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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. **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 **red underlined text**.

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 FOR *BREAST CANCER UPDATE* FOR SURGEONS

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer screening, diagnosis and treatment.
- Describe the current guidelines for, and ongoing clinical trials of, local and regional therapy for noninvasive and invasive breast cancer.
- Describe and implement an algorithm for HER2 and estrogen receptor testing in the primary breast cancer setting.
- Develop and explain a management strategy for local and systemic treatment of breast cancer in the adjuvant, neoadjuvant and recurrent disease settings.
- 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.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE* FOR SURGEONS

The purpose of Issue 1 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Bear, Howell, Mamounas and Perez on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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Harry D Bear, MD, PhD	Consultant: Aventis Pharmaceuticals Inc
Anthony Howell, MD, MSc, FRCP	No financial interests or affiliations to disclose
Eleftherios P Mamounas, MD, MPH, FACS	Consultant: Aventis Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Eli Lilly & Company, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation Honorarium: Aventis Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Ortho Biotech Products LP
Edith A Perez, MD	Grants/Research Support: Bristol-Myers Squibb Company, Genentech BioOncology, Aventis Pharmaceuticals Inc, Pharmacia Corporation

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals Corporation
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech BioOncology

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Editor's Note

The path ahead

In the next five to 10 years, which breast cancer clinical research strategy is most likely to result in tangible improvements in patient care?

This is one of my favorite questions to ask during interviews with research leaders for the *Breast Cancer Update* audio series. It has gotten to the point where I generally can predict the answer. Targeted therapy based on tumor tissue markers is clearly the mantra for current clinical trials, and in this issue, Dr Harry Bear discusses plans for a new NSABP neoadjuvant study that fully embraces this paradigm.

The new trial is very different from the two prior NSABP neoadjuvant studies (B-18 and B-27), which were very large, randomized, Phase III efforts attempting to determine both short-term tumor responses and long-term impact on disease-free and overall survival. In contrast, the new NSABP trial, as described by Dr Bear, will attempt to compare four different chemotherapy regimens and will focus on short-term clinical response rates and changes in various markers within the tumor. Because disease-free and overall survival are not endpoints, the trial will require far fewer patients and will be completed in a much shorter time than trials like B-18 and B-27.

Everywhere in cancer medicine, researchers refer to breast cancer as the model for targeted therapy. This message is reinforced in our current issue. Dr Tony Howell discusses fascinating new research data from the ATAC trial, presented at the 2003 San Antonio Breast Cancer Symposium, demonstrating that while all patients with ER-positive cancers had lower relapse rates with adjuvant anastrozole than tamoxifen, the difference was particularly significant in women with ER-positive, PR-negative tumors. A similar observation has not previously been reported and, therefore, requires confirmation, but Dr Howell speculates that these tumors may also have HER2 overexpression.

Another related trial reported in San Antonio was the IMPACT study, which is essentially a neoadjuvant version of ATAC. The data document a significantly greater rate of breast conservation in women receiving preoperative anastrozole compared to tamoxifen. These patients also exhibit a greater reduction in Ki67 — a marker of tumor proliferation. For patients with HER2-positive tumors, improved response was also seen, and this helps confirm other studies demonstrating greater antitumor effect of aromatase inhibitors versus tamoxifen in this subset. Dr Howell is now spearheading a major effort to collect tissue blocks from patients enrolled in the ATAC trial so other factors can be studied.

Dr Edith Perez comments on another critical tissue factor that is rapidly increasing in importance — HER2, which can be evaluated both by immunohistochemistry and fluorescence in situ hybridization (FISH). We have long known that women with HER2-overexpressing primary breast cancer have a worse prognosis and respond differently to systemic agents. A new generation of clinical trials is evaluating adjuvant trastuzumab, and for these studies, it is critical that patients are selected appropriately.

Dr Perez chairs one of the largest of the adjuvant trastuzumab trials, an Intergroup study being run out of the North Central Cancer Treatment Group (NCCTG). In this interview she chronicles her efforts, and those of the NSABP to ensure quality control in HER2 testing. The simple message that has emerged so far is that all primary breast cancers should be evaluated for HER2 overexpression, and that this testing should be performed in relatively high volume laboratories.

Many of us remember the "pre-ER" days of the 1970s when we administered endocrine agents like tamoxifen without really knowing whether our patients would benefit or not. We have now entered a new era in which many critical treatment decisions are determined by tissue testing. It is imperative that our patients receive state-of-the-art quality in these assays.

—Neil Love, MD

Bear HD et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 3.**

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 4.**

Dowsett M, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;**Abstract 2.**

Perez EA et al. **N98-32-52: Efficacy and tolerability of two schedules of paclitaxel, carboplatin and trastuzumab in women with HER2 positive metastatic breast cancer: A North Central Cancer Treatment Group randomized Phase II trial.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 216.**

Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 1.**

Wolmark N et al. **Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18.** *J Natl Cancer Inst Monogr* 2001;(30):96-102. **Abstract**

Edited comments by Harry D Bear, MD, PhD

NSABP-B-35: Tamoxifen versus anastrozole in patients with DCIS

This study builds on the series of DCIS trials: NSABP-B-17, which proved the value of radiation therapy, and NSABP-B-24, which demonstrated that the addition of tamoxifen improves recurrence rates. NSABP-B-35 builds on NSABP-B-24 and the ATAC trial, which demonstrated an advantage for anastrozole versus tamoxifen for invasive breast cancer.

The side-effect profile of anastrozole seems to be a little more acceptable than that of tamoxifen, particularly related to hot flashes. Patients also have concerns about uterine cancer, and anastrozole does not have that problem. However, there are tradeoffs. Anastrozole has the issue of osteoporosis, but that's the point of a randomized trial — to compare the two. I don't currently recommend anastrozole for DCIS outside of a trial. The NSABP-B-35 study is requiring ER testing because it appears that patients who have ER-negative DCIS probably don't benefit from taking tamoxifen.

Figure 1.1

NSABP-B-35: Tamoxifen versus Anastrozole in Postmenopausal Patients with Ductal Carcinoma In Situ **Open Protocol**

Eligibility:

Postmenopausal women with DCIS treated with lumpectomy, ER/PR-positive or borderline

R

- Tamoxifen + placebo qd x 5 y + XRT
- Anastrozole + placebo qd x 5 y + XRT

Projected Accrual: 3,000 Patients

Stratification: Age (<60 vs ≥60)

Study Contact:

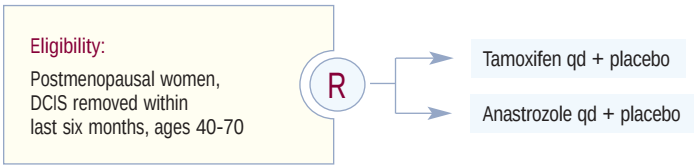
Richard Margolese, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI Physician Data Query, February 2004.

Dr Bear is the Chairman of the Division of Surgical Oncology, Professor of Microbiology and Immunology, Walter Lawrence Jr, Distinguished Professor in Oncology at the Massey Cancer Center, Virginia Commonwealth University School of Medicine in Richmond, Virginia.

Figure 1.2

IBIS-II DCIS: International, Multi-Center Study of Tamoxifen versus Anastrozole in Postmenopausal Women with Ductal Carcinoma In Situ (DCIS) **Open Protocol**



Projected Accrual: 4,000 patients

SOURCE: NCI Physician Data Query, February 2004.

Role of radiation therapy for DCIS

Surgeons and patients alike question whether radiation therapy is necessary for all patients with DCIS. The NSABP trials demonstrated radiation therapy conferred benefit in every subset of patients who had DCIS. On the other hand, Dr Silverstein's extensive experience suggests that some patients — particularly those with a wide margin resection — do not derive much benefit from radiation. In my practice I find that the cosmetic results of performing a limited resection and adding radiation therapy are superior to the results of a large excision with a wide margin.

There are individual patients in whom I might avoid radiotherapy, such as patients with a very small focus of DCIS or those who had a core biopsy of DCIS with cores from multiple sites. I'd do a definitive excision and, if there's no residual cancer in the breast, those patients probably will have acceptable outcomes without radiation therapy — particularly patients over 70 years old.

Another development that may apply to DCIS is the partial breast radiotherapy trial. That's a very exciting way to further improve the cosmetic result and decrease the concerns about going through six weeks of whole breast radiotherapy, which is, at best, inconvenient.

DCIS and sentinel lymph node biopsy (SLNB)

There's been a trend of performing SLNB in patients with DCIS, which is absurd for the majority of patients. However, in select patients, I'll consider doing a sentinel node biopsy. For example, in patients with a very aggressive-looking DCIS and microinvasion, when I do a definitive lumpectomy I know there's a chance the pathologist will find definitive invasion, and I can potentially avoid another operation by performing SLNB. I also do sentinel node biopsy in patients undergoing a mastectomy because if the pathologist finds invasive cancer in the definitive breast specimen, it is too late to perform a sentinel node biopsy because the breast has already been removed.

Neoadjuvant therapy and SLNB

Until recently, I've recommended most patients receiving neoadjuvant therapy have an axillary node dissection because we haven't known the accuracy rate of sentinel node biopsy in that setting.

Some have advocated performing sentinel node biopsy before chemotherapy, and have shown that it works. I think it's probably more useful to the patient to do it afterwards. We now have some of the data from NSABP-B-27, a trial in which 300 to 400 patients had sentinel node biopsies at the time of surgery followed by axillary node dissection. It was not designed as a part of the trial. It was simply coincidental that a lot of surgeons were performing sentinel node biopsies, perhaps to gain more experience with the technique. The false-negative rate was approximately 11 percent, which is similar to the rates in the multicenter trial performed by David Krag. The technique was not standardized and, again, it's likely some of the surgeons were still early in the learning curve.

Performing the sentinel node biopsy after neoadjuvant chemotherapy is preferable because it allows axillary node dissection to be avoided in the maximum number of patients. The sentinel node should be negative in patients in whom it was initially negative, and it will be negative in patients whose nodes have been sterilized by the chemotherapy. Regardless of whether those nodes were always negative or have been converted to negative, the prognostic significance is the same, or even greater, than it would have been from knowing the nodal status up front.

The problem with knowing the nodal status before treatment is that you don't know what to do with that information. If the patient was node-positive prior to systemic therapy, does that automatically mean the patient should have an axillary node dissection? I guess the answer is "yes," but if you do the axillary node dissections after chemotherapy you're going to perform a lot of axillary node dissections and find no tumor.

Proposed NSABP-B-27 neoadjuvant replacement trial

The NSABP-B-27 replacement study represents a paradigm shift in how we perform neoadjuvant trials, particularly with the advent of molecular markers and gene expression signatures as predictors of response. We felt it would be wasteful to put thousands of patients into a two-arm study and wait five to 10 years for the survival data to mature.

We will use the neoadjuvant studies as a discovery platform to compare multiple regimens in a very rapid-fire way. By using pathologic complete response as the primary endpoint and doing molecular marker analysis and gene expression profiles on all of the patients prior to, in the middle of and after chemotherapy, we hope to develop markers that can be used to predict responses to certain drugs.

We envision that the B-27 replacement trial will evaluate AC plus a taxane or

several taxane combinations to predict pathologic complete response. We'll also switch the order of treatment so that we can determine whether genetic profiles can predict response to either anthracyclines or taxanes.

Proposed NSABP trial evaluating chemotherapy for local recurrence

Local recurrence in patients who have undergone breast conservation surgery, or a chest wall or regional recurrence in patients who've had a mastectomy, is a signal that the patient is likely to develop metastatic disease in the near future.

We don't know whether giving chemotherapy in that setting will alter the outcome, particularly in patients who previously received adjuvant chemotherapy. We've decided to join a large international trial that will examine that question, and rather than specifying a specific chemotherapy regimen, we'll leave the chemotherapy up to the individual investigator.

Select publications

Clinical trials of SLNB and neoadjuvant chemotherapy

Aihara T et al. **Feasibility of sentinel node biopsy for breast cancer after neoadjuvant endocrine therapy: A pilot study.** *J Surg Oncol* 2004;85(2):77-81. **Abstract**

Balch GC et al. **Lymphatic mapping and sentinel lymphadenectomy after preoperative therapy for stage II and III breast cancer.** *Ann Surg Oncol* 2003;10(6):616-21. **Abstract**

Birdwell RL et al. **Breast cancer: Variables affecting sentinel lymph node visualization at preoperative lymphoscintigraphy.** *Radiology* 2001;220(1):47-53. **Abstract**

Breslin TM et al. **Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer.** *J Clin Oncol* 2000;18(20):3480-6. **Abstract**

Fernandez A et al. **Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme.** *Nucl Med Commun* 2001;22(4):361-6. **Abstract**

Kuerer HM et al. **Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy.** *Ann Surg* 1999;230(1):72-8. **Abstract**

Mamounas EP. **Sentinel lymph node biopsy after neoadjuvant systemic therapy.** *Surg Clin North Am* 2003;83(4):931-42. **Abstract**

Reitsamer R et al. **Sentinel lymph node biopsy in breast cancer patients after neoadjuvant chemotherapy.** *J Surg Oncol* 2003;84(2):63-7. **Abstract**

Schwartz GF, Meltzer AJ. **Accuracy of axillary sentinel lymph node biopsy following neoadjuvant (induction) chemotherapy for carcinoma of the breast.** *Breast J* 2003;9(5):374-9. **Abstract**

Tafra L et al. **Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer.** *Am J Surg* 2001;182(4):312-5. **Abstract**

Vigario A et al. **Primary chemotherapy effect in sentinel node detection in breast cancer.** *Clin Nucl Med* 2003;28(7):553-7. **Abstract**

Edited comments by Anthony Howell, MD, MSc, FRCP

ATAC analysis of response based on progesterone receptor assays

The analysis of recurrence according to estrogen and progesterone receptor status was the first translational research component of the ATAC trial to be reported. The data indicate patients with ER-positive and PR-negative tumors — approximately 20 percent of postmenopausal ER-positive patients with breast cancer — have a 50 percent reduction in the hazard for recurrence compared to tamoxifen, whereas those with ER/PR-positive tumors have about a 20 percent reduction in the hazard ratio (Figure 2.1).

We need to be cautious because there are early data and it's the first time this pattern has been reported. Biologically, it makes sense, because ER-positive/PR-negative tumors tend to be HER2-positive in other trials with which we've been involved. Additionally, in the letrozole preoperative trial and the IMPACT neoadjuvant anastrozole trial, patients with ER-positive, HER2-positive disease responded better to aromatase inhibitors than to tamoxifen. We haven't yet evaluated HER2 status in the ATAC trial.

Figure 2.1

Results of Analysis of Time to Recurrence in the ATAC Trial According to Estrogen- and Progesterone-Receptor Status

Receptor status	n	Anastrozole vs tamoxifen*
ER+PgR+	5704	0.82 (0.65-1.03)
ER+PgR-	1370	0.48 (0.33-0.71)
ER-PgR+	220	0.79 (0.40-1.50)
ER-PgR-	699	1.04 (0.73-1.47)

*Hazard ratios less than one indicate values in favor of anastrozole

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;**Abstract 4**.

Dr Howell is a Professor of Medical Oncology at the University of Manchester in Manchester, England.

Side effects and toxicities of anastrozole versus tamoxifen

The major difference between the two drugs is gynecologic — less bleeding and less endometrial cancer with anastrozole, and fewer strokes and deep vein thromboses. The down side of anastrozole is aching in the joints, vaginal dryness and effects on bone.

Aromatase inhibitors as initial therapy and sequence after tamoxifen

Increasingly, more data are emerging to support the superiority of aromatase inhibitors over tamoxifen. The NCIC-MA17 trial demonstrated the value of letrozole after five years of tamoxifen, and the Italian trial (Figure 2.2) just reported at San Antonio indicated that the switch from tamoxifen to anastrozole at two or three years results in a disease-free survival advantage and nearly results in a statistically significant survival advantage ($p = 0.06$).

I believe that if you're going to use an aromatase inhibitor, it is most appropriate to use it up front. The data in this setting are with anastrozole, so if I am going to use an aromatase inhibitor up front, I use anastrozole. The data for switching from tamoxifen at two to three years are with anastrozole, so I use anastrozole in that setting. After five years of tamoxifen, the data are with letrozole, so I use letrozole in those patients. Good clinical scientists treat patients according to the data.

Figure 2.2

Anastrozole (A) versus Tamoxifen (T) in Women Already Receiving Adjuvant Tamoxifen (Median Follow-Up, 24 months)[1]

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen (n=225)	1.0	0.0004	1.0	0.002
Anastrozole (n=223)	0.36 (95% CI 0.21-0.63)		0.35 (95% CI 0.18-0.69)	

"Conclusion: These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."[2]

SOURCES: [1]Boccardo F. Presentation, San Antonio Breast Cancer Symposium, 2003.
[2]Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1).**Abstract 3**.

IMPACT neoadjuvant trial: Anastrozole versus tamoxifen versus the combination

The IMPACT trial (Figure 2.3) can be thought of as preoperative ATAC, with treatment given for three months. Response rates were similar in all three arms — approximately 30 percent by calipers — but breast conservation rates were

significantly higher with anastrozole.

In the biological study reported, anastrozole resulted in approximately a 20 percent reduction in the proliferation index Ki67, compared to either tamoxifen or the combination, which was similar to the ATAC trial results. Additionally, the response rate was higher in patients with HER2-positive disease, which mirrors Matt Ellis' data with letrozole.

Figure 2.3

Anastrozole (A) versus Tamoxifen (T) versus the Combination (C) as Neoadjuvant Endocrine Therapy for Postmenopausal Patients with Estrogen-Receptor Positive Breast Cancer: The IMPACT Trial (N=330)

	A	T	A+T
Objective clinical tumor response[1]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after 3 months of treatment[1]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment[2]**	76%	59%	64%

*Of the 220 patients with surgeon's preferred surgery recorded at baseline, 56% were deemed to need a mastectomy.

**Reductions in Ki67 were virtually maximal at 2 weeks with only marginal changes between 2 and 12 weeks.

SOURCES: [1]Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;**Abstract 1**.

[2]Dowsett W, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;**Abstract 2**.

Select publications

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;**Abstract 3.**

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;**Abstract 4.**

Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;**Abstract 1.**

Dowsett M, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;**Abstract 2.**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Edited comments by Eleftherios P Mamounas, MD, MPH, FACS

NSABP sentinel node study

NSABP-B-32 is a large, randomized trial comparing sentinel node resection followed by conventional axillary node dissection with an accrual goal of approximately 5,400 patients. Many surgeons question whether we still need to prove that sentinel node biopsy is the standard of care. I believe until we have the results from larger, randomized trials, it will depend on the surgeon's level of experience. If the surgeon has performed hundreds of these procedures and convincingly demonstrated a very low false-negative rate and a high identification rate, then it's reasonable for that surgeon to perform sentinel node biopsy alone in a subgroup of patients with a low risk for axillary involvement.

NSABP partial breast irradiation trial

We are developing a trial to compare partial breast radiotherapy versus whole breast radiotherapy. The eligibility criteria will be broad and will include totally resected DCIS as well as invasive breast cancers up to three centimeters in size. We want to conduct this study now because there may only be a small window of opportunity before partial breast radiotherapy is widely adopted.

In this study, partial breast irradiation can be administered by brachytherapy catheters, the MammoSite® device or conformal external beam radiation therapy to only a portion of the breast. The physician and the hospital will determine which method is utilized, and it needs to be declared before randomization, although it can be changed if a patient is not eligible for a certain procedure. All three options are done in 10 fractions over five days, as opposed to the five or six weeks it takes to administer whole breast radiotherapy, with or without a boost. We hope to not only make it more convenient for patients but to increase the breast conservation rate, since some patients choose mastectomy because they can't travel to a radiotherapy facility.

There may be other subtle advantages of partial breast radiotherapy. Some data suggest that if we delay radiotherapy we may increase local recurrence, but on the other hand, when we delay systemic therapy we increase systemic

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

recurrence — so we choose to use systemic therapy first. Partial breast radiation takes only five days and is then followed by adjuvant chemotherapy. By moving radiotherapy earlier into the treatment schedule, we may actually decrease local recurrences.

The endpoint in this study is ipsilateral breast tumor recurrence (IBTR) and, based on our trials, we expect approximately six percent of the patients in the control arm will experience IBTR. We're trying to rule out approximately a 50 percent increase in the IBTR rate. Patients may be willing to accept this in order to receive partial breast irradiation. Because only a small portion of the breast is radiated, if they do experience IBTR, salvage therapy may consist of re-excision and full-breast radiotherapy rather than mastectomy, which is the current standard in patients who experience tumor recurrence after full breast radiotherapy. In addition, because partial breast irradiation delivers a higher dose in the vicinity of the tumor bed, it may even be more effective than whole breast radiotherapy.

NSABP-B-35: Tamoxifen versus anastrozole in patients with DCIS

The NSABP study comparing tamoxifen and anastrozole for patients with DCIS is essentially a trial aimed at preventing invasive breast cancer. Aromatase inhibitors have emerged as very good agents in the treatment of metastatic breast cancer, both second- and first-line, and the pivotal results from the ATAC trial demonstrated adjuvant anastrozole was more effective than tamoxifen in reducing recurrence rates and contralateral breast cancers. If patients with DCIS fail, it's usually in the ipsilateral or contralateral breast rather than in the regional nodes or distant sites.

Aromatase inhibitors are very well-tolerated in general. In the ATAC trial, the safety profile of anastrozole was impressive. Patients had fewer thromboembolic events, endometrial cancers and menopausal symptoms than with tamoxifen, but with aromatase inhibitors we need to monitor bone density and fractures.

Select publications

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analysis.** *Cancer* 2003;98(9):1802-10. **Abstract**

Mamounas EP. **Sentinel lymph node biopsy after neoadjuvant systemic therapy.** *Surg Clin North Am* 2003;83(4):931-42. **Abstract**

Vogel VG et al. **National Surgical Adjuvant Breast and Bowel Project Update: Prevention trials and endocrine therapy of ductal carcinoma in situ.** *Clin Cancer Res* 2003;9(1 Pt 2):495S-501S. **Abstract**

Edited comments by Edith A Perez, MD

Concordance between local and central laboratory HER2 testing

We published data on the first 119 specimens submitted to our adjuvant trial. We were surprised to find poor concordance between community and central laboratory testing, in terms of both HER2 protein expression and gene amplification.

In the same issue of the *Journal of the National Cancer Institute*, the NSABP published a paper evaluating specimens from their adjuvant trial (Figure 4.1). Amazingly, their data were almost identical to ours in terms of the discordance rate; however, they found the discordance rate to be much lower when experienced or certified laboratories for HER2 testing were used. Physicians in the community need to send specimens to experienced laboratories.

Figure 4.1

Comparison of Local HER2 Testing Performed for Study Entry to N9831 and Central FISH

	Central FISH result		
	Total	Not amplified	Amplified
Local HER2 testing			
IHC-positive (3+)	110	37	73
FISH-positive	9	3	6
Total	119	40	79

SOURCE: Roche PC et al. *J Natl Cancer Inst* 2002;94:855-7.

Algorithm for HER2 testing: IHC versus FISH

We recommend an algorithm that starts with immunohistochemistry, because it is an easier, less expensive test to do. If the tumor is IHC 0, 1+ or 3+, no further testing is necessary. If the tumor is IHC 2+, reflex FISH testing is recommended (Figure 4.2). At our facility, the pathologists automatically perform the FISH analysis.

Dr Perez is Professor of Medicine at the Mayo Medical School, Director of the Cancer Clinical Study Unit, Director of the Breast Cancer Program, Division of Hematology and Oncology, at the Mayo Clinic in Jacksonville, Florida.

Figure 4.2

Reproducibility of Community Laboratories' Results for HER2 Status of Tumor Specimens from NSABP-B-31

Central Laboratories' Results	Percent of Cases (n=104)
Strongly positive (3+) by the HercepTest™ assay	79%
Positive for gene amplification by the PathVysion™ FISH assay	79%
Neither strongly positive (3+) by the HercepTest™ assay nor positive for gene amplification	18%

SOURCE: Paik S et al. *J Natl Cancer Inst* 2002;94:852-4.

We believe perhaps it's not a good idea to do FISH testing for every tumor, because the majority will be negative. Should we test 100 percent of tumors to find 25 percent positive, or should we use immunohistochemistry to guide us in terms of FISH testing? The latter approach will save money and time.

Routine HER2 testing on breast cancer specimens

Our approach is to test all primary breast cancers for HER2 (Figure 4.3). This is part of the standard evaluation of all new invasive breast cancers diagnosed at the Mayo Clinic in Jacksonville.

Figure 4.3

Defining HER2 Positivity: *Breast Cancer Update* Patterns of Care Study

How do you interpret the following lab results?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	75%	5%	-
HER2-positive only with FISH confirmation	25%	95%	55%
HER2-negative	-	-	45%

How often do you obtain FISH to determine a tumor's HER2 status?

Always	35%
Commonly	38%
Occasionally	27%
Rarely	-
Have not done it	-

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2003.

Knowing a tumor's HER2 status helps in three ways. First, it may assist in determination of prognosis, especially in patients with node-positive breast cancer. Second, it may give us an idea of the potential benefit of anthracycline- versus non-anthracycline-based chemotherapy in the adjuvant setting. Finally, knowing the HER2 status allows us to identify patients who may be eligible for adjuvant trastuzumab protocols such as N-9831.

I do not know what fraction of breast tumors are being tested for HER2 nationwide, but some institutions only test tumors from patients who are node-positive. I believe this is changing as education has improved and there is increased awareness of the potential value of HER2 testing in the determination of prognosis and decisions for therapy.

The discordance rate becomes much lower by using experienced or certified laboratories for HER2 testing, which is good for clinical care because we need to remember that HER2 testing is not only being done for patients potentially eligible for clinical trials, but also for general clinical practice.

Intergroup adjuvant trial evaluating trastuzmab plus chemotherapy

This trial builds on several issues, including the relative importance of anthracyclines in patients with HER2-positive breast cancer, and the value of adjuvant taxanes. Patient randomly assigned to trastuzumab receive it for a year. I believe adjuvant trastuzumab currently should only be used in a clinical trial setting. Clinicians who use this therapy off protocol are essentially shooting in the dark, because we don't understand for how long this therapy should be given, what schedule should be used in combination with chemotherapy, and the potential risks or benefits patients may derive from such treatment. There are several major clinical protocols available, and I hope that every woman diagnosed with HER2-positive breast cancer asks her physician about participation in a clinical trial that will help answer those questions.

Select publications

Paik S et al. **Real-world performance of HER2 testing—National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94(11):852-4. **Abstract**

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the breast Intergroup trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7. **Abstract**

Zujewski JA. **"Build quality in" — HER2 testing in the real world.** *J Natl Cancer Inst* 2002;94(11):788-9. No abstract available.

Post-test: *Breast Cancer Update* for Surgeons, Issue 1, 2004

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the analyses of outcome according to estrogen and progesterone receptor status in the ATAC trial, patients with which phenotype had the largest relative reduction in the hazard for recurrence with anastrozole compared to tamoxifen?**
   a. ER-positive, PR-positive
   b. ER-positive, PR-negative
   c. ER-negative, PR-positive

2. **The IMPACT neoadjuvant trial randomly assigned patients to receive:**
   a. Anastrozole versus tamoxifen versus anastrozole plus tamoxifen
   b. Letrozole versus tamoxifen
   c. Exemestane versus tamoxifen

3. **The NSABP is joining an international trial of treatment for locoregional relapse (IBCSG-27-02) comparing chemotherapy versus no chemotherapy.**
   a. True
   b. False

4. **In NSABP-B-27, the false negative rate for sentinel lymph node biopsy was approximately:**
   a. 3 percent
   b. 11 percent
   c. 17 percent
   d. 22 percent

5. **NSABP-B-32 randomly assigns women with invasive breast cancer and negative sentinel node biopsies to either axillary dissection or no further surgery.**
   a. True
   b. False

6. **Multicentric disease is a standard indication for sentinel node biopsy.**
   a. True
   b. False

7. **The NSABP is planning a randomized trial comparing traditional external beam radiotherapy to which method of partial breast radiotherapy?**
   a. Brachytherapy catheters
   b. MammoSite® device
   c. Conformal external beam radiation therapy
   d. All of the above

8. **The NSABP-B-35 study for patients with DCIS compares tamoxifen to which of the following?**
   a. Anastrozole
   b. Exemestane
   c. Raloxifene
   d. Placebo

9. **The NCCTG and NSABP cooperative research groups found a significant number of tumors that were reported as HER2-positive by local laboratories to be HER2-negative when retested at a central laboratory.**
   a. True
   b. False

10. **Dr Perez recommends a HER2-testing algorithm to include reflexive FISH testing on which of the following specimens?**
    a. IHC 0+
    b. IHC 1+
    c. IHC 2+
    d. IHC 3+
    e. None of the above

11. **Knowing a primary tumor's HER2 status may be helpful in determining which of the following:**
    a. Prognosis
    b. Potential benefit of anthracycline-based chemotherapy
    c. Eligibility for adjuvant trastuzumab trials
    d. All of the above

Post-test Answer Key: 1b, 2a, 3a, 4b, 5b, 6b, 7d, 8a, 9a, 10c, 11d

Evaluation Form: *Breast Cancer Update* for Surgeons, Issue 1, 2004

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.

Please answer the following questions by circling the appropriate rating:

5 =	4 =	3 =	2 =	1 =	NA=
Outstanding	*Good*	*Satisfactory*	*Fair*	*Poor*	*not applicable to this issue of BCU Surgeons*

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer screening, diagnosis and treatment . . . . . 5 4 3 2 1 NA
- Describe the current guidelines for, and ongoing clinical trials of, local and regional therapy for noninvasive and invasive breast cancer . . . . 5 4 3 2 1 NA
- Describe and implement an algorithm for HER2 and estrogen receptor testing in the primary breast cancer setting . . . . . 5 4 3 2 1 NA
- Develop and explain a management strategy for local and systemic treatment of breast cancer in the adjuvant, neoadjuvant and recurrent disease settings . . . . . 5 4 3 2 1 NA
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings . . . . . 5 4 3 2 1 NA
- 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 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Anthony Howell, MD, MSc, FRCP	5 4 3 2 1	5 4 3 2 1
Harry D Bear, MD, PhD	5 4 3 2 1	5 4 3 2 1
Eleftherios P Mamounas, MD, MPH, FACS	5 4 3 2 1	5 4 3 2 1
Edith A Perez, 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: *Breast Cancer Update* for Surgeons, Issue 1, 2004

Please Print Clearly

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Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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

Signature: _____

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.

_____

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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?

_____

_____

Degree:

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

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 www.BreastCancerUpdate.com/CME.