

Breast Cancer[®]

U P D A T E

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

EDITOR

Neil Love, MD

FACULTY

Mark D Pegram, MD

Victor G Vogel, MD, MHS

Debu Tripathy, MD

Robert W Carlson, MD



Breast Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF BREAST CANCER UPDATE

The purpose of Issue 7 of Breast Cancer Update is to support these global objectives by offering the perspectives of Drs Pegram, Vogel, Tripathy and Carlson 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.

CREDIT DESIGNATION STATEMENT

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

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. BreastCancerUpdate.com includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in [blue underlined text](#).

3 EDITOR'S NOTE

Cancer Q&A

5 INTERVIEWS

Mark D Pegram, MD

Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Women's Cancer Program
UCLA/Jonsson Comprehensive Cancer Center
Los Angeles, California

14 Victor G Vogel, MD, MHS

Director, Magee/UPCI Breast Cancer Prevention Program
Professor of Medicine and Epidemiology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

22 Debu Tripathy, MD

Professor of Internal Medicine
Director, Komen UT Southwestern Breast Cancer Research Program
University of Texas Southwestern Medical Center
Dallas, Texas

30 Robert W Carlson, MD

Professor of Medicine
Division of Oncology and Stanford Medical Informatics
Stanford University Medical Center
Stanford, California

38 POST-TEST

39 EVALUATION FORM

If you would like to discontinue your complimentary subscription to *Breast Cancer Update*, please email us at Info@ResearchToPractice.net, or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Anne Jacobson, MPH, Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Margaret Peng, Lillian Sklaver Poltorack, PharmD, Ginelle Suarez, Chris Thomson, MD, MS, Erin Wall and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Marie Bialek, PharmD — freelance/contractor: McNeil Consumer & Specialty Pharmaceutica Products LP; salary (spouse): AstraZeneca Pharmaceuticals LP; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc and Genentech BioOncology. Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech BioOncology/OSI Pharmaceuticals Inc, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Pegram — Consulting Fees: AstraZeneca Pharmaceuticals LP, Genentech Inc, Sanofi-Aventis. **Dr Vogel** — Consulting Fees: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Genomic Health Inc; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Genomic Health Inc, Novartis Pharmaceuticals Corporation; Contracted Research: Abraxis Oncology, AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Genentech Inc, Novartis Pharmaceuticals Corporation. **Dr Tripathy** — Consulting Fees: Genentech Inc, Roche Laboratories Inc; Contracted Research: AstraZeneca Pharmaceuticals LP, Genentech Inc, Roche Laboratories Inc. **Dr Carlson** — Contracted Research: AstraZeneca Pharmaceuticals LP; Consulting Fees: AstraZeneca Pharmaceuticals LP, Genentech Inc, Genomic Health Inc; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

UPCOMING EDUCATIONAL EVENTS

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

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

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

American Society of Breast Disease
April 12-14, 2007
San Francisco, California
Event website: asbd.org

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

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



EDITOR'S NOTE

Neil Love, MD

Cancer Q&A

Our CME group recently launched an interesting pilot audio program for cancer patients, their loved ones, physicians, nurses and other oncology health-care professionals dedicated to improving cancer education. We call this Phase I initiative Cancer Q&A because, well, that's what we do...we ask questions and you hear the answers.

Like most of the series we produce for oncology professionals, the core of this patient ed series (available in both CD format and on the internet at CancerQandA.com) is the audio interview, and over the next few months, our hope is to distribute more than 18 hours of conversations about both breast and colorectal cancer. The goal is to supplement and reinforce what patients learn in the oncology office.

It's both scary and humbling to try to figure out what might be useful to people confronting cancer, but we have to believe that one source of important and relevant information would be experts in the field. So in breast cancer, our first shot at this includes five CDs worth of educational insights provided by Kathy Miller, Joyce O'Shaughnessy, Dennis Slamon, Rowan Chlebowski, George Sledge, Bill Gradishar and Hal Burstein. Our group has very high hopes for the long-term viability of this series, but we shall see.

While Q&A is an obvious aspect of our traditional audio programs, we also really like to ask people poll questions about what they think and do. The answers to these queries may not be as straightforward, but they are always interesting and, we believe, very valuable.

Our favorite pollees in this regard are clinical researchers, and this year alone we hosted five Think Tank meetings for which we utilized premeeting surveys to gauge clinical investigator opinion on a number of controversial issues. The results were incorporated into the discussion during the meetings and were often intriguing and thought provoking, particularly because of the considerable heterogeneity in perspectives that emerged among these elite investigators. I guess that's why they call these things controversies.

On this issue of *Breast Cancer Update*, we take the Q&A approach to another level and we ask Dr Bob Carlson to comment on the results of a survey generated prior to a recent breast cancer Think Tank. Dr Carlson was unfortunately not able to attend that meeting, and it was highly interesting and entertaining

to watch his evidence-based, NCCN guideline-trained mind chew up controversy after controversy post hoc. I personally found it hard to disagree with anything he said and was particularly interested in his answer to a question tossed his way toward the end of the interview:

“Agree, disagree or in between? Single-agent capecitabine is generally the optimal choice of first-line systemic chemotherapy for most patients with metastatic breast cancer, including patients with no prior exposure to chemotherapy.”

Bob paused for about three seconds, looked me straight in the eye and said, “Agree.” His explanation was evidence- and quality of life-based, and I couldn’t help but feel that Bob’s patients are truly lucky to have such a fine and caring oncologist to hold their hands and lead the way.

Another Q&A function our group serves is the implementation of polls of *patients*. Our most recent study was of 100 people who received adjuvant chemotherapy for colon cancer in the last five years. The interesting bottom line is that both oxali-receiving and nonoxali-receiving patients generally found the experience somewhat different than what they expected, and 40 percent would go through the same therapy again for a one percent reduction in their risk of relapse.

My favorite set of *oncologist* Q&As was from our August 2005 survey of 145 docs demonstrating that just a couple of months after the initial ASCO presentations of the adjuvant trastuzumab trials, a profound change in clinical practice had already occurred, and more than 90 percent of oncologists were adapting treatment patterns similar to clinical investigators. I like that. It makes me feel that the onco-world has efficient communication channels.

The next question is, “When are we going to find some answers? When are we going to put ourselves out of business? When are we going to get this thing done?”

— Neil Love, MD
NLove@ResearchToPractice.net
November 17, 2006

SELECT PUBLICATIONS

NCCN Clinical Practice Guidelines in Oncology™. *Breast Cancer* V.2.2006. nccn.org

Perez EA et al. **NCCTG N9831: May 2005 update**. Presentation. ASCO 2005. No abstract available

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

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



INTERVIEW

Mark D Pegram, MD

Dr Pegram is Associate Professor of Medicine at the David Geffen School of Medicine at UCLA and Director of the Women's Cancer Program at the UCLA/Jonsson Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-28

- Track 1 Introduction
- Track 2 Case discussion: A 68-year-old woman with HER2-positive, ER-positive, node-negative breast cancer averse to receiving chemotherapy
- Track 3 Counseling patients about the benefits of adjuvant chemotherapy
- Track 4 Estimating the risk of relapse for patients with HER2-positive, ER-positive, node-negative disease
- Track 5 Utility of the *Oncotype DX*[™] assay for treatment decision-making in HER2-positive and HER2-negative disease
- Track 6 Relative benefit of chemotherapy, hormonal therapy and trastuzumab for patients with HER2-positive, ER-positive disease
- Track 7 Clinical use of trastuzumab monotherapy in combination with hormonal therapy
- Track 8 Adjuvant trastuzumab for patients with small node-negative tumors
- Track 9 Selection of adjuvant hormonal therapy based on HER2 status
- Track 10 Biologic rationale for combining trastuzumab with fulvestrant
- Track 11 Delayed adjuvant trastuzumab
- Track 12 Concurrent versus sequential use of adjuvant chemotherapy and trastuzumab
- Track 13 Role of quantitative amplification of HER2 by FISH in treatment decision-making
- Track 14 Concordance between community and reference laboratory FISH testing
- Track 15 Use of FISH versus immunohistochemistry
- Track 16 Selection of a chemotherapeutic regimen to combine with adjuvant trastuzumab
- Track 17 Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy: BCIRG 006
- Track 18 Dose-dense AC → paclitaxel with trastuzumab
- Track 19 Adjuvant chemotherapy for patients with HER2-negative, node-positive disease
- Track 20 Prophylactic growth factor support with TAC chemotherapy
- Track 21 Docetaxel/cyclophosphamide (TC) versus AC
- Track 22 FinHER: Adjuvant docetaxel or vinorelbine with or without trastuzumab
- Track 23 Importance of protocol-defined cardiac monitoring in clinical practice
- Track 24 Counseling patients about risk of cardiotoxicity and cardiac follow-up after completion of therapy with trastuzumab
- Track 25 Current clinical trials evaluating the safety and efficacy of bevacizumab in breast cancer
- Track 26 Thromboembolic and cardiac side effects of bevacizumab
- Track 27 Potential role for adjuvant lapatinib
- Track 28 Potential role of cMYC amplification as a predictor of response to trastuzumab

A 68-Year-Old Woman with HER2-Positive, Weakly ER-Positive, Node-Negative Breast Cancer (from the Practice of Mark Pegram, MD)

“I’ve recently seen a 68-year-old woman who presented with a mammographically detected breast cancer. A core-needle biopsy was positive for infiltrating ductal carcinoma. She had a lumpectomy and the sentinel lymph node was negative.

The tumor size was around 1.5 centimeters, and the characteristics on histology were a poorly differentiated tumor with a small component of ductal carcinoma in situ. The HER2 gene was strongly amplified, with a HER2 gene-to-chromosome 17 centromere ratio of about 10. The ER was weakly staining and in a minority of the tumor cells — 30 to 40 percent of the cell nuclei were stained, but the staining was a weak intensity, which is classic for a HER2-amplified tumor to have downregulation of the estrogen receptor.

In past years, this might be someone, by virtue of her age, for example, who we might not even consider for chemotherapy treatment in the adjuvant setting; instead, we might have relied on endocrine therapy because of its smoother toxicity profile.

She loathed the idea of toxicity from chemotherapy but had a recommendation from her referring oncologist to consider chemotherapy. We also discussed it as an option in her case, but she had a close relative who had been through chemotherapy for breast cancer in the past and had an unpleasant experience. This was a person who really was thoughtful and well educated and had the capacity to understand data. She brought a thoughtful perspective to the whole case.”

SOURCE: Track 2.

Select Excerpts from the Interview



Track 3

► **DR LOVE:** Can you talk about the discussions that went on between you and the patient?

► **DR PEGRAM:** In this situation, whether or not to use adjuvant systemic chemotherapy is always a dilemma. That’s always the issue with small, mammographically detected, lymph node-negative tumors.

We had serious discussions about chemotherapy and its side effects and to what degree it would reduce the risk of relapse according to computer algorithms such as Adjuvant! Online, which don’t yet incorporate HER2 into the equation.

If you note the hazard ratios for tamoxifen therapy for a small, ER-positive tumor and then add in chemotherapy, you see that it adds very little in terms of percentage differences in these types of estimations. So patients who can view those data critically will often decline chemotherapy for small, node-negative tumors. This tumor was 1.5 centimeters, so she was a candidate for chemotherapy. However, in the end she declined it.

► **DR LOVE:** You mentioned Adjuvant! Online, which doesn’t currently incor-

porate HER2 as a prognostic factor or trastuzumab. Did you discuss with her what you thought her numbers were?

► **DR PEGRAM:** Absolutely. In many situations I'll print out the results from Adjuvant! Online and thoroughly discuss them with a patient. Because I give a number of second opinions in a university-based clinic, I find that generally patients are given what I consider to be overestimates of the utility of systemic adjuvant chemotherapy for small, lymph node-negative tumors.

When they see the real numbers, it is sometimes sobering, but I believe it empowers patients to make informed decisions. So I find these types of algorithms useful.

Tracks 6-7

► **DR LOVE:** What was your estimate of how the risk of relapse would have been affected if this patient had been willing to go “full bore” with endocrine therapy, chemotherapy and trastuzumab?

► **DR PEGRAM:** The hazard ratios for all the adjuvant trastuzumab trials that have been reported — all of which have used chemotherapy in combination with trastuzumab or chemotherapy followed by trastuzumab — are coming in at around a half, with remarkable consistency across the studies. Remember, that hazard ratio of 0.5 is above and beyond chemotherapy and hormone therapy.

In subset analyses, the hazard ratio in favor of trastuzumab is similar for ER-positive and ER-negative disease, and in the European HERA trial (Piccart-Gebhart 2005), it was similar for lymph node-negative and node-positive disease. So trastuzumab will be the workhorse for a patient like this in the modern era. Chemotherapy and endocrine therapy will have a much less robust effect compared to trastuzumab.

She felt comfortable that the efficacy of trastuzumab, which had recently been demonstrated, would be sufficient in her mind without chemotherapy to reduce her risk of recurrence when administered in combination with endocrine therapy.

If I were to have administered chemotherapy, I would have offered her a nonanthracycline-based regimen as one of the options, based on the BCIRG data, specifically TCH (Slamon 2005).

Track 10

► **DR LOVE:** What about endocrine therapy for this patient? When you look at tamoxifen, the aromatase inhibitors and fulvestrant, which seems to make the most sense in terms of combining with trastuzumab?

► **DR PEGRAM:** Fulvestrant makes the most sense because in HER2-positive breast tumor cells there is ligand-independent activation of the estrogen receptor. That is, the cross talk between HER2 signaling and the estrogen receptor can activate

estrogen-dependent genes in the absence of estradiol. That predicts an absence of estradiol with aromatase inhibitors — no ligand for the ER — but the ER can still be turned on by HER2 signaling. So that's a strike against aromatase inhibitors. Tamoxifen can also be more agonistic as a result of this cross talk mechanism.

The question is, how can you tackle such a complex issue? It would be ideal to eliminate the estrogen receptor, and that's exactly what fulvestrant does. Therefore, it is appealing from a theoretical point of view to incorporate HER2-directed therapy with fulvestrant, and we have a randomized Phase II trial under way in the metastatic setting comparing fulvestrant alone to trastuzumab alone to the combination. It's accruing slowly, unfortunately, and may have to be pared down to get some point estimate on the activity of the combination in the future.

► **DR LOVE:** When you see a postmenopausal patient with metastatic disease that's ER-positive and HER2-positive, do you use trastuzumab with hormonal therapy?

► **DR PEGRAM:** Absolutely. I have a number of patients on fulvestrant and trastuzumab who are doing well, although they were started on the treatment off protocol because our protocol wasn't open when they started. I've had some nice anecdotal responders on that combination. Remember that many of these patients have already received adjuvant aromatase inhibitors anyway. So fulvestrant is a reasonable consideration when they relapse.

Tracks 16-17

► **DR LOVE:** If your patient's disease had been multiply node-positive and she had no special concerns about chemotherapy, which chemotherapy would you have used?

► **DR PEGRAM:** It all depends on one's estimate of the cardiac risk. If it was for a healthy patient who had a lot of positive nodes and I thought that she could safely tolerate an anthracycline-based regimen, then I would consider it.

The lion's share of young, healthy patients will tolerate anthracycline-based regimens, and even in the BCIRG 006 cohort, the numerically — though not statistically — superior arm is clearly in favor of the anthracycline followed by docetaxel/trastuzumab regimen.

► **DR LOVE:** What are your thoughts on the TOPO II data that came out of that trial?

► **DR PEGRAM:** We realized, based on the design of BCIRG 006, that we had a unique opportunity because we had a nonanthracycline arm and an anthracycline arm, both of which included trastuzumab, in a pure population of patients with HER2-amplified disease.

Dennis Slamon presented the preliminary data on the amplification of TOPO II at the plenary session during the 2005 San Antonio meeting, and Mike

Press had a poster also summarizing the data (Press 2005; Slamon 2005; [1.2]).

It's important to realize that it was an interim subset analysis of only the first couple of thousand of the 3,200 patients, and longer follow-up is needed. With those caveats, the hypothesis that coamplification of TOPO II and HER2 does confer additional benefit from anthracyclines seems to be indicated by this preliminary analysis.

1.2

BCIRG 006: Events Based on Treatment and Amplification of TOPO II

Treatment	TOPO II amplified		Non-TOPO II amplified	
	N	Events	N	Events
AC → T	227	10%	458	20%
AC → TH	265	5%	472	10%
TCH	252	8%	446	12%

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 1](#).

Track 19

▶ **DR LOVE:** For a patient with *HER2-negative*, node-positive disease, what tends to be the chemotherapeutic regimen that you use off protocol?

▶ **DR PEGRAM:** It depends on the patient's age, performance status and comorbid medical conditions. We have any number of active regimens to choose from, and I usually give the patients a menu of options (1.3).

When I see patients in consultation as a second opinion, if someone has been referred to me with node-positive disease and it has been recommended they receive dose-dense adjuvant chemotherapy, TAC or FEC followed by docetaxel, I'd say those are perfectly good regimens for lymph node-positive, early-stage breast cancer.

▶ **DR LOVE:** What about the controversy over whether TAC is better than dose-dense chemotherapy for patients with ER-positive disease?

▶ **DR PEGRAM:** For ER-positive disease, I have a hard time justifying the dose-dense approach. Findings for that subset, which is fully two thirds of the N9741 cohort, are negative to date (Citron 2003; Hudis 2005).

If you look at the principle on which the dose-dense adjuvant regimen was devised — the Norton-Simon hypothesis — you see that substantial regrowth of tumor cell populations between cycles is necessary for the dose-dense approach to work. For an indolent, ER-positive, slow-growing tumor, there will not be a substantial difference in the number of cells in somebody's body over a one-week period.

The Norton-Simon hypothesis predicts a population of indolent, slow-

growing breast tumors, for which dose-dense treatment is not necessary, and that's exactly what the data set shows.

- ▶ **DR LOVE:** So what chemotherapy regimen do you tend to use for those patients with ER-positive disease?
- ▶ **DR PEGRAM:** For ER-positive patients, again, it depends on their age, et cetera. If they're getting on in years, I'm more likely to use AC followed by weekly paclitaxel, for example, because that's so well tolerated. If they are young, fit, in their thirties, have no comorbid medical illnesses and have a number of positive nodes, I would have no hesitation using TAC (Martin 2005) because we participated in some of those TAC trials and we're comfortable with the regimen when we use pegfilgrastim.

Trial	Chemotherapy regimens	DFS	p-value	OS	p-value
Hudis 2005	AC/paclitaxel q3wk	71.7%	0.012	79.5%	0.049
	AC/paclitaxel q2wk	76.7%		83.0%	
Martin 2005a	FAC	68%	0.001	81.0%	NR
	TAC	75%		87.0%	
Roche 2004	FEC 100 x 6	73.2%	0.014	86.7%	0.017
	FEC 100 x 3 → docetaxel x 3	78.3%		90.7%	
Martin 2005b	FE ₉₀ C x 6	79.2%	0.0009	91.8%	0.1375
	FE ₉₀ C x 4 → paclitaxel qwk x 8	86.9%		94.5%	

DFS = disease-free survival; OS = overall survival; NR = not reported

SOURCES: Hudis C et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 41](#); Martin M et al. *N Engl J Med* 2005a;352(22):2302-13. [Abstract](#); Roche H et al. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 27](#); Martin M et al. San Antonio Breast Cancer Symposium 2005b; [Abstract 39](#).

Track 21

- ▶ **DR LOVE:** What were your thoughts about Steve Jones' presentation at San Antonio 2005 of the US Oncology adjuvant trial of docetaxel/cyclophosphamide versus AC (Jones 2005; [1.4])?
- ▶ **DR PEGRAM:** It was an exciting presentation, and I'm not surprised at all by the data. Steve presented a randomized trial for patients with early-stage breast cancer, approximately 40 to 50 percent of whom had node-negative disease. They were randomly assigned to four cycles of AC versus four cycles of TC. They showed a significant relapse-free survival advantage with the TC compared to the AC arm, and a numeric trend even appeared in the survival analysis, although it hasn't reached statistical significance yet. Steve Jones concluded — and probably rightly so — that this constitutes a new regimen that replaces AC. If you're going to use a four-cycle regimen, you probably wouldn't want to use AC anymore, based on this data set.

I was also favorably surprised by the toxicity and safety data. The TC was well tolerated compared to AC. It goes to show that we probably underestimate the toxicity of AC routinely because we're so used to prescribing it.

I saw a young woman within the past couple of weeks in my clinic with newly diagnosed doxorubicin cardiotoxicity after adjuvant therapy for what will probably be curable breast cancer. It's sobering and scary when you see cases like this.

1.4

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 66 Months)

	TC (n = 506)	AC (n = 510)	Hazard ratio	p-value
Five-year disease-free survival	86%	80%	0.67	0.015
ER-/PR-	HR = 0.64 (95% CI: 0.38-1.04)			
ER+ or PR+	HR = 0.71 (95% CI: 0.47-1.03)			
Node-positive	HR = 0.67 (95% CI: 0.45-0.98)			
Node-negative	HR = 0.73 (95% CI: 0.42-1.27)			
Five-year overall survival	90%	87%	0.76	0.131

Hazard ratios < 1 indicate values in favor of TC.

“Based on this trial, TC should now be considered a standard nonanthracycline adjuvant regimen for operable breast cancer.”

Toxicities (Grades III/IV)	TC	AC	p-value
Neutropenia	59%	55%	NS
Neutropenic fever	6%	3%	0.03
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01
Congestive heart failure	0	0	NS

“TC was associated with more low-grade myalgias, arthralgias, edema and febrile neutropenia. AC was associated with significantly more nausea and vomiting.”

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

 **Track 23**

► **DR LOVE:** Let's talk about the cardiac issues and trastuzumab. It's difficult for a physician in practice to sort this out because each trial approached it differently (1.5).

► **DR PEGRAM:** If you're going to consider an anthracycline-based adjuvant regimen followed by trastuzumab with taxanes, you need to tell patients that it carries a defined risk of cardiotoxicity. In particular, in the NSABP-B-31

adjuvant trastuzumab trial, after four cycles of AC approximately four to five percent of the patients were ineligible for adjuvant trastuzumab at all. If you were in clinical practice, it would be important to measure the ejection fraction before and after the AC to make sure that your patient would have met the eligibility for the study and you could draw on that safety database.

Moreover, during the year of adjuvant trastuzumab for the patients who received the drug, an additional approximately 15 percent of the patients had to drop out because of decreases in ejection fraction, which I find alarming. My fear is that in the community, busy practitioners will forget to obtain those ECHOs and MUGAs every three months, which was done on all of the adjuvant trastuzumab trials.

I'm fearful of what might happen for patients who have marked decreases in ejection fraction but may not be having symptoms from heart failure yet, and because they didn't get their ECHO or MUGA they are simply continued on more trastuzumab. That scares me, and clinicians need to know that if they're going to prescribe adjuvant trastuzumab, they should do so following the same guidelines that were used in those protocols.

► **DR LOVE:** Can you go through exactly what those were?

► **DR PEGRAM:** It was an ejection fraction assessment every three months during the one year of trastuzumab. If the ejection fraction decreased to less

1.5

Cardiac Event Rates and Cardiac Monitoring in the Adjuvant Trastuzumab Trials

	NSABP-B-31 ¹	NCCTG-N9831 ¹	HERA ²	BCIRG 006 ³
Cardiac event rates	AC → T: 0.8% AC → TH: 4.1%	AC → T: 0% AC → TH: 2.9%	Ch → observation: 0% Ch → T x 1 yr: 0.54%	AC → T*: 0.95% AC → TH [†] : 2.34% TCH: 1.33%
Protocol-defined cardiac events	NYHA Class III or IV CHF or death from cardiac causes		NYHA Class III or IV CHF and ≥10% ↓ from baseline in LVEF to <50%	Grade III/IV CHF, cardiac ischemia/infarction and arrhythmias, or cardiac death
Test to assess LVEF	MUGA	MUGA or ECHO	MUGA or ECHO	NR
Frequency of assessment	Baseline, post-AC, 6, 9 and 18 months after randomization		Baseline, 3, 6, 12, 18, 24, 30, 36 and 60 months after randomization	NR

AC → T = doxorubicin/cyclophosphamide → paclitaxel; AC → TH = doxorubicin/cyclophosphamide → paclitaxel/trastuzumab; Ch = chemotherapy; T = trastuzumab; AC → T* = doxorubicin/cyclophosphamide → docetaxel; AC → TH[†] = doxorubicin/cyclophosphamide → docetaxel/trastuzumab; TCH = docetaxel/carboplatin/trastuzumab; CHF = congestive heart failure; NYHA = New York Heart Association; NR = not reported

SOURCES: ¹ Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**; ² Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353(16):1659-72. **Abstract**; ³ Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005; **Abstract 1**.

than institutional norms, patients had to drop out. If it dropped 15 points and was above institutional norms, they had to hold the trastuzumab, at least temporarily, and wait for recovery. If recovery was evident on a follow-up one month later, then they were allowed to attempt to reinstitute it, as long as they were not symptomatic or at lower than institutional norms. These protocol guidelines are available, and they should be strictly followed if you're going to use anthracyclines.

Track 25

- ▶ **DR LOVE:** I heard that the NSABP and BCIRG are interested in the concept of an adjuvant trial evaluating bevacizumab and trastuzumab. Do you think that will happen?
- ▶ **DR PEGRAM:** I believe it will, but it all hinges on the pilot adjuvant bevacizumab trial that's under way now through ECOG. So we're anxiously awaiting the safety analysis of that trial. Of course, the primary endpoint for that study is cardiac safety.

Practicing clinicians should probably wait on the sidelines to see these safety data sets before embarking on any of these combinations on their own. These types of combinations are of serious concern, and clinicians shouldn't do anything off protocol in the absence of the Phase II data. ■

SELECT PUBLICATIONS

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](#)

Ellis MJ et al. **Estrogen-independent proliferation is present in estrogen-receptor HER2-positive primary breast cancer after neoadjuvant letrozole.** *J Clin Oncol* 2006;24(19):3019-25. [Abstract](#)

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

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

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. [Abstract](#)

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. [Abstract](#)

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

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



INTERVIEW

Victor G Vogel, MD, MHS

Dr Vogel is Director of the Magee/UPCI Breast Cancer Prevention Program and Professor of Medicine and Epidemiology at the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania.

Tracks 1-16

- | | | | |
|---------|---|----------|--|
| Track 1 | Introduction | Track 9 | Use of bisphosphonates to prevent aromatase inhibitor-associated bone loss and fractures |
| Track 2 | Development of the <i>Oncotype</i> DX assay | Track 10 | Duration of adjuvant hormonal therapy |
| Track 3 | Clinical use of <i>Oncotype</i> DX to assist in the selection of adjuvant therapy | Track 11 | NSABP-P-4: Letrozole versus raloxifene for the prevention of breast cancer |
| Track 4 | Utility of the <i>Oncotype</i> DX assay for patients with HER2-positive disease | Track 12 | Clinical use of aromatase inhibitors for ductal carcinoma in situ |
| Track 5 | Case discussion: A woman with a 1.2-cm, ER-positive, node-negative breast tumor and a high <i>Oncotype</i> recurrence score | Track 13 | NSABP-P-2: Study of Tamoxifen and Raloxifene (STAR) for the prevention of breast cancer |
| Track 6 | Predictability of <i>Oncotype</i> recurrence score based on classic clinical factors | Track 14 | Tolerability of raloxifene versus tamoxifen in the STAR trial |
| Track 7 | Applicability of <i>Oncotype</i> recurrence score for patients with large tumors | Track 15 | Acceptance of tamoxifen by women at high risk for breast cancer |
| Track 8 | Side effects of tamoxifen versus aromatase inhibitors | Track 16 | Importance of discussing adherence with patients receiving adjuvant hormonal therapy |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Can you talk about the development of the *Oncotype* DX assay?

► **DR VOGEL:** Using archival tissue blocks from past trials, Genomic Health and Dr Soon Paik from the NSABP (Paik 2004) analyzed about 200 genes that were reported to possibly relate to outcome in breast cancer. They narrowed that set down to just 16 genes that could be sorted into logical groups based on the estrogen receptor, the HER2 protein and proliferation and invasion characteristics of the cells.

That set of 16 genes plus five reference genes were used to see if breast cancer patients could be sorted into prognostic and predictive groups. When I say “prognostic” I mean to predict the likelihood of recurrence, and when I say “predictive” I mean to predict patients who would benefit from chemotherapy.

So these investigators examined the archival subsets and were able to determine that those 16 genes and five reference genes could be used to sort patients along a continuum they called the recurrence score, which varies from zero to 100. Using simple mathematic regression procedures, that recurrence score could then be translated into a probability of recurrence over 10 years.

► **DR LOVE:** What does the recurrence score tell us?

► **DR VOGEL:** The investigators were able to determine that patients who had low recurrence scores — that is, scores lower than 18 — benefited from hormonal therapy but derived no additional benefit from the addition of chemotherapy to their hormonal therapy regimens.

Conversely, patients with high recurrence scores — scores of 31 or higher — showed a clear, statistically significant and large benefit when cytotoxic chemotherapy was added to hormonal therapy — that is, tamoxifen.

In the intermediate group, the group with scores between 18 and 30, no benefit was apparent from the addition of chemotherapy, but the confidence intervals — the statistical certainty of no benefit — were not established.

What came out of that work was the *Oncotype DX* assay from Genomic Health. It is commercially available and essentially allows selection of patients for hormonal therapy alone or hormonal therapy with chemotherapy in the high-risk group.

► **DR LOVE:** What further studies are being conducted among patients who fall in the intermediate group?

► **DR VOGEL:** In the intermediate-risk group, we’re left with some uncertainty. An Intergroup clinical trial, known as the TAILORx (2.1) study, is for patients with ER-positive, node-negative, early-stage — Stage I, small Stage II — breast cancer. Patients with intermediate recurrence scores will be randomly assigned to chemotherapy or no chemotherapy, in addition to their hormonal therapy.

Track 4

► **DR LOVE:** The *Oncotype DX* data came out before we found out that adjuvant trastuzumab works so well. At this point, to what extent, if any, do you think the *Oncotype* is useful for patients with HER2-positive tumors?

► **DR VOGEL:** That’s an interesting question because some of the data that are emerging from the *Oncotype DX* data are perhaps counterintuitive. We can all cite examples of patients who had HER2-positive disease and were incorpo-

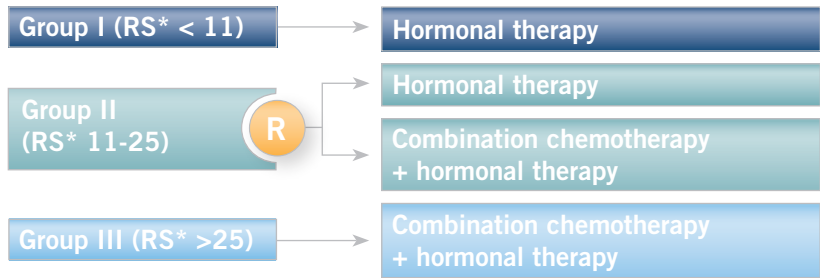
rated into the data set for *Oncotype DX*, yet their recurrence scores were not necessarily in the high-risk group. That is, the presence of HER2 doesn't, by itself, trump all the other genomic prognostic factors. That was a revelation to some of us because many of us had argued that the presence of the HER2 protein stratifies subsets. All the subsets appeared to indicate a worse prognosis for patients with HER2 overexpression compared to those whose disease was HER2-negative.

The question that remains unanswered by the available data is whether those patients who are HER2 overexpressors and will receive hormonal therapy alone should be receiving trastuzumab. Currently, we don't have an answer, but I believe trials have been envisioned to answer that question.

2.1

TAILORx: Phase III Randomized Study of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Node-Negative Breast Cancer with Various Levels of Risk for Recurrence

Protocol IDs: ECOG-PACCT-1, TAILORx, NCT00310180
 Target Accrual: 10,046 (Open)



* *Oncotype DX* recurrence score

Eligibility:

- Pre- or postmenopausal
- ER-positive and/or PR-positive
- HER2-negative

- Node-negative

Study Contact:

Eastern Cooperative Oncology Group
 Joseph Sparano, MD
 Tel: 718-920-4826

SOURCE: NCI Physician Data Query, July 2006.

Track 9

▶ **DR LOVE:** The NSABP just launched B-42, evaluating the duration of adjuvant aromatase inhibitor therapy. What's your take on the AIs?

▶ **DR VOGEL:** When we choose aromatase inhibitor therapy instead of tamoxifen, we tell patients that, compared to tamoxifen, aromatase inhibitors have a better safety profile. Fewer thromboembolic and uterine events are associated with

their use. We do have the issue of the bone events with the aromatase inhibitors.

Then we turn our attention to both the myalgias and arthralgias so patients are aware of those side effects when we start their therapy. Then we talk specifically about the bone data.

My impression of the bone data from the completed and reported adjuvant therapy trials is that, although it was known that the aromatase inhibitors could affect bone density and osteoporotic fractures, those adjuvant trials did not include a systematic, repeated search for bone loss or an attempt to treat that loss with calcium and bisphosphonates.

We tell all our patients that they should have baseline DEXA scans, and our intention will be to repeat their DEXA scans every 24 months, which is the recommendation of our osteoporosis experts. Then, if we see T-scores on the DEXA scans that are more severe than a minus two, we initiate therapy with bisphosphonates.

► **DR LOVE:** Do you use oral or IV bisphosphonates?

► **DR VOGEL:** Our strategy has been to offer oral bisphosphonates. For about half the patients, we also have been successful in getting their insurance payers to pay for IV bisphosphonates — that is, zoledronic acid.

Many patients like zoledronic acid because they don't have to take a weekly or a daily oral bisphosphonate. They don't have to endure the GI side effects that occur with oral bisphosphonates. When we can get it paid for, IV bisphosphonates have been well received by patients.

We also have some data from our practice with Adam Brufsky's Z-fast study (Brufsky 2006) showing that the initiation of zoledronic acid at the start of aromatase inhibitor therapy can prevent bone loss.

The data are not mature enough for fractures. So for us, the bone issue is one we talk about, but it doesn't dissuade us from using aromatase inhibitors, even in our elderly population, 65 and older, who are probably the majority of the users of the aromatase inhibitors.

Track 10

► **DR LOVE:** How do you approach the patients who have received five years of an adjuvant aromatase inhibitor?

► **DR VOGEL:** That's a challenging question.

Up until the 2005 San Antonio meeting, I wasn't certain what the answer was to that question. But I was heartened by the data that were presented, both by Paul Goss and Jim Ingle, on the continued follow-up of the MA17 trial patients and, particularly, those patients who had initially been assigned to placebo and then crossed over to letrozole (Goss 2005).

Two patterns were evident from those data. The first was that the longer a patient received the aromatase inhibitor following five years of tamoxifen, the greater the benefit. It is rare in medical oncology to see a benefit that increases as the duration of therapy increases. But it was clear that the longer the duration of therapy with letrozole was, the greater the benefit was.

Comparing two years to four years, the benefit almost doubled. So for our patients at high risk, especially those with larger tumors and those with positive nodes, based on those data, we're now telling them they should continue to take their aromatase inhibitor because we know they're at risk for a very long time — two decades or longer — for recurrence, and these data now show that longer therapy may improve their outcomes.

The other question those data helped us answer relates to patients who have a gap between the end of their tamoxifen therapy and the initiation of their aromatase inhibitor therapy.

The patients who were initially assigned to placebo after five years of tamoxifen in the MA17 trial crossed over to letrozole. Approximately 1,600 patients made the crossover, and their average duration off therapy — that is, the time between the end of their tamoxifen and the initiation of their letrozole — was about 30 months.

Even with that delay in the initiation of the aromatase inhibitor, a statistically significant benefit was demonstrated with the so-called delayed initiation of the aromatase inhibitor after tamoxifen (2.2).

2.2

Efficacy Outcomes for Women Who Were Initially Assigned to Placebo on the MA17 Trial (Median Follow-Up = 54 Months)

	Adjusted hazard ratio (95% CI) Switching to letrozole:continuing on placebo	p-value
Disease-free survival (DFS)	0.31 (0.18-0.55)	<0.0001
Distant DFS	0.28 (0.13-0.62)	0.002
Overall survival	0.53 (0.28-1.00)	0.05
Contralateral breast cancer	0.23 (0.07-0.77)	0.017

CI = confidence interval

SOURCE: Goss PE et al. Presentation. San Antonio Breast Cancer Symposium 2005: [Abstract 16](#).

 **Track 11**

▶ **DR LOVE:** How do you think aromatase inhibitors will “stack up” in the prevention setting?

▶ **DR VOGEL:** We've all been gratified by the reduced incidence in the adjuvant trials of second, contralateral breast primary tumors in patients receiving aromatase inhibitors compared to those receiving tamoxifen.

We know from 20 years of tamoxifen data that the reduction of the contralateral second primaries is about 50 percent (Horton 1996), but it's now evident that the aromatase inhibitors, compared to tamoxifen, bring an additional 20 or 30 percent reduction in the incidence of contralateral second tumors.

This, with preclinical data that show aromatase inhibitors effectively prevent the emergence of invasive breast cancers in animal models, has led to the emergence of two ongoing trials and a soon-to-be-started trial.

The IBIS-II prevention trial in the United Kingdom is comparing anastrozole to placebo. A North American trial compares exemestane to placebo — the so-called MAP.3 study — and the NSABP is proposing a third aromatase inhibitor primary prevention trial — the P-4 trial — which will compare the winner, if you will, of the STAR trial (Wickerham 2006), raloxifene, to letrozole.

Tracks 13-14

► **DR LOVE:** Can you discuss the initial findings from the STAR trial?

► **DR VOGEL:** Between 1999 and 2004 we enrolled 19,747 postmenopausal patients who were at high risk to the STAR trial (Wickerham 2006). Half of them received tamoxifen and half received raloxifene.

The trial was monitored by a Data and Safety Monitoring Committee, which, in December of 2005, declared that the trial had reached its pre stated number of invasive breast cancer events, 327, and so the trial was unblinded.

At the time of the unblinding the occurrence of invasive breast cancer incidents was essentially the same, comparing tamoxifen to raloxifene. The trial recorded 163 invasive breast cancer cases in the tamoxifen arm and 168 in the raloxifene arm. So there was no statistically significant difference.

Compared to the predicted number of invasive breast cancer events at the start of the trial, using the Gail model, the risk reduction was about 50 percent, so the effect of raloxifene was equal to that of tamoxifen. The effect of tamoxifen in the STAR trial was similar to what we had seen in the first breast cancer prevention trial (Fisher 1998).

It is interesting and perhaps surprising that raloxifene did not show as great an effect on the incidence of noninvasive breast cancer. With tamoxifen we saw 57 cases of in situ cancer — which included both ductal carcinoma in situ and lobular carcinoma in situ — and we saw 80 cases with raloxifene. Now, it was not statistically significant, but it did represent 40 percent more in situ cases with raloxifene compared to tamoxifen.

► **DR LOVE:** Can you discuss the safety data from the STAR trial?

► **DR VOGEL:** We saw approximately a 38 percent reduction in the incidence of invasive uterine cancer, comparing raloxifene to tamoxifen. Only 23 invasive uterine events were recorded (2.3) with raloxifene compared to 36 with tamoxifen. We saw a 50 percent reduction in the number of patients who

required hysterectomy with raloxifene compared to tamoxifen. Overall, far fewer uterine events occurred with raloxifene compared to tamoxifen.

Another major benefit with raloxifene was the rate of serious thromboembolic events (2.3) — deep-vein thrombosis and pulmonary emboli. Thirty percent fewer thrombotic events occurred with raloxifene compared to tamoxifen and also fewer cataracts.

The number of fracture events was about the same for each drug, and both tamoxifen and raloxifene are known to reduce fractures compared to placebo. The number of cardiac events was the same.

Overall, when we looked at the entire data set, it appeared to us that the benefit in terms of reducing the risk of invasive cancer was the same for both drugs. But a substantial improvement in toxicity, both for uterine events and for thromboembolic events, appeared with raloxifene compared to tamoxifen.

► **DR LOVE:** If a patient were to ask you if taking raloxifene would increase her baseline risk of endometrial cancer or deep vein thrombosis, how would you respond?

► **DR VOGEL:** No increased risk of uterine events is apparent using raloxifene. For clotting events, the risk is increased with raloxifene, but the amount of increase will be substantially less than what we would expect to see with tamoxifen.

► **DR LOVE:** If you don't believe there's an increased risk of endometrial cancer, you're indirectly comparing raloxifene to the placebo.

► **DR VOGEL:** Yes, and one of the criticisms that has been leveled at the STAR

2.3

Select Efficacy and Toxicity Endpoints During the NSABP-P-2 (STAR) Trial of Raloxifene or Tamoxifen as Breast Cancer Prevention in Postmenopausal Women

	No. of events		Rate per 1,000		RR (95% CI)
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	
Invasive breast cancer	163	168	4.30	4.41	1.02 (0.82-1.28)
DCIS and/or LCIS	57	80	1.51	2.11	1.40 (0.98-2.00)
Uterine cancer	36	23	2.00	1.25	0.62 (0.35-1.08)
Uterine hyperplasia*	84	14	4.69	0.76	0.16 (0.09-0.29)
Hysterectomy during follow-up*	244	111	13.57	6.04	0.44 (0.35-0.56)
Thromboembolic events	141	100	3.71	2.61	0.70 (0.54-0.91)

* Among women not diagnosed with uterine cancer

SOURCE: Vogel VG et al. *JAMA* 2006;295(23):2727-41. [Abstract](#)

trial is that it had no placebo arm, but we didn't believe it was ethical to conduct this trial with a placebo. So we're left with inferences between the two treatment arms in STAR and the placebo arms in other trials. When you put all those data together, it doesn't appear that raloxifene has a uterine effect. ■

SELECT PUBLICATIONS

Brufsky A. **Management of cancer-treatment-induced bone loss in postmenopausal women undergoing adjuvant breast cancer therapy: A Z-FAST update.** *Semin Oncol* 2006;33(Suppl):13-7. [Abstract](#)

Buzdar AU, on behalf of the ATAC Trialists' Group. **Clinical features of joint symptoms observed in the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Proc ASCO* 2006;[Abstract 551](#).

Coleman RE, on behalf of the ATAC Trialists' Group. **Effect of anastrozole on bone mineral density: 5-year results from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Proc ASCO* 2006;[Abstract 511](#).

Cuzick J et al. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomized prevention trial.** *Lancet* 2002;360:817-24. [Abstract](#)

Ettinger B et al. **Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene.** *JAMA* 1999;282:637-45. [Abstract](#)

Fisher B et al. **Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study.** *J Natl Cancer Inst* 2005;97(22):1652-62. [Abstract](#)

Fisher B et al. **Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.** *J Natl Cancer Inst* 1998;90(18):1371-88. [Abstract](#)

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

Horton J. **1995 Oxford breast cancer overview — Preliminary outcomes.** *Cancer Control* 1996;3:78-9. No abstract available

Howell A, on behalf of the ATAC Trialists' Group. **Analysis of fracture risk factors from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial: 5-year data.** *Proc ASCO* 2006;[Abstract 563](#).

Jordan VC. **Optimising endocrine approaches for the chemoprevention of breast cancer beyond the Study of Tamoxifen and Raloxifene (STAR) Trial.** *Eur J Cancer* 2006;[Epub ahead of print]. [Abstract](#)

Land SR et al. **Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.** *JAMA* 2006;295(23):2742-51. [Abstract](#)

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

Paik S. **Methods for gene expression profiling in clinical trials of adjuvant breast cancer therapy.** *Clin Cancer Res* 2006;12(3 Pt 2):1019s-23s. [Abstract](#)

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

Veronesi U et al. **Prevention of breast cancer with tamoxifen: Preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study.** *Lancet* 1998;352(9122):93-7. [Abstract](#)

Vogel VG et al. **Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.** *JAMA* 2006;295(23):2727-41. [Abstract](#)

Wickerham CL et al. **The study of tamoxifen and raloxifene (STAR): Initial findings from the NSABP P-2 breast cancer prevention study.** *Proc ASCO* 2006;LBA5.



INTERVIEW

Debu Tripathy, MD

Dr Tripathy is Professor of Internal Medicine and Director of the Komen UT Southwestern Breast Cancer Research Program at the University of Texas Southwestern Medical Center in Dallas, Texas.

Tracks 1-16

- | | | | |
|----------------|---|-----------------|--|
| Track 1 | Introduction | Track 9 | Future directions for adjuvant clinical trials in HER2-positive disease |
| Track 2 | BCIRG 006: Adjuvant AC followed by docetaxel (T) versus AC followed by T and trastuzumab (H) versus TCH | Track 10 | Potential use of trastuzumab in combination with epirubicin to mitigate cardiotoxicity |
| Track 3 | Counseling patients about the risk of cardiac toxicity associated with chemotherapy and trastuzumab | Track 11 | Continuation of trastuzumab after disease progression |
| Track 4 | Clinical use of trastuzumab as monotherapy or with single-agent chemotherapy | Track 12 | Clinical use of bevacizumab |
| Track 5 | Concurrent versus sequential use of chemotherapy and trastuzumab | Track 13 | Role of metronomic chemotherapy in the management of metastatic disease |
| Track 6 | Potential role of TOPO II and cMYC amplification as predictors of response | Track 14 | Efficacy, tolerability and benefits of nanoparticle albumin-bound (<i>nab</i>) paclitaxel |
| Track 7 | Time course for initiating delayed adjuvant trastuzumab | Track 15 | Clinical use of the <i>Oncotype</i> DX assay |
| Track 8 | Clinical use of dose-dense AC → paclitaxel and trastuzumab | Track 16 | ECOG-E1199: Adjuvant AC followed by paclitaxel or docetaxel, given every three weeks or weekly |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Can you talk about the results of the BCIRG 006 study comparing AC → docetaxel to AC → docetaxel/trastuzumab to TCH (docetaxel/carboplatin/trastuzumab)?

► **DR TRIPATHY:** Both of the trastuzumab-containing regimens lowered the risk of recurrence (Slamon 2005; [3.1]), and they're not statistically different from each other. The reduction is numerically greater in the AC → docetaxel and

trastuzumab arm compared to the nonanthracycline arm. But longer follow-up is needed to get the statistical power to find which one wins out.

► **DR LOVE:** It's approximately a 51 percent reduction with the anthracycline, and it's 39 percent with TCH. Dr Slamon showed the confidence intervals overlapping, yet a lot of people are looking at those numbers, saying, "Hmm. It looks as if TCH is not quite as good." Is that the way you see it?

► **DR TRIPATHY:** I must admit, I do see it that way as well. These are very early results, but we tend to project over time how these curves may continue to diverge. However, we all have to be cognizant that we've been wrong before and we must wait for all the data.

But it's a totally legitimate interpretation. After all, we have to make the best decisions we can for our patients. Sometimes, as an oncologist, you have to take your intuitions about what you sense might be better, even though the statistical rules don't apply. Here we have a 12-point difference between the

3.1 Phase III Study Comparing Doxorubicin/Cyclophosphamide/Docetaxel with or without Trastuzumab versus Docetaxel/Carboplatin or Cisplatin/Trastuzumab

Protocol ID: BCIRG 006
Accrual: 3,222 (Closed)

Eligibility:

- HER2-positive breast cancer
- Node-positive or high-risk node-negative

First interim efficacy analysis (N = 322 events)

Comparison	Relative reduction in risk of relapse	95% CI	p-value
AC → TH vs AC → T	51%	35%-63%	p < 0.0001
TCH vs AC → T	39%	21%-53%	p < 0.001

AC = doxorubicin/cyclophosphamide; T = docetaxel; H = trastuzumab
C = cisplatin or carboplatin; CI = confidence interval

SOURCES: NCI Physician Data Query, October 2005; BCIRG Press Release, bcirg.org.

hazard reductions. Although that's not statistically significant, I believe we need to keep it in mind.

Track 4

▶ **DR LOVE:** What about the possibility of using adjuvant trastuzumab monotherapy without chemotherapy?

▶ **DR TRIPATHY:** Theoretically, trastuzumab monotherapy may be a reasonable approach.

Remember that in the HERA study, a 50-percent reduction in recurrence was seen in all patient groups, which included all comers (Piccart-Gebhart 2005). But keep in mind that as a requirement of the HERA study, all patients received prior chemotherapy. We know that synergy exists between chemotherapy and trastuzumab, so we could argue that trastuzumab works best in the context of chemotherapy.

Although I would guess that trastuzumab monotherapy would reduce recurrence, we don't have any data to support that. Sometimes extrapolations require too much speculation, and I believe the leap to trastuzumab monotherapy is one of those situations.

Trastuzumab monotherapy would be good to include in a trial if we could identify an appropriate patient population. We currently have options for chemotherapy regimens that are nontoxic, like some of those used in the HERA trial.

Dr Heikki Joensuu has studied vinorelbine followed by FEC (Joensuu 2006), opening the door to studies of agents with preclinical synergy and great activity in the advanced setting. I would advocate a trial, maybe with vinorelbine plus trastuzumab in one arm and trastuzumab alone in another arm.

▶ **DR LOVE:** What about a taxane alone with trastuzumab?

▶ **DR TRIPATHY:** That is a little more reasonable, although again, we do not have the data. Technically, the HERA study would have allowed that, but I don't think there were any patients who received paclitaxel alone. In talking about where one would draw the line, taxane alone with trastuzumab, in my mind, would be reasonable.

Track 7

▶ **DR LOVE:** What about the delayed use of trastuzumab? For example, how would you approach a patient with HER2-positive disease who was treated six months or a couple of years ago but didn't receive trastuzumab?

▶ **DR TRIPATHY:** This is a dilemma. You have to decide one way or the other. If the patient comes to you, then you can't just throw up your arms and say you don't know. My approach is to individualize therapy.

We know that in both the HERA study and the North American studies (Piccart-Gebhart 2005; Romond 2005), the hazard rate in the entire population was still pretty high at two and three years — around 10 percent per year. Now, the question is, does the risk reduction still apply two years out? That we don't know.

I can make an analogy with hormonal therapy. I was surprised when the data came out for patients who had been on tamoxifen for five years and were then randomly assigned to placebo versus letrozole (Thürlimann 2005).

Even when initiating hormonal therapy after five years, approximately a 40 percent reduction was still evident, which is about what we expect of hormonal therapy anyway. So at least in the case of hormonal therapy, it looks as though the odds reduction is preserved whether treatment is given up front or much later.

Extending that to trastuzumab, patients at average risk would still have an annual reduction in hazard ratio of about five percent per year. So that would be 10 percent over two years and maybe even more as time goes on. We have to realize that even two or three years out, an odds reduction is likely.

Again, this is where you need to tailor treatment. For a patient with node-negative disease who is a borderline candidate, I would use trastuzumab up front or maybe six months out.

For patients with two or three nodes, I believe it's appropriate to consider trastuzumab even two years out. I know that's a stretch, but at least it is based on data on annual hazards and some extrapolations of the activities of other drugs.

► **DR LOVE:** How about beyond two years — say, three or four years?

► **DR TRIPATHY:** Again, I believe it's reasonable. We don't have hazard rates that far out. Right now, we have them as far as three years on the longest-running NSABP study (Romond 2005). Keep in mind that every year we will have more data on the annual hazards.

Currently I would say two, two and a half years is my limit. But a year from now, when we will have more data, I believe we can feel more comfortable. So it's a moving target, and we have to stay tuned.

Track 8

► **DR LOVE:** What are your thoughts about dose-dense AC → paclitaxel?

► **DR TRIPATHY:** The mathematical theory behind dose-dense chemotherapy is elegant. The idea is that because of the growth shape of the so-called Gompertzian curve, administering drugs in closer proximity in a dose-dense fashion would yield more tumor kill. When growth factors became available, we could test this.

Dose-dense AC → paclitaxel was better than an every three-week schedule (Citron 2003). But over time, that difference has not been as great, and the survival difference is now marginal (Hudis 2005). I still think it's a superior regimen, but the reason for that is unclear.

Data in the metastatic and neoadjuvant settings tell us that a weekly versus every three-week paclitaxel schedule is better. It's better tolerated and the effectiveness is better, certainly in terms of disease-free survival.

An important question is whether the AC part of it needs to be dose dense. In the European epirubicin/cyclophosphamide studies, dose density didn't seem to be a factor.

One could argue that maybe you could administer AC every three weeks followed by paclitaxel weekly, which is the way it was administered in the adjuvant trastuzumab trials. Because dose dense is a reasonably safe regimen — the toxicity is about equivalent — my practice is to use it in HER2-negative cases. I believe it is a better regimen.

Track 9

► **DR LOVE:** What is the next generation of clinical trials that will focus on HER2-positive disease?

► **DR TRIPATHY:** We'd like to improve the odds reduction and use drugs that target other aspects of the HER2 pathway. A leading candidate is lapatinib, a dual HER1 and HER2 kinase inhibitor that also inhibits the same target, HER2, but in a different way.

It works on the cytoplasmic kinase domain, which is part of the signaling initiator. Some early data show a higher response rate when you combine lapatinib and trastuzumab. We already know from early pilot trials that previously untreated patients with HER2-positive disease show good response rates with lapatinib.

I'm not enthusiastic about this trend for trials of other chemotherapies because we need to build on trastuzumab first. I'm concerned that we're simply adding more and more therapies without making an effort to find out who in particular needs them. I don't want to see a trend toward every adjuvant regimen involving 20 drugs. I don't believe that's the way we need to go.

► **DR LOVE:** What about clinical trials evaluating bevacizumab with trastuzumab?

► **DR TRIPATHY:** Bevacizumab with trastuzumab is a reasonable combination, again with the caveats I mentioned. I would prefer to try to isolate the patients who will benefit, but without that, I do believe it's reasonable. Some pilot studies also show that the bevacizumab/trastuzumab combination is safe and active (Ordonez 2006). We have no randomized studies yet, but I believe that would be a reasonable place to look.

Track 12

► **DR LOVE:** Can you discuss the ECOG-E2100 trial, which showed an advantage to adding bevacizumab to paclitaxel in the first-line metastatic setting?

► **DR TRIPATHY:** The main endpoint, progression-free survival, was significantly prolonged with the combination (Miller 2005c; [3.2]). The hazard rates indicate a more robust improvement than we've seen with single chemotherapy compared to chemotherapy doublets.

Much attention has been given to the survival difference, which was statistically significant when initially presented at ASCO (Miller 2005c) but was not

3.2 ECOG-E2100: Paclitaxel with or without Bevacizumab as First-Line Therapy

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



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

CI = confidence interval

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

Conclusions:

“In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and more than doubles the objective response rate. Overall survival data are still premature, and longer follow-up will be needed to assess the true impact of this therapy... .

It's now time to move bevacizumab into the adjuvant setting and explore its role there.”

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 3](#).

significant at the next two presentations at ECCO and San Antonio (Miller 2005a, 2005b). It's important to remember that the number of events was nowhere near what was projected for that analysis.

So although survival is an important endpoint, I don't believe the trial had enough power to demonstrate whether a survival advantage exists.

In the end, data on overall survival will be important in deciding whether to use it. But right now, you have to go with the data on progression-free survival.

► **DR LOVE:** How has that played out in your own practice?

► **DR TRIPATHY:** I have tried to practice the way the trial was designed, using bevacizumab for patients only as first-line therapy. I use it with paclitaxel, and I tend to reserve it either for patients who are symptomatic or for those who may not be symptomatic but whose disease trajectory is such that I would predict they might become symptomatic soon. It's a judgment call.

In terms of whether or not we might want to generalize this and combine bevacizumab with other chemotherapeutic drugs, I believe that's a reasonable consideration. For patients who have already received a taxane in the adjuvant setting, should we use a drug like capecitabine? I believe it would be reasonable.

Track 14

► **DR LOVE:** What are your thoughts about nanoparticle albumin-bound (*nab*) paclitaxel?

► **DR TRIPATHY:** *Nab* paclitaxel is a good alternative to paclitaxel and seems to be a more active drug, but I don't believe we know the optimal schedule yet for that drug. When it was tested on an every three-week schedule, it brought a little more neuropathy than standard paclitaxel (O'Shaughnessy 2003).

Some more recent data evaluating weekly schedules of 100 mg/m² or 125 mg/m² per week suggest less neurotoxicity (O'Shaughnessy 2004). For a patient who is symptomatic and you want to see a response, *nab* paclitaxel is a better choice, quite frankly, and I'm using it.

Can you extend that to combine it with trastuzumab for HER2-positive disease or with bevacizumab? You probably could, but I would likely wait for the data.

► **DR LOVE:** When you've used it in your practice, what kind of dose and schedule have you utilized?

► **DR TRIPATHY:** I've used both of the tested dosing schedules, although the standard 260 mg/m² every three weeks is probably what I use more often. For patients who are very concerned about neurotoxicity, I tend to use it at the lower dose — 100 mg/m² weekly on days 1, 8 and 15 of a 28-day schedule.

- ▶ **DR LOVE:** How has that played out in your practice in terms of the shorter infusion time and the lack of need for premedication?
- ▶ **DR TRIPATHY:** I can't comment much on my individual practice because we're fortunate in that we don't see patients with that much comorbid illness. Both are advantages, but I believe the big advantage is that you don't have to use steroids. Not only do they cause nuisance-type side effects, but in patients with diabetes, they also cause major problems. So that alone is a big advantage. ■

SELECT PUBLICATIONS

- 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](#)
- Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005; [Abstract 41](#).
- Joensuu H et al. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. [Abstract](#)
- Miller KD et al. **First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: A randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100).** Presentation. European Cancer Conference 2005a; [Abstract 275](#).
- Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial conducted by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005b; [Abstract 3](#).
- Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005c;23(4):792-9. [Abstract](#)
- Ordonez J et al. **Trastuzumab in combination with bevacizumab in advanced breast cancer patients resistant to chemotherapy.** *Proc ASCO* 2006; [Abstract 10762](#).
- O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004; [Abstract 1070](#).
- O'Shaughnessy JA et al. **ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs Taxol in MBC: A phase III trial.** San Antonio Breast Cancer Symposium 2003; [Abstract 44](#).
- Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER 2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. [Abstract](#)
- Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER 2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. [Abstract](#)
- 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](#).
- 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

Robert W Carlson, MD

Dr Carlson is Professor of Medicine in the Division of Oncology and Stanford Medical Informatics at the Stanford University Medical Center in Stanford, California.

Tracks 1-19

- Track 1 Introduction
- Track 2 Selection of up-front adjuvant hormonal therapy
- Track 3 Divergent perspectives on the role of aromatase inhibitors as adjuvant therapy
- Track 4 Selection of adjuvant endocrine therapy based on HER2 and PR status
- Track 5 Management of patients with ER-positive disease who become amenorrheic after chemotherapy
- Track 6 Ovarian suppression plus an aromatase inhibitor in premenopausal women
- Track 7 Clinical use of fulvestrant in patients with ER-positive metastatic disease
- Track 8 Variability in the effectiveness of LHRH agonists in suppressing ovarian function
- Track 9 Utilization of the *Oncotype* DX in patients with small, node-negative, ER-positive tumors
- Track 10 Adjuvant TC versus AC
- Track 11 Prophylactic growth factor support with TAC and dose-dense chemotherapy
- Track 12 Selection of adjuvant chemotherapy in patients with ER-positive, node-positive disease
- Track 13 Clinical use of dose-dense AC with growth factor support
- Track 14 Capecitabine as first-line therapy for patients with asymptomatic metastatic disease
- Track 15 Incorporation of bevacizumab into clinical practice
- Track 16 Rationale for the greater use of capecitabine by clinical research leaders than by community-based physicians
- Track 17 Combining bevacizumab with other chemotherapeutic agents
- Track 18 Use of TOPO II in clinical decision-making regarding adjuvant trastuzumab and chemotherapy
- Track 19 Selection of patients for treatment with adjuvant trastuzumab

EDITOR'S NOTE: *This interview focuses on a recent survey of 12 clinical investigators for a recent Breast Cancer Think Tank. For more information, go to BreastCancerUpdate.com/thinktank.*

Select Excerpts from the Interview

Track 2

▶ **DR LOVE:** Can you talk about the use of sequential tamoxifen/aromatase inhibitors versus up-front aromatase inhibitors in the adjuvant setting?

► **DR CARLSON:** The different methods of using aromatase inhibitors or incorporating them — initial aromatase inhibitor therapy versus sequential after two to three years of tamoxifen versus extended after five years — have never truly been studied in a randomized fashion, one against another. The BIG 1-98 trial (Thürlimann 2005) will give us the first look at that sort of comparison.

The real question is whether tamoxifen does something to prime the breast cancer cells and cause the aromatase inhibitor to be more effective. Or, rather, is it that the population of women and the characteristics of their breast cancer change over time in a way that would make the aromatase inhibitors — or any hormonal therapy — more effective?

I believe a substantial amount of data exists to support the selection bias theory that the population of breast cancer patients over time is changing. You would expect the endocrine-resistant, receptor-positive breast cancer to recur earlier, so those women are removed from the denominator.

If you have a sensitive population and an insensitive population with hormone receptor-positive tumors — even with no difference in efficacy between the hormonal therapies — you should expect to see an increasing effect the later in time you initiate the therapy. However, it's hard to have a drug that's so effective down the road that you are able to regain the loss of two to three absolute percentage points that women may experience when the drug is used in this context.

► **DR LOVE:** If you were to treat 100 postmenopausal women, what prescription would they likely receive before leaving your office?

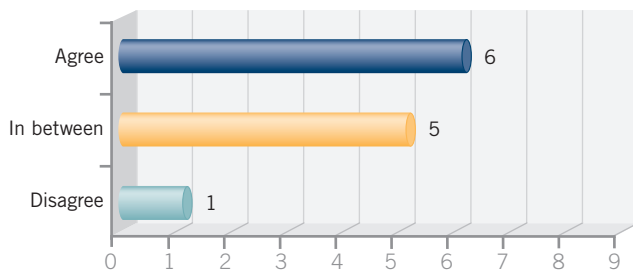
► **DR CARLSON:** The vast majority would walk out with a prescription for an aromatase inhibitor — usually anastrozole in my practice. We have to establish a practice pattern, and mine is to lead with an aromatase inhibitor. It is interesting how expert panels interpreted the emerging aromatase inhibitor data differently. Within 10 to 14 days of the initial ATAC presentation, the NCCN panel had modified the guidelines to allow anastrozole as an alternative to tamoxifen as initial hormonal therapy for postmenopausal patients with ER-positive disease.

The ASCO panel initially believed that tamoxifen should remain the standard hormonal therapy, but that guideline, over time, has also changed. Currently, the NCCN and the ASCO guidelines are essentially identical in terms of up-front hormonal therapy.

Track 5

► **DR LOVE:** Do you agree or disagree (4.1): “Premenopausal patients aged 40 to 45 with ER-positive, node-positive tumors who cease menstruation with chemotherapy should be treated with tamoxifen for two years and then, if still amenorrheic and chemically postmenopausal, should be switched to an aromatase inhibitor.”

Breast Cancer Think Tank Faculty Poll Question: Premenopausal Patients Age 40 to 45 with ER-Positive, Node-Positive Tumors Who Cease Menstruation with Chemotherapy Should Be Treated with Tamoxifen for Two Years and Then, If Still Amenorrheic and Chemically Postmenopausal, Should Be Switched to an AI.



SOURCE: Survey of 12 Think Tank Participants, February 25, 2006, Miami, Florida. <http://breastcancerupdate.com/thinktank/default.htm>

- ▶ **DR CARLSON:** I would feel comfortable switching a woman in that situation to an aromatase inhibitor based on the trial data that we have. The difficulty with that statement, of course, is that the crossover trials, the switching trials, did not include such women. The women had to be postmenopausal at the time of diagnosis. So one issue is how biologically similar we think women are who have gone through chemically induced menopause to those who are naturally postmenopausal at the time of diagnosis.
- ▶ **DR LOVE:** Do you usually switch such patients to an aromatase inhibitor?
- ▶ **DR CARLSON:** It is a strategy that I have used. More commonly, I tend to administer a full five years of tamoxifen and then cross over to letrozole, as in the MA17 trial (Goss 2005). The MA17 trial eligibility criteria did allow women who had become postmenopausal during the five years of tamoxifen.
- ▶ **DR LOVE:** What about a patient with 10 positive nodes? Would you still keep the tamoxifen going for five years?
- ▶ **DR CARLSON:** The higher the risk for recurrence, the more willing I would be to consider crossover to an aromatase inhibitor earlier. That's not necessarily logical because my confidence level doesn't increase in that situation.
- ▶ **DR LOVE:** Obviously the concern is that if the woman were to start menstruating again, you'd then have an ineffective therapy. The other option is, at some point, even at the beginning, to include an LHRH agonist or remove the ovaries — even if the woman has stopped menstruating — just to be sure.
- ▶ **DR CARLSON:** That's an option. The important point, however, that you're raising indirectly is that of the women who you believe have become postmenopausal, secondary to adjuvant chemotherapy, many will experi-

ence a resumption of ovarian function. In that context, if you're going to use an aromatase inhibitor, you must be confident not only that the woman is postmenopausal when you start it but also that she remains so as the treatment is continued.

🎧 Track 7

▶ **DR LOVE:** Do you agree or disagree with the following statement: “In a clinical setting, a loading dose of fulvestrant generally should be used.”

▶ **DR CARLSON:** I agree.

▶ **DR LOVE:** Is that something you do in your practice?

▶ **DR CARLSON:** Yes, it is.

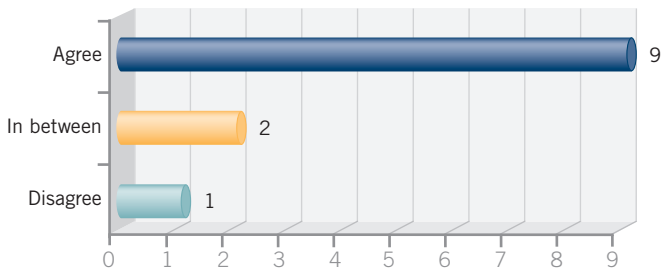
▶ **DR LOVE:** We're seeing a lot of that from both investigators and oncologists in practice (4.2). Where do you think we are heading with fulvestrant in terms of dose and schedule and use for premenopausal women?

▶ **DR CARLSON:** I continue to see an increase in the number of patients treated with fulvestrant. That's reasonable, and experience has confirmed the tolerability of the drug and the efficacy of the therapy. My expectation is we'll see nothing but increased use of fulvestrant. In terms of use for the premenopausal woman, I believe that in the metastatic setting, we will see increasing numbers of patients treated with fulvestrant after they are put in a menopausal state. In part this is because I believe the truly limited number of endocrine agents we have available for the treatment of premenopausal breast cancer means that, functionally, after a premenopausal woman has been treated with tamoxifen, you're obligated to make her postmenopausal.

Once she's postmenopausal, the whole spectrum of endocrine agents, which are effective in the postmenopausal woman, become available.

4.2

Faculty Poll Question: In a Clinical Setting, a Loading Dose of Fulvestrant Should Generally Be Utilized.



SOURCE: Survey of 12 Think Tank Participants, February 25, 2006, Miami, Florida. <http://breastcancerupdate.com/thinktank/default.htm>

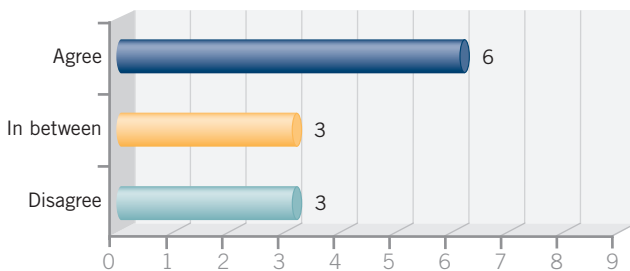
- ▶ **DR LOVE:** Do you have patients who are on an LHRH agonist and fulvestrant?
- ▶ **DR CARLSON:** In the metastatic setting. Because my expectation is that the women will be on hormone therapy for some length of time, I often send those women to the gynecologic oncologist for a laparoscopic oophorectomy.

🎧 Track 11

- ▶ **DR LOVE:** Here is another Think Tank poll question (4.3). “Putting cost and reimbursement issues aside, do you agree or disagree that if an oncologist elects to use adjuvant AC followed by docetaxel, the dose of docetaxel should be 100 mg/m² — every three weeks — and that preemptive myeloid growth factor should be used?”
- ▶ **DR CARLSON:** Docetaxel administered every three weeks at 100 mg/m² is a reasonable taxane to use following AC chemotherapy. I have no difficulty with that. ECOG trial E1199 suggested equal efficacy to paclitaxel in that setting (Sparano 2005). Perhaps a little more toxicity, especially febrile neutropenia, occurred with the every three-week regimen. Given the increased frequency of febrile neutropenia, growth factors would be reasonable to use with that dose and schedule.
- ▶ **DR LOVE:** Gary Lyman has data suggesting a surprising lack of use of preemptive growth factors in the adjuvant setting (Lyman 2003). I thought everyone knew you had to give growth factors when you use TAC. According to him, a significant number of patients are being treated with adjuvant TAC without growth factors. Any take on what’s going on?
- ▶ **DR CARLSON:** I don’t understand that. TAC certainly causes febrile neutropenia with high enough frequency that growth factors should be used. The NCCN Breast Cancer Treatment Guideline specifies the use of growth factors

4.3

Faculty Poll Question: When an Oncologist Elects to Use Adjuvant AC → Docetaxel, the Dose of Docetaxel Should Be 100 mg/m², and Preemptive Myeloid Growth Factors Should Be Utilized.



SOURCE: Survey of 12 Think Tank Participants, February 25, 2006, Miami, Florida. <http://breastcancerupdate.com/thinktank/default.htm>

with two of the adjuvant chemotherapy regimens. One would be TAC and the other would be a dose-dense chemotherapy regimen.

Track 12

▶ **DR LOVE:** Do you agree or disagree? “Patients with strongly ER-positive, PR-positive, node-positive tumors who require adjuvant therapy should generally receive TAC chemotherapy as opposed to dose-dense AC → paclitaxel and other regimens.”

▶ **DR CARLSON:** One of the difficulties in evaluating the adjuvant therapy studies and making cross-study comparisons is that the patient populations are often quite different. The doses and schedules of chemotherapy are almost by definition different.

The analyses of dose-dense chemotherapy and TAC in hormone receptor-positive patients are provocative. Dose-dense chemotherapy showed very little benefit in receptor-positive breast cancer, whereas not much difference in efficacy appeared between the patients with ER-negative and ER-positive disease in the TAC study. Those are indirect comparisons, so I’m not sure we can make much of that specific finding. It’ll be interesting to see, as ECOG-E1199 unfolds, if a differential responsiveness appears with docetaxel versus paclitaxel based on ER status, because that’s what you’d have to hypothesize.

▶ **DR LOVE:** Actually, most oncologists and clinical investigators agree with you, and they weren’t ready to abandon dose-dense AC → paclitaxel, which, according to our Patterns of Care studies with both investigators and oncologists, is by far the most common chemotherapeutic regimen being used for node-positive disease. The last time I spoke with you, that was your chosen treatment for patients with node-positive disease. Is that the case?

▶ **DR CARLSON:** Yes, and it continues to be the case.

I’ve been surprised at how nontoxic dose-dense AC followed by paclitaxel is to deliver. You can argue it’s even less toxic and easier to deliver than the every three-week regimens. My experience with TAC is that it’s a difficult regimen. It’s a tolerable regimen — women can get through it — but it’s a much more difficult regimen in terms of acute toxicities.

Track 13

▶ **DR LOVE:** Do you think that every two-week AC without a taxane with only growth factor support is a reasonable regimen?

▶ **DR CARLSON:** It’s a reasonable regimen, and I use it for the patients for whom I do not consider a taxane necessary. It’s based on the belief — and it’s just a belief, it’s not yet proven — that if dose-dense AC followed by paclitaxel, or the ATC dose-dense regimen, is superior, it’s likely that every two-week AC should be superior, or at least equal to every three-week AC. Again, I’m

impressed at how nontoxic it is when you use growth factors. I believe women like to get through these therapies quickly, and you shorten the duration of treatment with the dose-dense regimens.

Track 14

▶ **DR LOVE:** Do you agree or disagree with the following statement: “For patients with minimally symptomatic metastatic breast cancer in non-visceral sites, the optimal first-line chemotherapy regimen is single-agent capecitabine.”

▶ **DR CARLSON:** I would agree with that.

▶ **DR LOVE:** For patients with metastatic disease, we are seeing a lot more earlier use of capecitabine by clinical investigators and breast cancer specialists compared to those in community practice. In general, is capecitabine your first-line chemotherapeutic agent?

▶ **DR CARLSON:** Yes, capecitabine has efficacy that is in the ballpark of any single agent, and I tend to treat metastatic breast cancer that’s not in visceral crisis with single-agent therapy. The toxicity profile of capecitabine is favorable, and the women appreciate being able to take an oral medication, not having to go to the infusion center and not having to come back as frequently. It’s an agent that, at doses that are typically used, is associated with a predictable toxicity experience. I use 1,000 mg/m² twice daily — two weeks out of three weeks.

▶ **DR LOVE:** Capecitabine generally doesn’t cause alopecia. How important is that issue in the metastatic setting?

▶ **DR CARLSON:** That’s very important. If you’re going to use sequential single agents, it’s always nice to start with an agent that doesn’t cause alopecia. If the woman already has established alopecia, you don’t gain from the nonalopecia properties of the new therapy. That’s often an important component of treatment of metastatic disease.

The other reason I often will lead with capecitabine is that many of these women, because it’s the first-line therapy, have recently been diagnosed with their metastasis. They will go through all the turmoil and psychic trauma of the new diagnosis, and in that context, often it is easier to start with an agent that has acceptable toxicity, so they can become used to the chronic nature of the disease and the need for ongoing chemotherapy with an agent that has good efficacy and doesn’t affect their quality of life to a major degree.

Track 17

▶ **DR LOVE:** Do you agree or disagree? “Patients with ER-negative, PR-negative and HER2-negative tumors (triple negative) should be offered bevacizumab and chemotherapy in the first-line metastatic setting.”

► **DR CARLSON:** It's reasonable to offer such a patient chemotherapy and bevacizumab. The best evidence we have is with paclitaxel/bevacizumab. Kathy Miller's other ECOG study that evaluated capecitabine with or without bevacizumab showed a slightly higher response rate using the combination but no advantage in terms of relapse-free survival and overall survival (Miller 2005).

We may be seeing specific drug effects and different drug interactions between bevacizumab and chemotherapy. It may be a result of different patient populations. The patients in the capecitabine study were treated in the second-line setting, not the first-line setting, as with paclitaxel plus bevacizumab.

► **DR LOVE:** George Sledge is conducting a study right now of first-line capecitabine with bevacizumab (4.4).

► **DR CARLSON:** That's an important study. Based on the existing data evaluating capecitabine/bevacizumab, currently I'm not combining bevacizumab and capecitabine. We didn't see an advantage and although most patients tolerate bevacizumab well, it does have toxicity and expense. So I'm limiting bevacizumab use at the current time to concurrent use with paclitaxel. ■

4.4

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

Protocol ID: XCalibr
Target Accrual: 92 (Open)

Protocol

Capecitabine 1,000 mg/m² d1-14 +
Bevacizumab 15 mg/kg d1

Investigator/
patient choice
at progression

Vinorelbine +
bevacizumab

Paclitaxel +
bevacizumab

Eligibility:

- Newly diagnosed metastatic breast cancer

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

SELECT PUBLICATIONS

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

Lyman GH et al. **Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices.** *J Clin Oncol* 2003;21(24):4524-31. [Abstract](#)

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

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The Phase II XCalibr study is evaluating capecitabine with bevacizumab as first-line therapy followed by bevacizumab continuation with chemotherapy after disease progression.
 - a. True
 - b. False
2. Potential advantages to patients with capecitabine as first-line therapy include that _____.
 - a. Its oral administration obviates frequent office visits for infusion
 - b. It is not usually associated with alopecia
 - c. Its efficacy is comparable to other single-agent chemotherapeutic agents
 - d. All of the above
3. In the ATAC substudy of bone mineral density reported by Coleman et al, patients with normal BMD at baseline did not become osteoporotic after five years of adjuvant anastrozole.
 - a. True
 - b. False
4. NSABP-B-42 is a Phase III study evaluating the duration of adjuvant hormonal therapy in postmenopausal women with hormone receptor-positive early breast cancer.
 - a. True
 - b. False
5. In the adjuvant trial comparing docetaxel/cyclophosphamide to doxorubicin/cyclophosphamide, a disease-free survival advantage was seen with _____.
 - a. Docetaxel/cyclophosphamide
 - b. Doxorubicin/cyclophosphamide
6. The primary endpoint of the ECOG-E2104 pilot study of adjuvant bevacizumab and dose-dense doxorubicin and cyclophosphamide followed by paclitaxel is _____.
 - a. Disease-free survival
 - b. Overall survival
 - c. Cardiac safety
7. In the BCIRG 001 adjuvant TAC/FAC study, the rate of febrile neutropenia without prophylactic growth factor support in the TAC arm was approximately 24 percent.
 - a. True
 - b. False
8. The TAILORx study is randomly assigning patients with _____ Oncotype DX recurrence scores to hormonal therapy or combination chemotherapy followed by hormonal therapy.
 - a. Low
 - b. Intermediate
 - c. High
9. In BCIRG 006, no statistically significant difference was seen between AC followed by docetaxel/trastuzumab and TCH, but a trend for better three-year disease-free survival appeared with _____.
 - a. TCH
 - b. AC followed by docetaxel/trastuzumab
 - c. Neither
10. In ECOG-E2100, the addition of _____ to weekly paclitaxel as first-line therapy improved the median progression-free survival of patients with metastatic breast cancer by five months.
 - a. Capecitabine
 - b. Cetuximab
 - c. Bevacizumab
 - d. Gemcitabine
11. Which of the following is an advantage of *nab* paclitaxel?
 - a. Steroid premedications not required
 - b. Shorter infusion time
 - c. Both of the above
 - d. None of the above
12. According to the NCCN guidelines, the use of growth factor support is recommended for patients who receive adjuvant treatment with _____.
 - a. TAC chemotherapy
 - b. Dose-dense AC → paclitaxel
 - c. Both a and b
 - d. None of the above

EVALUATION FORM

Breast Cancer Update — Issue 7, 2006

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Mark D Pegram, MD	5 4 3 2 1	5 4 3 2 1
Victor G Vogel, MD, MHS	5 4 3 2 1	5 4 3 2 1
Debu Tripathy, MD	5 4 3 2 1	5 4 3 2 1
Robert W Carlson, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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

- Audio CDs Audio tapes Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 7, 2006

REQUEST FOR CREDIT — please print clearly

Name: Specialty:

Degree:

MD DO PharmD NP BS RN PA Other

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

Street Address: Box/Suite:

City, State, Zip:

Telephone: Fax:

Email:

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

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

Signature: Date:

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

Yes No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

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

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

BCU706 **To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at BreastCancerUpdate.com/CME.**

Breast Cancer®

U P D A T E

Editor/CME Director	Neil Love, MD
Associate Editors	Richard Kaderman, PhD Kathryn Ault Ziel, PhD
Writers	Lillian Sklaver Poltorack, PharmD Douglas Paley
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunniss Tamara Dabney Shantia Daniel
Senior Production Editor	Alexis Oneca
Managing Production Coordinator	Tere Sosa
Copy Editors	Dave Amber Mary DiNunzio Rosemary Hulce Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Patricia Kappes
Audio Production	Frank Cesarano
Technical Services	Arly Ledezma
Web Master	John Ribeiro
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: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

Copyright © 2006 Research To Practice. All rights reserved.

This program is supported by education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis.

The audio tapes, compact discs, internet content and accompanying printed material are protected by copyright. No part of this program may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or utilizing any information storage and retrieval system, without written permission from the copyright owner.

The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management.

Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Breast Cancer[®]

U P D A T E

Copyright © 2006 Research To Practice.

This program is supported by education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis.



Sponsored by Research To Practice.

Last review date: November 2006

Release date: November 2006

Expiration date: November 2007

Estimated time to complete: 4.25 hours