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Breast Cancer® UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Sandra M Swain, MD

Kathleen I Pritchard, MD

Martine J Piccart-Gebhart, MD, PhD

MEET THE PROFESSORS SESSIONS

Peter M Ravdin, MD, PhD

John Mackey, MD

Anthony Howell, MD

Nicholas J Robert, MD

Harold J Burstein, MD, PhD

CME Certified

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 2 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Swain, Pritchard, Piccart-Gebhart, Ravdin, Mackey, Howell, Robert and Burstein on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

6th Annual New Strategies in Breast Cancer Conference
April 28-29, 2006
Philadelphia, Pennsylvania
Event website: **www.thecbce.com/currentactivities.asp**

NSABP Group Meeting
April 28-May 1, 2006
Denver, Colorado
Event website: **www.nsabp.pitt.edu**

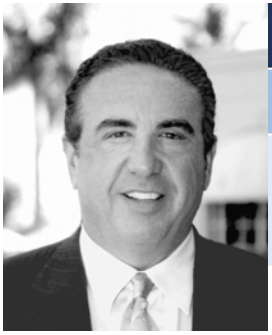
American Society of Clinical Oncology 42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**

23rd International Conference: Advances in the Application of Monoclonal Antibodies in Clinical Oncology
June 26-28, 2006
Mykonos, Greece
Event website: **www.immunology.org/meetings/mt54_05.htm**

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **www.worldcancerconferences.com**

5th Annual International Congress on the Future of Breast Cancer: Linking Therapeutic Strategies and Breast Cancer Subtypes
August 3-6, 2006
Kohala Coast, Hawaii
Event website: **www.cancerconferences.com**

31st ESMO Congress
September 29-October 3, 2006
Istanbul, Turkey
Event website: **www.esmo.org**



EDITOR'S NOTE

Neil Love, MD

San Antonio Scrapbook

This year's December stampede of breast cancer research was the usual mélange of the sublime and the repetitive. The meeting burst open with a provocative discussion of guidelines for adjuvant systemic therapy by Martine Piccart-Gebhart (see the enclosed interview) followed by possibly the most intriguing clinical research paper of the year — Dennis Slamon's presentation of the initial findings from the BCIRG 006 trial evaluating anthracycline- and nonanthracycline-based chemotherapy/trastuzumab adjuvant regimens.

The next morning, Paul Goss delivered perhaps the most interesting and discussed endocrine presentation, a subsequent analysis of the paradigm-shifting Canadian MA17 trial of letrozole after prior tamoxifen therapy. Paul, who now makes his home on this side of the border in Boston, expounded on the trial findings in an interview on the last issue of our series. San Antonio even brought some good news to the chemotherapeutic arena with Steve Jones' encouraging presentation of a US Oncology trial that demonstrated a disease-free survival advantage with docetaxel/cyclophosphamide compared to doxorubicin/cyclophosphamide.

Our CME team once again partnered with Kent Osborne and the San Antonio group to produce an educational poster exhibit entitled "Breast Cancer Clinical Trials: Past, Present and Future." During lunch breaks, we invited clinical investigators to a "Meet The Professor" session to review what was happening at the conference in real time while attendees quietly munched sandwiches and chips. Below, find a few snapshots from these sessions. ■

— Neil Love, MD
NLove@ResearchToPractice.net
March 20, 2006

Number king: Peter Ravdin (left), creator of Adjuvant! Online, expounds on emerging clinical trial data on aromatase inhibitors at various time points after diagnosis.

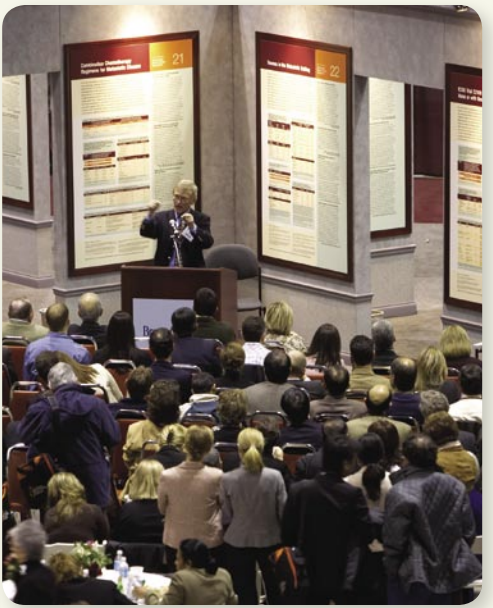






Adjuvant systemic therapy now has two molecular targets: (top) John Mackey and Harold Burstein review the recent explosion of clinical research data on adjuvant trastuzumab; Aman Buzdar takes on the St Gallenists in a transatlantic battle over the optimal long-term hormonal therapy for postmenopausal women; Terry Mamounas reviews his new NSABP trial evaluating the duration of adjuvant aromatase inhibitor therapy; Tony Howell discusses a poster demonstrating excess rates of hysterectomies and other gynecologic events in the tamoxifen treatment arm of ATAC; John Robertson comments on the next generation of endocrine research questions regarding fulvestrant.

Progress in cytotoxic therapy: Kathy Miller (below) updates the crowd on ECOG-E2100, evaluating bevacizumab with paclitaxel as first-line therapy for metastatic disease; Joyce O'Shaughnessy comments on a US Oncology trial demonstrating an advantage for TC over AC and a key ongoing adjuvant study evaluating AC → docetaxel/capecitabine; Cliff Hudis expounds on his update of CALGB-9741 evaluating dose-dense AC → paclitaxel; Nicholas Robert reviews a US Oncology report of dose-dense AC → nanoparticle albumin-bound (*nab*) paclitaxel.



INTERVIEW

Sandra M Swain, MD

Dr Swain is Chief of the Cancer Therapeutics Branch of the Center for Cancer Research at the National Cancer Institute in Bethesda, Maryland.

Tracks 1-20

Select Excerpts from the Interview

Track 2

DR LOVE: Could you review the initial adjuvant trastuzumab trials that preceded BCIRG 006?

DR SWAIN: At ASCO 2005, we heard presentations about three adjuvant trastuzumab trials. One of the presentations was actually a combined analysis

of NSABP-B-31 and NCCTG-N9831. I think everyone was stunned by the data and the *p*-value of 10^{-12} showing efficacy when you add trastuzumab to AC followed by paclitaxel (Romond 2005a; [1.1]). I was there, and I don't think there was a dry eye in the place. We have spent our lives working in breast cancer research and have never seen a result like this. It was just spectacular.

After that, the HERA trial was presented, which had a little different design in that it involved the sequential use of trastuzumab. That trial was also very positive (Piccart-Gebhart 2005a). These were also data that were early, without many events. It's clear that this is changing the paradigm in breast cancer.

The hazard rates for distant recurrence in the combined analysis of NSABP-B-31 and NCCTG-N9831 looked as if they're going down to almost zero. So we may really be curing patients with the use of adjuvant trastuzumab (Romond 2005b; [1.2]).

DR LOVE: In terms of combining the data from the two trials, some oncologists were initially questioning whether that was legitimate. What are your thoughts?

DR SWAIN: The original study design was that each trial would look at the disease-free survival separately. The groups got together before accrual was completed for both of the studies and presented an analysis plan to the FDA in order to get the results sooner. No one had any idea that we'd have the benefit that we do, so they thought they needed the combined analysis to get some results out there.

When they did the combined analysis, it was so spectacular that the results are still significant when the trials are analyzed separately (Romond 2005a; [1.3]). They did not need to do a combined analysis, but they didn't know that beforehand. So I believe it was clearly legitimate.

1.1 **Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data**

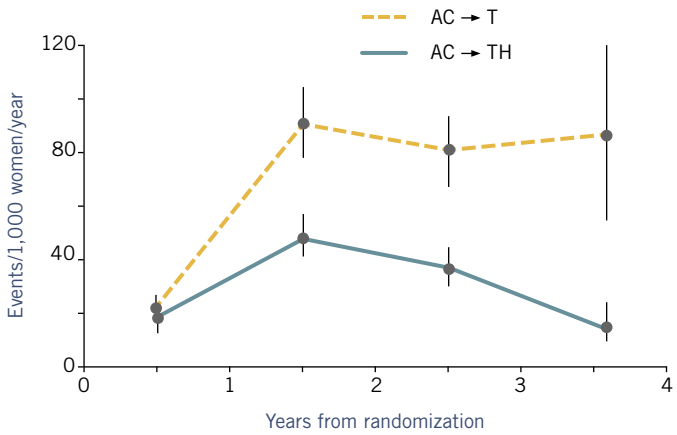
Parameters	Chemotherapy* (n = 1,679)	Chemotherapy* with trastuzumab (n = 1,672)	Hazard ratio	*p*-value
Disease-free survival				
Three-year disease-free survival	75%	87%		
Four-year disease-free survival	67%	85%	0.48	$3x10^{-12}$
Time to first distant recurrence				
Three years from randomization	81%	90%		
Four years from randomization	74%	90%	0.47	$8x10^{-10}$
Overall survival				
Three years from randomization	92%	94%		
Four years from randomization	87%	91%	0.67	0.015

* Chemotherapy = AC → paclitaxel

SOURCE: Romond EH et al. Presentation. ASCO 2005a. No abstract available

1.2

NSABP-B-31 and NCCTG-N9831 Combined Analysis: Hazard Rates for Distant Recurrence



SOURCE: With permission. Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER 2-positive breast cancer.** *N Engl J Med* 2005b;353(16):1673-84. Copyright © 2005 Massachusetts Medical Society. All rights reserved. **Abstract**

1.3

Disease-Free Survival for Patients Randomly Assigned to Adjuvant Chemotherapy with or without Trastuzumab

	NSABP-B-31		NCCTG-N9831	
	AC → T (n = 872)	AC → TH (n = 864)	AC → T (n = 807)	AC → TH (n = 808)
Three years from randomization	74%	87%	78%	87%
Four years from randomization	66%	85%	68%	86%
Hazard ratio	0.45		0.55	
p-value	1×10^{-9}		0.0005	

AC = doxorubicin plus cyclophosphamide; T = paclitaxel; TH = paclitaxel plus trastuzumab

SOURCE: Romond EH et al. Presentation. ASCO 2005a. No abstract available

Track 3

DR LOVE: In September 2005, there was a press release about BCIRG 006. Then the data were presented at the 2005 San Antonio Breast Cancer Symposium. Would you discuss that study?

DR SWAIN: Dennis Slamon performed this courageous trial, in which he chose to evaluate a nonanthracycline-containing regimen. He conducted the pivotal metastatic trial of trastuzumab, so he was extremely concerned that AC

followed by docetaxel/trastuzumab would cause cardiac toxicity. Therefore, he wanted a treatment that did not involve an anthracycline.

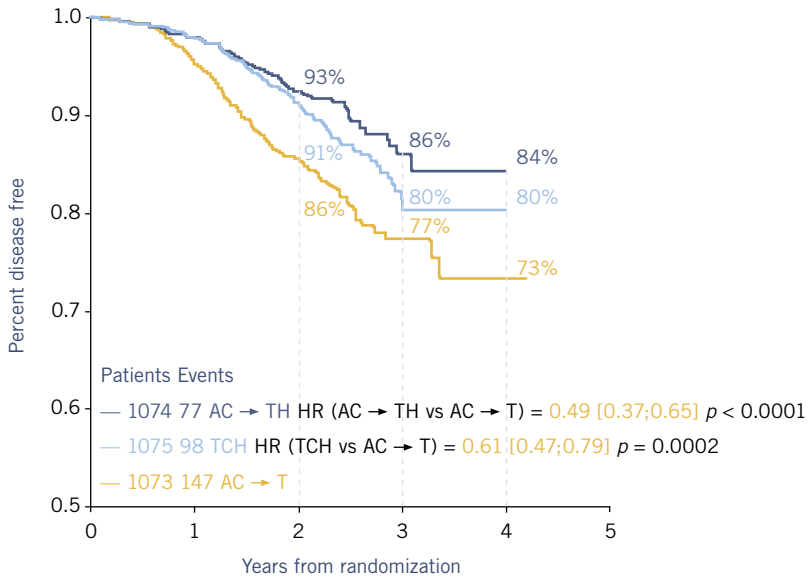
BCIRG 006 evaluated AC followed by docetaxel (T) with or without trastuzumab (H) and TCH (docetaxel/carboplatin and trastuzumab). It was a scientifically sound trial.

The interim analysis, conducted in September 2005, was presented at the 2005 San Antonio Breast Cancer Symposium. BCIRG 006 showed a strong benefit associated with the use of trastuzumab — a 51 percent reduction in the risk of recurrence for AC followed by docetaxel/trastuzumab and a 39 percent reduction for TCH (Slamon 2005; [1.4]).

If you evaluated the three curves, AC → TH was on top, TCH was in the middle and AC → T was on the bottom. There was not a statistically significant difference if you compared AC → TH to TCH. However, if you look on the graph, I think it's clear that TCH is in the middle (Slamon 2005; [1.4]).

1.4

BCIRG 006
Disease-Free Survival



SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005. With permission from CIRGC, www.bcirg.org;Abstract 1.

Track 4

DR LOVE: Another fascinating data set Dr Slamon presented evaluated topoisomerase II-alpha (TOPO II) amplification. Can you discuss that?

DR SWAIN: TOPO II is on the same amplicon as HER2. Mike Press evaluated TOPO II using FISH testing, and 35 percent of the tumors were coamplified for TOPO II and HER2. They found that regardless of the treatment, the patients who had TOPO II coamplification had a better prognosis than those who did not (Slamon 2005).

Furthermore, if you evaluate the patients who did not have coamplified tumors and look at the three treatment arms, you see that it didn't seem to matter whether they received TCH or AC → TH. They all did better compared to the nontrastuzumab-containing arm.

In the smaller group, with the 35 percent of patients whose tumors were coamplified, there was no significant difference between TCH and AC followed by docetaxel (Slamon 2005; [1.5]). They've only looked at approximately 2,000 out of the 3,000 patients, so these are preliminary but exciting data.

DR LOVE: The idea would be that if TOPO II is not amplified, you're not going to need an anthracycline and you won't need to be exposed to the cardiac risk?

DR SWAIN: That's the interpretation a lot of people are discussing right now. It is actually a great finding. If this were true, then TCH would be the treatment of choice in those patients, because you obviously don't want to expose people to a cardiotoxic agent.

They are extremely provocative data, and I've heard many people talking about the need to check TOPO II in patients. But I believe right now, we need to hold on. We have very early data with a very small number of events when we start subgrouping. We need the rest of the data with more events, and we need to look at them more carefully.

1.5

BCIRG 006: Disease-Free Survival Events in Patients with or without TOPO II Gene Amplification

	TOPO II amplified	TOPO II nonamplified
All patients (n = 744; n = 1,376)	57 (7.7%)	191 (13.9%)
AC → T (n = 227, n = 458)	23 (10.1%)	92 (20.1%)
AC → TH (n = 265, n = 472)	13 (4.9%)	45 (9.5%)
TCH (n = 252, n = 446)	21 (8.3%)	54 (12.1%)

SOURCE: Slamon D et al; on behalf of the BCIRG 006 Investigators. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

Track 5

DR LOVE: Where do you think we are right now in terms of the clinical application of these adjuvant trastuzumab data?

DR SWAIN: From the four large trials that have been presented (Romond 2005a; Piccart-Gebhart 2005a; Slamon 2005) we have a lot of data supporting the use of taxanes with trastuzumab. In clinical practice, the best plan is to utilize the regimen that you are most comfortable with. AC followed by weekly paclitaxel or by docetaxel are both effective treatments. I personally would recommend every three-week docetaxel rather than weekly docetaxel.

However, I would not recommend vinorelbine. The FinHer study showed that docetaxel had a better outcome compared to vinorelbine (Joensuu 2005, 2006). I thought that was an interesting finding. With all of the other strong data with the taxanes, a taxane would be my choice. I would use trastuzumab concurrently with a taxane when possible.

Track 5

DR LOVE: Would you summarize the data on patients with node-negative disease from the adjuvant trastuzumab trials?

DR SWAIN: In NCCTG-N9831, about 10 percent of the patients had node-negative disease (Romond 2005b), and none of those patients had tumors that were less than a centimeter. Probably one of the questions I am asked the most right now is, "What do you do with a patient who has a three-millimeter, HER2-positive tumor?"

In BCIRG 006, about 30 percent of the patients had node-negative disease (Slamon 2005), and some of those patients did have very small tumors. There was not a size limitation, but it's still, again, limited in number. In the HERA trial, approximately 30 percent of the patients had node-negative disease. The HERA trial was very strongly positive for efficacy with sequential trastuzumab in the patients with node-negative disease (Piccart-Gebhart 2005a; [1.6]).

Hence, strong data support the use of adjuvant trastuzumab in patients with node-negative disease. The nuances of its use are really about the tiny tumors. Do we need to treat those? I attended a meeting last night with Dennis Slamon, and he believes that even patients with the smallest HER2-positive tumors should receive trastuzumab.

I disagree with that a little bit because the data indicate that a patient with a two- or three-millimeter tumor has an extremely good prognosis. I have not been recommending adjuvant trastuzumab for those very tiny tumors because of the risk of cardiac toxicity. It's not like tamoxifen, with which you have minimal risk. You do have risk, and it requires intravenous therapy for a year.

Track 6

DR LOVE: What about the use of trastuzumab monotherapy in the patient whom you wouldn't want to treat with chemotherapy because of age and comorbid illnesses, perhaps a patient with an ER-negative tumor?

1.6 **HERceptin Adjuvant (HERA) Trial**

Protocol ID: BIG-01-01
Accrual: 5,090 (Closed)

Eligibility
Node-positive or node-negative, centrally confirmed HER2-overexpressed or amplified breast cancer in patients who completed ≥4 cycles of approved (neo)adjuvant chemotherapy regimen and have baseline LVEF ≥55% (Echo or MUGA)

R

- Trastuzumab 8 mg/kg → 6 mg/kg q3wk x 2y
- Trastuzumab 8 mg/kg → 6 mg/kg q3wk x 1y
- Observation

Disease-Free Survival Benefit in the HERA Adjuvant Trastuzumab Trial by Nodal Status: One Year of Trastuzumab versus Observation

Nodal status	N	Hazard ratio
Node-negative	1,100	0.51
1-3 positive	972	0.51
>4 positive	953	0.53

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353(16):1659-72. **Abstract**

DR SWAIN: I probably wouldn't use trastuzumab without chemotherapy. Most likely, even if there's comorbidity, paclitaxel can be tolerated very well if you use it weekly.

Such a large amount of synergy data exists with trastuzumab, even though the HERA trial is positive with sequential use (Piccart-Gebhart 2005b), I believe Dennis Slamon's laboratory data that indicate the synergy is important.

So I would try to use paclitaxel with trastuzumab in those patients, and if you're concerned about the anthracycline, just don't use that.

Track 7

DR LOVE: Another common question that comes up is about the patient with HER2-positive, node-positive disease who's been treated with adjuvant chemotherapy in the past — six months or a couple of years ago. What are your thoughts about guidelines for those patients?

DR SWAIN: Generally, if it's six months or less, I follow the guidelines from the trials and offer therapy. I have occasionally used trastuzumab in one or two patients who were farther out than that if they had high-risk disease. I think it's reasonable with such a huge benefit.

DR LOVE: Do you think it makes sense to try to estimate what the chance of recurrence is from that point in time for a patient who is out a year or two or more from her initial treatment?

DR SWAIN: I think the way I would look at it is exactly what you said. You take the risk that they had initially, a year ago, and the benefit of whatever you gave them to see where they are at that point. I think it is reasonable to do that, and you have to do that. I don't know how else you could do it. ■

SELECT PUBLICATIONS

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Flaherty KT, Brose MS. **Her-2 targeted therapy: Beyond breast cancer and trastuzumab.** *Curr Oncol Rep* 2006;8(2):90-5. **Abstract**

Hicks DG et al. **The incidence of topoisomerase II-alpha genomic alterations in adenocarcinoma of the breast and their relationship to human epidermal growth factor receptor-2 gene amplification: A fluorescence in situ hybridization study.** *Hum Pathol* 2005;36(4):348-56. **Abstract**

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Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER 2-positive breast cancer.** *N Engl J Med* 2005b;353(16):1673-84. **Abstract**

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Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

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INTERVIEW

Kathleen I Pritchard, MD

Dr Pritchard is Head of Clinical Trials and Epidemiology at Toronto Sunnybrook Regional Cancer Centre, Professor in the Department of Medicine and is Faculty of Medicine at the University of Toronto in Toronto, Canada.

Tracks 1-20

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: Dr Martine Piccart-Gebhart, in her presentation at the San Antonio Breast Cancer Symposium, suggested that some postmenopausal patients are better served with tamoxifen, at least initially (Piccart-Gebhart 2005). What are your thoughts on that?

DR PRITCHARD: That point of view relates to the fact that the hazard ratios in the switching trials looked somewhat better than those in the trials that compared an aromatase inhibitor to tamoxifen from the beginning. Also, many of us thought that priming with tamoxifen prior to treatment with an aromatase inhibitor might somehow be advantageous.

However, when you consider randomized studies of up-front AIs in which disease recurs more in patients on tamoxifen than in those on the aromatase inhibitor in the first two years, it's difficult to suggest that you should begin with tamoxifen (Howell 2005; Thürlimann 2005).

Until somebody shows in a randomized fashion that patients who begin with adjuvant tamoxifen are doing better at the end of five years than the patients who use an aromatase inhibitor initially, I will discuss with virtually all my patients the idea of beginning therapy with an aromatase inhibitor.

DR LOVE: How do you find tamoxifen and aromatase inhibitors compare with regard to toxicities?

DR PRITCHARD: The aromatase inhibitors probably have a better toxicity profile. The side effects of tamoxifen are different, and while some are not of concern for everyone, such as endometrial cancer for women who have had a hysterectomy, we still have to be concerned about deep vein thrombosis, which is a serious complication.

With the aromatase inhibitors, we're seeing more osteoporosis (2.1). In the MA17 data, Goss showed more fractures and osteoporosis in the patients on the placebo arm of the original trial who crossed over to letrozole in the last two years after unblinding compared to those who did not (Goss 2005a).

I think we will see some long-term complications from this unless these patients are properly treated for their osteoporosis. We have to consider how well we are prepared to either treat our patients or collaborate with primary caregivers to prevent osteoporosis, which I think is not well managed in the general population.

In Canada, increasingly, we find patients are not always screened or treated according to the guidelines. In addition, patients may not have a family doctor, or they don't follow their physician's recommendations, so it's a bit out of our control.

Track 8

DR LOVE: A number of ongoing trials are evaluating the efficacy of aromatase inhibitors in the prevention setting and in the treatment of DCIS. When the tamoxifen prevention data were released, they generated a lot of excitement, and yet people don't use it very much in that setting. What do you think is the potential of aromatase inhibitors in prevention?

DR PRITCHARD: People have opted not to take tamoxifen for prevention, which is actually quite startling. It seems women intuitively don't want to take

a pill to prevent something, and I'm not sure why that is, but I think we will see some of the same problems with the aromatase inhibitors.

People in general like to believe that maybe there's a lifestyle intervention that would be equally or more effective than taking a drug. If one exists for breast cancer, I don't think we know what it is. We are learning that exercise and keeping one's weight down may be important, and obviously these measures are good for patients in a number of ways.

I think the BRCA gene carriers are the only women who have really embraced the idea of chemoprevention. I suspect that will be true with the aromatase inhibitors as well, particularly if osteoporosis is an issue.

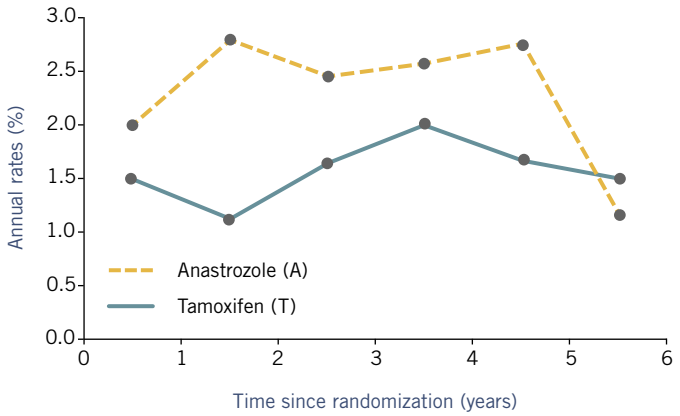
DR LOVE: How do you find that aromatase inhibitors compare with tamoxifen in terms of tolerability?

DR PRITCHARD: The hot flashes with tamoxifen are real. They show up in every placebo study, whereas weight gain and a number of other complaints do not. I believe patients similarly experience hot flashes on aromatase inhibitors, and while these may not bother some patients, they can be deal breakers for others.

If we're going to treat patients with an aromatase inhibitor long term in the adjuvant or prevention setting, we will probably use an aromatase inhibitor plus a bisphosphonate, which may double the potential for toxicity but may double the benefit as well.

2.1

Annual Fracture Rates with Anastrozole versus Tamoxifen



At risk:								
	A	3092	2923	2724	2553	2393	2070	845
	T	3094	2932	2741	2579	2401	2100	846

SOURCE: With permission. Howell A. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

Track 8

DR LOVE: In your practice, what has been your patients' experience with arthralgias and AIs?

DR PRITCHARD: The absolute difference between the arthralgias in patients on aromatase inhibitors versus tamoxifen is about five percent. I believe the aches and pains that patients experience with aromatase inhibitors are real, but it's such a peculiar phenomenon.

Some of these women become miserable, and when you discontinue the drug, for many, the symptoms disappear. However, I've had some patients that I've put back on tamoxifen, and they still have the aches and pains.

I guess this side effect is related to the lowering of estrogen. Aches and pains are reported as a menopausal symptom and are generally regarded as not all that common or serious, but maybe we don't always listen to what women tell us about their menopausal symptoms.

Track 9

DR LOVE: Putting reimbursement issues aside, how do you manage women who have received five years of an aromatase inhibitor or who switched at two or three years and get to the five-year point?

DR PRITCHARD: We're just starting to see these women now, and we don't know what to do. I told the last patient I saw to continue her aromatase inhibitor and come back in six months because we would have a clinical trial for her. Both Jim Ingle and Paul Goss have presented data from the MA17 trial that suggest year upon year, letrozole continues to add benefit (Ingle 2005; Goss 2005a; [2.2]).

However, until we see randomized studies, we're not going to know the best way to manage these cases. I think it's great that the NSABP is launching a study to evaluate patients who have had five years of any aromatase inhibitor

2.2 **MA17: Efficacy Outcomes for Women Who Initially Received Placebo and Were Offered Letrozole after Unblinding (Median Follow-Up = 54 Months)**

	Switching to letrozole: No further therapy Adjusted hazard ratio (95% CI)	*p*-value
Disease-free survival (DFS)	0.31 (0.18-0.55)	<0.0001
Distant DFS	0.28 (0.13-0.62)	0.002
Overall survival	0.53 (0.28-1.00)	0.05
Contralateral breast cancer	0.23 (0.07-0.77)	0.017

CI = confidence interval

SOURCE: Goss PE et al. Presentation. San Antonio Breast Cancer Symposium 2005a;**Abstract 16**.

or two or three years of tamoxifen followed by an aromatase inhibitor. These patients will then be randomly assigned to an additional five years of an aromatase inhibitor or not.

Track 10

DR LOVE: Can you talk about the data that were presented at the Oxford Trialists' meeting in September 2005, regarding disease-free survival curves for ER-positive and ER-negative breast cancer?

DR PRITCHARD: The most interesting piece of data I saw was a curve showing that disease in untreated patients with ER-negative disease recurs quickly in the first few years, but then their curves level out much more than patients with ER-positive disease.

On the other hand, untreated patients with ER-positive disease do much better in the first five years, and they're still ahead in the next five years. However, at approximately 10 years, the disease-free survival curves for ER-positive and ER-negative disease cross over each other, and at 15 years, the survival curves are crossing.

DR LOVE: So the untreated patients with ER-positive disease have a higher delayed relapse rate than those with ER-negative disease?

DR PRITCHARD: Yes. It's slower and steadier, but they keep recurring. It makes sense that we're now seeing that treatment after five years can be very helpful, because these patients have an ongoing risk. We haven't all appreciated this very well until the last few years. I believe that the Saphner paper showed this ongoing risk, and the Oxford Overview data have shown this before as well (Saphner 1996).

We all think of ER-positive disease as having a better natural history, but the fact is that by 10 years, more of the patients with ER-positive disease have recurred than the ER-negative group, both untreated. It's shocking because we thought we could treat these patients with tamoxifen and after that they would do well and we would not have to worry about them, but they continue on having recurrences.

So I think adding additional treatment with an aromatase inhibitor or certainly evaluating these patients in clinical trials is important.

Track 11

DR LOVE: Do you think the adjuvant aromatase inhibitor trials will eventually show a mortality benefit?

DR PRITCHARD: I believe that if these trials had gone on long enough, we definitely would have seen a mortality benefit. In the MA17 trial, when the trial was stopped, approximately 70 percent of the patients crossed over to letrozole. We're still seeing a significant overall survival benefit in patients

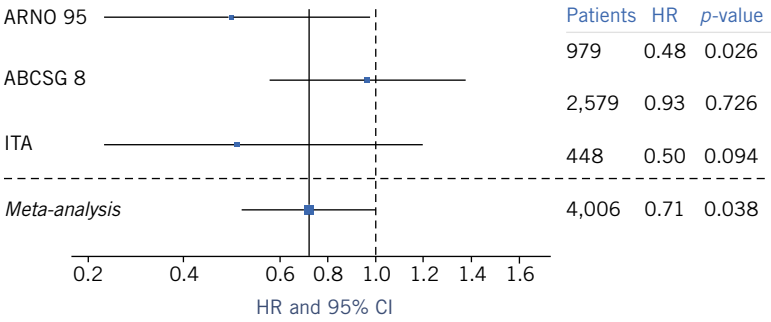
with node-positive disease who were randomly assigned to letrozole. Had the original trial continued another six or 12 months, we would have seen that much more clearly; however, now as patients cross over and receive the benefit but receive it later, that mortality benefit may be muted.

DR LOVE: Can you talk about the meta-analysis that was presented at the San Antonio Breast Cancer Symposium on the mortality data from the aromatase inhibitor trials?

DR PRITCHARD: The Austrian group presented an analysis of three of the switching trials — the ITA trial, the ARNO 95 trial and the ABCSG-8 trial — in which patients switched at two to three years from tamoxifen up front to anastrozole (Jonat 2005; [2.3]). The data showed a significant survival benefit among those patients who were switched to anastrozole versus those who remained on tamoxifen.

2.3

Meta-Analysis of ARNO 95, ABCSG-8 and ITA Trials: Overall Survival Benefit for Patients Switching to Anastrozole Following Two to Three Years of Adjuvant Tamoxifen



HR = hazard ratio; CI = confidence interval

SOURCE: With permission. Jonat W et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

Track 13

DR LOVE: What are your thoughts about some of the recent data that have come out in terms of cardiac issues and the aromatase inhibitors?

DR PRITCHARD: My view on this is probably controversial, but I think I'm right. I believe we're forgetting that tamoxifen is probably cardioprotective. I've been in the game long enough to remember that when we started studying tamoxifen as an adjuvant therapy, we knew it lowered lipids substantially, and we all believed that it was going to show a cardiac effect that was beneficial.

Indeed, the NSABP prevention study, P-1, was originally designed to examine cardiac endpoints, but since the women who enrolled in the study were

younger than expected, the cardiac component was dropped because the cardiac rate was not expected to be high enough to answer the question.

The cardioprotective effect of tamoxifen was a big hypothesis, and when you examine the available data, although they are a bit mixed, I think they consistently show either no detriment or that there is a benefit with tamoxifen compared to placebo or control.

Data from a study comparing five versus two years of tamoxifen were presented at ASCO a couple of years ago by one of the Scandinavian groups and were recently published in the *Journal of Clinical Oncology*. They showed that the patients randomly assigned to five years of tamoxifen had a lower rate of cardiac events and cardiac deaths. I believe that what we're seeing in all of these trials comparing aromatase inhibitors with tamoxifen is a small amount of cardioprotection from tamoxifen.

In the MA17 trial, the only study in which the aromatase inhibitor is compared to placebo, a lipid substudy shows virtually no difference in lipids or cardiac events between the two groups. I think that there's a protective effect from the tamoxifen and maybe an extremely small effect, if any, from the aromatase inhibitor, which I don't think is substantial. ■

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

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005b;97(17):1262-71. **Abstract**

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

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INTERVIEW

Martine J Piccart-Gebhart, MD, PhD

Dr Piccart-Gebhart is Head of the Medicine Department of the Breast International Group and Chair of the Medical Oncology Clinic at the Jules Bordet Institute in Brussels, Belgium.

Tracks 1-12

Select Excerpts from the Interview

Track 2

DR LOVE: What do you consider the optimal adjuvant chemotherapy regimen for a patient with a node-positive tumor?

DR PICCART-GEBHART: I believe that in the not-too-distant future, we will approach the choice of chemotherapy completely differently. We used to think according to risk, dividing the choice of chemotherapy regimens into the most appropriate for patients with node-positive versus node-negative disease (Piccart-Gebhart 2005a).

We are going to move away from that, because we are entering an era in cancer medicine with the development of superb tools to predict which tumors respond to which drug.

We are not there yet, but this is going fast. The technologies are exploding. If we, the clinicians, are smart enough to design the right studies to validate these technologies quickly, it's going to change the picture.

Instead of our habit of thinking that six positive nodes means dose-dense chemotherapy, we should look at the profile of the tumor first. And after that we can look at the nodes, because the number of nodes is related to risk.

I certainly would never administer dose-dense chemotherapy to a patient with a Grade I, highly endocrine-responsive tumor with maximum receptors and a very low proliferation index. On the contrary, if I see a young patient with negative nodes but an aggressive tumor with absolutely no endocrine receptors whatsoever, no HER2 and very high proliferation, I would be tempted to use dose-dense therapy.

DR LOVE: Does that same concept apply, for example, to using trastuzumab for patients with lower-risk, node-negative disease?

DR PICCART-GEBHART: This reinforces what I was saying. When a test tells you the tumor will have a good chance of responding to a targeted drug, you more readily use this drug in node-negative patients.

In the adjuvant trastuzumab studies, especially the HERA trial, which had 30 percent of node-negative patients, we saw a substantial degree of benefit from trastuzumab (HERA 2005; Piccart-Gebhart 2005b). The relative risk reduction was the same as among patients with node-positive disease; it was a substantial gain.

As we become smarter about identifying the drugs that work in particular tumors, we will still consider risk in the clinical decision-making process, but it will come second. Risk will be used to evaluate the tradeoffs between efficacy and toxicity, but it will no longer be the first consideration in treatment decision-making.

Track 3

DR LOVE: How do you view the results of the BCIRG adjuvant trastuzumab trial?

DR PICCART-GEBHART: The BCIRG 006 study is truly an interesting study. It is original in the sense that it's the only adjuvant trastuzumab trial that has at least one arm without an anthracycline, the TCH arm. I view the results of this arm as extremely positive. Several of my colleagues were disappointed, because everybody was expecting TCH to markedly surpass all the others in view of some interesting preclinical data (Slamon 2005).

My interpretation of the results is that the TCH arm is almost as good as the traditional AC followed by a taxane and trastuzumab, in terms of efficacy, and it clearly has the advantage of a much reduced risk of cardiac toxicity. I view this regimen as a good option for a woman at very high risk, for example, with many positive nodes, about whom I am very concerned about the cardiac toxicity risk.

DR LOVE: Can you summarize your take on the TOPO II data (Press 2005)? Do you think that right now it would be reasonable to utilize this test as a guide in clinical practice?

DR PICCART-GEBHART: You do some things in medicine before they are completely evidence based. In this case, it is not the first observation. Many others have been recorded, and the data already look pretty solid. So although you certainly cannot write that in a textbook or in guidelines, I will be tempted to use it for my patients.

Track 5

DR LOVE: How do you approach patients right now with small HER2-positive tumors and negative nodes?

DR PICCART-GEBHART: Women were allowed to enter the HERA trial if the tumor size was greater than one centimeter. This was the only criterion. We didn't require other aggressive features — it was purely based on pathological size. Of course, now the problem we have is with young women coming to us with eight-millimeter tumors and negative nodes. Usually, when you look at the pathology, you see other features of aggressiveness — for example, a high proliferation rate, Grade III tumors and so on.

Personally, I don't see why these women would not derive a substantial benefit from trastuzumab. Provided these women are well informed about cardiotoxicity risk, of course, we are discussing with them the possibility of trastuzumab.

Track 7

DR LOVE: What are your thoughts about the issue of delayed trastuzumab for the patient who was diagnosed one, two or five years ago with significant residual risk?

DR PICCART-GEBHART: That's a very difficult question. As we continue to follow the women in the control arms of the adjuvant trastuzumab trials, we will better understand the hazard rates over time. It's clear from the data we collected in HERA that women are at very high risk in the first two years — they have a high risk of experiencing a relapse every year (HERA 2005; Piccart-Gebhart 2005b; [3.1]). So up to two years, if a woman wants to start the drug, it makes sense to do it. Beyond two years, I have no idea.

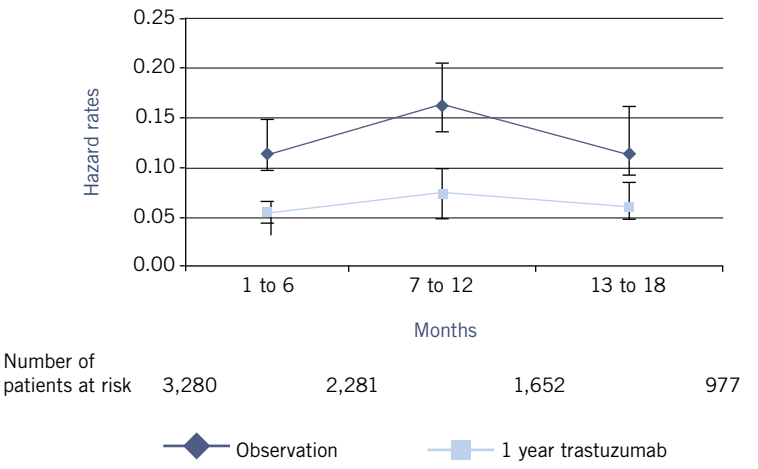
Our French colleagues demonstrated this with tamoxifen, another targeted agent. Dr Goss also presented fascinating data at the San Antonio meeting with delayed introduction of letrozole. So you start wondering whether a smart targeted drug will still provide benefit when you introduce it somewhat later. It would be interesting to design a trial looking at that (Goss 2005a, 2005b).

Track 9

DR LOVE: Where do you see bevacizumab fitting in with clinical management of metastatic breast cancer?

3.1

HERA Trial: Annual Hazard of Recurrence



SOURCE: With permission. Gelber R et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 11**.

DR PICCART-GEBHART: That's a difficult question, and I don't think I have an answer. I am embarrassed by the fact that it's not possible to identify the subset of patients that really benefits from the drug. To me, using such an expensive agent for metastatic disease without the possibility of targeting the drug is a little bit problematic.

Putting cost aside, I would use clinical judgment and I would probably be comfortable with the use of the drug for very aggressive, rapidly proliferating tumors with visceral metastasis for which, clearly, endocrine therapy cannot be beneficial.

I have no personal experience with the drug, because we have not had access to it in Europe, with the exception of a few investigators involved in Phase I/Phase II trials. It is also not reimbursed. So not having experience makes it difficult to answer.

But in my experience, sometimes women are exposed to endocrine treatments in sequence for prolonged periods of time. The day they exhaust all these possibilities, they are endocrine resistant, and you believe that chemotherapy is going to work, because they haven't seen it. My impression is that it doesn't work that well in that setting.

Based on that experience and given that there is this very well-conducted, highly positive randomized trial, I would have few problems prescribing bevacizumab combined with a taxane. If I were to use this drug today, I would use it with weekly paclitaxel as it was given in the ECOG-E2100 trial (Miller 2005; [3.2]).

3.2

E2100: Phase III Randomized Trial Comparing Paclitaxel with or without Bevacizumab as First-Line Therapy for Recurrent or Metastatic Breast Cancer

Efficacy	Paclitaxel + bevacizumab (n = 341)	Paclitaxel alone (n = 349)	Hazard ratio (95% CI)	*p*-value
Response rate				
All patients	29.9%	13.8%	--	<0.0001
Measurable disease	37.7%	16.0%	--	<0.0001
Progression-free survival	11.4 months	6.1 months	0.51 (0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months	0.84 (0.64-1.05)	0.12

CI = confidence interval

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 3**.

Track 10

DR LOVE: In general, what tends to be your first-line chemotherapy?

DR PICCART-GEBHART: The majority of first-line chemotherapy in Europe is taxane-based, because we give a lot of anthracyclines in the adjuvant setting. Many people use taxanes as soon as there is visceral disease — either docetaxel or paclitaxel.

For patients who received adjuvant taxanes, we tend to use them again if there is a long treatment-free interval.

DR LOVE: What about if there isn't a long treatment-free interval or if the patient progressed on a taxane?

DR PICCART-GEBHART: Then it would depend a little bit on the amount of anthracycline they had, and whether we can possibly use a liposomal anthracycline. Capecitabine, clearly, is among our choices. Vinorelbine may be another option.

DR LOVE: What has been your experience with capecitabine in the metastatic setting?

DR PICCART-GEBHART: For some patients this can really be a fabulous treatment. I have a few patients who have been on capecitabine for more than two years with very good stabilization of the disease, manageable toxicities and good quality of life. When the drug works, it can be really tremendously useful.

DR LOVE: How do you approach dosing?

DR PICCART-GEBHART: I usually start at 2,000 mg/m^2. In a very frail patient I might even start with 1,800 mg/m^2. I never start with 2,500 mg/m^2 — I reduce the dose.

Track 11

DR LOVE: What is your current take on adjuvant endocrine therapy, particularly for postmenopausal patients in a clinical setting?

DR PICCART-GEBHART: I have been very impressed by the results of MA17 (Goss 2003, 2005a; Ingle 2005; [3.3]). To me, this is an indication that hormone receptor-positive breast cancer is extremely difficult to cure — these women are at risk of relapse five, seven, 10, even 12 years after diagnosis. On the other hand, we clearly have an increasing number of very active endocrine agents.

I am biased. I believe that the optimal therapy for these women in the future will be a very smart sequence of endocrine agents, covering at least 10 years. Because of this bias, I don't like the idea of giving an aromatase inhibitor to everybody up front, because I don't know what to give after an AI, and I don't think an aromatase inhibitor will cure all these women. In addition, some patients will develop resistance to the drug.

In view of that, I tend to look at the profile of the tumor. If I'm dealing with a highly endocrine-responsive tumor with little worry about early relapse on therapy — a situation in which both ER and PR are very high, the proliferation genes are very low, the tumor is Grade I, and there is no HER2 overexpression — I believe there is a very low risk that the patient will relapse if you put her on tamoxifen for two years.

DR LOVE: What if the patient has node-positive disease? Do you believe that in the first two or three years there is an excess risk of relapse in those patients on tamoxifen?

DR PICCART-GEBHART: It might be that you will have a few early relapses, but on the other hand, given that the sequencing strategy is so effective and allows you to go for a seven- or eight-year treatment period, you might recover these losses later. The sequencing strategy might be more effective in the long term.

Of course, this is pure speculation and nobody knows. But I don't think it's so simple. An aromatase inhibitor for everybody up front is also expensive and cannot be afforded in many parts of the world. Certainly, this might not be the best strategy for everyone.

DR LOVE: How do you factor endometrial cancer and deep vein thrombosis versus potential effects on bone into your decision?

DR PICCART-GEBHART: It is very important. Clearly, before making a decision about adjuvant endocrine treatment, I do an in-depth evaluation of lipids, cardiovascular status and bone health.

All of these considerations need to be factored into the decision-making process.

DR LOVE: Putting aside the cost issue, what would you recommend for a 70-year-old woman with an ER/PR-positive tumor with two positive nodes?

3.3

Hazard Ratios of Disease Recurrence over Time for Patients on NCIC CTG MA17

Months after randomization	Hazard ratio Letrozole versus placebo*
12	0.52 (0.40-0.64)
24	0.45 (0.33-0.56)
36	0.35 (0.21-0.48)
48	0.19 (0.04, 0.34)

* Hazard ratios less than one indicate values in favor of letrozole.

Conclusions: This analysis of the hazard ratios for disease recurrence over time between the letrozole and placebo arms of MA17 indicates that, at least out to 4 years, the longer patients are exposed to letrozole, the greater the benefit. The increasing HR in the placebo group is of note and emphasizes the residual risk of recurrence that exists in women completing 5 years of tamoxifen. To further address the issue of duration of letrozole therapy, a rerandomization of all participants completing letrozole on MA17 to a further 5 years of treatment is underway.

SOURCE: Ingle JN et al. San Antonio Breast Cancer Symposium 2005;**Abstract 17**.

DR PICCART-GEBHART: This is clearly a woman for whom I am going to investigate the family history, look at lipid levels, ask for bone densitometry, ask whether she already has arthralgia and make sure that she has no history of deep venous thrombosis and embolism in the family.

If she's in very good health, very active, very fit, and I don't have to worry too much about bone and about cardiovascular disease, I would start with tamoxifen and go after that to an aromatase inhibitor, despite her two positive nodes. And this woman can still have a long life expectancy.

Starting with four positive nodes, I am more reluctant to go for tamoxifen. But a patient with one to three positive nodes is still in an intermediate risk group in the absence of HER2 overexpression.

DR LOVE: If we were able to conduct an international Patterns of Care study, I would expect to see a big difference in terms of US versus non-US physicians in how they answer that case.

DR PICCART-GEBHART: I agree. Although even in the US I see the controversy. I know colleagues who are very much in favor of the sequencing strategy in selected patients and others who are really in favor of an aromatase inhibitor. Some have killed tamoxifen and don't use it anymore. ■

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

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005b;97(17):1262-71. **Abstract**

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**

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MEET THE PROFESSORS

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 *Breast Cancer Update* Meet The Professors Session, held at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005

Track 2

DR LOVE: Can you review data presented here on biomarkers to identify subgroups of patients who would benefit from a specific endocrine therapy?

DR RAVDIN: The ATAC trial found that the extra advantage of an aromatase inhibitor — in this case, anastrozole — was seen strongly only in the patients with ER-positive, PR-negative disease (Dowsett 2005). This finding was based on 6,000 patients, and it had a very large *p*-value.

However, the BIG FEMTA study, which compared letrozole to tamoxifen as up-front therapy, did not find a significant difference in the efficacy of these agents relative to the status of the progesterone receptor (BIG 1-98 Collaborative Group 2005). The BIG investigators also evaluated the HER2 status of roughly 4,000 patients because data suggest that aromatase inhibitors may be more effective in tumors that are HER2-positive and ER-positive. They conducted a well-controlled study and found no significant difference on the basis of HER2, either.

The relationship between hormone receptor status and the impact of endocrine therapy was also examined in the NCIC-CTG MA17 trial. This

trial randomly assigned patients who had taken five years of adjuvant tamoxifen to five years of letrozole versus a placebo. Patients with ER- and PR-positive disease particularly benefited from letrozole (Goss 2005).

However, patients with ER-positive but PR-negative disease received no additional benefit from letrozole compared to tamoxifen. Interestingly enough, that observation is exactly opposite to the ATAC observation.

At this point, we have no way in clinical practice to specifically select patients, and in this state of uncertainty, an aromatase inhibitor is probably the better adjuvant endocrine therapy for postmenopausal patients with ER-positive breast cancer.

DR LOVE: An updated analysis was presented on the MA17 trial, which examined patients who had originally received a placebo and then switched to letrozole after the unblinding. Could you comment on that data?

DR RAVDIN: Paul Goss presented follow-up data on patients who participated in the Canadian trial comparing letrozole versus a placebo after completing five years of adjuvant tamoxifen. When they broke the code at two and a half years, some of the placebo patients decided to switch to letrozole and a few chose no further therapy. The patients who went on to take letrozole had much lower recurrence rates, even though some of them had been off any endocrine therapy for four years.

This analysis suggests that even years after stopping tamoxifen, patients can gain benefit from an aromatase inhibitor. In my practice, that means some of my patients, particularly the patients at high risk who have already been off tamoxifen for a year, should consider taking an aromatase inhibitor, specifically letrozole, because it's the only one that has been tested in this context.

DR LOVE: A rerandomization of all the patients who completed letrozole on MA17 is underway to compare another five years of letrozole to no further therapy. What do you think this will show?

DR RAVDIN: Aromatase inhibition probably should be continued indefinitely, and my opinion is based on two factors. One is that if a patient stops an aromatase inhibitor, her hormone levels will, of course, recover. Second, it may be more difficult to develop resistance to estrogen deprivation than it is to develop resistance to tamoxifen. Tamoxifen is an agonist/antagonist, and preclinical work has shown that it can be reinterpreted as an estrogen by cancer cells, but I can't conceive of a pathway that would reinterpret no estrogen as an estrogen. ■

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MEET THE PROFESSORS

John Mackey, MD

Dr Mackey is Medical Oncologist at the Cross Cancer Institute, Associate Professor of Oncology at the University of Alberta, Chair of the Northern Alberta Breast Cancer Program and Director of the Cancer International Research Group in Edmonton, Canada.

Tracks 1-6

Track 1	Introduction
Track 2	Background and design of BCIRG 006
Track 3	TOPO II amplification and the efficacy of anthracycline-based chemotherapy in BCIRG 006
Track 4	Schedule and duration of adjuvant trastuzumab
Track 5	Clinical implications of adjuvant trastuzumab trial results
Track 6	Delayed adjuvant trastuzumab

Select Excerpts from the *Breast Cancer Update* Meet The Professors Session, held at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005

Tracks 2-4

DR LOVE: Can you summarize the data presented by Dennis Slamon on the adjuvant trastuzumab trial, BCIRG 006?

DR MACKEY: The trial compared four cycles of doxorubicin/cyclophosphamide followed by four cycles of docetaxel (AC → T) — the control arm — versus four cycles of AC followed by docetaxel plus trastuzumab, which was administered concurrently with the taxane but then continued for one year (AC → TH), versus an intriguing third arm consisting of docetaxel, carboplatin and trastuzumab (TCH; [Slamon 2005]).

On the third arm, all three agents were begun on day one. Six cycles of chemotherapy were given, and the trastuzumab was continued for one year. The intent of the trial was to see if the preclinical synergy seen between docetaxel, carboplatin and trastuzumab would be borne out in the adjuvant setting and whether we could avoid major problems with cardiotoxicity by eliminating the anthracycline.

The trial demonstrated that both the AC → TH arm and the novel arm of TCH outperformed the control arm, with hazard ratios of 0.49 and 0.61, respectively. No statistically significant difference appeared between the two experimental arms.

In addition, the TCH arm had virtually no cardiotoxicity — only four out of more than 1,000 patients developed congestive heart failure.

DR LOVE: Could you comment on the TOPO II data?

DR MACKEY: The trial only allowed patients with HER2-positive disease identified by FISH. All of the tumor blocks were studied in two centers, so we were able to perform additional molecular analyses.

With HER2 amplification, a small strip of DNA is, by definition, amplified in this population; however, the HER2 amplicon can include the TOPO II gene, which is the target for anthracyclines.

Michael Press found that in about a third of patients, the HER2 amplicon included TOPO II (Press 2005). The really exciting finding was that the patients who had TOPO II amplification did very well if both targets, TOPO II and HER2, were hit by using an anthracycline and trastuzumab. In the two thirds of patients who did not have the amplified TOPO II, TCH performed just as well as the anthracycline-containing regimen and with no significant cardiotoxicity.

If we can validate this with additional follow-up, we may be able to select patients for an optimal adjuvant trastuzumab regimen on the basis of HER2 status in addition to TOPO II amplification by FISH, and these tests can be done simultaneously. If TOPO II is amplified, we might administer AC → TH; however, if TOPO II is not amplified, those women could perhaps optimally be treated with TCH and not exposed to any significant risk of cardiotoxicity.

DR LOVE: Is TOPO II ready for "prime time"?

DR MACKEY: I don't think so yet, although the data suggest we may finally have a third predictive assay in breast cancer. We have ER to tell us whether we should be using hormonal therapy, and we have HER2 to tell us whether we need trastuzumab. My prediction is that TOPO II amplification will become a validated predictive assay for benefit from anthracyclines, but we haven't proved that yet. ■

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MEET THE PROFESSORS

Anthony Howell, MD

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

Tracks 1-7

Track 1	Introduction
Track 2	Meta-analysis demonstrating a survival advantage in switching from tamoxifen to anastrozole
Track 3	Increased incidence of gynecological events with tamoxifen in ATAC
Track 4	Use of mathematical modeling to determine optimal up-front hormonal therapy
Track 5	Initiating therapy after five years of anastrozole
Track 6	Incidence of fractures and bone loss associated with aromatase inhibitors
Track 7	Time course for developing endometrial cancer with tamoxifen

Select Excerpts from the *Breast Cancer Update* Meet The Professors Session, held at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005

Tracks 2-3

DR LOVE: A number of adjuvant endocrine therapy trials were presented at the San Antonio Breast Cancer Symposium (2005). Can you summarize what those trials demonstrated?

DR HOWELL: The data from these trials created another epoch-making moment for aromatase inhibitors. To begin with, the data from Jakesz are important because they show that the effect of switching is not quite as big as we once thought. While the hazard ratio is approximately a 40 percent reduction in the switching studies, when they took into account the first two years, the reduction in the hazard ratio was about 24 percent (Jakesz 2005b).

Another significant finding was the survival advantage seen in the meta-analysis of the ARNO 95, ABCSG-8 and the ITA trials. It was an important analysis because it showed, for the first time in an unselected population, the survival advantage of switching to anastrozole. Based on that, I feel we should use anastrozole in that clinical setting (Jonat 2005).

Paul Goss and Jim Ingle's papers also presented some beautiful data — although some of that is selected — demonstrating the efficacy of letrozole for patients with hormone receptor-positive breast cancer (Goss 2005b, Ingle 2005).

Combined, I believe these data highlight the importance of the aromatase inhibitors therapeutically, and we've also seen that apart from the bone events and aching joints, aromatase inhibitors are better than tamoxifen as far as toxicity is concerned.

DR LOVE: Can you comment on the gynecologic events data from the ATAC trial?

DR HOWELL: The ATAC trial, because of its long follow-up, is providing us with some good gynecological data (Duffy 2005). Basically, it shows that gynecological events occur much more often with tamoxifen.

What really impress me are the data showing that women are undergoing many more investigations — hysteroscopies, dilatation and curettages, biopsies — and more hysterectomies on tamoxifen. The hysterectomy rate on the tamoxifen arm is 5.1 percent versus 1.3 percent among the patients taking anastrozole.

Tracks 6-7

DR LOVE: Can you discuss the issue of bone loss with aromatase inhibitors?

DR HOWELL: All three aromatase inhibitors are showing about two to three percent bone loss per year, and we need to do something about that.

What's interesting to us is that in the ATAC data, while the fracture rate was increased with anastrozole, it leveled off, and when the patient stopped treatment, the curves came right back together. If that's true, that's fantastic, but we need more data to confirm that.

I asked our bone specialists whether bone density can improve that quickly, and they pointed out that when steroids are stopped, bone reforms very rapidly, and they were not surprised by our findings.

DR LOVE: Would you comment on Delozier's data evaluating side effects and the duration of adjuvant tamoxifen?

DR HOWELL: Delozier et al showed there was no difference in the rate of endometrial cancer among patients who had taken two to three years of tamoxifen versus 13 years, which is very surprising (Delozier 2005). They're a good research group, so I suspect their finding is right. This suggests that the maximum induction might be in the first two to three years of therapy.

We found in the ATAC data that there is a bigger difference between tamoxifen and anastrozole in the first two and a half years than in the second two and a half years of treatment, which supports Delozier's finding, but obviously we need more data to see exactly what's happening. ■

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MEET THE PROFESSORS

Nicholas J Robert, MD

Dr Robert is Chairman of the Research Committee at Inova Fairfax Hospital's Cancer Center and is Chair of the Breast Cancer Committee of the US Oncology Research Network in Fairfax, Virginia.

Tracks 1-6

Track 1	Introduction
Track 2	Rationale for incorporating *nab* paclitaxel into the adjuvant setting
Track 3	Pilot study of dose-dense AC followed by *nab* paclitaxel in the adjuvant setting
Track 4	Utilization of growth factor support with dose-dense chemotherapy regimens
Track 5	Substituting epirubicin for doxorubicin in the adjuvant setting
Track 6	Schedule of *nab* paclitaxel

Select Excerpts from the *Breast Cancer Update* Meet The Professors Session, held at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005

Tracks 2-3

DR LOVE: Would you comment on your paper evaluating dose-dense AC → *nab* paclitaxel and the rationale for the study?

DR ROBERT: Right now, where I practice — and I believe throughout the United States — when we utilize adjuvant chemotherapy, we either use dose-dense chemotherapy or TAC. Paclitaxel with Cremophor® is a good drug but it requires steroid premedication, as patients can experience severe allergic reactions. The question is whether there is a better way to deliver it.

Nab paclitaxel is well tolerated — you don't have to worry about hypersensitivity or premedication with steroids. I think it was really novel to use albumin rather than Cremophor as the solvent. The interesting part of that story was the idea that albumin as a solvent might bring drugs closer to the tumor and be more effective in addition to being easier to administer.

We had a discussion about the standard in adjuvant chemotherapy and decided that the dose-dense AC → T regimen was here to stay — certainly the disease-free survival data are holding — and since *nab* paclitaxel looked better than paclitaxel in the Phase III trial (Gradishar 2005), we wanted to evaluate it in the dose-dense setting.

We started with a simple study of 30 patients and administered AC with growth factor support every two weeks and then *nab* paclitaxel, 260 mg/m^2, without growth factor support (Robert 2005) every two weeks.

All 30 patients got through the AC portion, with three requiring dose delays and two requiring dose reductions.

In the *nab* paclitaxel portion, 33 percent of the patients received growth factor support due to lack of recovery of ANC to at least 1,000 cells/mm^3 by the first day of the following cycle.

Also, of the patients who received *nab* paclitaxel, one patient went off study because the HER2 data were released and she wanted to receive trastuzumab, and two other patients were unable to complete the study. During *nab* paclitaxel treatment, approximately a third of the patients had a dose delay, and about a third experienced neurotoxicity.

However, as in the Phase III study (Gradishar 2005), in our trial, we found that once the patient develops neurotoxicity, if we reduce the dose, the neurotoxicity decreases.

We're still examining those data, but the majority of our patients improved their grade in terms of neurotoxicity within a month. So, by the time we finished administering all four cycles, the neurotoxicity was diminished.

In addition, the majority of patients were experiencing Grade II symptoms — which are livable — versus Grade III, which is when the patient is having problems with daily functioning. So it doesn't appear that neurotoxicity is a problem; the issue is whether we need to be concerned about dose delay with *nab* paclitaxel.

Preliminary results indicate that dose-dense AC for four cycles followed by *nab* paclitaxel, 260 mg/m^2, every two weeks was well tolerated in patients with early-stage breast cancer. However, further studies of that regimen in this population are indicated. ■

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MEET THE PROFESSORS

Harold J Burstein, MD, PhD

Dr Burstein is Assistant Professor of Medicine at the Dana-Farber Cancer Institute's Breast Oncology Center at Harvard Medical School in Boston, Massachusetts.

Tracks 1-7

Track 1	Introduction
Track 2	Clinical implications of adjuvant trastuzumab trial results
Track 3	Management of low-risk HER2-positive disease
Track 4	Adjuvant trastuzumab monotherapy
Track 5	Delayed adjuvant trastuzumab
Track 6	Duration of therapy with adjuvant trastuzumab
Track 7	Selection of adjuvant hormonal therapy for patients with ER-positive, HER2-positive disease

Select Excerpts from the *Breast Cancer Update* Meet The Professors Session, held at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005

Tracks 2-3

DR LOVE: Would you summarize the results of the adjuvant trastuzumab trials?

DR BURSTEIN: Within a span of eight months, the results from a number of randomized clinical trials, all with a fundamental design of chemotherapy with or without trastuzumab, were reported.

This experience cumulatively totals more than 10,000 patients: 3,200 in the BCIRG trial, roughly 3,000 from the pooled NSABP and Intergroup analysis, approximately 3,500 from two arms of the HERA trial, and a couple of hundred from the FinHer study (Slamon 2005; Romond 2005; HERA Study Team 2005; Joensuu 2005).

I'm sure that at some point, someone will do a meta-analysis, but I don't believe it's necessary because the hazard ratio for risk reduction when trastuzumab is added in the adjuvant treatment of HER2-positive disease has been remarkably consistent — approximately 50 percent. When you consider the scale of this research enterprise and the sample size, that's really quite astonishing.

It's also impressive that the absolute benefit has been incredibly consistent.

In all of these trials, the patients who received chemotherapy alone had approximately a 30 percent risk of recurrence, whereas the patients who received chemotherapy with trastuzumab had a 15 percent risk.

DR LOVE: Can you comment on the data from the BCIRG 006 adjuvant trial that compared AC followed by docetaxel versus AC followed by docetaxel plus trastuzumab versus docetaxel, carboplatin and trastuzumab?

DR BURSTEIN: The seminal question for that trial was how the triplet — docetaxel, carboplatin and trastuzumab (TCH) — would compare with AC followed by docetaxel/trastuzumab and whether we could avoid using an anthracycline.

Although the numbers were not statistically significant, it struck me that there is still an advantage for the anthracycline-based chemotherapy. The tradeoff that Dr Slamon reported is that there seems to be a slightly greater risk of cardiac toxicity for the women who received the anthracycline-based regimen, but only about a one percent difference in terms of clinical cardiotoxicity events.

I think the TCH regimen is provocative, and we should continue to watch the data as they mature. However, for the moment I will continue to use AC followed by taxane with trastuzumab as my principal adjuvant regimen for HER2-positive disease.

DR LOVE: What are your thoughts about the TOPO II data that Dr Slamon introduced?

DR BURSTEIN: TOPO II is a gene locus that's on the same chromosome as the HER2 gene locus, and when there is amplification of HER2, sometimes those amplicons, that stretch of DNA that gets amplified, include the TOPO II gene. Dr Slamon showed that the patients whose tumors are particularly enriched for TOPO II seem to selectively benefit from the anthracycline-based chemotherapy.

I think that is a provocative finding, and it fits with a good deal of preclinical and clinical literature. However, for the moment, it is not a commercially available test nor, frankly, one that is commercially necessary, because I think most patients should still get the anthracycline-based, trastuzumab-based regimen.

DR LOVE: How do you manage a HER2-positive tumor smaller than one centimeter in the adjuvant setting?

DR BURSTEIN: The honest answer is that we don't know whether these women need trastuzumab. We do need to be respectful of the fact that these women have a better prognosis because their tumors are so small. Certainly for women whose tumors are ER-positive and less than one centimeter, I've not offered trastuzumab.

For patients with ER-negative disease, I suppose one could consider trastuzumab, though the quantifiable gains from adding this agent are not known. It would be interesting to conduct a study evaluating trastuzumab with or

without chemotherapy in patients with very small tumors. Maybe we can begin to eliminate chemotherapy for the lower-risk patient population if we can alter the natural history of their disease. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Approximately what percentage of patients had node-negative disease in the HERA adjuvant trastuzumab trial?**
   a. 0
   b. 10
   c. 20
   d. 30

2. **Which of the following trials of adjuvant trastuzumab included randomization to a nonanthracycline-containing regimen?**
   a. NSABP-B-31
   b. HERA
   c. BCIRG 006
   d. NCCTG-N9831

3. **In patients with HER2-positive disease, amplification of TOPO II may increase sensitivity to anthracycline chemotherapy.**
   a. True
   b. False

4. **In the ECOG E2100 trial that evaluated paclitaxel with or without bevacizumab as first-line therapy, paclitaxel was administered _____ .**
   a. Weekly
   b. Every two weeks
   c. Every three weeks

5. **In untreated patients, the relapse rate is twice as high at 10 years in patients with ER-negative disease as those with ER-positive disease.**
   a. True
   b. False

6. **Jonat's meta-analysis of the switching trials ITA, ARNO 95 and ABCSG-8 showed a significant survival benefit in which group of patients?**
   a. Patients who remained on tamoxifen
   b. Patients who switched to anastrozole

7. **The hazard ratios for disease recurrence over time between letrozole and the placebo arms of MA17 indicated that, at least out to four years, the longer the duration of letrozole therapy, the greater the benefit.**
   a. True
   b. False

8. **Which nonanthracycline-containing regimen has been evaluated in combination with adjuvant trastuzumab?**
   a. Paclitaxel plus capecitabine
   b. Docetaxel plus capecitabine
   c. Docetaxel plus carboplatin
   d. Paclitaxel plus carboplatin
   e. All of the above

9. **According to a preliminary analysis of BCIRG 006, patients whose tumors express TOPO II amplification appear to have a better prognosis compared to those whose tumors are not amplified for TOPO II.**
   a. True
   b. False

10. **In the FinHer trial, which chemotherapeutic agents were evaluated in combination with trastuzumab?**
    a. Vinorelbine
    b. Docetaxel
    c. Gemcitabine
    d. Both a and b
    e. All of the above

11. **Data from the ATAC trials show a higher rate of recurrence during the first two years in patients taking which adjuvant therapy?**
    a. Tamoxifen
    b. Anastrozole

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

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Breast Cancer Update — Issue 2, 2006

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GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Sandra M Swain, MD	5 4 3 2 1	5 4 3 2 1
Kathleen I Pritchard, MD	5 4 3 2 1	5 4 3 2 1
Martine J Piccart-Gebhart, MD, PhD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
John Mackey, MD	5 4 3 2 1	5 4 3 2 1
Anthony Howell, MD	5 4 3 2 1	5 4 3 2 1
Nicholas J Robert, MD	5 4 3 2 1	5 4 3 2 1
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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

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.....

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

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UPDATE

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