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Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

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SPECIAL ISSUE

SECOND OPINION OF CASES FROM COMMUNITY PRACTICE WITH DRS VOGEL AND SWAIN

CME Certified

Breast Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging research advancing breast cancer treatment, and incorporate these data into management strategies in the neoadjuvant, adjuvant and metastatic settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Describe the risks and benefits of neoadjuvant and adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen in the setting of ER-positive breast cancer, and discuss these findings with your patients.
- Counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dosing and selection of taxanes with or without anthracyclines, and explain the absolute risks and benefits of these regimens to patients.
- Counsel appropriately selected patients with metastatic disease about evidence-based selection and sequencing of endocrine therapy and chemotherapies, and evaluate the risks and benefits of these agents as either monotherapy or combination regimens.
- Review the emerging data for biologic therapies and explain how these findings should be incorporated into the treatment algorithm for appropriately selected patients with metastatic disease.
- Describe the evidence to support the use of genetic and other molecular markers as prognostic and predictive tools to guide therapy decisions.
- Discuss the impact of standard oncologic interventions on patient quality of life, and offer supportive or alternative management strategies to improve tolerability.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 7 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Smith, Vogel, Swain, Goss and Linden on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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

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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.

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EDITOR'S NOTE

Neil Love, MD

Survivors

survivor |sər vīvər| a person who survives, esp. a person remaining alive after an event in which others have died: *the sole survivor of the massacre.*

Walking through malls, airports and grocery stores in this country, I am often struck by the massive proliferation of the pink ribbon and the impressive power of the breast cancer advocacy movement to garner attention and get things done. When one considers the prevalence of various tumors by age (Figure 1), it becomes evident why a disease that represents less than 10 percent of all cancer mortality has become so top-of-mind to the public.

More than 10 million citizens in the United States are "cancer survivors" — an interesting term that has become a permanent part of our lexicon, even though many of these people will eventually die of this disease and almost all live with concerns and fears about cancer recurrence.

What is particularly striking about these statistics is how the age of incidence and the "lethality" of a tumor type create a formula for survivorship. At one end of the spectrum, we have breast and prostate cancer, with long natural histories — even in many patients destined to succumb to progressive disease — and relatively high "cure" rates. On the other hand, we have lung and pancreatic cancer, where most patients are dead in a couple of years and the pool of survivors is minuscule.

1 US Cancer Prevalence, Incidence and Mortality

Cancer	Prevalence by age				Incidence	Mortality
	All	≤49	50-69	70+		
All	10,495,999	1,476,018	3,902,861	5,117,120	1,444,920	559,650
Breast	2,369,035	240,505	1,020,237	1,108,293	180,510	40,910
Prostate	1,937,808	14,803	639,593	1,283,412	218,890	27,050
Colorectal	1,068,203	49,601	317,900	700,702	153,760	52,180
Lung	354,988	17,395	148,640	188,953	213,380	160,390

SOURCES: National Cancer Institute's SEER Program. Prevalence was calculated using the First Malignant Primary Only for a person. http://seer.cancer.gov; Hayat MJ et al. **Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program.** *Oncologist* 2007;12(1):20-37. Abstract

This has led to an unequal balance, with an eye-opening 4.2 million breast and prostate cancer survivors, yet even these two subpopulations can't be grouped together because there are far more younger survivors of breast cancer who historically have proven to be ready, willing and able to push for change.

The constant threat of recurrence and progression means that most cancer survivors keep an anxious eye on developments in cancer research, despite the recent *NCI Cancer Bulletin* proudly reporting "a 2.1-percent decrease in cancer mortality rates between 2002 and 2004, an approximate doubling of the 1.1-percent decline seen each year from 1993 to 2002." *

These anxious survivors would be dismayed to learn of a recent poll we conducted with the 11 clinical investigators who participated in our breast cancer think tank last summer, suggesting that most experts don't expect a meaningful drop in breast cancer mortality in the next 15 years (Figure 2).

This is not a subject that is frequently discussed. Physicians don't like to be reminded of the shortcomings of their treatment tools, particularly when they spend the day trying to reassure desperate patients, and investigators don't want to constantly revisit the tribulations of obtaining adequate support for cancer research.

As a result, we often accept the outrageous and unacceptable, such as the fact that two years after Rowan Chlebowski's first presentation of the WINS trial data (Chlebowski 2005) demonstrating a 24 percent reduction in cancer recurrence in patients randomly assigned to instruction to lower dietary fat, a follow-up study is not being planned, and Rowan still doesn't even have the funds needed to study the sera of the WINS patients to help figure out what's going on.

Perhaps even more distressing than this somewhat bleak perspective on breast cancer — our research vanguard —

2

Breast Cancer Think Tank Faculty Poll
July 19, 2007

If the current structure, funding base and strategy of clinical breast cancer research remain essentially the same, how will annual US breast cancer deaths change over the next 15 years?

Faculty member	+ 5 years (mean 7%)	+ 10 years (mean 11%)	+ 15 years (mean 16%)
A	0%	1%	2%
B	0%	1-2%	1-2%
C	0%	10%	20%
D	2%	4%	6%
E	3%	5%	10%
F	5%	10%	15%
G	6%	12%	20%
H	5-10%	5-10%	5-10%
I	10%	20%	30%
J	10%	20%	30%
K	10%	25%	35%

SOURCE: Survey of Think Tank Participants, July 19, 2007, Miami, Florida. Howard A Burris III, MD, Harold J Burstein, MD, PhD, Melody A Cobleigh, MD, William J Gradishar, MD, Frankie A Holmes, MD, Joyce O'Shaughnessy, MD, Peter M Ravdin, MD, PhD, Lee S Schwartzberg, MD, Andrew D Seidman, MD, Dennis J Slamon, MD, PhD and George W Sledge Jr, MD

* *www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_102307/page2?cb_email=1*

is the lack of progress in other tumor types (Figure 3) that threaten breast cancer survivors and the rest of us.

So maybe it's time to replace the pink ribbon with a multicolored version that represents the complex spectrum of related neoplasms that currently comprise the profound public health catastrophe that is cancer today.

Perhaps if these 10 million strong and their loved ones unite together regardless of primary cancer, we would see the necessary resources allocated to find quicker solutions to this very grave problem. ■

3

Annual Cancer Mortality by Age

Age	Breast	Lung	Other cancers
All ages	42,000	158,086	356,816
<25 years	16	29	3,149
25-34 years	407	154	3,180
35-44 years	2,716	2,478	10,315
45-54 years	6,365	12,376	31,104
55-64 years	8,267	30,956	56,469
65-74 years	8,338	49,386	83,524
75-84 years	9,644	48,619	109,354
85+ years	6,245	14,088	59,713

SOURCES: Hoyert DL et al. *Natl Vital Stat Rep* 2006;54(13):1-120. **Abstract**; Office of Statistics and Programming, Centers for Disease Control and Prevention. Data Source: NCHS, National Vital Statistics System.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
November 30, 2007

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INTERVIEW

Ian E Smith, MD

Dr Smith is Professor of Cancer Medicine in the Department of Medicine's Breast Unit at The Royal Marsden Hospital, London and Surrey, United Kingdom.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss what we know about preoperative hormone therapy?

DR SMITH: Neoadjuvant endocrine therapy is clinically important in the role of downstaging to avoid mastectomy or perhaps for elderly patients when you're not completely certain if the patient will be fit enough for surgery. Without a doubt, the need for mastectomy is significantly reduced with neoadjuvant endocrine therapy.

Two or three trials have shown that the aromatase inhibitors are more effective than tamoxifen for neoadjuvant treatment (Eiermann 2001; Smith 2005; Cataliotti 2006).

It's not that tamoxifen is ineffective, but the aromatase inhibitors seem to yield higher response rates. More than that, they yield higher breast conservation rates (1.1).

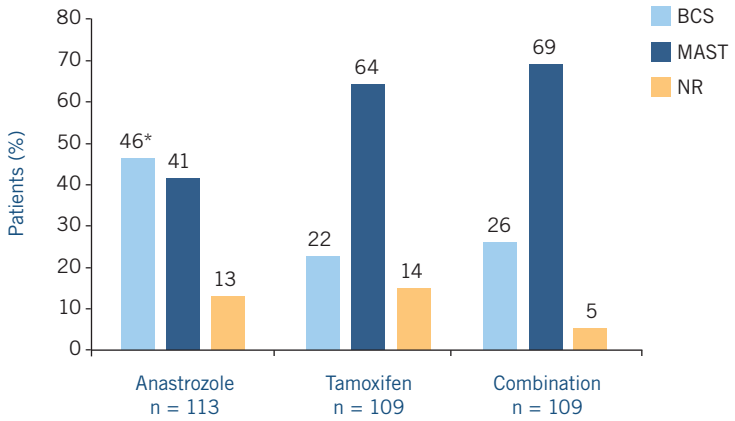
One question is whether this is an underused treatment modality. With postmenopausal women who are in their late fifties or early sixties and have large breast tumors, the use of chemotherapy can be a knee-jerk reaction.

Neoadjuvant endocrine therapy is clearly much more acceptable in terms of quality of life. It's easier to deliver, you see good responses and you achieve your aim of avoiding mastectomy.

The question is whether such a woman loses out by not receiving up-front chemotherapy. Trials to compare the two scenarios have not been conducted, but patients with strongly ER-positive disease respond well to endocrine therapy, and we know that at least some of them may not need chemotherapy. It's even plausible that neoadjuvant endocrine therapy could be a "test bed" for that comparison.

1.1

Breast Conservation and Neoadjuvant Endocrine Therapy: The IMPACT Trial (Anastrozole versus Tamoxifen versus the Combination)



* OR = 2.94 (95% CI; 1.11 to 7.81) (p = 0.03)
BCS = breast-conserving surgery; MAST = mastectomy; NR = Not recorded

".....The third-generation aromatase inhibitors are significantly more effective than tamoxifen in downstaging large breast cancers and reducing the need for mastectomy in post-menopausal women."

SOURCE: Smith IE et al. *J Clin Oncol* 2005;23(22):5108-16. **Abstract**

For example, after treatment with neoadjuvant endocrine therapy, groups of patients with good remission rates could be randomly assigned to trials evaluating whether or not chemotherapy is needed. Such a trial has not yet been conducted.

Track 6

DR LOVE: Where are we in terms of clinical research of fulvestrant?

DR SMITH: It seems to be as good as tamoxifen in up-front trials (Howell 2004). It also seems to be as good as anastrozole, but it isn't any better (Howell 2005).

One question is about the estrogen receptor becoming hypersensitized when it is reset. If the estrogen receptor is exposed to low doses of estrogen for a long time — as, for example, during prolonged aromatase inhibitor therapy — the receptor then seems to become hypersensitive to minute amounts of estrogen.

So the question is whether fulvestrant would work better if you used an aromatase inhibitor concomitantly. Two or three trials address this — one in the UK is called SoFEA (4.1, page 28). Patients who experience relapse on aromatase inhibitors are randomly assigned to fulvestrant or fulvestrant in combination with the aromatase inhibitor to test this question.

Another issue is if prolonged exposure to low estrogen doses hypersensitizes the receptor, then maybe we should be administering these therapies intermittently. So the latest idea being tested in clinical trials is intermittent aromatase inhibitor therapy — for example, three months on, three months off.

In metastatic disease, the tumor marker CA15-3 may be useful in guiding therapy. As soon as levels go down, you stop and wait. Treatment can be restarted when the marker levels go up again to determine whether that approach is superior.

The Breast International Group trial 1-07 — the Study of Letrozole Extension (SOLE) — is like the MA17 trial (Goss 2005), in which people who've been receiving endocrine therapy for five years are switched to either continuous or intermittent (three months on, three months off) aromatase inhibitor therapy.

Track 10

DR LOVE: What is your perception of the clinical role of capecitabine in the bevacizumab era (Miller 2005)? Prior to that time, many breast cancer investigators like yourself were using capecitabine in the metastatic setting.

DR SMITH: In the United Kingdom, the bevacizumab data haven't influenced the use of capecitabine either way. I believe capecitabine is a useful drug for metastatic breast cancer for all the obvious reasons.

Women who've already experienced relapse after standard adjuvant therapy are demoralized, and the problems of returning to all the standard chemotherapy options are obvious. Capecitabine is, by and large, well tolerated.

I believe dose is important. To be technical, the standard dose is 2,500 mg/m^2 in divided doses (ie, 1,250 mg/m^2 twice a day). That dose can cause a lot of toxicity. MD Anderson published data a few years ago (Hennessy 2005; [1.2]) showing outcomes if the dose was reduced a little, to 1,000 mg/m^2 twice daily.

This wasn't a randomized trial — they simply reviewed the data — but the outcome was as good, and the toxicity with capecitabine is dose dependent. We now start patients with a dose of 1,000 mg/m^2 twice daily for 14 days, and most people tolerate that well.

DR LOVE: You published a study describing a series of patients who received that dose of capecitabine (Yap 2007). Was what you saw in terms of efficacy similar to what you would see at a higher dose (1.3)?

1.2

MD Anderson Retrospective Analysis: Capecitabine for Metastatic Breast Cancer

	Starting dose of capecitabine	
	2,500 ± 5% mg/m^2/day (n = 49)	≤2,000 + 5% mg/m^2/day (n = 41)
Response		
Improved disease	18%	24%
Stable disease	35%	37%
Progressive disease	47%	39%
Median time to progression	2.8 months	3.5 months
Adverse events (Grade III/IV)		
Hand-foot syndrome	33%	20%
Diarrhea	13%	3%
Stomatitis	8%	3%
Nausea/vomiting	4%	5%
Neutropenia	3%	9%
Thrombocytopenia	3%	0
Anemia	12%	3%

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

1.3

Retrospective Analysis of Efficacy and Side Effects of Lower-Dose Capecitabine in Patients with Metastatic Breast Cancer

"Our retrospective audit on first line capecitabine monotherapy in metastatic breast cancer using a lower dose of 1,000 mg/m^2 twice daily every 2 out of 3 weeks is consistent with a previously published study using a higher dose and suggests that this is a more practical and realistic schedule. For a subgroup of patients with predominantly soft tissue or bone disease, capecitabine can result in prolonged TTP with minimal toxicity."

SOURCE: Yap YS et al. *The Breast* 2007;16(4):420-4. **Abstract**

DR SMITH: I believe so. In adjuvant therapy with curative intent, the dose is crucial. You don't want to shortchange patients. Once you're dealing with metastatic disease, it's a balance.

Obviously, patients want to stay alive, but patients can stay alive using a little dose reduction — it's hard for me to imagine that a small dose reduction will make a big difference in terms of survival. However, you can see that the lower dose makes a big difference in terms of quality of life.

Track 13

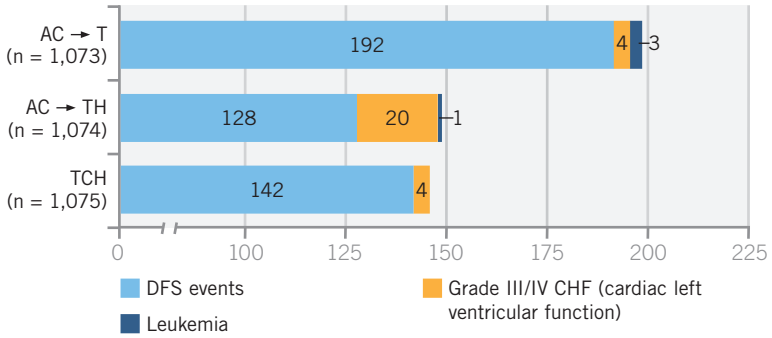
DR LOVE: What is your view of the data presented at the San Antonio meeting from the CIRG trial evaluating TCH (Slamon 2005, 2006)?

DR SMITH: Cardiotoxicity is the only seriously potential problem with trastuzumab. Other than that, it's an extraordinarily safe and easy-to-administer drug. Cardiotoxicity is virtually always associated with anthracycline use — no anthracyclines, no problem.

Occasionally, an elderly patient with bad heart disease might not fare well with trastuzumab, but by and large, if you don't use anthracyclines, you don't have a problem. Many of those data come from the TCH arm of the CIRG trial (1.4).

1.4

BCIRG 006: Disease-Free Survival (DFS) Events and Critical Adverse Events at Second Interim Analysis



"Considering the published data just this month from the US Oncology trial that Steve Jones led that showed that docetaxel and cyclophosphamide outperforms significantly Adriamycin and cyclophosphamide for all breast cancers, and now the recent data we have from our update of BCIRG 006, the question becomes this: What is the role of anthracyclines in the adjuvant treatment of breast cancer?"

— Dennis J Slamon, MD, PhD
San Antonio, December 14, 2006

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Why are we using anthracyclines? I think that's a tough question to answer. I'm sympathetic to the results of the BCIRG 006 trial (1.4). In the second interim analysis, the data appeared convincing that TCH is statistically as good as AC followed by TH.

The problem is that it was an interim analysis. The first interim analysis showed that TCH was inferior, at least in some subgroups. The data have not been published yet, so I don't believe there's enough evidence for the world to say, "OK, let's switch."

I believe we do have enough data to say, "Let's use TCH if you anticipate potential cardiac problems." The main cardiac risk factors from the other trials were age (older than 55 years), history of antihypertensive therapy or at least having hypertension and reduced left ventricular ejection fraction prior to starting therapy — anything less than 55 percent is associated with an increased risk.

One practice in the United Kingdom is to focus on the ejection fraction following AC therapy, and I believe that we have that the wrong way around. We need to check the ejection fraction *before* we start any chemotherapy.

If someone has a left ventricular ejection fraction of 55 percent or less at that stage, I believe we have enough data to support the use of TCH right away because a significant dropout occurs. You have to remember that many patients never even made it into the trials because after AC their ejection fraction was too low (1.5). ■

1.5

Impact of Cardiotoxicity on Initiation and Completion of Adjuvant Trastuzumab in NSABP-B-31/NCCTG-N9831

"Of 3497 patients who had an evaluation of LVEF after doxorubicin and cyclophosphamide therapy, 233 (6.7 percent) had an LVEF that declined at least 16 percentage points from baseline or that declined below the lower limit of normal or had cardiac symptoms during such treatment that would preclude the initiation of trastuzumab therapy...

Of 1159 patients with an adequate LVEF after doxorubicin and cyclophosphamide treatment who began treatment with trastuzumab and have completed therapy, 364 (31.4 percent) discontinued the treatment before 52 weeks. Reasons for discontinuation were...

A confirmed asymptomatic decline in LVEF in 164 (14.2 percent), symptoms of congestive heart failure or other adverse cardiac effect in 54 (4.7 percent)..."

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

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

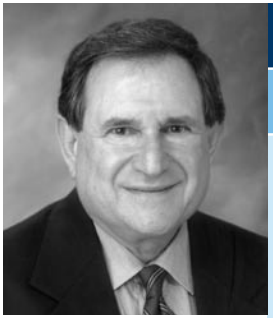
Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive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

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

Sledge GW et al. **Pilot trial of paclitaxel-Herceptin adjuvant therapy for early stage breast cancer (E2198).** San Antonio Breast Cancer Symposium 2001;**Abstract 4**.

Smith IE et al. **Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial.** *J Clin Oncol* 2005;23(22):5108-16. **Abstract**

Yap YS et al. **Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer — How low can you go?** *The Breast* 2007;16(4):420-4. **Abstract**



INTERVIEW

Charles L Vogel, MD

Dr Vogel is Senior Research Advisor for Breast Cancer of Aptium Oncology at Boca Raton Community Hospital's Lynn Regional Cancer Center West Campus and Scientific Advisor at the Cancer Research Network Inc in Boca Raton, Florida.

Tracks 1-22

Track 1 *Second opinion case:* A 74-year-old man initially treated with mastectomy and adjuvant chemotherapy followed by tamoxifen for a node-positive infiltrating ductal carcinoma (IDC) presents with metastatic disease

Track 2 SWOG-S0511 Phase II study of goserelin with anastrozole in advanced male breast cancer

Track 3 Fulvestrant in male breast cancer

Track 4 *Second opinion case:* A 53-year-old woman with a newly diagnosed 2.2-cm, ER-negative, PR-positive IDC associated with lymphovascular invasion and one of 16 positive nodes

Track 5 US Oncology Phase III trial of adjuvant TC versus TAC

Track 6 Weekly compared to every three-week taxane dosing

Track 7 Complications of corticosteroid premedications

Track 8 Randomized Phase II study comparing *nab* paclitaxel to docetaxel

Track 9 Selecting endocrine therapy in the presence of chemotherapy-induced amenorrhea

Track 10 Chemotherapy with bevacizumab for first-line metastatic disease

Track 11 Overview of XCaliBr: Phase II trial of capecitabine and bevacizumab

Track 12 Practical use and future directions with capecitabine in advanced breast cancer

Track 13 *Second opinion case:* A 64-year-old woman with an ER-positive, PR-positive, HER2-negative, node-positive IDC treated with FAC 100 followed by anastrozole

Track 14 Presentation and management of AI-associated arthralgias

Track 15 *Second opinion case:* A 45-year-old premenopausal woman with ER-negative, PR-negative, HER2-negative inflammatory breast cancer and a 5-cm palpable lymph node

Track 16 The evolving role of platinum salts in breast cancer

Track 17 Clinical trial data in triple-negative disease

Track 18 *Second opinion case:* A 53-year-old woman with mild hypertension and a 0.8-cm, poorly differentiated ER-negative, PR-negative, HER2-positive, lymph node-negative breast tumor

Track 19 Treatment options for ER-positive, HER2-positive disease

Track 20 Sorting out the TOPO II puzzle

Track 21 Next-generation adjuvant trials with trastuzumab

Track 22 Subclinical brain metastases in primary HER2-positive breast cancer

Tracks 5-12

Case Discussion 1

A 53-year-old postmenopausal woman who, as part of a clinical trial, received dose-dense AC, nanoparticle albumin-bound (*nab*) paclitaxel and tamoxifen for a 2.2-cm, Grade III, ER-negative, PR-positive, HER2-negative invasive ductal carcinoma with lymphovascular invasion and one of 16 positive nodes. Within a year, she developed a subpectoral mass.

SOURCE: *Meet The Professors* 2007;5(1):4. Case 1. Available at: **www.MeetTheProfessors.com**

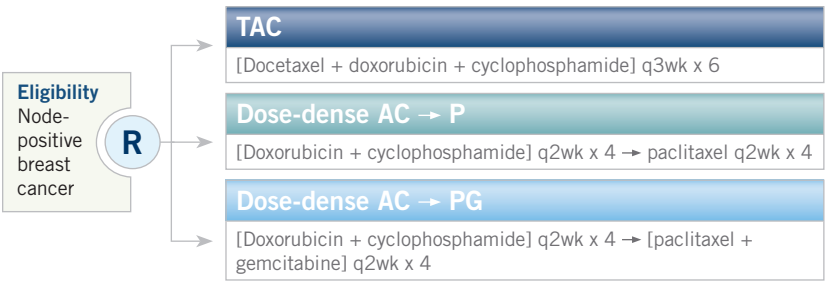
DR LOVE: For a patient like this, what would you have considered for adjuvant chemotherapy?

DR VOGEL: That's a difficult question to answer until we obtain the results from NSABP-B-38 (2.1). Currently, the two major contenders are TAC and dose-dense AC followed by paclitaxel. Those regimens are close in terms of their efficacy in clinical trials (Citron 2003; Martin 2005). The major difference is that in a prospectively defined subset analysis, TAC was statistically significantly better than FAC for patients with hormone receptor-positive disease (Martin 2005).

The problem is that this is a third-generation versus a second-generation protocol. And the data with dose-dense AC followed by paclitaxel are third-generation versus third-generation. However, the CALGB trials have not shown a statistically significant benefit from this regimen for patients with hormone receptor-positive disease. A benefit exists, but it is not statistically significant (Berry 2006). If I were to be a purist and go with the data, I would

2.1 Phase III Randomized Trial of Three Different Adjuvant Chemotherapy Regimens

Protocol IDs: NSABP-B-38, CTSU
Accrual: 4,800 (Closed)



Patients with ER-positive and/or PR-positive disease receive hormonal therapy.

SOURCE: NCI Physician Data Query, October 2007.

probably use TAC. I believe that most US oncologists would use dose-dense AC followed by paclitaxel.

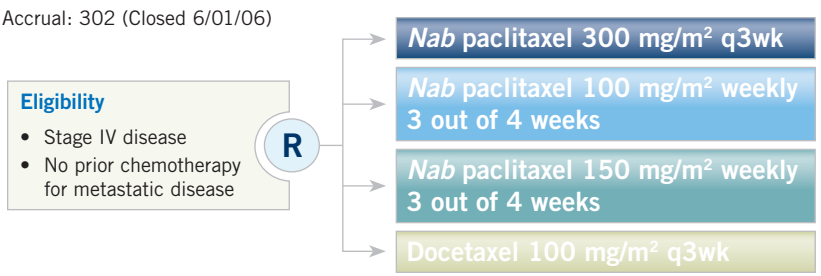
DR LOVE: What are your thoughts about Bill Gradishar's randomized Phase II trial comparing weekly *nab* paclitaxel to every three-week docetaxel?

DR VOGEL: Weekly *nab* paclitaxel showed better activity, with approximately double the response rate (Gradishar 2006b, 2007; [2.2]). Investigators are trying to mount a major trial in the US because much of this trial was conducted outside of the US. However, I've been impressed with the European and South American investigators, and I believe they had enough control over those trials to make them viable. If those data hold up, then *nab* paclitaxel could become the dominant taxane.

DR LOVE: For this patient who had a local recurrence in the axilla about a year after adjuvant dose-dense AC → *nab* paclitaxel, what would you consider in terms of chemotherapy, and would you consider bevacizumab?

2.2

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



	Nab paclitaxel 300 mg/m² q3wk n = 76	*Nab* paclitaxel 100 mg/m² weekly 3 out of 4 weeks n = 76	*Nab* paclitaxel 150 mg/m² weekly 3 out of 4 weeks n = 74	Docetaxel 100 mg/m² q3wk n = 76
Objective response rate	33%*	58%†	62%‡	36%
RECIST	43%	62%	70%	38%
IRR	35%	45%	47%	28%
Grade III/IV neutropenia	44%	25%	43%	94%
Grade III/IV peripheral neuropathy	17%	9%	16%	11%
Grade III/IV fatigue	4%	0%	3%	19%

* p-value < 0.001 versus weekly *nab* paclitaxel; † p-value = 0.004 versus docetaxel arm; ‡ p-value = 0.016 versus docetaxel arm

SOURCES: Gradishar W et al. Presentation. San Antonio Breast Cancer Symposium 2006b;**Abstract 46**; Gradishar W et al. *Proc ASCO* 2007;**Abstract 1032**.

DR VOGEL: I would be considering bevacizumab. Because she finished her adjuvant chemotherapy more than a year ago, I might be tempted to go back and treat her with *nab* paclitaxel and bevacizumab.

DR LOVE: This patient was enrolled in a study with the UCLA network in which she received docetaxel and bevacizumab. She had a good response — tumor shrinkage and symptom improvement.

How are you approaching the decision about using bevacizumab for women with metastatic breast cancer? How do you make the decision about which agent to combine it with, specifically when a relapse quickly follows paclitaxel?

DR VOGEL: We were fortunate to participate in the RIBBON 1 trial, and many of our patients were enrolled in that trial. RIBBON 1 allowed an anthracycline, *nab* paclitaxel, docetaxel or capecitabine. Before the XCaliBr trial results (Sledge 2007; [2.3]), from the standpoint of quality of life and given the choice of these different agents, I was choosing capecitabine.

I use a lot of capecitabine in my practice, but I wasn't impressed with the results for the eight or nine patients whom I treated with capecitabine/bevacizumab. Most of the patients in the RIBBON 1 trial were allowed to cross over to open-label bevacizumab.

So you could then move to second-line *nab* paclitaxel or paclitaxel, if you wished, with open-label bevacizumab. I did that, and most of my patients who crossed over to the taxane/bevacizumab have fared nicely.

I have one or two of my original patients still on capecitabine/bevacizumab. However, I view the XCaliBr trial as a relatively negative trial (Sledge 2007; [2.3]).

The interesting part of the trial — an unexpected finding — was that the patients with hormone receptor-positive disease seemed to do much better than those with hormone receptor-negative disease when treated with capecitabine/bevacizumab (Sledge 2007; [2.3]).

2.3

XCaliBr: Efficacy of Capecitabine/Bevacizumab as First-Line Therapy According to ER Status (Median Follow-Up: 12.9 months)

	Overall (n = 106)	ER-negative (n = 49)	ER-positive (n = 57)
Objective response rate	38%	27%	47%
Median time to progression (95% CI)	5.7 months (4.9-8.4)	4 months (3.0-4.9)	8.9 months (7.5-13.6)
Median overall survival (95% CI)	16.0+ months (12.9-*)	7.5 months (5.6-16)	16.6+ months (15.1-*)

* Not reached; CI = confidence interval; $p < 0.0001$ for ER-positive versus ER-negative

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

Tracks 13-17

Case Discussion 2

A 64-year-old woman presented in December 2001 with a 2.7-cm, strongly ER-positive, PR-positive, HER2-negative infiltrating ductal carcinoma with one of 19 positive nodes and was treated with an MRM and FAC_{100}. She has nearly completed five years of an aromatase inhibitor.

SOURCE: *Meet The Professors* 2006;4(4):4. Case 7. Available at: **www.MeetTheProfessors.com**

DR LOVE: When you are making this decision in a clinical setting, how do you think it through?

DR VOGEL: This woman had a positive node, which puts her at a somewhat greater risk. If I had a patient with a good-risk, node-negative tumor who was having symptoms with an aromatase inhibitor, I would probably take her off. If she was tolerating the aromatase inhibitor, I would discuss the question of delayed relapse. If this particular patient were tolerating the drug well, I would encourage her to participate in NSABP-B-42. As part of the informed consent process, patients usually declare which way they want to go.

DR LOVE: What has been your experience with the arthralgias associated with the aromatase inhibitors (2.4)?

DR VOGEL: It's highly variable. Approximately 30 percent of my patients have to be switched to another therapy or discontinue the aromatase inhibitor. Aman Buzdar and I had an agreement not to agree. He told me, "It is a class effect. If you get it with one aromatase inhibitor, you will get it with another." I absolutely do not agree because I have seen patients respond to a second aromatase inhibitor.

DR LOVE: Does it make a difference if it is steroidal or nonsteroidal?

DR VOGEL: No. I see no rhyme or reason. If you take any one of them and have a problem, you can switch to one of the others, and the patients can sail through it.

DR LOVE: What percent of those 30 percent do you end up having to take off aromatase inhibitors?

DR VOGEL: I'd say approximately five percent.

DR LOVE: Is there a typical clinical pattern or set of complaints that people tell you about?

DR VOGEL: Not really. It can occur in any joint, more frequently in the fingers and toes. I've had some patients who have been on exemestane develop what sounds like paresthesias, which I haven't heard about with the nonsteroidals. That makes that toxicity pattern a little different.

2.4

Prospective Characterization of Musculoskeletal Symptoms in Patients with Early Breast Cancer Treated with Adjuvant Letrozole or Exemestane

"Median time to onset of symptoms was 1.6 months (range 0.4–10 months). Clinical and laboratory evaluation of patients evaluated by rheumatology suggested that the majority developed either non-inflammatory musculoskeletal symptoms or inflammation localized to tenosynovial structures. Musculoskeletal side effects were common in AI-treated patients, resulting in therapy discontinuation in more than 10% of patients. There are no identifiable pre-therapy indicators of risk, and the etiology remains elusive."

SOURCE: Henry NL et al. *Breast Cancer Res Treat* 2007;[Epub ahead of print]. **Abstract**

Tracks 18, 21

Case Discussion 3

A 53-year-old woman with a history of hypertension and hypercholesterolemia who underwent a lumpectomy for a 0.8-cm, poorly differentiated, ER-negative, PR-negative, HER2-positive, node-negative, invasive ductal carcinoma. She received six cycles of TCH followed by trastuzumab for a year.

SOURCE: *Meet The Professors* 2007;5(1):4. Case 6. Available at: **www.MeetTheProfessors.com**

DR VOGEL: I would treat this patient with adjuvant chemotherapy and trastuzumab, but we don't have much data in this area. The only source of data is BCIRG 006 (Slamon 2006) because they allowed patients with small, node-negative, HER2-positive tumors.

So we have data with TCH, which includes carboplatin. If you're thinking "inside the box" and you intend to treat, then it would be with TCH. If you were thinking "outside the box," an interesting combination would be docetaxel/cyclophosphamide and trastuzumab.

DR LOVE: How do you feel about the new NSABP/CIRG study — the BETH trial — evaluating TCH (docetaxel/carboplatin/trastuzumab) with or without bevacizumab (2.5)?

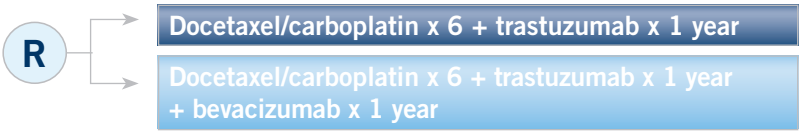
DR VOGEL: I will be participating in that trial. I do have concerns about the brain and brain metastases in these patients. A study from Poland obtained an MRI of the brain from 80 patients with HER2-positive breast cancer.

Thirty-six percent of the MRIs were positive for brain metastases (Niwinska 2007). We have data with lapatinib suggesting that perhaps it could provide some protection in the brain. That story must play out over the next few years.

In the ALTTO trial (2.6), you have the advantage in several of the arms of learning whether you can reduce brain metastases with lapatinib in patients with HER2-positive disease. I would have loved to have another randomization in the BETH trial to lapatinib or no lapatinib, after the other therapies were completed. ■

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

Target Accrual: 2,875



Eligibility

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

Stratification

- Number of positive nodes
- Hormone receptor status

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

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

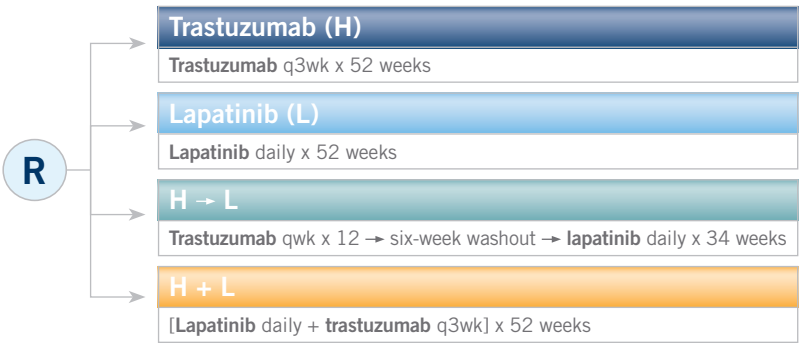
Protocol IDs: BIG 2-06, NCCTG-N063D, IBCSG 36-07; Target Accrual: 8,000

Eligibility

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

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

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



Study Contacts

Martine J Piccart-Gebhart, MD, PhD

Edith A Perez, MD

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

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Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Burstein HJ. **Aromatase inhibitor-associated arthralgia syndrome.** *Breast* 2007;16(3):223-34. **Abstract**

Carmona-Bayonas A. **Potential benefit of maintenance trastuzumab and anastrozole therapy in male advanced breast cancer.** *Breast* 2007;16(3):323-5. **Abstract**

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

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

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

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

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

Lynn Henry N et al. **Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors.** *Breast Cancer Res Treat* 2007;[Epub ahead of print]. **Abstract**

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

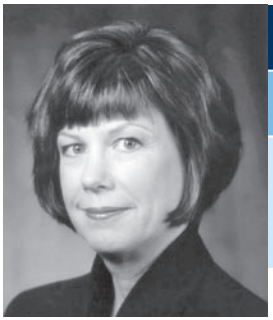
Miller K et al. **Capecitabine plus bevacizumab in first line metastatic breast cancer: An interim safety and efficacy report of the first phase of Xeloda plus Avastin 1st line metastatic breast cancer trial.** San Antonio Breast Cancer Symposium 2006;**Abstract 2068**.

Miller KD et al. **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**.

Niwinska A et al. **Effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival.** *Proc ASCO* 2007;**Abstract 1015**.

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

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



INTERVIEW

Sandra M Swain, MD

Dr Swain is Professor of Medicine at Georgetown University and Medical Director at the Washington Hospital Center's Washington Cancer Institute in Washington, DC.

Tracks 1-10

Select Excerpts from the Interview

Track 1

Case Discussion 4

A 58-year-old woman with a 2-cm, ER-negative, PR-negative, node-negative breast tumor with lymphovascular invasion who refused adjuvant chemotherapy and presented six months later with hepatomegaly, back pain, abnormal liver function tests and imaging that indicated bone and liver metastases.

SOURCE: *Meet The Professors* 2006;4(2):4. Case 1. Available at: **www.MeetTheProfessors.com**

DR SWAIN: A number of treatment options are available. What comes to mind first is to treat her with an anti-angiogenic agent like bevacizumab. So my first choice would be paclitaxel or paclitaxel/bevacizumab (Miller 2005; [3.1]).

DR LOVE: What are your thoughts about platinum agents for patients with triple-negative disease?

DR SWAIN: Utilizing a carboplatin-based regimen crossed my mind, but I believe the anti-angiogenic agent is more appealing because it's a different class of drugs and we know these patients don't fare well. That's why I would try bevacizumab first.

3.1

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

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-MAC3, 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 (d1, 8 and 15) + **bevacizumab** 10 mg/kg (d1 and 15) q4wk

T
Paclitaxel (d1, 8 and 15) q4wk

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

CI = confidence interval

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

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

Tracks 4-7

Case Discussion 5

A 65-year-old woman who underwent mastectomy for a 5-cm, Grade II, ER-positive, PR-positive, HER2-negative, node-negative, infiltrating lobular carcinoma. Her Onco*type* DX score was eight.

SOURCE: *Meet The Professors* 2007;5(2):4. Case 1. Available at: **www.MeetTheProfessors.com**

DR SWAIN: This is exactly the kind of patient I would send for an Onco*type* DX assay (3.2).

DR LOVE: Even for a 5-cm tumor?

DR SWAIN: Yes — I believe we need to consider the biology, not the size.

DR LOVE: Our *Meet The Professors* faculty held a spectrum of opinions on this case. Nancy Davidson concurred with you in that she would not use chemotherapy if the patient's recurrence score was low. Edith Perez indicated she would use chemotherapy and wouldn't even want the Onco*type* assay performed. Martine Piccart-Gebhart said that if the pathologist read the grade as low, she would consider not administering chemotherapy.

This patient's Onco*type* score was eight. What would you do if this patient had a high recurrence score?

3.2 Analysis of NSABP-B-20 with the Recurrence Scores Utilized in TAILORx: Recurrence Score and Response to Chemotherapy

Recurrence score	Number of patients	Tam 10-year DDFS	Tam + chemo 10-year DDFS	Hazard ratio (95% CI) for recurrence by addition of chemo	*p*-value
<11	177 (27%)	98%	95%	1.788 (0.360, 8.868)	0.471
11-25	279 (43%)	95%	94%	0.755 (0.313, 1.824)	0.531
>25	195 (30%)	63%	88%	0.285 (0.148, 0.551)	<0.0001

Tam = tamoxifen; DDFS = distant disease-free survival; CI = confidence interval; chemo = chemotherapy (which included cyclophosphamide, methotrexate and 5-fluorouracil or methotrexate in combination with 5-fluorouracil)

Risk of Relapse Associated with a Recurrence Score (RS) in the 11-25 Range

"Although a trend favoring the addition of chemotherapy becomes evident at an RS of approximately 11 when the risk of relapse is analyzed in a linear fashion, the 95% confidence intervals completely overlap in the 11–25 RS range...

An RS of 11 is associated with a risk of both local and distant relapse of about 10%, a threshold that has been typically used for recommending adjuvant chemotherapy."

SOURCE: Sparano JA. *Community Onc* 2006;3:494-6. **Abstract**

DR SWAIN: I would use chemotherapy. I've been using TC frequently for patients with node-negative disease.

DR LOVE: Is there a role for AC in your practice?

DR SWAIN: I don't use AC at all.

DR LOVE: Sharon Giordano gave a presentation at ASCO 2006 that drew attention to anthracycline-related cardiotoxicity in women with breast cancer (Giordano 2006). What risk are we exposing women to — even with four cycles of AC — particularly in the next 20 to 30 years?

DR SWAIN: That presentation was recently published in the *Journal of Clinical Oncology* (Pinder 2007; [3.3]). Women aged 60 to 70 who received adjuvant anthracyclines bore an increased risk of congestive heart failure. Some people have argued that patients gained a survival benefit and lived longer, which is why they had heart failure.

I don't believe that. I don't believe anthracyclines are benefiting those patients with HER2-negative disease. An Oxford meta-analysis demonstrated an overall benefit for anthracyclines (Mano 2005), but it didn't consider HER2, so I believe those data are flawed.

DR LOVE: If approximately 20 percent of these patients have HER2-positive disease, could it add up to that being the source of the advantage?

DR SWAIN: That would be my opinion, yes.

DR LOVE: What about the issue of what happens to patients in the long term, with the dynamics of hypertension, aging, et cetera, and the question of how anthracycline damage might tie in here?

3.3

Congestive Heart Failure in Older Women Treated with Adjuvant Anthracycline Chemotherapy for Breast Cancer

"In this large, observational data set, we found that women aged 66 to 70 years treated with adjuvant anthracycline chemotherapy had a statistically significant increase in the risk of being diagnosed with CHF. At 5 years of follow-up, we observed absolute differences of 1% and 4.6% respectively in rates of CHF between anthracycline-treated women in this age group and those who received other adjuvant chemotherapy or no chemotherapy.

After 10 years, the increased risk of CHF in anthracycline-treated patients was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when comparing anthracycline-treated patients to the other or no adjuvant chemotherapy groups, respectively.

This effect emerged even though anthracycline treated patients appeared to have been selected for a more favorable cardiac risk profile and were not subjected to more rigorous surveillance for cardiac complications..."

SOURCE: Pinder MP et al. *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

DR SWAIN: Even with one dose of an anthracycline, you damage myocytes and the heart. If you're administering 240 mg/m^2, the damage may be significant, especially in older patients.

Tracks 8-9

Case Discussion 6

An 86-year-old woman was found to have a 1.9-cm, Grade II, ER-negative, PR-negative, HER2-positive IDC with six of 15 positive axillary nodes. Extent-of-disease evaluation showed no evidence of distant metastases and medical history was notable for controlled hypertension and mild Parkinsonism.

SOURCE: *Meet The Professors* 2007;5(3):4. Case 10. Available at: **www.MeetTheProfessors.com**

DR SWAIN: I would definitely administer trastuzumab and chemotherapy to this woman, but I wouldn't administer an anthracycline. I'd probably treat her with weekly paclitaxel and trastuzumab for 12 weeks and then continue the trastuzumab alone for a year.

DR LOVE: What about administering paclitaxel to a woman with Parkinson's disease?

DR SWAIN: I would be concerned, but I'd be more concerned about the cardiac effects in someone that age, so I would choose the taxane. Vinorelbine would be a consideration, but it's never been used in the adjuvant setting. ■

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

Pinder MC et al. **Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer.** *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

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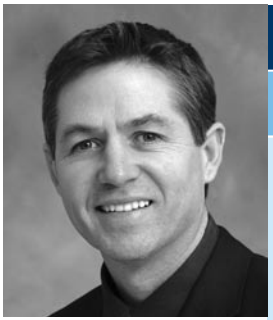


INTERVIEW

Paul E Goss, MD, PhD

Dr Goss is Professor of Medicine at Harvard Medical School, Director of the Breast Cancer Program at MGH Cancer Center, Co-director of the Breast Cancer Disease Program, Dana-Farber/Harvard Cancer Center and Avon Foundation Senior Scholar in Boston, Massachusetts.

Tracks 1-19

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What is our current understanding of estrogen and breast cancer?

DR GOSS: The dynamics among cancer cells, the estrogen pathway and the ambient estrogen concentration are interesting.

It turns out that in cell culture, and probably clinically, prolonged treatment changes the affinity of the estrogen pathway for estrogen, and that's how the cancer adapts to living at a lower level of estrogen. For example, after a long treatment with an aromatase inhibitor, the cancer grows as efficiently at a low level of estrogen as it would on the higher, pretreatment level, and that's probably a major mechanism of resistance, involving alternative signaling pathways.

Imagine a scenario in which you are trying to prevent schoolchildren from leaving a building that has a front door and multiple windows. With endocrine therapy, you are closing the front door and keeping it closed, but eventually the children get fed up and open the windows, so these pathways are switched on.

This concept led me to examine in clinical trials the idea of administering aromatase inhibitors intermittently rather than continuously. This concept of alternating suppression with letting go has been tested in the laboratory, where we're essentially moving the goalpost. By turning on alternative signaling, we're preventing the cancer cell from adjusting.

DR LOVE: Would it make any sense to use another endocrine intervention, such as fulvestrant, as opposed to doing nothing?

DR GOSS: Absolutely. Part of the strategy is to use a so-called total estrogen blockade, or the estrogen clamp, and alternate it with actual estrogen therapy. That's what Steven Come at Beth Israel is doing in his trial in which patients experiencing disease progression on aromatase inhibitors receive high-dose estrogen for 12 weeks and then fulvestrant. The plan is to examine tissue and sera from these patients, but we don't have any data yet.

Track 6

DR LOVE: Can you elaborate on the role of HER2 in endocrine therapy?

DR GOSS: The trial in which tamoxifen or letrozole was randomly assigned to patients with metastatic breast cancer showed that letrozole was superior to tamoxifen by a fairly significant amount (Mouridsen 2001). In that trial they collected serial sera, and Allan Lipton's laboratory measured serum-circulating HER2 at baseline and on disease progression (Lipton 2003).

He found that among patients with HER2-negative disease treated with tamoxifen or letrozole, at the point of progression, 25 percent had developed easily measurable, circulating HER2, and the animal models concur with this finding.

DR LOVE: Do you think that the disease literally converts from HER2-negative to HER2-positive?

DR GOSS: Yes, I do.

DR LOVE: If that's the case, then many patients might be out there who could benefit from anti-HER2 therapy but are being missed.

DR GOSS: That could be true. One of the most important metastatic breast cancer trials in the world right now is a study in which women are randomly assigned to letrozole versus letrozole with lapatinib (NCT00073528).

It's a 1,200-patient trial, stratified by the tumor's HER2 status, and 800 patients have ER-positive, HER2-negative breast cancer. The idea is to prolong the time to progression by inhibiting the conversion to HER2-positive.

If that trial is positive, we're opening the door to the question, "Are all patients with HER2-negative disease who receive adjuvant aromatase inhibitor therapy potential candidates for anti-HER2 therapy over time?" The answer might be yes.

Tracks 7-8

DR LOVE: What do you think about the SoFEA trial, which compares fulvestrant to fulvestrant with anastrozole to exemestane in postmenopausal women whose disease progressed during endocrine therapy with a nonsteroidal aromatase inhibitor (4.1)?

DR GOSS: I believe these types of trials will be positive in favor of the combination over the single agent and will provide proof of the concept that complete estrogen blockade is superior.

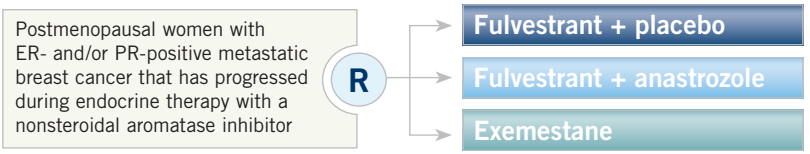
DR LOVE: Why would fulvestrant be helpful when combined with an aromatase inhibitor?

DR GOSS: The estrogen pathway itself is not completely blocked by the aromatase inhibitors. Residual estrogen and exogenous estrogen are still present. People ignore the presence of exogenous estrogens, but it's important.

4.1

SoFEA: A Phase III Trial of Fulvestrant with or without Concomitant Anastrozole versus Exemestane After Disease Progression on Nonsteroidal Aromatase Inhibitors

Protocol IDs: ISRCTN44195747, SoFEA, NCT00253422
Target Accrual: 750 (Open)



Study Contact

Institute of Cancer Research-UK
Stephen Johnston, MD, Protocol Chair
Tel: 44-20-7808-2748

SOURCES: National Cancer Research Network Trials Portfolio. Available at http://www.controlled-trials.com/ISRCT44195747/sofea; NCI Physician Data Query, November 2007.

My concern is that in the laboratory, when we culture MCF-7 cells in an ever-depleting estrogen concentration, creating long-term estrogen-deprived cells, these cells become stimulated.

They increase their sensitivity of growth promotion 10,000-fold, so you can imagine that if a patient has been on an aromatase inhibitor for four years and uses a vaginal estrogen cream, she could stimulate the growth of her cancer.

Track 9

DR LOVE: We haven't yet seen data from the crossover arms of the BIG 1-98 trial. What do you expect to observe in the patients who began on letrozole and cross over to tamoxifen?

DR GOSS: I predict that arm will be a bust, based on the metastatic trial of tamoxifen versus letrozole, in which approximately 50 percent of the patients crossed over at disease progression (Mouridsen 2003). The patients who received tamoxifen followed by letrozole showed a respectable response rate. However, among the patients who crossed over to tamoxifen after letrozole, virtually none showed a response. In the metastatic setting, there's no hint that tamoxifen works after letrozole.

DR LOVE: What do you think would happen if, rather than switching to tamoxifen after an aromatase inhibitor, patients received an estrogen?

DR GOSS: That is a great idea and is similar to what Steven Come is doing in his trial, in which patients who experience disease progression on aromatase inhibitors receive high-dose estrogen for 12 weeks and then receive fulvestrant.

DR LOVE: I was hopeful that the letrozole-to-tamoxifen regimen in the BIG 1-98 trial might work, thinking that maybe the agonist effect of tamoxifen would kick in. However, you're saying that we don't see those results clinically, correct?

DR GOSS: Not in metastatic disease, but you can never be sure that it won't happen. You're saying that the low agonist effect of tamoxifen could, in theory, stimulate and act as estrogen therapy, and that's an interesting thought. You may be correct.

Track 11

DR LOVE: Overall, what is the biggest misconception of oncologists in practice with regard to endocrine therapy?

DR GOSS: I'm heavily biased here, but I believe the greatest disservice to women with breast cancer — other than possibly overtreating with chemotherapy in certain circumstances — is the lack of understanding of the chronicity of relapse in hormone-dependent breast cancer, the benefits that can be obtained by aromatase inhibition and the easily manageable level of toxicity that's associated with that therapy.

DR LOVE: Do you believe that aromatase inhibitors are underutilized?

DR GOSS: Very much so, specifically with regard to the use of extended adjuvant endocrine therapy. In the MA17 trial, postunblinding, we offered letrozole to 2,500 patients who had been on the placebo arm, and we found a continuing benefit to introducing letrozole in patients who had finished tamoxifen one to 10 years prior (Goss 2005a).

DR LOVE: What about investigating even beyond that? Is that in the realm of chemoprevention?

DR GOSS: You put your finger right on the misunderstanding of this disease. Most oncologists imagine that with the passage of time, the proportion of relapses, including metastatic relapses, declines. However, we do not see that in the Oxford overview (EBCTCG 2005) or the MA17 data (Goss 2005b).

Two thirds of all recurrences in node-positive, hormone-dependent breast cancer, no matter how far out you go, are metastases. Among the patients with node-negative disease, if you add up local-regional, contralateral, new primary and ipsilateral recurrences, they come to 60 percent, but 40 percent of all recurrences and the most frequent single site of recurrence are metastases, and they're fatal.

The benefit that we've shown for letrozole is an absolute median disease-free survival advantage of 4.5 percent in four years, and all the data suggest that this will continue for 15 or 20 years. You can erase the chances of recurrence of breast cancer with aromatase inhibition if you keep administering it for long enough.

Track 12

DR LOVE: Many women were treated 15, 20 or 25 years ago, yet it seems like an uncommon event for these women to experience a clinical relapse. Am I wrong about that?

DR GOSS: You are wrong. Two phenomena occur. First, the annual hazard of recurrence is lower, so the number of women per year who experience relapse is definitely lower than in the first five years.

Second, many doctors discharge their patients, and the patients are lost to follow-up. We don't directly record the source of patients with metastatic breast cancer, but they come relentlessly from late recurrences of previous hormone-dependent breast cancer.

Richard Peto understands this better than anybody. He has published the 15-year follow-up for five years of adjuvant tamoxifen (EBCTCG 2005). If you take his event-rate data and compare them to the data for the placebo group in the MA17 trial, the curves are superimposable.

Whereas the MA17 trial is defined as including four or five years, the overview goes out 15 years, and the event rate is two percent per annum from

five to 15 years in patients with node-negative breast cancer. For node-positive disease, the rate is four percent per annum all the way out to 15 years.

When you add that up, it's a huge pool of recurrences. When you examine our data on patients who received letrozole over four years, in the first 12 months after tamoxifen, comparing the recurrence rate to no treatment, you find that the hazard rate is 0.52. In year four — patients who have received nine years of therapy — the patients on letrozole have a recurrence hazard rate of 0.19 compared to the control patients.

DR LOVE: In terms of absolute risk, are you saying that a woman 15 years after primary treatment for node-positive breast cancer has a four percent chance of developing a relapse that year?

DR GOSS: Yes, and Richard Peto believes that would continue indefinitely because there's no evidence, not even a flick on the graph, that suggests it will change.

DR LOVE: How far out from diagnosis would you consider starting an aromatase inhibitor-naïve patient on an adjuvant aromatase inhibitor?

DR GOSS: I believe that when we see patients who had receptor-positive disease and are between years five and 11 since diagnosis on no therapy, then it behooves us to talk to them about this.

Tracks 18-19

DR LOVE: Would you discuss the work you have been doing with triple-negative breast cancer and platinums?

DR GOSS: This is a special interest of ours at MGH Cancer Center. Everyone recognizes that triple-negative disease is a disproportionately fatal form of breast cancer and that it's particularly refractory to our current anticancer therapies, and we are frustrated by the lack of progress with this dangerous subtype.

You might recall that cisplatin was once tried in breast cancer and produced a low response rate in an "all-comers" setting, so it was taken off the table as a single agent or even as an active drug in breast cancer.

However, Leif Ellisen, the new head of translational research at MGH Cancer Center, has a career interest in cell survival pathways in breast cancer, and he has discovered a p63/p73 marker that we believe identifies 30 to 40 percent of patients with triple-negative breast cancer who are exquisitely and specifically sensitive to cisplatin (Leong 2007). These genes are in the same family and pathway as p53.

DR LOVE: Does it make biologic sense that a platinum would be particularly effective in this subgroup of patients?

DR GOSS: It absolutely does. It's not that it's an incidental marker. Rather, there is a biological explanation. These two genes interact with the tumor in

such a way that the platinum, with its mechanism of action, will be effective. So it's more than simply a predictor of response — it's actually involved in the response mechanism.

DR LOVE: Would you use this strategy for patients with triple-negative breast cancer in the clinical setting?

DR GOSS: I would not use single-agent cisplatin before standard chemotherapy, but I would afterward. I've seen responses with the strategy, and I believe that this will be one of these phenomena in which the marker may be found in only 15 or 20 percent of patients. Among those patients, we'll see an 80 or 85 percent response rate with this drug, which would be fantastic. ■

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Goss P et al. **The effects of atamestane and toremifene alone and in combination compared with letrozole on bone, serum lipids and the uterus in an ovariectomized rat model.** *Breast Cancer Res Treat* 2007;103(3):293-302. **Abstract**

Goss P et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** San Antonio Breast Cancer Symposium 2005a;**Abstract 16**.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005b;97(17):1262-71. **Abstract**

Leong CO et al. **The p63/p73 network mediates chemosensitivity to cisplatin in a biologically defined subset of primary breast cancers.** *J Clin Invest* 2007;117(5):1370-80. **Abstract**

Lipton A et al. **Serum HER-2/neu and response to the aromatase inhibitor letrozole versus tamoxifen.** *J Clin Oncol* 2003;21(10):1967-72. **Abstract**

Lipton A et al. **Elevated serum Her-2/neu level predicts decreased response to hormone therapy in metastatic breast cancer.** *J Clin Oncol* 2002;20(6):1467-72. **Abstract**

Ma XJ et al. **A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen.** *Cancer Cell* 2004;5(6):607-16. **Abstract**

Mouridsen H et al. **Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2003;21(11):2101-9. **Abstract**

Mouridsen H et al. **Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2001;19(10):2596-606. **Abstract**

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Thürlimann B et al; Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. **Abstract**

INTERVIEW

Hannah M Linden, MD

Dr Linden is Associate Professor of Medicine at the University of Washington's Harborview Medical Center and Seattle Cancer Care Alliance in Seattle, Washington.

Tracks 1-20

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss your research on molecular imaging of estradiol?

DR LINDEN: We have a grant to study the molecular imaging technology Dave Mankoff developed (Mankoff 2001). PET-fluorodeoxyglucose (FDG) imaging uses a fluoridated sugar to detect glycolysis in tumors. With the same tracer, we use [^{18}F]fluoroestradiol (FES) to image the ER.

We can examine whether the ER functions in the tumor. The PET-FES studies show uptake in an intact uterus because that's an ER-rich target. It doesn't show in a lung because the lung does not have enough ER. It shows whether a tumor can concentrate and bind estrogen. It provides a macroscopic picture of different tumor sites in the whole body where estrogen is being taken up.

DR LOVE: How is it at detecting tumors that aren't visible with other types of imaging?

DR LINDEN: I'm sure it will be used in that context. Estrogen is metabolized in the liver, and we can't examine tumors in the liver because the liver is full of the isotope and all its metabolites. We can examine bone and every other site. The gut is problematic for FDG. It has the same limitations as a PET scan — about a centimeter-sized tumor, depending on how concentrated the ERs are. It will not pick up tiny metastases from an infiltrating lobular cancer.

Everybody in practice knows that breast cancer is heterogeneous, and ER uptake is heterogeneous. Patients have appeared to have ER-negative disease when their primary tumor was diagnosed, possibly due to sampling error. Then they develop bone-dominant disease, which isn't their basal phenotype. I believe this is where we can help in the future. Sampling bone is difficult. I do it, but it's difficult.

DR LOVE: What do you see in terms of the distribution of widespread metastatic disease? Does the imaging correlate with what you see, or is there variability within the tumors?

DR LINDEN: The imaging correlates with what you see by an FDG study in general, but there is heterogeneity of uptake (5.1). Interestingly, it correlates nicely with what we know histologically. We know that a low level of ER is still a meaningful finding. When uptake of estrogen is significant, the chance of responding to hormone therapy is better, even if there is no uptake at heterogenic sites of disease.

Track 7

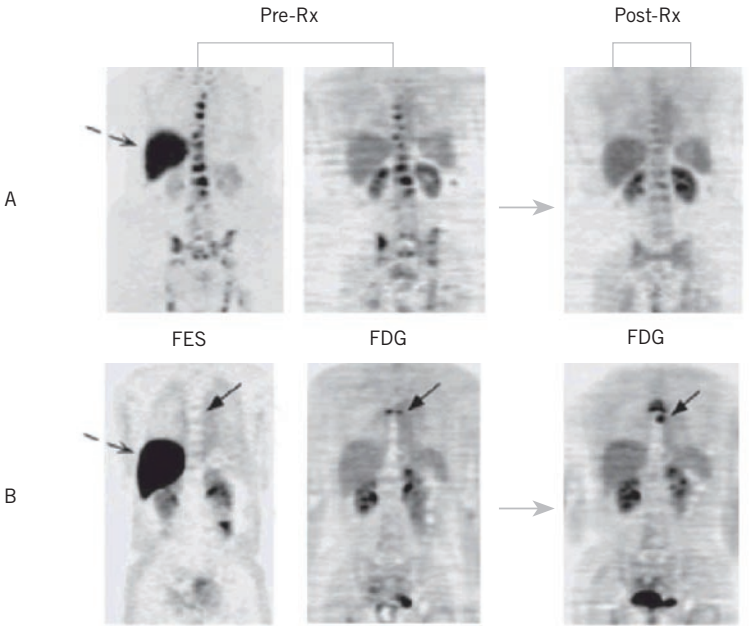
DR LOVE: Can you discuss the issue of endocrine therapy for premenopausal women?

DR LINDEN: It will be great to have data from the international cooperative trials evaluating this in the adjuvant setting, and we will settle the issue with the SOFT and TEXT studies (5.2).

The age of menopause is increasing and people need to be careful. You can't assume that a woman in her fifties is in menopause because she hasn't

5.1

Pretreatment and Post-treatment [^{18}F]fluoroestradiol (FES) and Fluorodeoxyglucose (FDG) Images



Legend: Pretreatment FES (left) and FDG (middle) scans and post-therapy FDG (right) scans. A: Bone metastasis with FES and FDG uptake, and response at 3 months. Dashed arrows show normal liver FES uptake. B: Bone metastasis without FES but with FDG uptake, and progressive disease at 6 months.

SOURCE: Linden HM et al. *J Clin Oncol* 2006;24(18):2793–9. **Abstract**

had a period for a year. We can offer ovarian suppression and administer an aromatase inhibitor. Clinically it makes sense that this would be the most potent endocrine manipulation, but it needs to be proven.

Track 15

DR LOVE: Can you comment on the use of capecitabine alone or with bevacizumab in metastatic disease?

DR LINDEN: Breast cancer is a heterogeneous disease. If your clinical judgment is that this is an aggressive tumor, what does it matter if it's ER-positive? Administer aggressive therapy. That's a reasonable option. I have administered bevacizumab with capecitabine. I try to not pull out all the stops at once. The advantage of capecitabine for many patients is that they aren't in the infusion suite and they aren't facing much in the way of toxicities.

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

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	T x 5y OFS + T x 5y OFS + E x 5y
IBCSG-25-02 (TEXT trial)	1,845 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + T x 5y Triptorelin ± chemotherapy + E x 5y

T = tamoxifen; OFS = ovarian function suppression with triptorelin, surgical oophorectomy or ovarian irradiation; E = exemestane

SOURCES: www.ibcsg.org; NCI Physician Data Query, November 2007.

I use bevacizumab because I believe it adds benefit to therapy, but it's expensive and it has some toxicities. When you're addressing metastatic disease, if a patient who is responding will be on therapy a long time, you may have to manage these toxicities.

DR LOVE: Have you observed problems with hypertension?

DR LINDEN: Not everybody seems to develop hypertension, which is intriguing. I worry about someone who's suffered other renal "hits" and whether we add to that by using bevacizumab. Generally the hypertension has been easy to manage with medication. When we stop the bevacizumab, the hypertension usually resolves.

The challenge of bevacizumab is selecting the best patient group to benefit. Some believe patients with ER-positive disease may receive extra benefit. Some believe it's the patients with triple-negative disease — perhaps because the patients with triple-negative disease are at such high risk, they are the best candidates.

DR LOVE: Have you seen any other problems with bevacizumab?

DR LINDEN: Shockingly, no. I've feared intracranial bleeds or simply a wound-healing crisis, but it's a pretty well-tolerated drug.

Tracks 16-17

DR LOVE: How does *nab* paclitaxel fit into your practice?

DR LINDEN: I believe it is an exciting drug, and I hope it's an opportunity for us to learn more about paclitaxel. By the end of its patent life and the randomized studies, we had learned that weekly paclitaxel is the best schedule. I hope we can build on that to learn more.

With Bob Livingston, our group has evaluated *nab* paclitaxel and vinorelbine in patients with metastatic disease. We saw some surprising toxicity and

neurotoxicity, although it's an active combination. We need to learn how to use it, but it's a nice drug. The neuropathy is less, and you don't need steroid premedication.

DR LOVE: In our Patterns of Care study of 150 randomly selected oncologists in the US, 30 percent of them were using corticosteroids with *nab* paclitaxel. We also surveyed 51 clinical investigators, and none of them were using it. Does that surprise you?

DR LINDEN: Yes. It shocks me. We're all creatures of habit. The steroids are good antinausea drugs, and for your lung cancer patient who will receive only four doses, it's trivial. But for your breast cancer patient who will receive it for a long time, the steroids are not a trivial load, whether you're using docetaxel or paclitaxel. The breast cancer patient will receive more steroid doses and will live longer, so it's a bigger issue.

DR LOVE: I wonder whether the insomnia and agitation from corticosteroids might have some subtle impact — whether the postagitation "down" contributes to the overall fatigue or bad feeling.

DR LINDEN: I don't believe we understand the insomnia of chemotherapy well enough. It's certainly one of the contributing factors. I don't use a lot of dexamethasone with my chemotherapy, and I still have patients who can't sleep during chemotherapy.

They don't like the high they get with it and the low that follows it. So many of my patients who are receiving steroid premedication tell me that they don't sleep that night or that they have strange dreams.

I also worry about an allergic reaction to paclitaxel. I believe it's a great drug for breast cancer. It's a particularly active drug, so I'm excited about *nab* paclitaxel. ■

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

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Linden HM et al. **PET FES measures in vivo pharmacodynamics of endocrine therapy.** *Proc ASCO* 2007;**Abstract 14110**.

Linden HM et al. **Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer.** *J Clin Oncol* 2006;24(18):2793-9. **Abstract**

Mankoff DA et al. **[^{18}F]fluoroestradiol radiation dosimetry in human PET studies.** *J Nucl Med* 2001;42(4):679-84. **Abstract**

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial, the rate of breast-conserving surgery was highest for patients who received _____.**
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole and tamoxifen
2. **The Study of Letrozole Extension (SOLE) trial will evaluate continuous or intermittent therapy with an aromatase inhibitor after completion of four to six years of adjuvant endocrine therapy in postmenopausal patients with hormone receptor-positive early breast cancer.**
   a. True
   b. False
3. **In a retrospective analysis by MD Anderson, capecitabine at 1,000 mg/m^2 BID resulted in _____ compared to capecitabine at 1,250 mg/m^2 BID.**
   a. Inferior efficacy
   b. Equivalent efficacy
   c. Improved side-effect profile
   d. Both a and c
   e. Both b and c
4. **In the second interim analysis of BCIRG 006, AC → TH was associated with significantly prolonged disease-free and overall survival compared to TCH.**
   a. True
   b. False
5. **In a randomized Phase II trial, women with metastatic breast cancer who were treated with weekly *nab* paclitaxel had a better response rate than those who received _____.**
   a. Docetaxel weekly
   b. Docetaxel every three weeks
   c. Both a and b
   d. None of the above
6. **The XCaliBr trial evaluated the efficacy of bevacizumab in combination with _____ as first-line therapy for metastatic breast cancer.**
   a. *Nab* paclitaxel
   b. Gemcitabine
   c. Capecitabine
   d. All of the above
   e. None of the above
7. **Patients with hormone receptor-positive, node-negative breast cancer and a(n) _____ recurrence score on the Onco*type* DX assay have a high likelihood of benefiting from adjuvant chemotherapy.**
   a. High
   b. Intermediate
   c. Low
   d. Both a and c
   e. None of the above
8. **The proposed NSABP/CIRG BETH trial of adjuvant monoclonal therapy in patients with HER2-positive early breast cancer will evaluate TCH with or without _____.**
   a. Cisplatin
   b. Bevacizumab
   c. Lapatinib
9. **In the SoFEA trial, postmenopausal women with hormone-receptor positive metastatic breast cancer that has progressed on a nonsteroidal aromatase inhibitor are randomly assigned to fulvestrant versus fulvestrant with anastrozole versus exemestane.**
   a. True
   b. False
10. **PET-FES imaging _____.**
    a. Uses fluoridated estradiol to detect ER
    b. Indicates whether a tumor can bind estrogen
    c. Is not useful for imaging ER-rich tumors in the liver
    d. All of the above

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

EVALUATION FORM

Breast Cancer Update — Issue 7, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this Evaluation Form. A certificate of completion will be issued upon receipt of your completed Post-test and Evaluation Form.

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging research advancing breast cancer treatment, and incorporate these data into management strategies in the neoadjuvant, adjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Describe the risks and benefits of neoadjuvant and adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen in the setting of ER-positive breast cancer, and discuss these findings with your patients . . . . . 5 4 3 2 1 N/A
- 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
- Implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dosing and selection of taxanes with or without anthracyclines, and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients with metastatic disease about evidence-based selection and sequencing of endocrine therapy and chemotherapies, and evaluate the risks and benefits of these agents as either monotherapy or combination regimens. . . . 5 4 3 2 1 N/A
- Review the emerging data for biologic therapies and explain how these findings should be incorporated into the treatment algorithm for appropriately selected patients with metastatic disease. . . . . 5 4 3 2 1 N/A
- Describe the evidence to support the use of genetic and other molecular markers as prognostic and predictive tools to guide therapy decisions. . . . . 5 4 3 2 1 N/A
- Discuss the impact of standard oncologic interventions on patient quality of life, and offer supportive or alternative management strategies to improve tolerability . . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Ian E Smith, MD	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, MD	5 4 3 2 1	5 4 3 2 1
Sandra M Swain, MD	5 4 3 2 1	5 4 3 2 1
Paul E Goss, MD, PhD	5 4 3 2 1	5 4 3 2 1
Hannah M Linden, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 7, 2007

REQUEST FOR CREDIT — please print clearly

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

Degree:

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

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

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

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

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 fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

BCU707

Breast Cancer® UPDATE

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