, can you review the current Intergroup neoadjuvant study and how this relates to translational research?

DR CAREY: In the trial for patients with HER2-positive breast cancer, all patients will receive weekly paclitaxel combined with trastuzumab, lapatinib or both in the neoadjuvant setting. The patients all undergo surgery, and in the postoperative period, they receive dose-dense AC and a year of trastuzumab.

5.2

BCIRG 006: Disease-Free Survival Events in Patients with or without TOPO II Gene Amplification

	TOPO II amplified	TOPO II nonamplified
All patients (n = 744, n = 1,376)	57 (7.7%)	191 (13.9%)
AC → T (n = 227, n = 458)	23 (10.1%)	92 (20.1%)
AC → TH (n = 265, n = 472)	13 (4.9%)	45 (9.5%)
TCH (n = 252, n = 446)	21 (8.3%)	54 (12.1%)

SOURCE: Slamon D et al, on behalf of the BCIRG 006 Investigators. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

The primary endpoint is predicated on the idea that the pathologic complete response rate will be higher for the combination than either single agent alone.

DR LOVE: Do you think people will wait for the data from this study before bringing lapatinib into trials in the adjuvant setting?

DR CAREY: No, I don't think so. Lapatinib is such an interesting drug that the adjuvant trials will be conducted concurrently with the neoadjuvant trials.

We will collaborate with the European trial that José Baselga is conducting, which is called Neo-Aphrodite. It has a similar trial design, except their adjuvant chemotherapy regimen is FEC and the adjuvant biologic therapy is whatever the patient is randomly assigned to in the beginning. They will have patients who will receive a year of lapatinib. In terms of the preoperative portion of the protocols, they're deliberately similar in design. We're trying to dovetail the correlative science component so that each trial can serve as a validation of the other.

CD 3, Track 22

DR LOVE: What do we know about the combination of lapatinib and trastuzumab?

DR CHANG: We have a lot of preclinical data about the synergism between lapatinib and trastuzumab. Our group evaluated MCF-7 HER2-overexpressing xenografts and found that with the combination of lapatinib, trastuzumab and endocrine therapy, in ER-positive disease, the tumors all went away. We had almost a 100 percent response rate with the combination of these targeted molecules.

That is strong evidence of cross talk between these different pathways and that pan-HER inhibition is probably necessary. ■

SELECT PUBLICATIONS

Carey LA et al. **Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study.** *JAMA* 2006;295(21):2492-502. **Abstract**

Geyer CE et al. **A phase III randomized, open-label, international study comparing lapatinib and capecitabine vs capecitabine in women with refractory advanced metastatic breast cancer (EGF100151).** *Proc ASCO* 2006. No abstract available

Kim C et al. **Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

Perou CM et al. **Molecular portraits of human breast tumours.** *Nature* 2000;406(6797):747-52. **Abstract**

Slamon D et al, on behalf of the BCIRG 006 Investigators. **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.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

Sørlie T et al. **Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.** *Proc Natl Acad Sci USA* 2001;98(19):10869-74. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **NSABP-B-42 will evaluate the optimal duration of therapy with an adjuvant aromatase inhibitor.**
   a. True
   b. False

2. **The Breast International Group (BIG) 2-06 randomized study will evaluate the use of trastuzumab versus _____ versus the combination versus sequential therapy in patients with HER2-positive disease who have been treated with chemotherapy.**
   a. Bevacizumab
   b. Lapatinib
   c. Erlotinib
   d. Gefitinib

3. **The Intergroup has proposed a Phase III adjuvant study for patients with HER2-negative, node-positive or high-risk node-negative breast cancer, evaluating AC followed by paclitaxel with or without _____.**
   a. Cetuximab
   b. Trastuzumab
   c. Bevacizumab
   d. Lapatinib

4. **In ECOG-E2100, patients with triple-negative, metastatic breast cancer treated with first-line paclitaxel/bevacizumab showed a significant improvement in progression-free survival compared to those treated with paclitaxel alone.**
   a. True
   b. False

5. **A retrospective analysis of CALGB adjuvant chemotherapy trials for patients with node-positive disease reported by Berry and colleagues demonstrated less antitumor benefit among patients with ER-positive disease compared to those with ER-negative disease.**
   a. True
   b. False

6. **In a Phase III neoadjuvant study of patients with locally advanced or inflammatory breast cancer, the pathologic complete response rate was significantly higher among those receiving standard every three-week AC followed by weekly paclitaxel compared to continuous AC + G followed by weekly paclitaxel.**
   a. True
   b. False

7. **A Phase III study of patients with metastatic breast cancer demonstrated that standard paclitaxel resulted in a higher response rate and time to progression than *nab* paclitaxel.**
   a. True
   b. False

8. **In NSABP-B-27, the addition of four cycles of preoperative docetaxel to four cycles of preoperative AC almost doubled the pathologic complete response rate.**
   a. True
   b. False

9. **In a subset analysis of NSABP-B-27, patients with _____ to AC benefited from the addition of preoperative docetaxel.**
   a. A clinical complete response
   b. A clinical partial response
   c. No response
   d. Both a and b
   e. All of the above

10. **NSABP-B-40 will evaluate the role of neoadjuvant bevacizumab in combination with _____.**
    a. Docetaxel alone
    b. Docetaxel with gemcitabine
    c. Docetaxel with capecitabine
    d. All of the above
    e. None of the above

11. **Which of the following are biologic subtypes of breast cancers?**
    a. Basal-like
    b. Luminal A
    c. Luminal B
    d. Both b and c
    e. All of the above

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

EVALUATION FORM

Breast Cancer Update — Issue 8, 2006

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = Not applicable to this issue of *BCU*

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Robert Livingston, MD	5 4 3 2 1	5 4 3 2 1
Harry D Bear, MD, PhD	5 4 3 2 1	5 4 3 2 1
Lisa Carey, MD	5 4 3 2 1	5 4 3 2 1
Jenny C Chang, 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

Breast Cancer Update — Issue 8, 2006

REQUEST FOR CREDIT — please print clearly

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

Degree:

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

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Research To Practice designates this educational activity for a maximum of 4.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

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

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

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

BCU806

Breast Cancer® UPDATE

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