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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

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INTERVIEWS

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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 medical oncology. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — clinicians 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.

LEARNING OBJECTIVES

- Formulate an approach to identify and present chemopreventive options to healthy women who are at risk for the development of breast cancer.
- Evaluate issues related to the accuracy, reliability and interpretation of the ER and HER2 status of breast tumors, in the context of local laboratory practices and national guidelines.
- Assess the benefits and challenges of neoadjuvant endocrine therapy, chemotherapy and biologic therapies.
- Counsel patients with one to three positive lymph nodes about the benefits of postoperative radiation therapy.
- Evaluate the risks and benefits of partial breast irradiation therapy, and develop a plan to identify patients for whom the procedure is contraindicated.
- Utilize magnetic resonance imaging for patients with breast cancer, considering the appropriate role of this technology.
- Identify the rationale for and benefits of extended adjuvant endocrine therapy for patients with hormone receptor-positive breast cancer.
- Utilize the Onco*type* DX™ assay for appropriately selected patients, to collect prognostic information that guides treatment decision-making.
- Summarize the risks and benefits of adjuvant trastuzumab for patients with HER2-positive early breast cancer.
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials, based on an awareness of the latest research.

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

The purpose of Issue 1 of *Breast Cancer Update* for Surgeons is to support the learning objectives by offering the perspectives of Drs Morrow, Smith, Carlson and Paik on the integration of emerging clinical research data into the management of breast cancer.

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This program is supported by educational grants from Genentech BioOncology and Genomic Health Inc.

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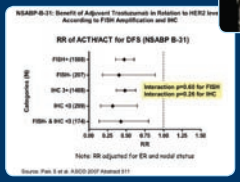
DOES ADJUVANT TRASTUZUMAB RESULT IN TREATMENT BENEFIT FOR PATIENTS WITH HER2-LOW TUMORS?



Review RTP's special multimedia presentation featuring Dr Soonmyung Paik discussing his and other work evaluating HER2 expression and its correlation with the impact of trastuzumab in the adjuvant setting. Watch or read Dr Paik's comments and hear related discussion on this topic from the most recent *Breast Cancer Update* Clinical Investigator Think Tank at www.BreastCancerUpdate.com/Video08Paik

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FACULTY — **Dr Morrow** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Prof Smith** — Advisory Committee: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi-Aventis; Lecturing: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, GlaxoSmithKline; Speakers Bureau: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr Carlson** — Advisory Committee: Genomic Health Inc; Consulting Agreements: AstraZeneca Pharmaceuticals LP, Pfizer Inc; Paid Research: AstraZeneca Pharmaceuticals LP, Genentech BioOncology. **Dr Paik** — Advisory Committee: Genentech BioOncology, GlaxoSmithKline.

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INTERVIEW

Monica Morrow, MD

Dr Morrow is Chief of Breast Surgery and Co-Director of the Breast Program at Memorial Sloan-Kettering Cancer Center and is Professor of Surgery at Weill Cornell Medical College in New York, New York.

Tracks 1-19

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What are your thoughts on chemoprevention and the STAR trial (NSABP-P-2)?

DR MORROW: Chemoprevention is something that both funding agencies and medical organizations have held as an important ideal, but in practice it hasn't come to pass.

We started with tamoxifen, a drug that produces a 50 percent risk reduction in the development of breast cancer in women who are at increased risk and approximately an 80 percent risk reduction in those who are at risk on the basis of atypical hyperplasia (Fisher 1998).

Because of tamoxifen's side-effect profile, we never saw a wide uptake in its use by healthy women.

I found the results from the STAR trial — a direct comparison of tamoxifen and raloxifene in postmenopausal women at increased risk of developing breast cancer — to be exciting. Raloxifene was equivalent to tamoxifen as a chemoprevention agent, and it had a significantly improved side-effect profile (Vogel 2006; [1.1]).

We saw no evidence of increased risk of endometrial cancer or deep vein thrombosis, but a beneficial antiosteoporosis effect was observed in patients treated with raloxifene.

I believe that any woman who has a biopsy that shows atypical hyperplasia or a patient who has more than one first-degree relative with breast cancer definitely needs to have a discussion about chemoprevention. For postmenopausal women who can receive the antiosteoporosis benefit, raloxifene is a win-win situation.

1.1

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

	Number 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

RR = risk reduction; CI = confidence interval; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ

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

Track 4

DR LOVE: What are your thoughts on the 100-month update of the ATAC trial?

DR MORROW: Clearly, the results are holding up long term. A question was whether there would be a "carryover" effect with the aromatase inhibitors, as we've seen with tamoxifen, in terms of the long-term reduction in contralateral breast cancer and survival benefits.

The 100-month ATAC trial data suggest that the same carryover effect is present, and that's reassuring (ATAC Trialists' Group 2008; [3.1, page 12]).

The idea that the osteoporosis and fracture problems appear to stabilize over time is also reassuring (ATAC Trialists' Group 2008), although it doesn't obviate the increased risk of osteoporosis in the early treatment period. This needs to be monitored and is an issue in the chemoprevention setting.

Most of the side-effect profile of the aromatase inhibitors appears to be preferable to that of tamoxifen, with the exception of the bone and joint problems, which for some women can be significantly disabling.

Tracks 7-8

DR LOVE: It is my understanding that the Onco*type* DX assay is going to start reporting quantitative ER. What are your thoughts on this development?

DR MORROW: Several studies suggest that when you use RT-PCR to measure ER, you obtain a result that correlates better with response than if you measure it by immunohistochemistry. When you have a single laboratory engaged in quality control, you have a better chance of obtaining a valid result.

DR LOVE: What is your opinion of the study evaluating the Onco*type* DX assay in patients with ER-positive, node-positive disease?

DR MORROW: I thought it was fascinating. For so long, node-positive disease has been the hallmark of a bad outcome and more treatment. But in our practices we have these patients, some of whom have had large numbers of positive nodes, who are still alive 15 and 20 years later.

The Onco*type* DX report indicates that the biology of the disease is equally diverse in patients with node-negative and node-positive disease and that a phenomenon of regional disease exists that is not necessarily systemic.

The level of the recurrence score may be a useful guide for the intensity of the chemotherapy needed, but it may not be the same for all patients with node-positive disease (Albain 2007; [4.2, page 17]).

Track 14

DR LOVE: What are your thoughts on the role of sentinel lymph node biopsy in the patient who has received neoadjuvant therapy?

DR MORROW: That's a controversial issue that we debated at a recent meeting almost more than any other subject in local therapy. Neoadjuvant therapy will reduce the incidence of positive nodes. So you're saving women an axillary dissection.

The data Terry Mamounas published from NSABP-B-27, which evaluated 428 patients who had a sentinel lymph node biopsy after neoadjuvant therapy, suggest that the accuracy rate is the same as it is for women who had a primary sentinel node biopsy (Mamounas 2005). Granted, we do not have long-term follow-up data on axillary failure rates in that population, but I am comfortable with that.

I am not comfortable with a sentinel lymph node biopsy for the patient who starts pretreatment with either a clinically positive axillary node or a node that is documented by needle biopsy to be positive but is downstaged to clinically node-negative after neoadjuvant therapy.

You have a higher false-negative rate in that population, and it may be as high as 20 or 30 percent. Most patients with one grossly positive node have other positive nodes, and the likelihood of an axillary pathologic complete response is only about 20 or 25 percent. Putting that together, I consider it an indication for axillary dissection. ■

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

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Bear HD et al. **Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2006;24(13):2019-27. **Abstract**

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

Mamounas EP et al. **Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results from National Surgical Adjuvant Breast and Bowel Project protocol B-27.** *J Clin Oncol* 2005;23(12):2694-702. **Abstract**

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Rastogi P et al. **Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27.** *J Clin Oncol* 2008;26(5):778-85. **Abstract**

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INTERVIEW

Ian E Smith, MD

Prof Smith is Professor of Cancer Medicine in the Department of Medicine's Breast Unit at The Royal Marsden Hospital, London and Surrey, United Kingdom.

Tracks 1-13

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you summarize what we currently know about neoadjuvant endocrine therapy?

PROF SMITH: Nearly all the work conducted with neoadjuvant endocrine therapy has been with postmenopausal women. Three large trials have compared the aromatase inhibitors to tamoxifen (Cataliotti 2006; Dowsett 2005; Ellis 2003; Smith 2005), all of which demonstrated that the aromatase inhibitors are more effective in terms of tumor regression and reducing the need for a mastectomy.

DR LOVE: How do you approach the choice between neoadjuvant chemotherapy and endocrine therapy?

PROF SMITH: That's the real crunch. The more I administer neoadjuvant endocrine therapy, the more I wonder why we don't utilize it more frequently. When it works, it's extremely effective. Anecdotally, I recently treated a woman in her sixties with a 5-cm, hormone receptor-positive tumor who did not want to receive chemotherapy but wished to avoid mastectomy. I treated her disease with an aromatase inhibitor, and she underwent breast-conserving surgery with only a small, 1-cm residual tumor.

The question was whether or not she needed chemotherapy. Until recently, no data existed to address this question, but we are beginning to evaluate our results from the IMPACT trial, which compared neoadjuvant anastrozole to tamoxifen. Matt Ellis is also evaluating the data from the P-024 trial of letrozole versus tamoxifen.

We are putting together an algorithm that suggests that patients with node-negative breast cancer, a good tumor response (smaller than one centimeter at surgery) and good suppression of Ki-67 while the tumor remains hormone receptor-positive have an excellent long-term outcome (Dowsett 2007). Patients with node-negative breast cancer at surgery with these parameters almost never experience relapse.

Track 3

DR LOVE: Can you discuss the issue of extended adjuvant endocrine therapy beyond five years?

PROF SMITH: The cleanest, most important data of the aromatase inhibitor trials addressing this issue are from MA17, which demonstrated that patients who had received tamoxifen for five years and were switched to letrozole fared better than those who received placebo (Goss 2008; Ingle 2008). The evidence suggests that the longer you treat beyond five years, the greater the benefit.

Another interesting aspect of MA17 is that when the results were first presented after two and a half years — because the benefit was more dramatic than imagined — patients on the placebo were offered the opportunity to switch. Some switched and some did not, but those who did had worse prognostic features in their original disease. Those patients are now faring better than the ones who didn't switch, even though they had poorer prognoses (2.1). That's a powerful message regarding the long-term use of aromatase inhibitors. Some women may need to receive these agents for an extended period of time.

Tracks 7-8

DR LOVE: Can you provide an overview of neoadjuvant therapy for patients with HER2-positive tumors?

PROF SMITH: For surgeons dealing with large tumors, the most spectacular data on trastuzumab are in the neoadjuvant setting. A small but influential

MD Anderson study showed a pathologic complete response rate of approximately 60 percent with the use of trastuzumab in addition to neoadjuvant chemotherapy (Buzdar 2007; [2.2]).

The results were almost too good to be true, but now a large European trial in inflammatory breast cancer (NOAH) has also demonstrated a high pathologic complete response rate with the addition of trastuzumab compared to neoadjuvant chemotherapy alone (Gianni 2007).

If a patient has a large, HER2-positive breast tumor and you are considering neoadjuvant treatment, then you must administer trastuzumab up front with the chemotherapy rather than waiting until after surgery.

Track 9

DR LOVE: What is your approach for the patient with a node-negative, HER2-positive tumor (Press 1997; [2.3])?

PROF SMITH: The issue that's beginning to emerge — and I've been impressed because it's changed my thinking — is that the prognosis with

2.1

MA17 Trial: Outcomes for Women Initially Assigned to Placebo (Median Follow-Up = 5.3 Years)

	Adjusted hazard ratio Switch to letrozole: Continue placebo	*p*-value
Disease-free survival (DFS)	0.37 (95% CI: 0.23-0.61)	<0.0001
Distant DFS	0.38 (95% CI: 0.20-0.73)	0.004
Overall survival	0.30 (95% CI: 0.17-0.53)	<0.0001
Contralateral breast cancer	0.18 (95% CI: 0.06-0.58)	0.004

Hazard ratio < 1.0 favors switching to letrozole; CI = confidence interval

SOURCE: Goss PE et al. *J Clin Oncol* 2008;[Epub ahead of print]. **Abstract**

2.2

Neoadjuvant Paclitaxel (P) Followed by FEC with or without Concurrent Trastuzumab (H)

		P + FEC + H		
	P + FEC (n = 19)	First cohort (n = 23)	Second cohort (n = 22)	Combined (n = 45)
Pathologic complete response (95% CI)	26.3% (9-51)	65.2% (43-84)	54.5% (32.2-75.6)	60% (44.3-74.3)
One-year disease-free survival (95% CI)	94.7% (85.2-100)	100% (85.2-100)	100% (83.9-100)	100% (92-100)

SOURCE: Buzdar AU et al. *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

HER2-positive tumors of one centimeter or less is approximately a 15 to 20 percent risk of relapse within 10 years (Press 1997). So we probably need to be more aggressive with these small, node-negative, HER2-positive tumors and bias ourselves toward using chemotherapy and trastuzumab. ■

2.3 **Treatment of Smaller HER2-Positive, Node-Negative Tumors**

"Since the 1990 National Institutes of Health Consensus Conference on breast cancer recommended that women with node-negative breast cancers ≤1.0 cm in diameter not be treated, the relative risk of poor outcome for this group with regard to gene amplification was examined. Patients with breast cancers ≤1.0 cm in diameter who had HER-2/neu gene amplification had a significantly higher rate of both recurrence (log-rank test, $P = .030$) and disease-related death (log-rank test, $P = .019$)."

SOURCE: Press MF et al. *J Clin Oncol* 1997;15(8):2894-904. **Abstract**

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Ellis MJ et al. **Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status.** *Cancer Res* 2003;63(19):6523-31. **Abstract**

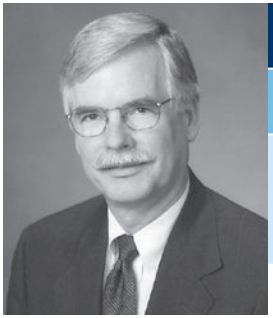
Gianni L et al. **Neoadjuvant trastuzumab in locally advanced breast cancer (NOAH): Antitumour and safety analysis.** *Proc ASCO* 2007;**Abstract 532**.

Goss PE et al. **Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen.** *J Clin Oncol* 2008;[Epub ahead of print]. **Abstract**

Ingle JN et al. **Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17.** *Ann Oncol* 2008;[Epub ahead of print]. **Abstract**

Press MF et al. **HER-2/neu gene amplification characterized by fluorescence in situ hybridization: Poor prognosis in node-negative breast carcinomas.** *J Clin Oncol* 1997;15(8):2894-904. **Abstract**

Smith IE et al. **Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial.** *J Clin Oncol* 2005;23(22):5108-16. **Abstract**



INTERVIEW

Robert W Carlson, MD

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

Tracks 1-17

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Where are we right now in terms of the risks and benefits of aromatase inhibitors for postmenopausal women with breast cancer?

DR CARLSON: The 100-month follow-up of the ATAC trial was one of the most important abstracts presented at San Antonio. The results were encour-

aging and reassuring. From the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis, we know that the benefits of tamoxifen, in terms of risk reduction for recurrence and death, persist well beyond the period of actual tamoxifen administration (EBCTCG 2005). Some were concerned that this might not be the case with the aromatase inhibitors — that you might win the short game but lose the long game.

The efficacy data from the ATAC trial suggest substantial benefit from anastrozole beyond the five years of actual therapy (ATAC Trialists' Group 2008; [3.1]). The long-term differences were larger in the ATAC trial than in the EBCTCG analysis of the tamoxifen carryover effect. It's an indirect comparison, so we have to be cautious, but it is reassuring to observe sustained benefits from anastrozole after treatment is completed.

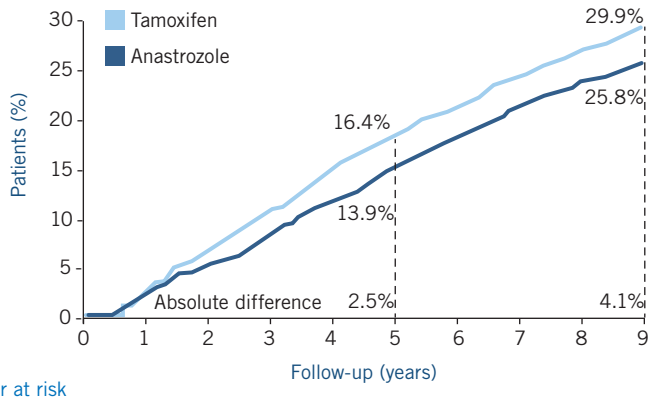
The toxicity data were also reassuring. No unexpected toxicities, especially bone events, were recorded on long-term follow-up (ATAC Trialists' Group 2008; [3.1]).

Patients received the initial five years of anastrazole or tamoxifen, and in the subsequent five years, the fracture rates for the women treated with tamoxifen and those treated with anastrozole were superimposable.

DR LOVE: We forget that these patients did not receive bone monitoring and were not administered bisphosphonate therapy. Now that's part of clinical practice.

3.1

ATAC Trial 100-Month Update — Carryover Effect: Increased Absolute Difference Favoring Anastrozole Over Tamoxifen at Five Years and Nine Years of Follow-Up



Number at risk

Tamoxifen	2598	2516	2400	2306	2196	2075	1896	1711	1396	547
Anastrozole	2618	2541	2453	2361	2278	2159	1995	1801	1492	608

SOURCE: Reprinted from *The Lancet Oncology*, Vol 9, ATAC Trialists' Group et al, **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial**, Pages 45-53, Copyright 2008, with permission from Elsevier. **Abstract**

DR CARLSON: One of the possible explanations for the fracture curves coming together with the extended follow-up in the ATAC trial is that we have learned that you need to evaluate bone health. Women in the aromatase inhibitor arm may have had their bones assessed and may have received an off-protocol intervention.

DR LOVE: That's an interesting thought. Another important finding involved the incidence of endometrial cancer during years five through nine: One case versus 12 cases in the anastrozole and tamoxifen arms, respectively (ATAC Trialists' Group 2008). The presenters posed the question of whether the absence of tamoxifen increases the risk or whether anastrozole has a preventive effect on endometrial cancer, which doesn't seem that far fetched. What are your thoughts on this?

DR CARLSON: It's hard to sort out from the data we have, but one would surmise from those numbers that it's a little of both.

Track 11

DR LOVE: Can you describe how the Onco*type* DX assay has influenced your practice?

DR CARLSON: In my practice, I consider using it for women with ER-positive, HER2-negative, lymph node-negative disease, especially in situations in which the woman is reluctant to consider chemotherapy and when the result of the assay would make a difference to her or to me in terms of the confidence with which we approach the therapy.

Women with T1A and probably T1B tumors fare well regardless of what the biomarkers show. It's for the women who have the T1C, the 1- to 2-cm or even the 3-cm node-negative tumors, that we hope these newer biological systems will be helpful.

Track 14

DR LOVE: Can you summarize what's happened recently in terms of anti-HER2 therapy for patients with HER2-positive tumors?

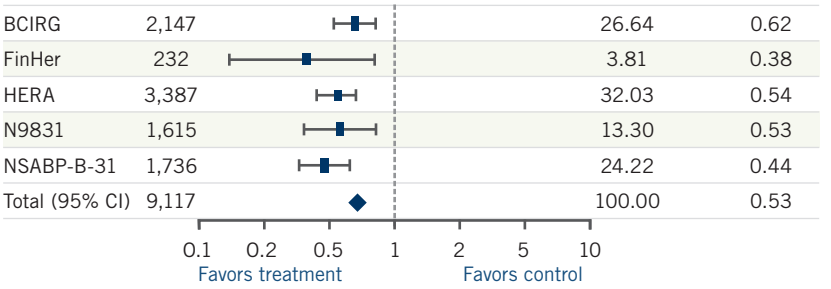
DR CARLSON: We have seen a tremendous paradigm shift in how we approach HER2-positive breast cancer, especially in the adjuvant setting. We now have six or seven major randomized trials evaluating combination chemotherapy with or without trastuzumab in the adjuvant setting. Those studies, with the exception of one that was recently reported, are remarkably consistent in the finding that the addition of trastuzumab decreases the risk of recurrence by about 50 percent and decreases the risk of death from breast cancer by about 35 percent (Smith 2007; Slamon 2006; Perez 2007; Viani 2007; [3.2]).

Those are tremendous risk reductions, the types we see with endocrine therapy in hormone receptor-positive breast cancer. They have resulted in

the rapid adoption of trastuzumab-containing adjuvant regimens in HER2-overexpressed breast cancer. ■

3.2

Disease-Free Survival in a Meta-Analysis of Published Randomized Trials of Adjuvant Trastuzumab in the Treatment of HER2-Positive Early Breast Cancer



SOURCE: Viani GA et al. *BMC Cancer* 2007;7:153. **Abstract**

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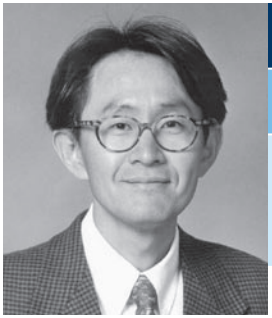
Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Smith I et al; HERA study team. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

Viani GA et al. **Adjuvant trastuzumab in the treatment of HER-2-positive early breast cancer: A meta-analysis of published randomized trials.** *BMC Cancer* 2007;7:153. **Abstract**

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *J Clin Oncol* 2007;25(1):118-45. **Abstract**



INTERVIEW

Soonmyung Paik, MD

Dr Paik is Director of the Division of Pathology for the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, Pennsylvania.

Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: Can you comment on the current assays being used to evaluate ER and HER2?

DR PAIK: The most important take-home lesson is that none of these tests is perfect.

It is almost frightening to receive data from places where, depending on which day the tissue is processed or which operation was performed, the ER result changes. Tumors removed on Friday have a much lower rate of ER positivity compared to the rest because they were in formula longer — over the weekend — and were not immediately processed into the tissue block.

DR LOVE: Is that relevant mainly to IHC testing?

DR PAIK: Yes. Unfortunately the ER assessment is done by IHC. This problem has fewer implications for FISH testing of HER2.

DR LOVE: How does a surgeon in a community hospital ensure that a patient will have appropriate ER and HER2 testing?

DR PAIK: Surgeons have a duty to communicate with the pathology department to demand quality control and quality assurance data. They have to understand which test is used at that particular lab. Is it reliable? It has to meet certain standards. For example, for HER2, I believe testing must meet the ASCO/CAP testing guideline (Wolff 2007). The quality control checks must be made.

DR LOVE: How do you check on certification?

DR PAIK: For HER2 testing, CAP will enforce the quality control beginning this year. If labs cannot meet the certification requirements, they are not supposed to perform the HER2 test.

Track 7

DR LOVE: Can you discuss your work with the Onco*type* DX assay and its role in clinical decision-making regarding the use of adjuvant chemotherapy?

DR PAIK: When we examined the gene list that the Onco*type* DX assay comprised, we realized that it was heavily populated by ER-related and proliferation-related genes. We hypothesized that this test might be predictive of chemotherapy response (Paik 2006; [4.1]).

DR LOVE: The Onco*type* DX assay has been integrated into the clinical management of the node-negative tumor. But in the last few months, we've begun to see data emerge from patients with node-positive tumors. Can you talk about what's been observed?

4.1

Impact of Adding Chemotherapy to Tamoxifen According to Onco*type* DX Recurrence Score in Women with ER-Positive, Node-Negative Disease

	10-year distant recurrence-free survival		
Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	*p*-value
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF; RS = recurrence score

"The clinical implications of these results for patients with low or relatively high RSs are relatively clear. For many women with low RSs, the anticipated benefit of adding chemotherapy to hormonal therapy may not exceed the risks. For many women with high RSs, the anticipated benefit of adding chemotherapy appears to be very favorable when compared with the risks. However, for women with intermediate RSs, it is uncertain that the benefits of chemotherapy exceed the risks. Additional study of the benefits and risks of chemotherapy in this middle range of patients is needed."

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

DR PAIK: The SWOG study Dr Kathy Albain presented has reinforced the idea that the Onco*type* DX assay is a predictor of chemotherapy response (Albain 2007). I believe it has a significant role in supporting the data we had from the NSABP-B-20 study.

We compared our chemotherapy findings to the tamoxifen arm, which was used for the gene findings, so in one sense it was a highly biased population. It is reassuring to see a similar finding in node-positive disease, in which a high recurrence score from the Onco*type* DX assay correlates with a higher degree of benefit from chemotherapy (Albain 2007; [4.2]).

The clinical utility of the Onco*type* DX assay for patients with node-positive disease is still questionable. We need much more study because even the patient with a node-positive tumor determined to be at low risk by Onco*type* DX profiling has a high baseline risk. Clinicians may have a hard time not administering chemotherapy to these patients, although biologically their expected benefit from it is minimal. ■

4.2

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

	10-year disease-free survival estimates (95% CI)	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low recurrence score (<18)	60% (40%, 76%)	64% (50%, 75%)
Intermediate recurrence score (18-30)	49% (32%, 63%)	63% (48%, 74%)
High recurrence score (≥31)	43% (28%, 57%)	55% (40%, 67%)

CI = confidence interval

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

SELECT PUBLICATIONS

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

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. **Real-world performance of HER2 testing — National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94(11):852-4. No abstract available

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *J Clin Oncol* 2007;25(1):118-45. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The NSABP-P-2 (STAR) trial for women at risk for developing breast cancer evaluated tamoxifen versus _____.**
   a. Anastrozole
   b. Raloxifene
   c. Toremifene

2. **On the two arms of the NSABP-P-2 trial for women at risk of developing breast cancer, invasive breast cancer events were equivalent.**
   a. True
   b. False

3. **In the MD Anderson neoadjuvant study, approximately _____ of patients with HER2-positive breast cancer who received chemotherapy and trastuzumab had a pathologic complete response.**
   a. 20 percent
   b. 30 percent
   c. 40 percent
   d. 60 percent

4. **In the MA17 trial, continued letrozole after completion of adjuvant tamoxifen resulted in significant improvements in _____ compared to placebo.**
   a. Disease-free survival
   b. Distant disease-free survival
   c. Overall survival
   d. Contralateral breast cancer
   e. All of the above

5. **In the 100-month follow-up of the ATAC trial, the off-treatment rate of _____ was higher among patients in the tamoxifen group than in the anastrozole group.**
   a. Endometrial cancer
   b. Fractures
   c. Both a and b
   d. None of the above

6. **The 100-month follow-up of the ATAC trial demonstrated a carryover benefit with anastrozole for recurrence in the hormone receptor-positive population that is greater than that previously shown with tamoxifen.**
   a. True
   b. False

7. **In the ATAC trial, the rate of fractures was equivalent with tamoxifen and anastrozole in the five years after completing adjuvant endocrine therapy.**
   a. True
   b. False

8. **In the adjuvant setting, trastuzumab decreases the risk of recurrence by approximately _____ among women with HER2-positive breast cancer.**
   a. 10 percent
   b. 20 percent
   c. 50 percent

9. **For postmenopausal women with node-positive, ER-positive breast cancer, a high recurrence score according to the Onco*type* DX assay correlates with a _____ degree of benefit from chemotherapy.**
   a. Higher
   b. Lower
   c. Negligible

10. **Though the Onco*type* DX assay has been integrated into the clinical management of node-negative tumors, only recently have data emerged suggesting its potential utility in the treatment of patients with node-positive tumors.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update for Surgeons — Issue 1, 2008

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

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

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Developments in neoadjuvant therapy** 4 3 2 1
- **ATAC 100-month update and the use of extended adjuvant endocrine therapy** 4 3 2 1
- **Onco*type* DX assay and clinical decision-making** 4 3 2 1
- **Clinical implications of (neo)adjuvant trastuzumab data** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Developments in neoadjuvant therapy** 4 3 2 1
- **ATAC 100-month update and the use of extended adjuvant endocrine therapy** 4 3 2 1
- **Onco*type* DX assay and clinical decision-making** 4 3 2 1
- **Clinical implications of (neo)adjuvant trastuzumab data** 4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

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

As a result of this activity, I will:

- Formulate an approach to identify and present chemopreventive options to healthy women who are at risk for the development of breast cancer. ..... 4 3 2 1 N/M N/A
- Evaluate issues related to the accuracy, reliability and interpretation of the ER and HER2 status of breast tumors, in the context of local laboratory practices and national guidelines. ..... 4 3 2 1 N/M N/A
- Assess the benefits and challenges of neoadjuvant endocrine therapy, chemotherapy and biologic therapies. ..... 4 3 2 1 N/M N/A
- Counsel patients with one to three positive lymph nodes about the benefits of postoperative radiation therapy. ..... 4 3 2 1 N/M N/A
- Evaluate the risks and benefits of partial breast irradiation therapy, and develop a plan to identify patients for whom the procedure is contraindicated. ..... 4 3 2 1 N/M N/A
- Utilize magnetic resonance imaging for patients with breast cancer, considering the appropriate role of this technology. ..... 4 3 2 1 N/M N/A
- Identify the rationale for and benefits of extended adjuvant endocrine therapy for patients with hormone receptor-positive breast cancer. ..... 4 3 2 1 N/M N/A
- Utilize the Onco*type* DX™ assay for appropriately selected patients, to collect prognostic information that guides treatment decision-making. ..... 4 3 2 1 N/M N/A
- Summarize the risks and benefits of adjuvant trastuzumab for patients with HER2-positive early breast cancer. ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials, based on an awareness of the latest research. ..... 4 3 2 1 N/M N/A

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

.....

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

.....

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

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

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
Monica Morrow, MD	4 3 2 1	4 3 2 1
Ian E Smith, MD	4 3 2 1	4 3 2 1
Robert W Carlson, MD	4 3 2 1	4 3 2 1
Soonmyung Paik, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Degree:

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

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

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City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this educational activity for a maximum of 3.0 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

Signature:..... Date:.....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.BreastCancerUpdate.com/Surgeons/CME.

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