BCU SURGEONS | 2006 VOL 5 | ISSUE 3

Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

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Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

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 adjuvant and neoadjuvant disease.
- 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 aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen.
- 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.
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy.
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients.

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 Simmons, Ravdin, Kuerer, Tripathy, Wickerham and Sainsbury on the integration of emerging clinical research data into the management of breast cancer.

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Dr Simmons — Consulting Fees: Sanarus Medical Inc. **Dr Ravdin** — Consulting Fees: AstraZeneca Pharmaceuticals LP, Sanofi-Aventis; Ownership Interest: Adjuvant Inc. **Dr Kuerer** — Contracted Research: Cytyc Corporation, Genentech Inc. **Dr Tripathy** — Consulting Fees: Genentech Inc, Roche Laboratories Inc; Contracted Research: AstraZeneca Pharmaceuticals LP, Genentech Inc, Roche Laboratories Inc. **Dr Wickerham** — Consulting Fees: AstraZeneca Pharmaceuticals LP; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP. **Dr Sainsbury** — Consulting Fees: Roche Laboratories Inc.

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UPCOMING EDUCATIONAL EVENTS

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

Current Controversies in the Management of Early and Advanced Breast Cancer
December 16, 2006
San Antonio, Texas
Event website: **BreastCancerUpdate.com/SABCS06**

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

Society of Surgical Oncology Annual Meeting
March 15-18, 2007
Washington, DC
Event website: **surgonc.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**

American Society of Clinical Oncology 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

INTERVIEW

Rache M Simmons, MD

Dr Simmons is Associate Professor of Surgery at The New York Presbyterian Hospital-Weill Medical College of Cornell University in New York, New York.

Tracks 1-9

Select Excerpts from the Interview

Track 2

DR LOVE: Can you provide an overview of the new developments in the local management of breast cancer?

DR SIMMONS: One particularly exciting area is alternatives to surgical lumpectomy, such as percutaneous excision. Several devices currently on the market do a good job of excising lesions. At this point, they're only approved to excise benign lesions, but it wouldn't surprise me if, in the future, we see these technologies used to excise breast tumors as an alternative to surgical lumpectomy.

Several ablation therapy technologies are currently available and are being evaluated in the treatment of primary breast cancer. These include laser ablation, radiofrequency (RF) ablation and cryoablation. Two other modalities being evaluated are focused ultrasound and microwave, for which we have limited data. The two heat technologies — laser and RF — have been shown to be pretty good at killing cancer. I find cryoablation most interesting. Good data evaluating cryoablation in the treatment of fibroadenomas have emerged. We started using it years ago and have accumulated enough data that it's now FDA approved to treat fibroadenomas without resection.

Currently, one pilot study is applying this technology to breast tumors. In 27 patients with T1 invasive breast tumors, we performed cryoablation and then a resection. We found that if we limited the patients to those with purely invasive ductal carcinoma, without extensive intraductal components and with tumors smaller than 1.5 centimeters, we achieved 100 percent complete ablation (Sabel 2004).

Track 7

DR LOVE: What are some other new areas of emerging clinical research that are important for surgeons in practice?

DR SIMMONS: We've been talking about what we can do from an oncologically safe perspective to maximize the cosmetic results for patients who require a mastectomy. Skin-sparing mastectomy has been around for a decade, and multiple studies demonstrate that skin sparing is oncologically as safe as a nonskin-sparing mastectomy, except for patients with inflammatory cancer.

Certainly we achieve better cosmetic results with those patients undergoing a skin-sparing mastectomy. When I talked to my patients about skin-sparing mastectomy, they used to ask, "Why do you have to take the nipple and areola?" The only data I could provide were old data suggesting that if you didn't take the nipple-areola complex, you had a higher chance of recurrence. Of course, the nipple and the areola are different from one another. The nipple is the convergence of all the ductal tissue from the breast, and the areola is just different-colored skin that doesn't have ductal glands.

So we conducted a study in which we evaluated how often the nipple and the areola were involved for more than 200 patients who underwent mastectomies (Simmons 2002) and discovered that the nipple was frequently involved, even for patients with ductal carcinoma in situ (DCIS). The areola, however, was almost never involved. We found that fewer than one percent of the patients had areolar involvement. These patients had large, invasive breast tumors located right behind the areola. I've modified my skin-sparing mastectomy to be, for many patients, an areola-sparing mastectomy. ■

SELECT PUBLICATIONS

Cunnick G, Mokbel K. **Oncological considerations of skin-sparing mastectomy.** *Int Semin Surg Oncol* 2006;3:14. **Abstract**

Sabel MS et al. **Cryoablation of early-stage breast cancer: Work-in-progress report of a multi-institutional trial.** *Ann Surg Oncol* 2004;11(5):542-9. **Abstract**

Simmons RM et al. **Analysis of nipple/areolar involvement with mastectomy: Can the areola be preserved?** *Ann Surg Oncol* 2002;9(2):165-8. **Abstract**

Woerdeman LA et al. **Skin-sparing mastectomy and immediate breast reconstruction by use of implants: An assessment of risk factors for complications and cancer control in 120 patients.** *Plast Reconstr Surg* 2006;118(2):331-2. **Abstract**

INTERVIEW

Peter M Ravdin, MD, PhD

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

Tracks 1-7

Select Excerpts from the Interview

Track 2

DR LOVE: Can you review where we are with the Onco*type* DX assay?

DR RAVDIN: A recent publication in the *JCO* described a study of the ability of that test to predict sensitivity to chemotherapy (Paik 2006). The study was conducted in collaboration with the NSABP.

They found that patients with a low recurrence score appeared not to benefit from chemotherapy, but the patients who had high recurrence scores clearly were substantial winners in receiving adjuvant treatment.

In that trial, the absolute risk of distant recurrence in 10 years was reduced by roughly 30 percent among patients with high recurrence scores who received chemotherapy. For the patients with low recurrence scores, the risk of recurrence was similar between the groups, irrespective of whether they received chemotherapy. So that group didn't appear to benefit (2.1).

DR LOVE: What are the clinical situations in which you think the Onco*type* DX can be most useful?

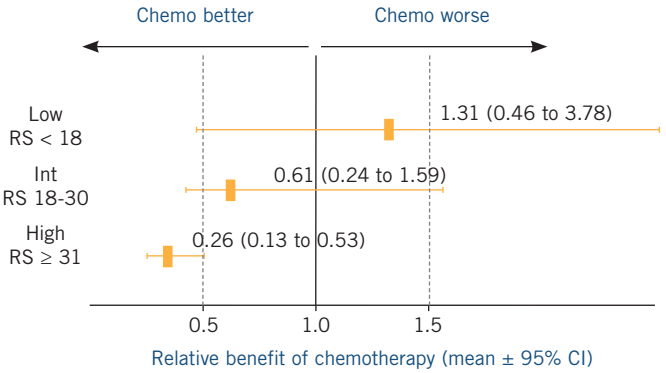
DR RAVDIN: This test was designed to be used by and was developed with

patients who have node-negative, estrogen receptor-positive disease.

Like any test, the Onco*type* DX assay should be used when the result might affect the treatment decision. For most of us, irrespective of what a recurrence score showed, if a patient had a T3 tumor, we simply wouldn't be satisfied with relying on the Onco*type* test result.

2.1

Adjuvant Chemotherapy Benefit According to the Onco*type* DX Recurrence Score



SOURCE: 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. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

Track 4

DR LOVE: These patients will also receive adjuvant endocrine therapy. Where are we now with aromatase inhibitors in postmenopausal patients?

DR RAVDIN: I believe we are at a transition point, and I expect it will become more and more clear that aromatase inhibitors are the way to go. The reason why we're at a transition point is that, up until this time, the improvements with aromatase inhibitors have been mainly limited to disease-free survival. Individual trials and meta-analyses are now showing that this is converting into an overall survival benefit (Mauri 2006).

These follow-up data strengthen the major guidelines from agencies in the United States, which now say that adjuvant therapy for a postmenopausal woman with ER-positive disease should include an aromatase inhibitor. The guidelines don't specify that it is best to start with and to administer five years of aromatase inhibitors.

Many open questions have arisen. One trial will address whether you should start with an aromatase inhibitor and switch to tamoxifen. The other question that occurs to all of us is the follow-up question to the one that we faced 10

years ago with tamoxifen: If five years is good, is 10 years better? We don't have any data to address that issue yet, but ongoing clinical trials are investigating what to do after five years of therapy with an aromatase inhibitor.

Track 7

DR LOVE: What about the side effects and toxicities of aromatase inhibitors versus tamoxifen?

DR RAVDIN: Basically, aromatase inhibitor profiles look better than tamoxifen. If you consistently look across studies, you see that the dropout rate is always higher in the tamoxifen arm than it is in the aromatase inhibitor arm. That tells you right away that the tolerability of the drug is at least as good as tamoxifen. It's not a dramatic difference, but it is always in favor of the aromatase inhibitor.

To me, that speaks deeply. We can all talk about aromatase inhibitor side effects like the arthralgias, and to be frank, the number of arthralgias you see depends on how hard you look. The real question is whether or not the patient had to stop the medication because she just couldn't tolerate it.

DR LOVE: Can you contrast the more serious side effects of the two drugs?

DR RAVDIN: Tamoxifen increases the risk of thrombotic events and endometrial cancer. Neither of those is an issue using an aromatase inhibitor. Tamoxifen confers a benefit, which is that it seems to help retain bone mass. Aromatase inhibitors tend to accelerate bone loss, and every single trial you can review shows a trend — not a dramatic trend but about a one third increase in the number of fractures that patients experience.

In the trials, it's well documented that people receiving aromatase inhibitors are losing bone mass faster, but growing evidence suggests that the use of bisphosphonates can block that effect. ■

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

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

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** San Antonio Breast Cancer Symposium 2003;**Abstract 16**.

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

Henry M Kuerer, MD, PhD

Dr Kuerer is Director of the Breast Surgical Oncology Training Program in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-8

Select Excerpts from the Interview

Track 4

DR LOVE: What's your take on ER testing in DCIS, an issue that was first presented by Craig Allred at the San Antonio meeting a couple years ago (Allred 2002)?

DR KUERER: It makes sense to me that tamoxifen will have an effect on DCIS with estrogen expression, but many of us in the community would like to see those data published. It's one of the few studies that has been presented only in abstract form, at least in the United States, and changed our standard therapy of only offering patients tamoxifen in the setting of DCIS with positive estrogen receptors.

DR LOVE: One of the things that bothered me is that when *he* tested tumors and found them to be ER-negative, they did not respond to or benefit from tamoxifen, but because there were so many false-positive results, among those tumors tested in the *community*, for example, benefit was recorded in ER-negative tumors. What are your thoughts about that?

DR KUERER: It's a big concern — that is, testing and whether or not we are accurately identifying the right patients to treat. The same problem arises with HER2 testing.

DR LOVE: It would seem that surgeons would want patients seeing a medical

oncologist for a postoperative visit to discuss adjuvant therapy and have as accurate as possible ER and HER2 test results at that time. How do you approach that situation?

DR KUERER: In general, unless we know the testing laboratory, we repeat everything at MD Anderson prior to sending the patient to the medical oncologist. A discrepancy occurs for about 20 percent of the patients, so we feel comfortable repeating it. Of course you have to trust your labs, but you have to employ a lab that has a lot of experience using the right positive and negative controls. You have to demand that for your patients.

Track 8

DR LOVE: What are your thoughts on neoadjuvant endocrine therapy?

DR KUERER: In Europe, a lot of postmenopausal women with ER-positive disease have been treated with endocrine therapy in the neoadjuvant setting. A good study was published five years ago (Eiermann 2001) with postmenopausal women who had large primary tumors that were ER-positive — in fact, these patients were ineligible for breast-conserving surgery. It was a randomized study of tamoxifen versus an aromatase inhibitor.

The results never fully made it to the surgical community, but 45 percent of the patients in the aromatase inhibitor group were converted from needing a mastectomy to being able to undergo safe breast-conserving surgery. It's remarkable because it's a higher conversion rate than we see with unselected patients who are receiving neoadjuvant chemotherapy. Many patients in our country are not interested in undergoing systemic chemotherapy. This is something that we surgeons need to consider and get more experience with.

The American College of Surgeons Oncology Group is opening a trial now (ACOSOG-Z1031). It's a three-arm study of approximately 300 patients who are postmenopausal with ER-positive disease and will receive neoadjuvant aromatase inhibitor therapy in a randomized manner using one of the three current agents: anastrozole, letrozole or exemestane.

We're hoping we'll be able to convert some of these patients from needing a mastectomy. It will also give surgeons experience on how to follow these patients — that is, initial examinations, follow-up visits using ultrasound and mammography and marking the area where the tumor is so we'll know where to resect with percutaneously placed clips. ■

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Eiermann W et al. **Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study.** *Ann Oncol* 2001;12:1527-32. **Abstract**

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 1-12

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Can you present one of your own patients for whom you obtained the Onco*type* DX assay?

DR TRIPATHY: I saw a 42-year-old woman who had a biopsy of a lump in her left upper, outer breast, which revealed ER-positive, PR-positive, HER2-negative intermediate-grade cancer. She ultimately underwent a lumpectomy and a sentinel node biopsy. All three of the sentinel nodes were negative, and the tumor was 1.2 centimeters.

Before any additional testing, I outlined for her our general approach for balancing chemotherapy's side effects with the projected benefits. We knew clearly we would recommend hormonal therapy. This would be a decision about how much benefit the chemotherapy would provide.

I had projected that her risk of recurrence was around 15 percent. We could lower that to maybe seven or eight percent with hormonal therapy and maybe by another two or three percent with chemotherapy. In her mind, at that point it was not something for which she would want to receive chemotherapy.

She was concerned about cardiovascular side effects of chemotherapy and leukemia. It became apparent to me that she had a clear threshold for which she was going to take chemotherapy, and I suggested that we obtain an Onco*type* DX recurrence score. I don't use this test for everybody. However, once it's evident that the range of risk will matter to the patient and we may want a more precise definition of it, that's exactly the kind of person who needs this test.

DR LOVE: What was this patient's recurrence score?

DR TRIPATHY: She had a high Onco*type* DX recurrence score of 33, which corresponds to a distant recurrence risk at 10 years of more than 25 percent. For this patient, therefore, we ended up using chemotherapy. She felt more comfortable about the decision. She was obviously concerned and scared that she was at a higher risk, but it gave her more resolve to move ahead with chemotherapy.

DR LOVE: The relative risk reduction is estimated to be about 75 percent for the patients with high recurrence scores, with three out of four relapses avoided with chemotherapy in the higher-risk group (Paik 2006).

DR TRIPATHY: The benefit is dramatic in these patients and is probably diluted in clinical trials. It could be that only a third of the patients benefit and that they are actually getting a 75 percent reduction, as suggested in the study (Paik 2006; [2.1]). These numbers may not hold up in larger analyses. We shouldn't take the 75 percent reduction too literally at this point, but we can say that the benefit is not distributed equally across the population.

Track 4

DR LOVE: What endocrine therapy are you planning for this patient?

DR TRIPATHY: We plan to use tamoxifen because she is premenopausal and still having menstrual periods. Even if she stops having periods, I feel that many of these women will still have ovarian function and continue to make estrogen. Their disease needs to be treated with tamoxifen instead of an aromatase inhibitor.

DR LOVE: Can you talk about the current clinical approach to both premenopausal and postmenopausal women in the adjuvant setting?

DR TRIPATHY: Hormonal therapy is effective in all age groups. We used to think it was mostly for older patients. Over the years, we have realized that what matters is the hormone receptor content. Clearly, ER or PR positivity indicates the possibility of a risk reduction with hormonal therapy. We now

know that the optimum duration of adjuvant hormonal therapy is five years, which provides around a 40 percent risk reduction in all age groups. The use of tamoxifen continues to be the gold standard. For postmenopausal women, however, the aromatase inhibitors are showing a marginal advantage, with a 20 to 40 percent additional risk reduction compared to tamoxifen. This translates into an absolute improvement of between two and five percent in recurrence-free outcome over the next five years (Howell 2005; Thürlimann 2005).

DR LOVE: For a postmenopausal patient, generally, what's your first-line hormonal therapy in the adjuvant setting?

DR TRIPATHY: I will typically start someone off with an aromatase inhibitor. I tend to use anastrozole as the drug of choice, but the other two aromatase inhibitors — exemestane and letrozole — are in the same league.

Track 6

DR LOVE: What about the duration of therapy with adjuvant aromatase inhibitors?

DR TRIPATHY: One approach that has been evaluated is head-to-head comparisons of tamoxifen to an aromatase inhibitor for five years (Howell 2005; Thürlimann 2005). The other studies have been crossover studies. Patients either take tamoxifen for two to three years and then cross over to an aromatase inhibitor (Coombes 2003; Jakesz 2005), or after five years of tamoxifen they cross over to placebo or an aromatase inhibitor for five years (Goss 2003, 2005).

On that basis, the ASCO Technology Assessment Panel recommended that an aromatase inhibitor be considered as part of adjuvant hormonal therapy for postmenopausal women. They recommend a duration of two to five years as long as there is a total of five years of any hormonal therapy. They also make the point that the effects of therapy beyond five years with an aromatase inhibitor are not known (Winer 2005). I generally recommend five years of an aromatase inhibitor. In fact, when I cross patients over after two to three years of tamoxifen, I still go ahead with a full five years of an aromatase inhibitor. When I'm using it instead of tamoxifen altogether, I use five years.

Track 10

DR LOVE: Can you summarize the recent trial results of trastuzumab in the adjuvant setting for women with HER2-positive disease?

DR TRIPATHY: It's clear that trastuzumab reduces the risk of recurrence. Four large randomized studies have all reported roughly equivalent reductions in risk, cutting the risk of recurrence in half (Piccart-Gebhart 2005; Romond 2005; Slamon 2005). These translate into large absolute reductions because these patients generally have a high risk of recurrence. It looks as if the recurrence risk is reduced by anywhere from 40 to 50 percent. Some of

those studies are now showing mortality differences with longer follow-up (Romond 2005).

The question is, what is the lower end of risk for which one would treat? We are seeing cardiac toxicity associated with trastuzumab as expected. We saw it in the metastatic setting, and we're seeing it in the adjuvant setting. It seems to be different from the cardiotoxicity associated with chemotherapy. It tends to be more reversible and treatable.

In the adjuvant trastuzumab trials, no cardiac deaths were associated with trastuzumab, but clinical congestive heart failure rates of two to four percent were observed (Piccart-Gebhart 2005; Romond 2005; Slamon 2005). Most of these patients recover over time, but many of them have to stay on cardiac medications. It's also becoming clear that older patients are at a higher risk. ■

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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**

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

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

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

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.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

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

D Lawrence Wickerham, MD

Dr Wickerham is Associate Chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and Associate Professor of Human Oncology at the Drexel University School of Medicine in Pittsburgh, Pennsylvania.

Tracks 1-5

Select Excerpts from the Interview

Track 2

DR LOVE: Can you summarize the findings from the STAR trial (Wickerham 2006; Vogel 2006; [5.1])?

DR WICKERHAM: The primary objective was to compare the effectiveness of tamoxifen and raloxifene in the prevention of primary invasive breast cancer for postmenopausal women at high risk. The results are clear that these drugs are equally effective. Overall, the safety profile of raloxifene appears to be better (5.1). The primary hope was that it would not increase the risk of endometrial cancer.

Although the difference didn't quite reach statistical significance, it's clear that raloxifene has less of an impact on the endometrium. More than 50 percent of the women coming into the STAR trial had prior hysterectomies, and that is not by chance.

Not only did the women have a Gail model score given to them to qualify for the trial, we also gave them an estimate of their benefit and risk of entering the trial. It's obvious that if you don't have a uterus, you are not at risk for endometrial cancer. So in many ways we were selecting for the absence of a uterus, but that 50 percent reduction lowers the power to demonstrate no excess in endometrial cancer.

During the course of the trial, more than twice as many hysterectomies for

benign conditions were performed among the tamoxifen-treated women, further reducing the ability to show a difference. Hyperplasia was 84 percent higher in the tamoxifen-treated group. The atypical hyperplasias were 12 to one comparing tamoxifen to raloxifene, and all these facts are consistent with the lack of an endometrial risk associated with raloxifene (5.1).

Fewer cataracts and fewer thromboembolic events, DVTs and pulmonary emboli were also observed with raloxifene. This was the first head-to-head comparison of tamoxifen and raloxifene, and it appears that raloxifene has a lowered risk of thromboembolic events compared to tamoxifen. So these findings combine to make raloxifene a more attractive drug in the prevention of this disease.

DR LOVE: What about the incidence of DCIS?

DR WICKERHAM: In the STAR trial, raloxifene wasn't as effective as tamoxifen in the reduction of LCIS and DCIS. The magnitude of that difference is relatively small, and the clinical impact remains to be seen. It may have no clinical impact, but it's biologically intriguing. How could a drug be effective in preventing invasive disease but be less effective on the precursors of that invasive disease? ■

5.1

Comparative Efficacy and Side Effects of Raloxifene and Tamoxifen in the NSABP-P-2 STAR Prevention Study

	No. of events		Rate per 1,000		
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	RR (95% CI)
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)

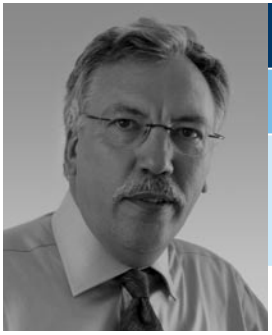
* Among women not diagnosed with uterine cancer

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

SELECT PUBLICATIONS

Vogel VG et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). **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 DL et al. **The study of tamoxifen and raloxifene (STAR): Initial findings from the NSABP P-2 breast cancer prevention study.** *Proc ASCO* 2006;**Abstract LBA5**.



INTERVIEW

Richard Sainsbury, MD

Dr Sainsbury is Senior Lecturer in the Department of Surgery at University College London in London, United Kingdom.

Tracks 1-8

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Can you discuss the side effects and complications of tamoxifen versus the aromatase inhibitors?

DR SAINSBURY: Vasomotor symptoms are less troublesome with the aromatase inhibitors. They're not absent completely, but they seem to disappear more quickly than when our patients were on tamoxifen. Lesley Fallowfield has shown that the patients stop complaining about those symptoms earlier than when they take tamoxifen (Fallowfield 2004).

Gynecologic problems are seen much less often with the aromatase inhibitors. The data that Sean Duffy produced from the ATAC endometrial subprotocol have clearly shown a reduced number of investigations, a reduced number of hysterectomies and therefore a much better gynecologic side-effect profile (Duffy 2006).

The serious complications for tamoxifen are ones that are difficult to manage, such as thromboembolic events, which cause major morbidity. The major side effects for the aromatase inhibitors appear to be the joint and bone problems, but at least those are manageable. While patients are receiving the aromatase

inhibitors, we have also seen an increase in fracture rate of approximately 1.5 to two percent per year (Locker 2003). Once they stop the aromatase inhibitor, the fracture rate drops dramatically and quickly. These are preliminary data, but in the ATAC bone subprotocol, many patients returned to normal a year after finishing therapy.

DR LOVE: The ATAC trial and the other studies of aromatase inhibitors didn't include preventive bone density monitoring or the use of bisphosphonates. When those kinds of strategies are used, do you believe the fracture rate will still be increased?

DR SAINSBURY: I don't believe we'll see that. If we identify the patients who are already at risk up front and treat them appropriately, I don't think we will see an excess risk of fractures.

Track 6

DR LOVE: Can you comment on what's been seen in terms of cardiovascular events in the adjuvant trials using the aromatase inhibitors?

DR SAINSBURY: When BIG 1-98 was first reported, a slight excess of nonbreast cancer deaths was observed, and that appeared to be related to cardiac deaths with letrozole (Thürlimann 2006). That seemed to be different from the ATAC trial. The ATAC Safety Monitoring Committee observed that specifically and found no excess deaths with anastrozole (ATAC Trialists' Group 2006). The other main difference between the anastrozole and letrozole randomized studies was the excess of Grade I hypercholesterolemia seen with letrozole. Whether that is clinically significant is uncertain because this was just a biochemical increase, which was not seen nearly as much with anastrozole. The adjuvant exemestane study (IES) also showed a slight excess of cardiac events but not to the same extent as letrozole (Coombes 2004). ■

SELECT PUBLICATIONS

The ATAC Trialists' Group. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006;7(8):633-43. **Abstract**

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Duffy S et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: First results of the endometrial sub-protocol following 2 years of treatment.** *Hum Reprod* 2005;21(2):545-53. **Abstract**

Fallowfield L et al. **Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) adjuvant breast cancer trial.** *J Clin Oncol* 2004;22(21):4261-71. **Abstract**

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Skin-sparing mastectomy provides better cosmetic results and is as oncologically safe as nonskin-sparing mastectomy, even in patients with inflammatory breast cancer.**
   a. True
   b. False

2. **The Onco*type* DX assay uses a total of _____ cancer genes and five reference genes to determine a patient's recurrence score.**
   a. 400
   b. 40,000
   c. 16
   d. 200

3. **Patients with a _____ recurrence score on the Onco*type* DX assay are likely to benefit from the addition of chemotherapy to adjuvant hormonal therapy.**
   a. Low
   b. Intermediate
   c. High
   d. Both a and b
   e. None of the above

4. **Several large, randomized trials demonstrated that adjuvant chemotherapy/trastuzumab resulted in approximately a 50 percent reduction in risk of recurrence compared to patients receiving chemotherapy alone.**
   a. True
   b. False

5. **In the STAR trial, more than twice as many hysterectomies for benign conditions were observed among women receiving tamoxifen compared to those receiving raloxifene.**
   a. True
   b. False

6. **Compared to tamoxifen, the use of adjuvant aromatase inhibitors has been associated with improvements in _____ _____.**
   a. Disease-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above

7. **The ASCO Technology Assessment Panel recommends that an aromatase inhibitor be considered as part of adjuvant hormonal therapy for postmenopausal women with ER-positive tumors.**
   a. True
   b. False

8. **The ACOSOG trial Z1031 randomly assigns postmenopausal patients with ER-positive breast cancer to neoadjuvant anastrozole, letrozole or exemestane.**
   a. True
   b. False

9. **A study that evaluated postmenopausal women with large, ER-positive primary tumors found that _____ of patients treated with a neoadjuvant aromatase inhibitor underwent breast-conserving surgery instead of mastectomy even though they were initially ineligible for breast-conserving surgery.**
   a. 25 percent
   b. 35 percent
   c. 45 percent
   d. 55 percent

10. **The IBIS-2 prevention study is evaluating anastrozole compared to tamoxifen in postmenopausal women at high risk for developing breast cancer.**
    a. True
    b. False

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

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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 adjuvant and neoadjuvant disease. . . . . 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 aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing 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 decisions. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients. . . . . 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Henry M Kuerer, MD, PhD	5 4 3 2 1	5 4 3 2 1
Debu Tripathy, MD	5 4 3 2 1	5 4 3 2 1
D Lawrence Wickerham, MD	5 4 3 2 1	5 4 3 2 1
Richard Sainsbury, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

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This program is supported by education grants from AstraZeneca Pharmaceuticals LP and Genomic Health Inc.

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Sponsored by Research To Practice.

Last review date: December 2006
Release date: December 2006
Expiration date: December 2007
Estimated time to complete: 2.75 hours