BCU SURGEONS | 2005 VOL 4 | ISSUE 3

Breast Cancer® UPDATE

Conversations with Clinical Research Leaders

Bridging the Gap between Research and Patient Care

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CME Certified

Breast Cancer Update for Surgeons
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic techniques, 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 breast surgeon must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* for Surgeons utilizes one-on-one discussions with leading breast cancer investigators. By providing access to the latest research developments and expert perspectives, this CME program assists breast surgeons 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 in order to incorporate these data into management strategies in the adjuvant and neoadjuvant disease settings.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- 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* FOR SURGEONS

The purpose of Issue 3 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Chlebowski, Mamounas, Margolese and Love on the integration of emerging clinical research data into the management of breast cancer.

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

CREDIT DESIGNATION STATEMENT

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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. **www.BreastCancerUpdate.com/Surgeons** 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**.

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UPCOMING EDUCATIONAL EVENTS

Radiation Therapy Oncology Group Meeting
January 19-22, 2006
Miami Beach, Florida
Event website: **www.rtog.org**

American Society of Clinical Oncology
2006 Gastrointestinal Cancers Symposium
January 26-28, 2006
San Francisco, California
Event website: **www.asco.org**

Miami Breast Cancer Conference
February 22-25, 2006
Miami Beach, Florida
Event website: **www.cancerconf.com**

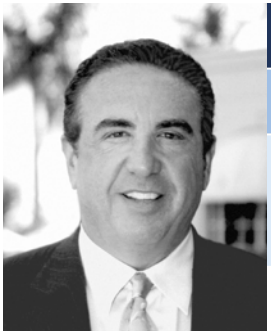
National Comprehensive Cancer Network
11th Annual Conference
March 8-12, 2006
Hollywood, Florida
Event website: **www.nccn.org**

Fifth European Breast Cancer Conference
March 21-25, 2006
Nice, France
Event website: **www.fecs.be**

Society of Surgical Oncology
Annual Meeting
March 23–26, 2006
San Diego, California
Event website: **www.surgonc.org**

American Association for Cancer Research
97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: **www.aacr.org**

American Society of Clinical Oncology
42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**



EDITOR'S NOTE

Neil Love, MD

Wizard boy

Rowan T Chlebowski, MD, PhD

Rowan Chlebowski reminds me of the mop-haired kid in your class who always had the correct answers and wasn't shy about raising his hand when the teacher asked a question.

When I see Rowan at ASCO or other onco-events, he never fails to tell me great new stories about his clinical research adventures. His latest tale, featured on this issue of *Breast Cancer Update* for Surgeons, does not disappoint.

Interviewing cancer researchers like Rowan has become considerably more interesting over the last few years because they have much more to talk about than just trials of different chemo combinations with perky nicknames (my favorite was always "MOPP"). Rowan in particular is involved in a number of innovative research efforts. Perhaps his most public role is as the key oncology investigator in the massive Women's Health Initiative (WHI) trials, and on this program, Rowan summarizes some of the fascinating and to some extent baffling results of these studies.

He begins with the WHI findings related to estrogen/progestin-based postmenopausal hormone replacement therapy (HRT), which was associated with more breast cancers, myocardial infarctions, strokes and dementia but fewer colon cancers and fractures than placebo. On balance, the news was not good, and subsequent to the dissemination of these data, physicians have written 33 million fewer prescriptions for HRT. The WHI also evaluated menopausal hormone replacement with estrogen alone, which also resulted in more strokes and dementia but ***fewer*** breast cancers. While these data balance out as a deterrent to use of this therapy, the biologic implication of the decline in breast cancer incidence is compelling.

Rowan postulates what might be called an estro-stat concept, in which breast cancer cells may survive only in a narrow range of local estrogen concentrations, and decreasing the level (eg, with an aromatase inhibitor) or increasing it by giving (big gulp) estrogen may lead to cell death.

Rowan is also principal investigator of the landmark Women's Intervention Nutrition Study (WINS) that he presented at ASCO and later on *The Today Show*. While the adjuvant trastuzumab trials appropriately garnered our rapt attention at ASCO in Orlando, the WINS study may prove to be equally important and potentially save more lives. WINS addressed a seemingly simple yet important question that had never been asked in a large-scale randomized clinical trial: Will reduction in dietary fat intake reduce the risk of cancer recurrence in early breast cancer? The answer, interestingly enough, is "yes," but even more intriguing is that most of the overall 24 percent reduction in recurrence rate was observed in women with ER-negative primary tumors, and there was no significant benefit in patients with ER-positive breast cancer.

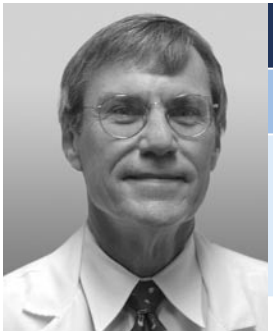
While we ponder the biology of these spectacular findings, women receiving our pricey adjuvant therapies will be very interested to find out that the modest and achievable nutritional change utilized in WINS could result in a benefit that is comparable to that expected from adjuvant chemotherapy, endocrine treatment and antibody therapy. Rowan's interview also touches on the rapidly evolving aromatase inhibitor (AI) story in the adjuvant setting (he chairs the ASCO Breast Cancer Risk Reduction Technology Assessment Committee and sits on the ASCO AI Tech Assessment Committee), and the other speakers on this program — Terry Mamounas, Richard Margolese and Susan Love — contribute their perspectives on what is perhaps the most important public health advance in breast cancer research of the last two decades.

All four interviewees favor an AI as the preferred initial adjuvant endocrine therapy in postmenopausal women, and Rowan trashes the oft-discussed theory that in some patients, one might improve the long-term outcome by starting with two to three years of tamoxifen and then switching to an AI. Dr Chlebowski not only shoots holes in the statistical methods used for these theoretical calculations but also notes the questionable logic of starting with a therapy that will result initially in more relapses, endometrial cancers and deep vein thromboses.

Woven between the research findings of the WHI, WINS and AI trials like ATAC is another story, namely the almost complete shift in current cancer research strategy toward targeted biologic therapy. The estrogen/breast cancer link is the most well-studied example of a targeted molecular strategy, and this century-old treatment approach now serves as a model for many other effective targeted therapeutic options in the future.

I'm mighty grateful to research wizards like Rowan. Not only are they able to make complex topics understandable and interesting, but their creative, open-minded approach to clinical investigation offers hope and encouragement to every person with breast cancer. ■

— Neil Love, MD
NLove@ResearchToPractice.net



INTERVIEW

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is a Professor of Medicine at the David Geffen School of Medicine at UCLA and is Chief of Medical Oncology at Harbor-UCLA Medical Center in Torrance, California.

CD 1, Tracks 1–15

Select Excerpts from the Interview

CD 1, Tracks 2–3

DR LOVE: Can you discuss the Women's Intervention Nutrition Study (WINS) that you presented at ASCO?

DR CHLEBOWSKI: The issue of dietary fat intake and breast cancer has been around for about 25 years. The prevailing thought was that obesity or dietary fat could be related to estrogen levels. So to address this issue, we conducted a randomized clinical trial and entered 2,437 women aged 48 to 79 from 37

clinical centers in the United States. They all received standard breast cancer management, including surgery, radiation therapy if indicated, tamoxifen for five years if estrogen receptor-positive and a defined chemotherapy if estrogen receptor-negative. The ER-positive patients could also receive chemotherapy.

Our primary study endpoint was relapse-free survival, which included all breast cancer recurrence sites, including contralateral breast cancers. We found that the dietary change group had a longer relapse-free survival than the control population, with a 24 percent reduction in risk of recurrence at five years (Chlebowski 2005; [1.1]).

We did a subgroup analysis by receptor status. The hazard ratio for relapse-free survival for patients with estrogen receptor-positive tumors was 0.85 and not statistically significant. In the 478 patients with ER-negative disease, there was a hazard ratio of 0.58, with a 42 percent reduction in risk and an eight percent absolute difference at five years. This is hypothesis generating but very intriguing to us.

DR LOVE: Do you think this is now something that should be presented to women with breast cancer?

DR CHLEBOWSKI: We're not quite there yet, in that we recognize the need for further follow-up, a peer-reviewed publication and probably a confirmatory study. Having said that, this diet was associated with nutritional adequacy, can be recommended for other health reasons and would also have no appreciable side effects.

1.1

WINS Relapse-Free Survival by Treatment Group

Groups	Diet (events/n)	Control (events/n)	HR (95% CI)	*p*-value*
All patients	96/975	181/1,462	0.76 (0.60-0.98)	0.034
ER-positive	68/770	122/1,189	0.85 (0.63-1.14)	0.277
ER-negative	28/205	59/273	0.58 (0.37-0.91)	0.018

* All *p*-values from adjusted Cox proportional hazards model. Consideration of disease-free survival as endpoint (adding other cancers and all deaths) including 389 events with similar outcomes (adjusted Cox HR 0.81, 95% CI 0.65-0.99, $p = 0.042$ favoring dietary intervention).

HR = hazard ratio; CI = confidence interval

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005;**Abstract 10**.

CD 1, Track 4

DR LOVE: Can you update us on the WHI trials and summarize some of the most important findings that have come out in the last couple of years, particularly related to breast cancer?

DR CHLEBOWSKI: The initial data reported for the WHI hormone trials was the comparison of estrogen plus progestin versus placebo in women who had

a uterus (Rossouw 2002). Basically, the surprising finding was that coronary heart disease was increased by approximately 25 to 30 percent, as opposed to the prestudy estimates that anticipated it would be reduced with hormone use.

Breast cancers were also increased, as expected, but surprisingly, prognostic characteristics worsened. After one year of estrogen plus progestin use, abnormal mammograms increased by 74 percent (McTiernan 2005).

The other very interesting finding was that *estrogen-only* therapy ended up showing a trend toward a decrease in breast cancers. There were approximately 24 percent fewer breast cancers on the estrogen-only arm. We're in the process of further analysis, and I believe this trend may well represent a real event. Short-term estrogen may well be associated with a reduction in breast cancer risk.

CD 1, Track 13

DR LOVE: Let's talk about recent research on adjuvant aromatase inhibitors for postmenopausal women. Putting aside toxicities, a lot of discussion has emerged about whether the long-term relapse rate — at 10, 15 or 20 years — would be lower in some patients starting with tamoxifen for some period of time, followed by an aromatase inhibitor. What are your thoughts on that hypothesis?

DR CHLEBOWSKI: If you start with tamoxifen, after two and a half, three or five years, more patients will have relapsed than on an aromatase inhibitor. A substantial number of those patients will be irretrievable — they have incurable disease — and so you're banking on the fact that you'll be able to capture more patients later, but we don't have any data for that. It's just speculation.

While I believe that some type of sequencing may be better ultimately, I still don't see any reason not to start with the most effective therapy. An aromatase inhibitor followed by tamoxifen or an aromatase inhibitor alone makes more sense to me. We have to wait to see the data from the BIG FEMTA trial, which includes an arm with letrozole as initial treatment followed by tamoxifen (Thürlimann 2005). ■

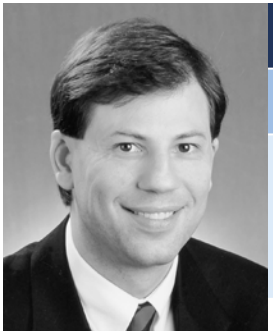
SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS).** Presentation. ASCO 2005;**Abstract 10**.

McTiernan A et al. **Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial.** *J Natl Cancer Inst* 2005;97(18):1366-76. **Abstract**

Rossouw JE et al. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Thürlimann B et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 511**.



INTERVIEW

Eleftherios P Mamounas, MD, MPH

Dr Mamounas is an Associate Professor of Surgery at Northeastern Ohio Universities College of Medicine and is Medical Director of the Aultman Cancer Center in Canton, Ohio.

CD 1, Tracks 16–25 — CD 2, Tracks 1–4

CD 1

Track 16 Introduction by Dr Love

Track 17 Background and development of Onco*type* DX™ assay

Track 18 Initial NSABP study of Onco*type* DX assay to predict recurrence rates in patients treated with tamoxifen

Track 19 Impact of HER2 status on Onco*type* DX recurrence score

Track 20 Potential cost effectiveness of Onco*type* DX assay

Track 21 Lack of benefit from tamoxifen in patients with high recurrence scores based on the Onco*type* DX assay

Track 22 NSABP study to assess ability of Onco*type* DX to predict response to chemotherapy

Track 23 Incorporation of Onco*type* DX into clinical practice

Track 24 False-negative rate with sentinel lymph node biopsy (SLNB)

Track 25 Strategies to decrease false negatives with SLNB

CD 2

Track 1 Studies evaluating aromatase inhibitors in the adjuvant setting

Track 2 Future NSABP trial to determine optimal duration of adjuvant aromatase inhibitors

Track 3 Potential benefit of anastrozole in patients with DCIS

Track 4 Design of future NSABP prevention trial

Select Excerpts from the Interview

CD 1, Tracks 17–18

DR LOVE: Can you review the first major presentation of the Onco*type* DX assay data by Dr Soon Paik at the 2003 San Antonio Breast Cancer Symposium?

DR MAMOUNAS: The initial study looked at the value of the recurrence score as it was developed based on three data sets. We wanted to see which genes were differentially expressed between the patients with and without a recurrence.

By putting the data in a multivariate analysis, we found the genes that were the most predictive of recurrence, and 16 cancer-related genes and five reference genes ended up being the most predictive. So a 21-gene index was developed. The next step was to validate the index prospectively in another data set. For that data set, we chose to use 668 tamoxifen-treated patients from NSABP-B-14. The goal was to see whether the recurrence score would separate patients at lower risk of recurrence from those at higher risk (Paik 2004a).

DR LOVE: What specifically was seen when you looked at the tamoxifen arm of the NSABP-B-14 study in terms of the recurrence score?

DR MAMOUNAS: The recurrence score ranges from zero to 100. Patients with a recurrence score of less than 18 had a 10-year distant recurrence rate of 6.8 percent, with very narrow confidence intervals. Patients with a high recurrence score (31 or greater) had a 30.5 percent 10-year distant recurrence rate. Patients with a recurrence score that fell between 18 and 31 had an intermediate risk of 10-year recurrence, which was around 15 percent (Paik 2004a; [2.1]).

The next step was to see whether the recurrence score went above and beyond prognosis; maybe it would provide a prediction of response to therapy. There was good reason, obviously, to look at that, because the recurrence score contains genes that have traditionally been associated with response to therapy.

For example, low ER positivity versus high ER positivity — we know from neoadjuvant chemotherapy studies that ER negativity has been associated with higher rates of pathologic complete response. Studies have shown that high proliferation and poor nuclear grade are factors associated with chemotherapy response.

So there were genes in the recurrence score that made us think that maybe it would be more than prognostic. Therefore, the subsequent goal was to try to assess the benefit from adjuvant tamoxifen and adjuvant chemotherapy according to the recurrence score.

2.1

Estimates of Recurrence Rate Based on Multigene Assay in Patients Who Received Tamoxifen in NSABP-B-14 (N = 668)

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

RS = recurrence score
$p < 0.001$ for comparison between high- and low-risk groups

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26. **Abstract**

CD 1, Track 22

DR LOVE: In December 2004, Dr Paik presented the second data set in this project. Can you review that?

DR MAMOUNAS: For this analysis, we evaluated patients in the NSABP-B-20 trial, which compared tamoxifen alone to tamoxifen plus one of two chemotherapy regimens — either methotrexate and 5-FU (MF) or CMF — in patients with node-negative, ER-positive disease.

In this second Onco*type* DX study, we evaluated the benefit of adjuvant chemotherapy according to the recurrence score. Patients with a low recurrence score received no benefit from chemotherapy. In fact, at 10 years the distant disease-free survival rate was 96 percent for patients on tamoxifen alone and 95 percent for patients on tamoxifen plus chemotherapy.

Patients with an intermediate recurrence score also did not seem to receive much benefit. The 10-year distant recurrence-free survival was 90 percent for patients treated with tamoxifen alone and 89 percent for those treated with tamoxifen plus chemotherapy (Paik 2004b; [2.2]).

What was interesting was the benefit seen in patients with a high recurrence score. In those patients, the absolute improvement in distant disease-free survival with chemotherapy was 28 percent, or a 75 percent relative reduction in the odds of recurrence. The group that received tamoxifen alone had a 60 percent distant disease-free survival at 10 years, and it was 88 percent when they received tamoxifen plus chemotherapy with CMF or MF (Paik 2004b; [2.2]).

2.2

Ten-Year Distant Recurrence-Free Survival According to Recurrence Score in NSABP-B-20 (N = 651)

Risk group	Tamoxifen (n = 227)	Tamoxifen plus chemotherapy (n = 424)	*p*-value
Low (RS < 18)	96%	95%	0.76
Intermediate (RS = 18-30)	90%	89%	0.71
High (RS ≥ 31)	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. San Antonio Breast Cancer Symposium 2004;**Abstract 24**.

DR LOVE: Those numbers were shocking and, to many people, unexpected.

DR MAMOUNAS: We've never seen such differences in any subset of patients with breast cancer. I like to quote what George Sledge said when he saw these data. He said, "This makes CMF look like a targeted regimen." In fact, that's

true. In other words, we found the signature predicting for huge benefit to a regimen that otherwise was almost ready to become obsolete.

The importance of the recurrence score is that it identifies about half of the patients and puts them in a lower-risk category. That's a big departure from what we could have done in our office before. Also, at the 2004 ASCO meeting, it was demonstrated that this is a cost-effective strategy in that you save money two ways: first, by not using chemotherapy in patients who don't need it, and second, by preventing recurrences in patients who otherwise would not have received adjuvant chemotherapy.

CD 2, Track 2

DR LOVE: What is the future direction of the NSABP in terms of the next generation of adjuvant endocrine therapy trials?

DR MAMOUNAS: We believe that this is an important time to study the question of duration of aromatase inhibitor therapy. So the NSABP has designed a study to take patients that complete five years of an aromatase inhibitor — either anastrozole, letrozole or exemestane — or patients that complete five years of hormonal therapy that consists of at least two to three years of an aromatase inhibitor and randomly assign them to an aromatase inhibitor — in this case, letrozole — versus placebo.

Essentially, we are repeating what was done in the NSABP-B-14 trial with tamoxifen, but now with aromatase inhibitors. I believe that this question should be studied prospectively, and the existing databases or continuation of current trials will not provide a definitive answer. We are planning on continuing the aromatase inhibitor therapy for five years.

DR LOVE: So this trial is addressing the question, "What do I do with a patient who's received an aromatase inhibitor for five years?"

DR MAMOUNAS: Right. The ATAC data were presented at the end of 2001. As a result, patients started taking aromatase inhibitors in the early part of 2002. Therefore, 2007 will be the first time we'll see these patients at close to five years of treatment. ■

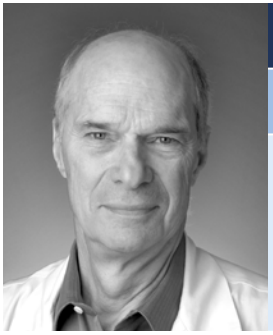
SELECT PUBLICATIONS

Fisher B et al. **Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer.** *J Natl Cancer Inst* 1997;89(22):1673-82. **Abstract**

Julian TB et al. **Preliminary technical results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 14**.

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

Paik S et al. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium 2004b;**Abstract 24**.



INTERVIEW

Richard G Margolese, MD

Dr Margolese is the Herbert Black Chair in Surgical Oncology, Director of the Department of Oncology at McGill University's Jewish General Hospital and Executive Committee Member of the National Surgical Adjuvant Breast and Bowel Project in Montreal, Quebec.

CD 2, Tracks 5–14

Track 5 Introduction by Dr Love

Track 6 Background of NSABP-B-35: Anastrozole versus tamoxifen for DCIS

Track 7 Mastectomy for patients with DCIS

Track 8 Design and eligibility of NSABP-B-35

Track 9 Rationale for excluding patients with ER-negative DCIS from NSABP-B-35

Track 10 Importance of quality control in ER testing

Track 11 Tolerability of anastrozole versus tamoxifen

Track 12 Implications of false-negative rate with SLNB observed in NSABP-B-32

Track 13 Decrease in morbidity associated with SLNB versus axillary dissection

Track 14 SLNB for patients with DCIS

Select Excerpts from the Interview

CD 2, Tracks 8–11

DR LOVE: What was the rationale for comparing anastrozole to tamoxifen in the NSABP-B-35 DCIS trial (3.1)?

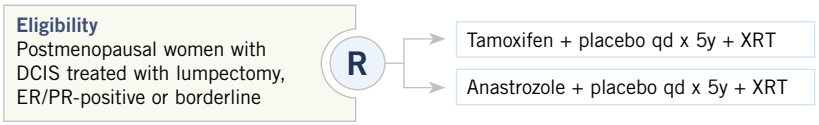
DR MARGOLESE: With the full armamentarium we use in DCIS, the local recurrence rates are low and the chances of dying from this cancer are very low; however, it may be that using the aromatase inhibitors would be even better.

There is evidence that the overall prevention effect of aromatase inhibitors is very powerful in terms of contralateral breast cancer. In the studies of patients with invasive breast cancer, the aromatase inhibitors were superior to tamoxifen at lowering the incidence of new primaries in the contralateral breast (Howell 2005) and with better safety profiles.

To be eligible for NSABP-B-35, patients must have ER-positive DCIS and no invasive cancer. The tumor must be resected with lumpectomy and clear margins, and there must be no contraindication to radiation therapy or either of the drugs (3.1).

3.1 Tamoxifen versus Anastrozole in Postmenopausal Patients with Ductal Carcinoma In Situ

Protocol ID: NSABP-B-35 (Open)
Accrual: 3,000



Study Contact:
Richard Margolese, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI Physician Data Query, October 2005.

3.2 ATAC Trial 68-Month Analysis: Adverse Events*

	Anastrozole (percent)	Tamoxifen (percent)	Odds ratio (anastrozole vs tamoxifen)	*p*-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Hysterectomy	1.3	5.1	—	<0.0001
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/arthralgia	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001

AE = adverse events; SAE = serious adverse events

* Adverse events on treatment or within 14 days of discontinuation
† Fractures occurring before recurrence (includes patients no longer on treatment)

SOURCES: Howell A et al; ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. **Abstract**
Howell A. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

DR LOVE: What are your thoughts on the safety profile of anastrozole versus tamoxifen?

DR MARGOLESE: Anastrozole and the other aromatase inhibitors result in fewer problems with thromboembolism than tamoxifen. In the tamoxifen versus placebo trials, patients on tamoxifen experienced a significantly higher rate of thromboembolic problems — more deep vein thromboses and pulmonary emboli (Fisher 1998). This was somewhat age related. The early tamoxifen studies accepted premenopausal and postmenopausal patients — women who were 50 years or younger didn't have an excess of thromboembolic problems. It wasn't until the patients were older than 65 years that a worrisome difference became evident.

From that sense, anastrozole is probably a safer drug. However, myalgias and arthralgias are a problem, and the risk of osteoporosis must be kept in mind. There is a difference in fracture rates in patients who received anastrozole compared to patients who received tamoxifen (3.2). Yet, even in the ATAC study and in short-term follow-up, the difference is not large (Howell 2005). ■

SELECT PUBLICATIONS

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47. **Abstract**

Duffy S, on behalf of the ATAC Trialists' Group. **Gynecological adverse events including hysterectomy occur less frequently with anastrozole than with tamoxifen: Data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2005;**Abstract 723**.

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**

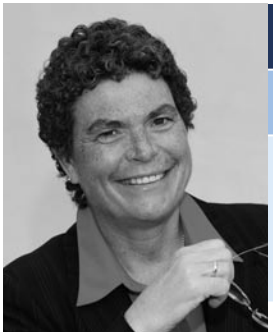
Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

Kudachadkar R, O'Regan RM. **Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer.** *CA Cancer J Clin* 2005;55(3):145-63. **Abstract**

Mouridsen HT, Robert NJ. **The role of aromatase inhibitors as adjuvant therapy for early breast cancer in postmenopausal women.** *Eur J Cancer* 2005;41(12):1678-89. **Abstract**

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status Report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**



INTERVIEW

Susan M Love, MD, MBA

Dr Love is President and Medical Director of the Dr Susan Love Research Foundation and is Clinical Professor of Surgery at the David Geffen School of Medicine at UCLA in Los Angeles, California.

CD 2, Tracks 15–27

Select Excerpts from the Interview

CD 2, Track 18

DR N LOVE: What do you see right now as the clinical role, if any, for ductal lavage?

DR S LOVE: I believe that ductal lavage is best utilized for women at high risk for breast cancer who are trying to make decisions about intervention (4.1). If you're a gene carrier trying to decide, "Should I have a prophylactic mastectomy or not?" and you're on the fence, ductal lavage showing atypia will certainly push you over.

If you're debating, "Should I take tamoxifen or maybe, if it comes on line, raloxifene to prevent breast cancer?" again, finding atypia on ductal lavage may be enough to push you over, and it may be something that we can follow. But that's really its role right now. I don't think we understand enough of the

physiology of the nonlactating breast to be able to take it very much further than that.

4.1

Role of Ductal Lavage in the Management of Women at High Risk for Breast Carcinoma

"Ductal lavage (DL) provides information similar to that obtained by cytologic examination of nipple aspiration fluid and random periareolar fine needle aspiration. Women who demonstrate cytologic atypia on these tests can be assumed to be at higher risk for breast cancer and may benefit from prophylactic medication. … Early data do not suggest that DL is an effective screening tool for breast cancer on the basis of cytologic interpretation of DL samples, although this may change if effective molecular markers are validated for cancer detection in women at high risk."

SOURCE: Khan SA. *Curr Treat Options Oncol* 2004;5(2):145-51. **Abstract**

CD 2, Track 20

DR N LOVE: What have you observed in terms of how aromatase inhibitors are tolerated compared to tamoxifen?

DR S LOVE: Initially, it was believed that the aromatase inhibitors would have no side effects. They don't cause uterine cancer. They don't cause clots. In actual fact, some women have problems with the aromatase inhibitors, primarily with muscular aches and pains. As physicians, we tend to downplay these issues just as we downplay hot flashes. However, when you're experiencing them, they can really interfere with your quality of life, particularly for active patients. On the other hand, the big worry of most women with tamoxifen was always the uterine cancer.

CD 2, Track 21

DR N LOVE: What's your take on the practice implications of clinical research on aromatase inhibitors?

DR S LOVE: It's complicated. You could make an argument that it's better to start with an aromatase inhibitor than tamoxifen. But I tell women if they find they can't tolerate aromatase inhibitors, tamoxifen is still a very reasonable option.

In the adjuvant setting, we know the most about anastrozole. I believe that we should use what we know the most about, so I would select anastrozole as the first line.

CD 2, Track 24

DR N LOVE: What's your take on the Onco*type* DX assay reported by Soon Paik and the NSABP?

DR S LOVE: It's terrific, and we've needed this for a long time. We've been treating everybody as though "one size fits all." However, it is clear that there certainly are different kinds of breast cancer. It's not just whether they're ductal or lobular, but we can now categorize them more effectively.

The Onco*type* DX assay provides us with a much better way to categorize patients. It's not perfect, but it's as good as or better than what we have had until now, which is our gut feeling and how the tumor looked under the microscope.

I think it's a real step forward into individualizing therapy and will take us away from "one size fits all." But I worry that the medical oncologists won't give up their chemotherapy easily.

DR N LOVE: Do you think this is something that should be incorporated into daily patient care at this point?

DR S LOVE: It's not unreasonable to test women who are node-negative and estrogen receptor-positive, particularly if you're debating about chemotherapy. ■

SELECT PUBLICATIONS

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47. **Abstract**

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 658**.

Fabian CJ et al. **Breast-tissue sampling for risk assessment and prevention.** *Endocr Relat Cancer* 2005;12(2):185-213. **Abstract**

Howell A et al. **Results of the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Khan SA. **The role of ductal lavage in the management of women at high risk for breast carcinoma.** *Curr Treat Options Oncol* 2004;5(2):145-51. **Abstract**

Kurian AW et al. **Ductal lavage of fluid-yielding and non-fluid-yielding ducts in BRCA1 and BRCA2 mutation carriers and other women at high inherited breast cancer risk.** *Cancer Epidemiol Biomarkers Prev* 2005;14(5):1082-9. **Abstract**

Mokbel K et al. **Mammary ductoscopy: Current status and future prospects.** *Eur J Surg Oncol* 2005;31(1):3-8. **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**

Paik S et al. **Expression of 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 24**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The WHI trial, comparing estrogen plus progestin versus placebo in women who had a uterus, showed that coronary heart disease significantly _____ with hormone use.**
   a. Increased
   b. Decreased
2. **In the WHI hormone trials, estrogen-only therapy showed a trend toward a/an _____ in breast cancers.**
   a. Increase
   b. Decrease
3. **The Onco*type* DX assay may help to individualize a patient's therapy.**
   a. True
   b. False
4. **The five-year toxicity data from the ATAC trial favor _____ because the life-threatening toxicities — endometrial cancer, arterial and venous vascular events — were all significantly less with this agent.**
   a. Tamoxifen
   b. Anastrozole
5. **The Onco*type* DX assay can be used to predict which patients have a high, low or intermediate risk of 10-year distant recurrence.**
   a. True
   b. False
6. **Patients with a low recurrence score according to the Onco*type* DX assay have been shown to benefit from adjuvant _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Chemotherapy
   d. All of the above
7. **Patients with a high recurrence score according to the Onco*type* DX assay have been shown to benefit from adjuvant _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Chemotherapy
   d. All of the above
8. **According to the preliminary technical results from NSABP-B-32, the false-negative rate is approximately _____.**
   a. One percent
   b. Ten percent
   c. Fifty percent
   d. Ninety percent
9. **Which of the following trials compared up-front adjuvant therapy with an aromatase inhibitor and tamoxifen?**
   a. ATAC
   b. BIG 1-98/BIG FEMTA
   c. IES
   d. Both a and c
   e. Both a and b
10. **In postmenopausal women with ER-positive DCIS, NSABP-B-35 is comparing _____ to tamoxifen as adjuvant therapy.**
    a. Raloxifene
    b. Exemestane
    c. Anastrozole
    d. Letrozole
    e. Fulvestrant
11. **In the WINS trial, women randomly assigned to the dietary intervention group had a significantly lower incidence of breast cancer relapse.**
    a. True
    b. False
12. **The NSABP-B-32 trial randomly assigns patients with clinically node-negative breast cancer to sentinel node biopsy followed by standard axillary dissection or to sentinel node biopsy alone, provided the sentinel node was negative.**
    a. True
    b. False
13. **In the WINS trial subgroup analysis, the hazard ratio for relapse-free survival for patients with _____ disease was 0.58.**
    a. ER-positive
    b. ER-negative

Post-test answer key: 1a, 2b, 3a, 4b, 5a, 6a, 7c, 8b, 9e, 10c, 11a, 12a, 13b

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 3, 2005

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

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in the adjuvant and neoadjuvant disease 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 in the adjuvant and neoadjuvant settings, and discuss the risks and benefits of sequencing adjuvant aromatase inhibitors after tamoxifen. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer. . . . . 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 decision. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Rowan T Chlebowski, MD, PhD	5 4 3 2 1	5 4 3 2 1
Eleftherios P Mamounas, MD, MPH	5 4 3 2 1	5 4 3 2 1
Richard G Margolese, MD	5 4 3 2 1	5 4 3 2 1
Susan M Love, MD, MBA	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

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 3, 2005

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

☐ Yes ☐ No

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.....

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

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.....

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

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

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