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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Melvin J Silverstein, MD

Norman Wolmark, MD

Hope S Rugo, MD

Lisa A Carey, MD

CME Certified

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Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Historically, surgery has been the primary mode of treatment for women with early breast cancer. The diagnostic, surgical and medical management of breast cancer, however, has escalated in complexity because of numerous advances in novel technologies and available adjunctive medical therapies. Hence, the multifaceted treatment of breast cancer now requires the input of an interdisciplinary group of expert care providers. This paradigm shift has created the challenge of ensuring that major clinical advances in local and systemic breast cancer therapy are effectively disseminated among all members of the cross-functional team. To bridge the gap between research and patient care, *Breast Cancer Update* for Surgeons utilizes one-on-one interviews with leading breast cancer investigators to translate the latest research developments into clinical practice. By providing access to cutting-edge data and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Assess the evolving role of oncoplastic breast surgery.
- Counsel women requiring breast biopsy about the diagnostic precision of the image-guided needle versus the excisional approach.
- Identify women with breast cancer who may be candidates for partial breast irradiation, and discuss ongoing clinical trials evaluating intraoperative radiation therapy.
- Develop an algorithm for the treatment of node-negative, HER2-positive early breast cancer, considering the tumor size and the ER status.
- Advise postmenopausal patients with hormone receptor-positive early breast cancer about the benefits and risks of (1) initial adjuvant therapy with an aromatase inhibitor, tamoxifen or a sequence of both agents and (2) extended adjuvant hormonal therapy.
- Use tissue-based genomic assays to aid in the selection of individualized treatment strategies, when applicable, for patients with ER-positive early breast cancer.
- Summarize the emerging data on select novel therapeutic agents or regimens in the treatment of breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing adjuvant and neoadjuvant clinical trials.

ACCREDITATION STATEMENT

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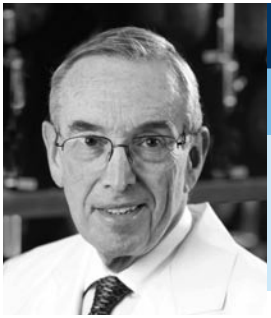


INTERVIEW

Melvin J Silverstein, MD

Dr Silverstein is Director of the Hoag Hospital Breast Program in Newport Beach, California and Professor of Surgery at the Keck School of Medicine at the University of Southern California in Los Angeles, California.

Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the role of oncoplastic surgery in breast cancer?

DR SILVERSTEIN: This has become a hot topic at the American Society of Breast Surgeons annual meeting. Oncoplastic surgery is a combination of oncologic surgery and plastic surgery with two opposing goals that are in a tug of war with each other. The goal of oncologic surgery is to excise the tumor with the best margins you can obtain — the bigger the margins, the better. Cosmetic surgery, however, doesn't remove a lot of breast tissue. Many surgeons have not been trained to consider that the appearance of the breast after tumor removal is important. The philosophy has been to remove the tumor at all cost to tissue.

I started performing oncoplastic surgery 20 years ago because I was in a clinical practice group that included two plastic surgeons. It became apparent to me that they were doing all sorts of exciting things in cosmetic surgery that I might incorporate into oncologic surgery. In the late 1990s through early 2000s, I started to talk about the subject, and interest in the topic has slowly increased.

Track 5

DR LOVE: Would you discuss the article about breast biopsies to which you wrote an editorial in the *Journal of the American College of Surgeons*?

DR SILVERSTEIN: The article, from a major teaching hospital in New York City, demonstrated approximately a 36 percent rate of open biopsies as the first diagnostic test for breast abnormalities among private practice breast surgeons and general surgeons (Clarke-Pearson 2009; [1.1]).

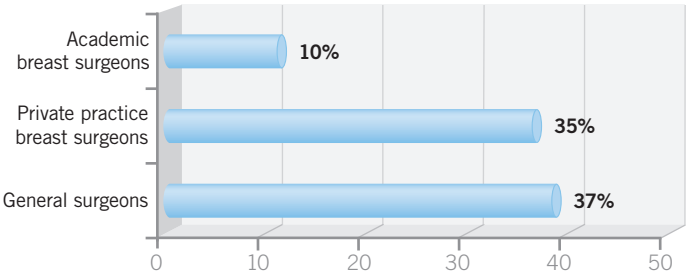
I thought this number was appallingly high. So I wrote an editorial that was published right along with the paper (Silverstein 2009) entitled, "Where's the Outrage?"

If these findings extend to current practice across the United States, and I believe they do, then approximately 40 percent of all diagnostic biopsies are open procedures. This would translate into almost 600,000 open biopsies per year, when the vast bulk of those diagnoses could be made with a needle biopsy (1.2)

I believe that the operating room should be reserved for a definitive surgical operation. The surgeon's goal ought to be to go to the operating room one time.

DR LOVE: In the editorial (Silverstein 2009), you said that you believe the rate for excisional biopsies should be less than five percent. What is it in your own practice?

1.1 **Rate of Excisional Biopsies as the Initial Diagnostic Procedure**



SOURCE: Clarke-Pearson EM et al. *J Am Coll Surg* 2009;208(1):75-8.

DR SILVERSTEIN: It's even less than that. If the surgeon can perform a needle biopsy with ultrasound or use a radiologist he or she trusts, then it ought to be close to zero, one or two to three percent — quite a low number.

1.2

American Society of Breast Surgeons: Consensus Statement on Percutaneous Needle Biopsy for Image-Detected Breast Abnormalities

"A major goal of modern breast medicine is to minimize the number of patients with benign lesions who undergo open surgical breast biopsies for diagnosis. Image guided percutaneous needle biopsy is the diagnostic procedure of choice for image-detected breast abnormalities. It should be readily available to all patients with image-detected lesions.

There are relatively few patients for whom excisional biopsy should be the initial procedure for diagnosis. For patients with a diagnosis of breast cancer, the goal is to make the diagnosis with a needle and to go to the operating room one time for definitive treatment. A definitive diagnosis of breast cancer made using a minimally invasive needle biopsy permits optimal preoperative work-up, patient counseling, and surgical planning."

SOURCE: American Society of Breast Surgeons. Available at: **www.breastsurgeons.org/statements/mibb.php**.

Tracks 6-7

DR LOVE: Would you discuss partial breast irradiation (PBI)?

DR SILVERSTEIN: It's a growing field. I believe that the future of PBI will be intraoperative radiation therapy (IORT). We've been using IORT at USC for the past four years. We prefer the procedure because it is uncomplicated and we've seen no side effects. In the first 40 cases, one patient had a red breast for about five or six days after the procedure, and then it returned to normal. Other than that, we have seen no problems whatsoever, and it only adds about one hour of OR time.

I believe that the ideal patients for this procedure are the ones who are least likely to experience a recurrence. Therefore, they ought to be older, have small, node-negative breast cancer and not have lymphovascular invasion. They ought to have wide margins. I believe that patients with DCIS can also be included if you excise it with good margins. ■

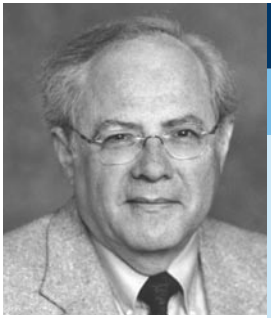
SELECT PUBLICATIONS

American Society of Breast Surgeons. **Official consensus statement of percutaneous needle biopsy for image detected breast abnormalities.** Approved June 2006. Available at: **www.breastsurgeons.org/statements/mibb.php**.

Anderson BO et al. **Oncoplastic approaches to partial mastectomy: An overview of volume-displacement techniques.** *Lancet Oncol* 2005;6(3):145-57.

Clarke-Pearson EM et al. **Quality assurance initiative at one institution for minimally invasive breast biopsy as the initial diagnostic technique.** *J Am Coll Surg* 2009;208(1):75-8.

Silverstein M. **Where's the outrage?** *J Am Coll Surg* 2009;208(1):78-9.



INTERVIEW

Norman Wolmark, MD

Dr Wolmark is Chairman of the National Surgical Adjuvant Breast and Bowel Project, Chairman of the Department of Human Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania and Professor of Human Oncology at Drexel University College of Medicine in Philadelphia, Pennsylvania.

Tracks 1-14

Track 1 **CASE DISCUSSION:** An 80-year-old woman with a 4-mm, node-negative, ER-positive, PR-negative, HER2-positive invasive ductal carcinoma (IDC) who underwent segmental mastectomy

Track 2 Clinical use of adjuvant trastuzumab for small, node-negative, HER2-positive breast cancer (BC)

Track 3 BETH trial: Adjuvant chemotherapy/trastuzumab with or without bevacizumab for HER2-positive BC

Track 4 Clinical use of the Onco*type* DX assay

Track 5 **CASE DISCUSSION:** A 60-year-old woman who developed a 1-cm, in-scar recurrence two years after resection without adjuvant therapy for a 2.5-cm, node-negative, ER/PR-positive, HER2-negative BC

Track 6 NSABP-B-37: A Phase III randomized trial of adjuvant chemotherapy for resected, locoregional BC recurrence

Track 7 Change in the Onco*type* DX Recurrence Score® from primary to recurrent BC

Track 8 Update on adjuvant aromatase inhibitors (AIs) from the 2008 San Antonio Breast Cancer Symposium

Track 9 Duration of adjuvant hormonal therapy

Track 10 **CASE DISCUSSION:** A 50-year-old premenopausal woman who underwent segmental mastectomy for a 5-mm focus of ER-negative, PR-negative, HER2-positive DCIS with comedonecrosis

Track 11 Incidence of ER-positive or HER2-positive DCIS

Track 12 NSABP-B-43: A Phase III randomized trial of radiation therapy with or without trastuzumab after lumpectomy for HER2-positive DCIS

Track 13 **CASE DISCUSSION:** An 80-year-old woman with a 1.5-cm, node-positive, ER-positive, PR-positive, HER2-negative lobular carcinoma

Track 14 Clinical use of the Onco*type* DX assay for node-positive, ER-positive BC

CASE DISCUSSION: An 80-year-old woman with a 4-mm, node-negative, ER-positive, PR-negative, HER2-positive invasive ductal carcinoma (IDC) who underwent segmental mastectomy

Select Excerpts from the Interview

Tracks 1, 4

DR LOVE: What were your thoughts about the next steps of treatment for this woman?

DR WOLMARK: Here's the dilemma: Are we going to take this individual who's 80 years old — without any comorbid conditions and with a life expectancy of approximately 11 years — and treat her disease with chemotherapy and trastuzumab?

From my standpoint, we have another assay that could allow us to examine the risk for this patient, and that's Onco*type* DX. The impression among physicians is that Onco*type* should not be performed for patients with HER2-positive disease because they all fall into a high-risk category. That's not true — some of these patients fall into an intermediate-risk category. However, for this particular patient the germane issue was whether to take an IHC3+ result from a local laboratory at face value when deciding upon therapy for an 80-year-old woman with a 4-mm tumor. The laboratory did not want to perform FISH, as she had an IHC3+ result, so I ordered the Onco*type* DX assay.

Surprisingly, Onco*type* DX indicated that HER2 fell in the normal range. So, armed with those data, we convinced our lab to conduct FISH and it confirmed that the tumor was HER2-negative.

DR LOVE: What was the Recurrence Score?

DR WOLMARK: The Recurrence Score was 18, and the assay results compelled us to reassess our therapeutic considerations. She was able to avoid chemotherapy and trastuzumab, which is not an easy regimen and, considering her tumor characteristics, would not have helped her.

DR LOVE: Obtaining accurate and reliable information about ER and HER2 is a critical component of the current breast cancer treatment algorithm. What role do you think RT-PCR and tests such as Onco*type* DX will have in trying to obtain better information to help guide decision-making?

DR WOLMARK: I believe that Onco*type* DX or other objective molecular-based assays will drive therapeutic decision-making, and I'm always amazed and amused that the morphologic pathologists rant and rave at statements of that nature. Pathologists should be embracing these developments and be on the leading edge for moving the state of the art toward a molecular taxonomy of breast cancer.

Track 3

DR LOVE: Can you discuss the NSABP/CIRG collaborative adjuvant trial — BETH — for patients with HER2-positive breast cancer?

DR WOLMARK: The BETH trial is evaluating the addition of bevacizumab to chemotherapy/trastuzumab, based on compelling data from preclinical studies and Phase II clinical trials (Pegram 2006).

DR LOVE: The chemotherapy doesn't include an anthracycline. Can you review the discussions that took place in selecting a nonanthracycline-containing regimen for the BETH trial?

DR WOLMARK: We were influenced by the results from BCIRG 006 (Slamon 2006). When adding bevacizumab to trastuzumab, our bias was to pick a regimen that had the least cardiotoxicity because we didn't want to encounter a situation in which cardiotoxicity would undermine the entire trial. However, the trial does make allowances for the use of an anthracycline-containing regimen if the investigator so desires. Our preference was to proceed with a nonanthracycline-containing regimen.

Tracks 8-9

DR LOVE: What are your thoughts on the results presented at the 2008 San Antonio Breast Cancer Symposium from the meta-analyses of the trials with adjuvant aromatase inhibitors (Ingle 2008) and the BIG 1-98 trial evaluating letrozole versus tamoxifen versus a switching strategy (Mouridsen 2008)?

DR WOLMARK: They were interesting papers, but will my standard change as far as starting postmenopausal patients on aromatase inhibitors as adjuvant therapy? No. I believe starting with an aromatase inhibitor is standard, and the data presented, even with the somewhat unconventional and original endpoints, reinforced it.

DR LOVE: Can you review the issue of the duration of adjuvant therapy with aromatase inhibitors?

DR WOLMARK: I believe it's an important question. We don't want another dilemma like we had with tamoxifen, for which it took NSABP-B-14 to determine that 10 years of tamoxifen added no benefit compared to five years of tamoxifen for patients with node-negative, ER-positive disease (Fisher 2001). Not only did it not add an advantage, but the adverse events such as endometrial carcinoma and deep venous thrombosis (DVT) also continued between five and 10 years. Those results determined the five-year duration of adjuvant tamoxifen.

For postmenopausal women, we started using adjuvant aromatase inhibitors, and the duration of adjuvant tamoxifen lost its relevance. To address the issue relative to the aromatase inhibitors, we're conducting the NSABP-B-42 study comparing five versus 10 years of adjuvant hormonal therapy. We are enrolling patients who have received five years of either an aromatase inhibitor or a combination of tamoxifen followed by an aromatase inhibitor. They will be randomly assigned to five years of letrozole or placebo (2.1). ■

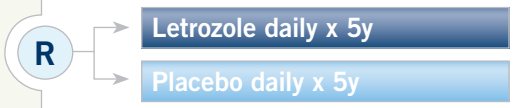
2.1

NSABP-B-42: Adjuvant Letrozole After Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor or Tamoxifen Followed by an Aromatase Inhibitor

Protocol IDs: NSABP-B-42; NCT00382070

Eligibility

- Postmenopausal
- No later than six months after completion of five years of hormonal therapy
- ER-positive and/or PR-positive
- Invasive breast cancer



Primary Endpoint
- Disease-free survival

Secondary Endpoints
- Survival, recurrence-free interval, distant recurrence-free interval, osteoporotic fracture rate, arterial thrombosis

Target Accrual: 3,840 over 5.25 years

Date Activated: August 14, 2006

Study Contact
National Surgical Adjuvant Breast and Bowel Project
Eleftherios P Mamounas, MD, MPH
Protocol Chair

SOURCES: NSABP-B-42 Protocol, June 2009; **www.nsabp.pitt.edu**; NCI Physician Data Query, June 2009.

SELECT PUBLICATIONS

Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-90.

Ingle JN et al. **Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies.** San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

McCaskill-Stevens W et al. **Contralateral breast cancer and thromboembolic events in African American women treated with tamoxifen.** *J Natl Cancer Inst* 2004;96(23):1762-9.

Mouridsen HT et al. **BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

Pegram M et al. **Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 301**.

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**.

Wapnir IL et al. **Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials.** *J Clin Oncol* 2006;24(13):2028-37.

Wickerham L et al. **Tamoxifen — An update on current data and where it can now be used.** *Breast Cancer Res Treat* 2002;75(Suppl 1):7-12.

INTERVIEW

Hope S Rugo, MD

Dr Rugo is Clinical Professor of Medicine and Director of Breast Oncology and Clinical Trials Education at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco in San Francisco, California.

Tracks 1-13

Track 1 **CASE DISCUSSION:** A 66-year-old woman with a 0.7-cm, node-negative, intermediate-grade, ER-positive, PR-positive, HER2-positive IDC

Track 2 Risk of recurrence associated with small, node-negative, HER2-positive BC

Track 3 Clinical use of the Onco*type* DX assay for node-negative, ER-positive BC

Track 4 Clinical use of adjuvant docetaxel/cyclophosphamide

Track 5 Combining adjuvant trastuzumab with a nonanthracycline-containing regimen

Track 6 Effect of the Onco*type* DX Recurrence Score on treatment selection for patients with ER-positive, node-positive BC

Track 7 Arthralgias as potential predictors of benefit from adjuvant AIs

Track 8 Tamoxifen metabolism by CYP2D6 and treatment efficacy

Track 9 Viewpoint on the relationship between therapy-related side effects and efficacy

Track 10 Compliance with adjuvant hormonal therapy

Track 11 **CASE DISCUSSION:** A 44-year-old premenopausal woman who underwent mastectomy for a 4.2-cm, node-positive, Grade II, ER-positive, PR-positive, HER2-negative invasive mixed ductal and lobular carcinoma

Track 12 ECOG-E5103: Adjuvant AC → weekly paclitaxel with or without bevacizumab for node-positive or high-risk, node-negative BC

Track 13 T-DM1: Trastuzumab linked with a derivative of maytansine 1

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the risk of recurrence for patients with small, node-negative, HER2-positive breast cancers?

DR RUGO: The most recent data presented at the 2008 San Antonio Breast Cancer Symposium from MD Anderson evaluated patients who had small (one centimeter or smaller), node-negative breast cancers. These data suggested that small HER2-positive tumors have a relatively high relapse risk with a five-year recurrence rate of 23 percent (Rakkhit 2008; [3.1]).

3.1

Recurrence-Free Survival (RFS) and Distant Recurrence-Free Survival (DRFS) in Subgroups of Patients with Small (≤1 cm), Node-Negative Breast Cancer

	Five-year estimate	
Breast cancer subgroup	RFS $p < 0.0001$	DRFS $p < 0.0001$
HER2-positive	77.1%	86.4%
Triple-negative	85.2%	95.6%
ER/PR-positive	95.2%	97.5%

SOURCE: Rakkhit R et al. San Antonio Breast Cancer Symposium 2008;**Abstract 701**.

Track 6

DR LOVE: What are your thoughts about using the Onco*type* DX assay for patients with node-positive, ER-positive disease?

DR RUGO: The Onco*type* DX assay can be used more safely for patients who have minimal disease in their nodes. I'm sure we're using chemotherapy for patients with node-positive disease who are not benefiting. I don't, however, believe that we know who those patients are yet, either by an Onco*type* DX Recurrence Score or MammaPrint®.

I would be comfortable using the Onco*type* DX assay for postmenopausal women with strongly ER-positive, PR-positive, low-grade disease and a micrometastasis in a node. Those are patients for whom a low Onco*type* DX Recurrence Score would convince me to use hormonal therapy alone. For patients with truly node-positive disease, the relapse rate was still high with a FAC-type regimen for the patients who had low Onco*type* DX Recurrence Scores in SWOG-8814 (Albain 2007; [3.2]). Rather than not using chemotherapy, the lesson is that we need to use chemotherapy in a smarter way.

3.2

Effect of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to the Onco*type* DX Recurrence Score

	10-year disease-free survival estimates	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low Recurrence Score (<18)	60%	64%
Intermediate Recurrence Score (18-30)	49%	63%
High Recurrence Score (≥31)	43%	55%

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Track 12

DR LOVE: Would you review the ECOG-E5103 adjuvant trial (3.3)?

DR RUGO: This study is evaluating whether bevacizumab improves the efficacy of adjuvant chemotherapy for HER2-negative, early breast cancer. The basis for the trial design includes preclinical data and two first-line trials in the metastatic setting. ECOG-E2100 demonstrated a marked improvement in response rate and a doubling in time to disease progression when bevacizumab was combined with paclitaxel (Miller 2007).

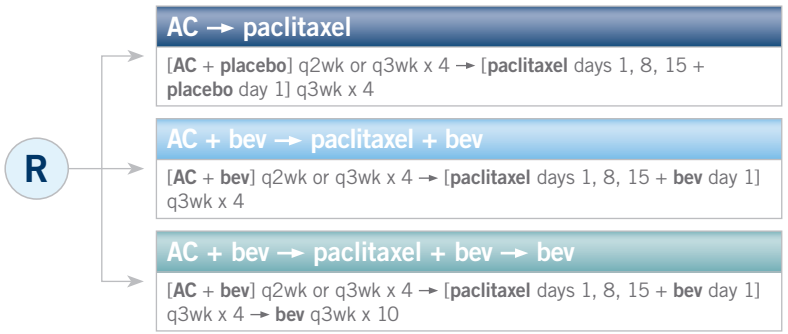
The AVADO trial found some improvement when bevacizumab was combined with docetaxel, even though the chemotherapy was discontinued before patients' disease progressed (Miles 2008).

ECOG-E5103 involves a randomization to three arms, in which patients receive AC → paclitaxel. Patients on Arm A receive a placebo infusion, whereas those on Arms B and C receive bevacizumab during chemotherapy. At the end of the chemotherapy, patients on Arm C continue to receive one year of bevacizumab (3.3).

3.3

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

Protocol IDs: ECOG-E5103, NCT00433511; Accrual: 4,950



Eligibility

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

SOURCE: NCI Physician Data Query, June 2009.

Track 13

DR LOVE: Would you review the novel agent for HER2-positive disease, T-DM1?

DR RUGO: This is a fascinating drug, a smart-bomb approach. It's trastuzumab linked to a chemotherapy agent called derivative of maytansine 1 (DM1). DM1 is similar to the vinca alkaloids, such as vincristine or vinorelbine. It destabilizes the microtubules that are important for cell division and causes cell death. DM1 has been around for a long time and was tested in Phase I trials, but it was too toxic and caused hepatic toxicity and thrombocytopenia. When trastuzumab binds to the HER2 receptor, the T-DM1 complex is internalized. The linker is digested inside the cell to release the DM1, and little free drug exposure occurs.

In our Phase II trial, we've seen patients respond to the drug with minimal toxicity — some thrombocytopenia, an increase in liver enzymes and a bit of nausea and vomiting occur, but no hair loss. The responses are dramatic in patients who have disease refractory to both trastuzumab and lapatinib (Vukelja 2008; [3.4]). ■

3.4

Phase II Study of Trastuzumab-DM1 (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer That Had Progressed on Trastuzumab/Chemotherapy: Interim Efficacy Data

Median follow-up, 4.4 months (19 weeks)

Tumor response	N	Overall objective response rate*	Confirmed† objective response rate*
All efficacy-evaluable patients	107	39.3%	27.1%
Centrally confirmed HER2-positive disease	64	50.0%	34.4%
Antitumor activity in lapatinib-treated patients	60	38.3%	21.7%

* Partial response plus complete response
† Complete or partial response determined on two consecutive occasions ≥4 weeks apart

SOURCE: Vukelja S et al. San Antonio Breast Cancer Symposium 2008;**Abstract 33**.

SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76.

Rakkhit R et al. **Significant increased recurrence rates among breast cancer patients with HER2-positive, T1a,bN0M0 tumors.** San Antonio Breast Cancer Symposium 2008;**Abstract 701**.

Vukelja S et al. **A phase II study of trastuzumab-DM1, a first-in-class HER2 antibody-drug conjugate, in patients with HER2+ metastatic breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 33**.

INTERVIEW

Lisa A Carey, MD

Dr Carey is Medical Director of the UNC Breast Center at the University of North Carolina at Chapel Hill's Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-15

Select Excerpts from the Interview

Track 3

DR LOVE: What are some of the new research strategies being evaluated as adjuvant therapy for HER2-positive disease?

DR CAREY: The agent we now use in the adjuvant setting is trastuzumab, but a number of large trials are evaluating the role of the oral tyrosine kinase inhibitor lapatinib. It wouldn't surprise me if the preclinical hypothesis — that the combination of two HER2-targeted drugs is better than one — proves to be true. A number of large adjuvant trials will answer that question.

DR LOVE: We're starting to see hints from data in the metastatic setting that perhaps combining trastuzumab and lapatinib may be better.

DR CAREY: Among patients with disease progression while receiving trastuzumab, those who continue trastuzumab with the addition of lapatinib fare better than those switched to lapatinib alone (O'Shaughnessy 2008; [4.1]).

George Sledge once stated, "One dumb tumor is still smarter than 10 smart oncologists." As tumors figure out ways around our drugs, we may have to keep blocking the first pathway as we start blocking the alternate mechanisms that the cell uses to stay alive.

DR LOVE: Can you discuss how trastuzumab and lapatinib target the cancer cell?

DR CAREY: Trastuzumab, a monoclonal antibody, binds to the outside of the cell. Originally, it was thought to work entirely by receptor downregulation. This may be true in part, but it also induces apoptosis, has hypoproliferative effects and induces a favorable immune response. Lapatinib, a small molecule, operates on the inside of the cell. It is an inhibitor of tyrosine kinase. Lapatinib and trastuzumab may be synergistic because they operate at two different parts of the signaling pathway.

4.1

Phase III Study of Lapatinib with or without Trastuzumab for Heavily Pretreated Patients with HER2-Positive Metastatic Disease Progressing on Trastuzumab

Efficacy parameter	Lapatinib alone	Lapatinib + trastuzumab	Odds ratio	*p*-value
Response rate[1]	6.9%	10.3%	1.5	0.46
Clinical benefit ratio[2]	12.4%	24.7%	2.2	0.01
Efficacy parameter	**Lapatinib alone**	**Lapatinib + trastuzumab**	**Hazard ratio**	***p*-value**
Progression-free survival	8.1 weeks	12.0 weeks	0.73	0.008
Overall survival	39 weeks	51.6 weeks	0.75	0.106
Adjusted overall survival	NR	NR	0.71	0.0596

[1] Confirmed complete response (CR) + partial response (PR)
[2] CR + PR + stable disease ≥ 6 months

SOURCE: O'Shaughnessy J et al. *Proc ASCO* 2008;**Abstract 1015**.

Track 7

DR LOVE: What new strategies are being evaluated for patients with triple-negative breast cancer?

DR CAREY: ECOG-E2100 demonstrated that patients with metastatic disease benefited from the addition of bevacizumab to paclitaxel in terms of a longer

progression-free survival. In the subset analysis by hormone receptor status, patients with triple-negative disease showed a benefit similar to or maybe a little better than the average patient in the trial (Miller 2007; [4.2]). This suggests that a targeted agent with anti-angiogenic properties may be effective for patients with triple-negative disease. The concept is being tested directly in CALGB-40603, a neoadjuvant study for patients with triple-negative, Stage II or III breast cancer. Patients are randomly assigned to paclitaxel with or without bevacizumab followed by dose-dense AC prior to surgery. In addition, patients are randomly assigned to receive carboplatin or not.

4.2

ECOG-E2100: Paclitaxel/Bevacizumab versus Paclitaxel Alone as First-Line Therapy for HER2-Negative Metastatic Breast Cancer

Progression-free survival according to hormone receptor status

	Number of patients	Paclitaxel/ bevacizumab	Paclitaxel alone	Hazard ratio (95% CI)
ER-negative/PR-negative	233	8.8 months	4.6 months	0.53 (0.40-0.70)
ER-positive/PR-negative	109	12.6 months	9.3 months	0.88 (0.58-1.33)
ER-positive/PR-positive	289	14.4 months	8.0 months	0.54 (0.44-0.70)

SOURCE: Miller K et al. *N Engl J Med* 2007;357(26):2666-76.

Track 10

DR LOVE: Would you talk about the use of genomic assays such as Onco*type* DX in the neoadjuvant setting?

DR CAREY: The Onco*type* DX assay has been evaluated in the neoadjuvant setting. Luca Gianni — in one of the first studies evaluating chemotherapy sensitivity via the Onco*type* DX Recurrence Score — demonstrated that a pathologic complete response was associated with a high score (Gianni 2005; [4.3]). These patients had extremely high Recurrence Scores because many of them had ER-negative, locally advanced disease.

4.3

Onco*type* DX Recurrence Score (RS) as a Predictor of Response to Neoadjuvant Chemotherapy

"The RS has been validated to quantify the risk of recurrence in tamoxifen-treated patients with node-negative, ER-positive breast cancer. We show here that RS strongly correlated with pCR. This has a provocative clinical implication, namely, that patients with high RS values, who are most likely to experience recurrence, are the very patients most likely to receive the greatest clinical benefit from chemotherapy treatment."

SOURCE: Gianni L et al. *J Clin Oncol* 2005;23(29):7265-77.

Track 13

DR LOVE: Would you discuss your viewpoint on adjuvant endocrine therapy for postmenopausal patients with ER-positive disease?

DR CAREY: The bottom line is that the inclusion of aromatase inhibitors is a crucial component of therapy. The issue of using a switching strategy with tamoxifen followed by an aromatase inhibitor versus an up-front aromatase inhibitor is a common question. For patients at higher risk, I incorporate an aromatase inhibitor early. For patients at lower risk, a switching strategy is reasonable.

The most pressing question currently is, how long should treatment be continued? The hazard rates of relapse examined on a year-to-year basis indicate that the risk continues over time. So a certain group of patients are at risk for relapse after five, 10 or 15 years, and for those patients prolonged endocrine strategies are probably appropriate.

DR LOVE: How do you approach the continuation or discontinuation of an adjuvant aromatase inhibitor for a patient who's been receiving it for five years?

DR CAREY: Outside of a protocol setting, I'm comfortable with patients receiving five years of an aromatase inhibitor, regardless of how much tamoxifen they have received before. I believe you have to gauge it by their risk. For small Stage I cancer, the absolute risk is probably relatively low — hence the absolute benefit after that fifth year is also fairly low.

For those with higher-risk disease, I have a conversation with each patient, and for some we continue it. It is, however, something we have a specific discussion about in the fifth year. ■

SELECT PUBLICATIONS

Dowsett M, Dunbier AK. **Emerging biomarkers and new understanding of traditional markers in personalized therapy for breast cancer.** *Clin Cancer Res* 2008;14(24):8019-26.

Gianni L et al. **Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer.** *J Clin Oncol* 2005;23(29):7265-77.

Gordon CR et al. **A review on bevacizumab and surgical wound healing: An important warning to all surgeons.** *Ann Plast Surg* 2009;62(6):707-9.

Goss PE et al. **Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen.** *J Clin Oncol* 2008;26(12):1948-55.

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76.

Muss HB et al. **Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG Intergroup trial MA.17.** *J Clin Oncol* 2008;26(12):1956-64.

O'Shaughnessy J et al. **A randomized study of lapatinib in combination with trastuzumab versus lapatinib monotherapy in heavily pretreated HER2+ metastatic breast cancer patients progressing on trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1015**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A teaching hospital in New York City recently reported that _____ are performed as the initial diagnostic test by private practice breast surgeons and general surgeons in 36 percent of patients with breast abnormalities.**
   a. Excisional biopsies
   b. Image-guided needle biopsies
   c. Both a and b
   d. None of the above
2. **Which procedure should be performed as the initial diagnostic test for the majority of women with image-detected breast abnormalities?**
   a. Excisional biopsies
   b. Image-guided needle biopsies
   c. Either a or b
   d. None of the above
3. **The BETH trial is evaluating adjuvant chemotherapy/trastuzumab with or without _____ for patients with HER2-positive breast cancer.**
   a. Lapatinib
   b. Bevacizumab
   c. T-DM1
   d. Pertuzumab
4. **NSABP-B-42 is evaluating the duration of adjuvant _____ for early breast cancer.**
   a. Hormonal therapy
   b. Trastuzumab
   c. Chemotherapy
   d. All of the above
5. **Trastuzumab and lapatinib are believed to affect different segments of the HER2-signaling pathway.**
   a. True
   b. False
6. **ECOG-E5103 is evaluating _____ in combination with adjuvant chemotherapy for HER2-negative early breast cancer.**
   a. Trastuzumab
   b. Bevacizumab
   c. T-DM1
   d. Lapatinib
7. **T-DM1 is an investigational biologic agent consisting of _____ linked to a chemotherapy drug known as DM1.**
   a. Trastuzumab
   b. Bevacizumab
   c. Lapatinib
   d. Tamoxifen
8. **Among patients with heavily pretreated, HER2-positive metastatic breast cancer that progressed on trastuzumab, those who received lapatinib/trastuzumab had a _____ outcome compared to those treated with lapatinib alone.**
   a. Better
   b. Similar
   c. Worse
9. **Data from MD Anderson suggest that node-negative, HER2-positive breast tumors that are one centimeter or smaller have a five-year recurrence rate of about _____ percent.**
   a. Five
   b. 10
   c. 20
   d. 40
10. **CALGB-40603 will be evaluating chemotherapy with or without bevacizumab in the _____ setting for triple-negative breast cancer.**
    a. Neoadjuvant
    b. Adjuvant
    c. Metastatic
    d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update for Surgeons — Issue 2, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Amount of additional time required in the operating room for the use of intraoperative radiation therapy	4 3 2 1	4 3 2 1
Efficacy and safety of extending adjuvant hormonal therapy beyond five years for patients with ER-positive disease	4 3 2 1	4 3 2 1
Risk of recurrence for small, node-negative, HER2-positive breast cancer	4 3 2 1	4 3 2 1
NSABP-B-43: Radiation therapy with or without trastuzumab after lumpectomy for HER2-positive DCIS	4 3 2 1	4 3 2 1
ECOG-E5103: Adjuvant AC → weekly paclitaxel with or without bevacizumab for node-positive or high-risk, node-negative breast cancer	4 3 2 1	4 3 2 1
Use of genomic assays to select patients with ER-positive breast cancer for adjuvant chemotherapy	4 3 2 1	4 3 2 1
Mechanism of action of trastuzumab-DM1	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Assess the evolving role of oncoplastic breast surgery. . . . . 4 3 2 1 N/M N/A
- Counsel women requiring breast biopsy about the diagnostic precision of the image-guided needle versus the excisional approach. . . . . 4 3 2 1 N/M N/A
- Identify women with breast cancer who may be candidates for partial breast irradiation, and discuss ongoing clinical trials evaluating intraoperative radiation therapy. . . . 4 3 2 1 N/M N/A
- Develop an algorithm for the treatment of node-negative, HER2-positive early breast cancer, considering the tumor size and the ER status. . . . . 4 3 2 1 N/M N/A
- Advise postmenopausal patients with hormone receptor-positive early breast cancer about the benefits and risks of (1) initial adjuvant therapy with an aromatase inhibitor, tamoxifen or a sequence of both agents and (2) extended adjuvant hormonal therapy. . . . . 4 3 2 1 N/M N/A
- Use tissue-based genomic assays to aid in the selection of individualized treatment strategies, when applicable, for patients with ER-positive early breast cancer. . . . 4 3 2 1 N/M N/A
- Summarize the emerging data on select novel therapeutic agents or regimens in the treatment of breast cancer. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about participation in ongoing adjuvant and neoadjuvant clinical trials. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?

Additional comments about this activity:

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.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Melvin J Silverstein, MD	4 3 2 1	4 3 2 1
Norman Wolmark, MD	4 3 2 1	4 3 2 1
Hope S Rugo, MD	4 3 2 1	4 3 2 1
Lisa A Carey, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

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

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

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

Breast Cancer®

UPDATE

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