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Breast Cancer® UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Eric P Winer, MD

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Anthony Howell, MD

Soonmyung Paik, MD

TUMOR PANEL CASE DISCUSSION

Brian Leyland-Jones, MD, PhD

Mark D Pegram, MD

CME Certified

Breast Cancer Update
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 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 neoadjuvant, adjuvant 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.
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- 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 3 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Winer, Buzdar, Howell, Paik, Leyland-Jones and Pegram on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Website: **www.asco.org**

The 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Website: **www.asco.org**

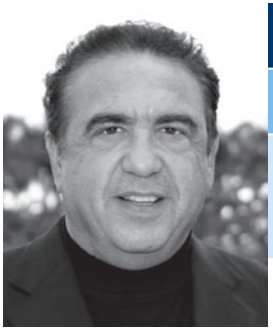
2007 California Breast Cancer Research Symposium
September 7-9, 2007
Los Angeles, California
Website: **www.cbcrp.org**

14th European Cancer Conference (ECCO)
September 23-27, 2007
Barcelona, Spain
Website: **www.fecs.be**

SWOG Semi-Annual Meeting
October 4-7, 2007
Huntington Beach, California
Website: **www.swog.org**

The Clinical Trials Workshop
October 26-28, 2007
Denver, Colorado
Website: **www.asco.org**

30th Annual San Antonio Breast Cancer Symposium
December 13-16, 2007
San Antonio, Texas
Website: **www.sabcs.org**



EDITOR'S NOTE

Neil Love, MD

Visionary

(Excerpt from a *Breast Cancer Update* interview conducted on May 22, 2002)

DR LOVE: Have you treated any patients in a nonprotocol setting with adjuvant trastuzumab?

DR SLAMON: Yes, quite a few, but if we see node-negative tumors that are less than 1.5 centimeters, it gets into a gray zone.

DR LOVE: Wow! So you'll treat a patient with a 1.5-cm, node-negative, HER2-positive tumor? How long do you continue the trastuzumab?

DR SLAMON: We use one year as in our BCIRG 006 trial, until we obtain more data. I recently treated a patient with newly diagnosed HER2-positive breast cancer — a young, premenopausal woman with a 1.7-cm, node-negative tumor. Her biggest concern was her heart because she wanted to continue to be a competitive runner.

I explained to her that this would be off-study therapy — that this is not the way to answer the question, and we need to answer the question scientifically — but for her individual case, understanding all the caveats, we would recommend TCH. She chose to be treated and is now out three years and doing fine.

DR LOVE: So you are offering adjuvant trastuzumab outside a protocol setting, even for patients with node-negative disease?

DR SLAMON: My belief is that a HER2-positive tumor is a HER2-positive tumor — nodes involved, nodes not involved, it doesn't matter. Clearly, the right way to answer the question, Neil, is in a study.

We tell the patient what we know and also that this depends on whether the payer will pay, because we don't want to put that burden on a patient.

But for the patient who's coming to you now with a HER2-positive tumor and can't wait six years for an answer from the studies, we are open to off-protocol therapy.

Dennis J Slamon, MD, PhD

DR LOVE: What about the potential for cardiac toxicity?

DR SLAMON I don't use trastuzumab with anthracyclines. I use TCH as in our BCIRG trial.

During this conversation five years ago, I distinctly remember my eyes opening wide with surprise as Dennis Slamon reeled off some of the boldest comments recorded during my 20-year CME journey. At the time of the interview and right up until the data explosions at the 2005 ASCO meeting, virtually every other breast cancer clinical investigator worshipped at the altar of the evidence base and steadfastly recommended against the nonprotocol use of adjuvant trastuzumab.

Our Patterns of Care studies during that time also consistently demonstrated that the vast majority of practicing oncologists were following the advice of their investigator colleagues, relegating adjuvant trastuzumab to trial use only. As evidenced in the aforementioned comments, the father of anti-HER2 therapy was one of the notable exceptions to that line of thinking.

On this issue of our series, we are reminded that as is frequently the case, Father knows best. To make that point, I asked Dr Slamon's UCLA colleague Dr Mark Pegram and new Emory arrival and "Hotlanta" resident Dr Brian Leyland-Jones to present patients from their practices who typify how in 2007 they approach some of the most challenging issues in adjuvant therapy for HER2-positive disease.

Among the cases discussed were two women with 0.5-cm, node-negative tumors who received trastuzumab. Five years ago, this situation was a "gray zone" for even Dr Slamon, and just two years ago, patients with multiple node-positive disease would be unlikely to receive anti-HER2 therapy outside of a study. But the rapidity of change in clinical practice with regard to trastuzumab is unprecedented in recent breast oncology history (Figure 1).

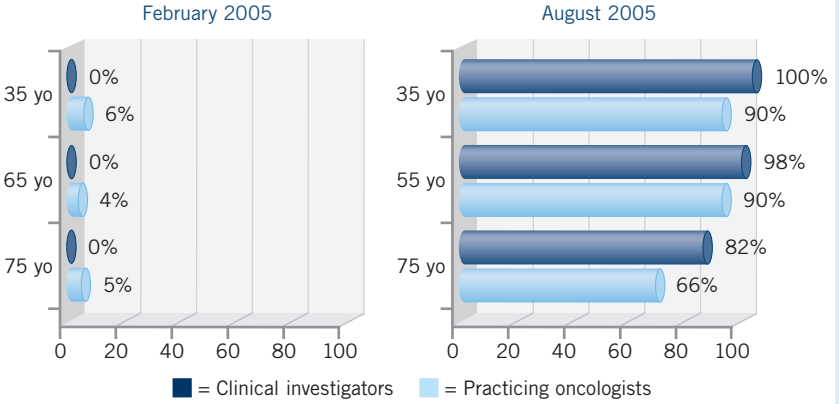
Over the years, we have observed that most important advances in the BCA clinical practice (Figure 2) have taken root much more gradually than with trastuzumab, and even a year after the initial presentation of most of these groundbreaking studies, less than a third of oncologists had changed their practices accordingly. With time, however, clinicians incorporated all of these innovations into daily patient care.

Adjuvant trastuzumab was much different, and the almost instantaneous use of this new treatment strategy was multifactorial but concentrated on two important factors: (1) the data were impressive and highly credible, and (2) everyone expected the trials to be positive based on the background research in metastatic disease. Now that we have quickly moved past the paradigm shift toward adjuvant trastuzumab, it will be fascinating to observe what people do with the latest piece of the HER2 puzzle, Dr Slamon's provocative presentation of the second data analysis of BCIRG 006 during the December 2006 San Antonio Breast Cancer Symposium.

1

Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150)

Case: A patient with a 1.2-cm, ER-positive, HER2-positive, Grade II tumor with three positive nodes. Would you use adjuvant trastuzumab off protocol for this patient? (Percent responding "yes")



SOURCE: Love N; Research To Practice. *Breast Cancer Clinical Trials Resource Guide* 2006.

2

Important Recent Breast Cancer Trial Data That Have Changed BCA Clinical Practice

December 2001	ATAC trial demonstrates superiority of anastrozole over tamoxifen[1]
December 2002	CALGB-9741 demonstrates advantage to dose-dense versus nondose-dense AC → paclitaxel[2]
December 2003	NSABP/Genomic Health collaboration reports on Onco*type* DX[3]
May 2005	First report of US and European randomized trials of adjuvant trastuzumab[4, 5]
	ECOG-E2100 demonstrates advantage of paclitaxel/bevacizumab versus paclitaxel in first-line therapy of metastatic disease[6]
December 2005	US Oncology reports advantage for TC (docetaxel/cyclophosphamide) over AC[7]
December 2006	BCIRG 006 reports equivalent tumor-related endpoints with TCH (docetaxel/carboplatin/trastuzumab) and AC → TH[8]

SOURCES: [1] Baum M et al. Presentation. San Antonio Breast Cancer Symposium 2001. No abstract available; [2] Citron ML et al. Presentation. San Antonio Breast Cancer Symposium 2002. No abstract available; [3] Paik S et al. Presentation. San Antonio Breast Cancer Symposium 2003. No abstract available; [4] Romond EH et al. Presentation. ASCO 2005. No abstract available; [5] Piccart-Gebhart MJ et al. Presentation. ASCO 2005. No abstract available; [6] Miller KD et al. Presentation. ASCO 2005. No abstract available; [7] Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 40**; [8] Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

As is often the case with presentations by this legendary investigator, the conclusions were controversial — specifically that, in essence, TCH should be the new standard adjuvant treatment for HER2-positive disease and that the time has come to put the nail into the anthracycline/trastuzumab coffin.

A think tank held by our group one month later demonstrated an immediate rift in the clinical research community on this issue, and BCIRG standard bearer John Mackey seemed perplexed that so many at the table were still hanging on to their anthracycline-based security blankets. To this end, I can't wait to see how investigators, community oncologists and patients react to the new BCIRG-NSABP trial that randomly assigns patients with HER2-positive disease to TCH alone or with bevacizumab.

Anyone can administer penicillin for pneumococcal pneumonia, but it takes a master physician to sort through the increasingly complex tumor biology and menu of options in contemporary oncology and be as objective as possible in making crucial life recommendations for patients. As part of that painstaking process, we sometimes choose to weigh the risks involved and educate our patients about the unknowns in order to walk outside the normal barriers of decision-making.

The wisdom and courage that this requires sometimes yield highly satisfying results, and in that regard, somewhere in the hills outside Los Angeles, a woman glides effortlessly on her daily jog, silently aware that the uncertain steps she and her physician took some years ago may have avoided the nightmare of cancer recurrence. ■

— Neil Love, MD
NLove@ResearchToPractice.com
April 13, 2007

SELECT PUBLICATIONS

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Love N; Research To Practice. **Management of breast cancer in the adjuvant and metastatic settings.** *Patterns of Care in Medical Oncology* 2005;2(1).

Love N; Research To Practice. **Management of breast cancer in the adjuvant and metastatic settings.** *Patterns of Care in Medical Oncology* 2005;2(3).

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

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. **Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: Second interim efficacy analysis.** Presentation. 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**

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**

INTERVIEW

Eric P Winer, MD

Dr Winer is Director of the Breast Oncology Center at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-16

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the BCIRG 006 trial results that were updated at the 2006 San Antonio Breast Cancer Symposium?

DR WINER: Dr Slamon presented the second analysis of BCIRG 006. Once again, it was clear that the use of adjuvant trastuzumab improved outcomes compared to no trastuzumab. Many people thought the big news was the update on the TCH regimen. The trial compared three treatment regimens in women with HER2-positive breast cancer as defined by FISH (Slamon 2006).

One group of women received four cycles of AC followed by four cycles of docetaxel. The second group of women received four cycles of AC followed by four cycles of docetaxel administered concurrently with trastuzumab and then followed by the completion of one year of trastuzumab. The third arm was the TCH regimen, which was docetaxel, carboplatin and trastuzumab (Slamon 2006).

In the TCH arm, no anthracycline was used and trastuzumab was administered from the beginning of the chemotherapy. The other two arms included an anthracycline, which did not allow for the concurrent administration of trastuzumab from the start (Slamon 2006).

When these data were initially presented at the 2005 San Antonio Breast Cancer Symposium, the addition of trastuzumab was found to improve disease-free survival. A suggestion emerged that the patients receiving AC followed by docetaxel/trastuzumab seemed to do better than those receiving the nonanthracycline-containing regimen. The differences were not statistically significant, but the suggestion was that more recurrences occurred in the TCH arm (Slamon 2005).

I believe that led many people to feel cautious about using TCH other than for the patient who had a contraindication to the use of an anthracycline. However, in the December update, the two trastuzumab-containing arms appeared to behave similarly. Both of the trastuzumab-containing arms recorded fewer recurrences than the nontrastuzumab-containing arm, and no dramatic difference seemed evident (Slamon 2006).

Two perspectives on these data are possible. One would be, "This is great, and we don't have to use an anthracycline." The other would be, "These are encouraging data, and they are a sign that perhaps we will be able to eliminate the anthracycline. At the same time, maybe it's best not to forget that in all the other adjuvant trastuzumab studies an anthracycline was used, and we still have a lot more experience with anthracycline- than nonanthracycline-containing regimens."

Maybe it's not time to throw out the anthracycline yet, although it certainly gives us courage to examine that issue further. I am in that second camp. In my practice, for most patients I would continue to use an anthracycline followed by a taxane and trastuzumab. I am, however, a little more comfortable than I was a year ago in skipping the anthracycline if a patient has a reason not to receive it.

Track 2

DR LOVE: Can you review the data from BCIRG 006 evaluating TOPO II amplification?

DR WINER: It is worth bearing in mind that these are subset analyses, and at our center we don't perform TOPO II testing. In my view, this is not ready for prime time.

A year ago, the suggestion emerged from 006 that for those women with TOPO II amplification in addition to HER2 amplification, the anthracycline seemed to matter more. The women who received AC followed by docetaxel/trastuzumab and had TOPO II amplification had the best outcome, and women who received TCH in the presence of TOPO II amplification perhaps didn't do quite as well (Slamon 2005).

This year, Dr Slamon presented two findings. First, in general, women whose tumors were TOPO II and HER2 amplified seemed to have a better outcome than those whose tumors were not TOPO II amplified. Second, among those women whose tumors were TOPO II amplified, a difference didn't seem to appear between TCH and AC → TH. It is also worth pointing out that among those women whose tumors were TOPO II amplified, those who didn't receive trastuzumab also did quite well (Slamon 2006).

Track 8

DR LOVE: How do you approach patients with small (<1 cm), HER2-positive, node-negative disease?

DR WINER: For a woman with a 9-mm, ER-negative, node-negative, HER2-positive tumor, a number of people — and I am one of them — would at least consider using trastuzumab.

I would also be more inclined to consider a nonanthracycline-containing regimen. In fact, we are developing a large Phase II trial evaluating weekly paclitaxel with trastuzumab for these patients. The trial will simply try to achieve a recurrence rate below a certain percentage.

If we achieve that rate, we will consider it a success. A success could either mean we would go on to another study, which I believe is unlikely, or we would feel comfortable with the regimen.

Track 10

DR LOVE: Where are we with the adjuvant trials evaluating bevacizumab?

DR WINER: Within the Intergroup, we have all endorsed a study (ECOG-E5103) comparing AC followed by paclitaxel/bevacizumab to AC followed by paclitaxel alone. That study will also have a randomization between six and 12 months of bevacizumab (1.1).

DR LOVE: Are you allowing dose-dense AC → paclitaxel in that study?

DR WINER: That decision is left to the physician. We in CALGB pushed hard for dose-dense AC → paclitaxel, so there is flexibility about how the AC is administered.

DR LOVE: What do we know from the pilot studies that have been conducted?

DR WINER: One pilot study conducted by ECOG (E2104) had two arms: (1) bevacizumab administered concurrently with AC and paclitaxel or (2) AC followed by bevacizumab administered concurrently with paclitaxel only. To my knowledge, we do not have any data yet, but we will before the other study starts. It will be important to make sure that administering bevacizumab during the AC is acceptable from a cardiac toxicity standpoint.

DR LOVE: Do we know anything about cardiac safety?

DR WINER: Concern has arisen about cardiac safety with bevacizumab. The number of events is by no means large, but a handful of cases of symptomatic cardiac toxicity have been reported with the use of bevacizumab, typically in conjunction with chemotherapy, although not with an anthracycline.

Also, a poster presentation by Mark Pegram at the 2006 San Antonio Breast Cancer Symposium evaluated trastuzumab and bevacizumab, which is a different issue because it involved combining the two antibodies. Some suggestion of cardiac toxicity appeared (Pegram 2006), although how much

1.1

Phase III Randomized Study of Adjuvant AC → Paclitaxel with or without Bevacizumab (Bev)

Protocol IDs: ECOG-E5103, NCT00433511
Accrual: 4,950 (Approved — not yet active)

R

AC → paclitaxel

[**AC** + **placebo**] q2wk or q3wk x 4 → [**paclitaxel** days 1, 8, 15 + **placebo** day 1] q3wk x 4

AC + bev → paclitaxel + bev

[**AC** + **bev**] q2wk or q3wk x 4 → [**paclitaxel** days 1, 8, 15 + **bev** day 1] q3wk x 4

AC + bev → paclitaxel + bev → bev

[**AC** + **bev**] q2wk or q3wk x 4 → [**paclitaxel** days 1, 8, 15 + **bev** day 1] q3wk x 4 → **bev** q3wk x 10

Eligibility

- Pre- or postmenopausal
- ER and PR status known, HER2-negative
- Node-positive or high-risk, node-negative

Study Contacts

Eastern Cooperative Oncology Group
Kathy Miller, MD, Protocol Chair
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Ramona Swaby, MD, Protocol Co-Chair
Tel: 888-369-2427

North Central Cancer Treatment Group
Donald Northfelt, MD, Protocol Chair
Tel: 507-538-7623

Cancer and Leukemia Group B
Chau Dang, MD, Protocol Co-Chair
Tel: 800-525-2225

SOURCE: NCI Physician Data Query, March 2007.

of it was caused by trastuzumab versus bevacizumab versus the combination is difficult to say.

We know bevacizumab causes hypertension in some women, and hypertension puts an added strain on the heart. It is not inconceivable that a problem could exist for at least a small number of women.

Track 13

DR LOVE: What do you recommend for the patient who received an adjuvant taxane less than one year ago and now experiences a relapse?

DR WINER: I struggle with what to do with that patient. Fortunately, it doesn't come up too often. Those types of patients were excluded from ECOG-E2100. About 20 percent of the patients in ECOG-E2100 had received a prior taxane but not in the past year (Miller 2005).

I am unenthusiastic about using a taxane again for that patient. So that would be a setting in which I would still want to use bevacizumab. I would use it either with capecitabine or vinorelbine. We conducted a Phase II trial with vinorelbine demonstrating that it was safe and reasonably effective (Burstein 2002), but I still don't believe we know what to do with these patients. ■

SELECT PUBLICATIONS

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Burstein HJ et al. **Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer.** San Antonio Breast Cancer Symposium 2002;446. No abstract available

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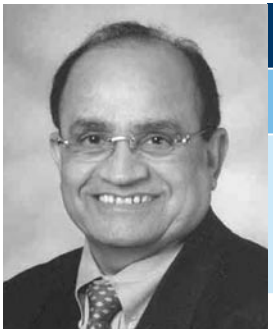
Pegram M et al. **Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 301**.

Slamon D et al, on behalf of the BCIRG 006 Investigators. **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**.

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.



INTERVIEW

Aman U Buzdar, MD

Dr Buzdar is Professor of Medicine and Deputy Chairman in the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-18

Select Excerpts from the Interview

Track 3

DR LOVE: How do you approach the sequencing of hormonal therapies for postmenopausal patients with metastatic disease?

DR BUZDAR: It all depends on the patient's prior exposure to endocrine therapy and her age. For a postmenopausal patient who has never received adjuvant endocrine therapy, I believe the first choice now is an aromatase inhibitor.

Anastrozole (Bonneterre 2000; Nabholtz 2000) and letrozole (Mouridsen 2003) both have clearly demonstrated better antitumor activity than tamoxifen in the metastatic setting. With the aromatase inhibitors, a higher fraction of patients obtain control of their disease for a longer period of time, and the patients overall experience fewer side effects.

DR LOVE: If a patient receiving an aromatase inhibitor as first-line therapy had a response and then her disease progresses, what's your usual second-line therapy?

DR BUZDAR: You have two choices. You can go from a nonsteroidal aromatase inhibitor to either a steroidal aromatase inhibitor or an estrogen receptor downregulator like fulvestrant. Those are the two choices with significant antitumor activity in this type of situation. Some patients will say, "I want to receive a therapy that I can control." Some patients want to receive therapy for which they don't have to do anything. You can administer an injection at the regular intervals, and they don't have to worry about taking something every day to remind them of their cancer.

Tamoxifen would be a reasonable option in that type of setting. However, considering the safety profile of tamoxifen versus an aromatase inhibitor, overall I would say that the aromatase inhibitor has a better safety profile.

Tracks 4-6

DR LOVE: Can you talk about the eligibility, design and results of the EFECT trial?

DR BUZDAR: Data show that the steroidal aromatase inhibitors are active in patients who have been previously treated with anastrozole or letrozole (Lonning 2000). Phase II data demonstrate that fulvestrant also has antitumor activity in patients who have received aromatase inhibitors (Ingle 2006).

We didn't, however, have any Phase III data to show whether exemestane and fulvestrant had similar efficacy. So EFECT was a bold attempt to compare them head to head. It was a double-blind, randomized, placebo-controlled trial. Neither the patient nor the doctor knew which drug the patient was receiving (Gradishar 2006; [2.1]).

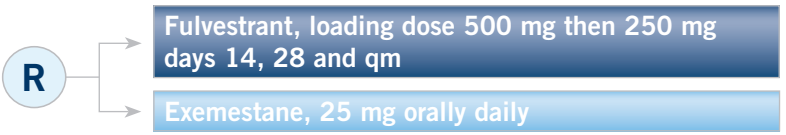
The results were not surprising. As third-line therapy, both drugs showed a modest degree of activity, and approximately one third of the patients obtained a clinical benefit. The benefit was identical between the two groups of patients (Gradishar 2006; [2.1]).

DR LOVE: EFECT used a loading dose of fulvestrant (2.1). Is a loading dose now standard with fulvestrant?

DR BUZDAR: We don't know whether that is the best approach. We can only say that it was the way fulvestrant was administered when we compared it to exemestane, and their efficacy was similar. If I have to use fulvestrant in clinical practice in this type of setting, I will use the drug as it was administered in the protocol.

2.1 **EFECT: Evaluation of Fulvestrant and Exemestane Clinical Trial**

Protocol IDs: EFECT, NCT00065325, 9238IL/0048
Accrual: 660 (Closed)



Eligibility
Postmenopausal, hormone receptor-positive, progression on a nonsteroidal aromatase inhibitor

Efficacy results

	Fulvestrant	Exemestane	*p*-value
OR	7.4%	6.7%	0.7364
CB	32.2%	31.5%	0.8534
TTP	3.7 months	3.7 months	0.6531
DOR	13.5 months	9.8 months	
DCB	9.3 months	8.3 months	

OR = objective response; CB = clinical benefit; TTP = median time to progression
DOR = median duration of response; DCB = median duration of clinical benefit

SOURCE: Gradishar W et al. San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

Track 9

DR LOVE: What about resistance to endocrine therapy? We hear more and more about the cross talk between HER2 and other pathways. Anything along those lines that you think is clinically meaningful?

DR BUZDAR: One study evaluating this question was the TAnDEM trial, in which postmenopausal patients with estrogen receptor-positive, HER2-positive, metastatic disease received anastrozole alone or anastrozole and trastuzumab. The patients who received the combination showed longer control of the disease and a higher incidence of clinical benefit (Mackey 2006; [2.2]).

Close to two thirds of the patients receiving anastrozole alone subsequently received trastuzumab, and we may not be able to evaluate the survival data. However, evidence suggested that patients receiving trastuzumab tended to have a slightly better survival, numerically (Mackey 2006).

DR LOVE: Does this new information mean that patients like this should generally start on trastuzumab and hormonal therapy?

DR BUZDAR: I believe these data are real. The TAnDEM trial did provide a strong positive lead. I would discuss that approach with a patient who is starting both therapies. We may be able to control the disease for a longer period of time. Six months ago I would not have done it.

2.2

TAnDEM: Randomized Trial Comparing Anastrozole with or without Trastuzumab for Patients with HER2-Positive, Hormone Receptor-Positive, Metastatic Breast Cancer (N = 208)

Parameter	Anastrozole	Anastrozole + trastuzumab	*p*-value
Median progression-free survival	2.4 months (95% CI: 2.0-4.6)	4.8 months (95% CI: 3.7-7.0)	0.0016
Partial response rate	6.8%	20.3%	0.018
Clinical benefit rate	27.9%	42.7%	0.026
Overall survival	23.9 months (95% CI: 18.2-37.4)	28.5 months (95% CI: 22.8-42.4)	0.325
Overall survival for patients without liver metastasis*	32.1 months (95% CI: 22.0-38.6)	41.9 months (95% CI: 30.3-52.8)	0.0399

* Unplanned subgroup analysis

SOURCE: Mackey JR et al. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

Track 11

DR LOVE: Can you provide an update of your neoadjuvant study for HER2-positive disease that you presented a couple of years ago at ASCO?

DR BUZDAR: Our study clearly demonstrated that close to 60-plus percent of the patients receiving chemotherapy with trastuzumab showed a pathological complete remission with no invasive cancer remaining in the breast or lymph nodes (Buzdar 2005).

We recently updated that study, and we have treated another 22 patients with the identical approach of chemotherapy and trastuzumab. Of the 19 patients who were in the control group and received chemotherapy alone, three have experienced disease recurrence and one of those three has died (Buzdar 2007). Of the initial 23 patients assigned to chemotherapy and trastuzumab, not a single patient has experienced recurrence during three years of follow-up. All of those patients remain alive and free of disease (Buzdar 2007).

Among the 22 additional patients we treated with chemotherapy and trastuzumab, the pathological complete response rate was similar to our earlier experience (2.3). Also, that subgroup of patients still continues alive and free of disease. Of 45 patients we treated with trastuzumab and chemotherapy, we

have not seen a single patient with a recurrence or clinical cardiac dysfunction (Buzdar 2007). ■

2.3

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 DFS (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**

SELECT PUBLICATIONS

Bonneterre J et al. **Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study.** *J Clin Oncol* 2000;18(22):3748-57. **Abstract**

Buzdar AU et al. **Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen.** *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

Gradishar W et al. **Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: First results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

Ingle JN et al. **Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032.** *J Clin Oncol* 2006;24(7):1052-6. **Abstract**

Lonning PE et al. **Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial.** *J Clin Oncol* 2000;18(11):2234-44. **Abstract**

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

Mouridsen H et al. **Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2003;21(11):2101-9. **Abstract**

Nabholtz JM et al. **Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. Arimidex Study Group.** *J Clin Oncol* 2000;18(22):3758-67. **Abstract**

TUMOR PANEL CASE DISCUSSION

Brian Leyland-Jones, MD, PhD and Mark D Pegram, MD

Tracks 1-23

Track 1 Case discussion: A 34-year-old woman (ER+/PR+/HER2+/N-)

Track 2 Estimating prognosis and benefit from therapy for patients with small, HER2-positive tumors

Track 3 Treatment of smaller, ER-positive, PR-positive, HER2-positive, node-negative breast cancer

Track 4 Clinical implications of BCIRG 006 in selection of adjuvant therapy

Track 5 Case discussion: A 53-year-old woman (ER+/PR-/HER2+/N-)

Track 6 Degree of HER2 amplification and responsiveness to trastuzumab

Track 7 Ovarian suppression/AI with trastuzumab for premenopausal patients with hormone receptor-positive, HER2-positive disease

Track 8 Trastuzumab monotherapy for lower-risk, HER2-positive disease

Track 9 Duration of adjuvant trastuzumab

Track 10 Case discussion: A 60-year-old woman (ER+/PR+/HER2+/N+)

Track 11 Adjuvant chemotherapy/trastuzumab in patients with very high-risk breast cancer and cardiac disease

Track 12 Case discussion: A 49-year-old woman (ER-/PR-/HER2+)

Track 13 Neoadjuvant chemotherapy/trastuzumab for locally advanced, HER2-positive disease

Track 14 Treatment of residual disease after induction therapy and surgery

Track 15 Case discussion: A 31-year-old woman with inflammatory breast cancer and metastatic disease

Track 16 Selection of therapy for a patient with HER2-positive inflammatory breast cancer and de novo metastatic disease

Track 17 Treatment after progression on first-line chemotherapy/trastuzumab

Track 18 Combination therapy with trastuzumab and lapatinib

Track 19 BIG 2-06: ALTTO adjuvant trial of trastuzumab, lapatinib or the combination

Track 20 Potential CNS-protective effect of lapatinib in HER2-positive disease

Track 21 Lapatinib and cardiotoxicity

Track 22 Case discussion: A 67-year-old woman with asymptomatic lung and liver metastases

Track 23 Treatment of trastuzumab-naïve metastatic disease after treatment with adjuvant AC → docetaxel

Tracks 1-4

Case Discussion 1

A 34-year-old woman who presented with a 0.5-cm, high-grade, ER-positive (90 percent), PR-positive (30 percent), HER2-amplified (FISH+), node-negative tumor with lymphovascular invasion and DCIS throughout the breast (Dr Leyland-Jones)

DR LOVE: If this patient had asked you what her risk of recurrence would be without any systemic therapy, what would you have told her?

DR LEYLAND-JONES: It is difficult to project for these cohorts with HER2-positive tumors that are smaller than one centimeter. Having said that, pathology drives everything, and this case had one of the most aggressive pathologies I have ever seen. I believe her chances of recurrence were extremely high and that her tumor would have already seeded vascularly.

DR LOVE: Mark, if this women had asked, "What do you think is my best choice for treatment?" what would you have said?

DR PEGRAM: I probably would have recommended the combination of endocrine therapy and trastuzumab. I would have put chemotherapy on the table as an option but showed her my best guess of its absolute benefits.

It is important to point out absolute benefits rather than relative risk reductions from adjuvant chemotherapy to put it into a perspective that patients can understand. Then I would let the patient weigh in on the decision. I'm not going to tell a patient "yea" or "nay" when it comes to these gray areas.

DR LOVE: Brian, what actually happened with this patient?

DR LEYLAND-JONES: We ended up treating her with FEC followed by trastuzumab, mainly because she was young and wanted to preserve her cardiac function.

Mark, what did you think about the TAnDEM data (Mackey 2006) evaluating trastuzumab with an aromatase inhibitor in metastatic disease?

DR PEGRAM: Adding trastuzumab doubled the time to tumor progression. This demonstrates a measurable treatment effect of the addition of trastuzumab to an aromatase inhibitor in first-line metastatic breast cancer that's HER2-positive and ER-expressing. That establishes precedent in my mind that those types of combinations would probably have as much or more activity in the adjuvant setting.

You could argue that the TAnDEM data set could be used as the basis for my recommendation, even though the results are modest and it's in metastatic breast cancer (Mackey 2006; [3.1]).

DR LEYLAND-JONES: I'm going to be "tongue in cheek" now and argue against myself.

If you consider the control arm of the TAnDEM study with those who had centrally confirmed ER-positive tumors, the time to progression was approximately 3.8 months, whereas for a HER2-negative population it is on the order of 11 to 12 months, so there is a significantly reduced effect for hormone therapy in the HER2-positive population.

DR PEGRAM: This is exactly as we predicted based on publications on this

issue of HER2 and estrogen receptor cross talk in laboratory models, which we first published in 1995 (Pietras 1995). HER2 would confer relative endocrine resistance.

DR LEYLAND-JONES: One of the conclusions that José Baselga drew from that study is that those patients probably need chemotherapy as opposed to hormone therapy. So in the way that we're administering it, the chemotherapy and trastuzumab is the major treatment modality, and the hormone therapy is the additive part of treatment.

DR PEGRAM: I believe the key to success of adjuvant therapy for this patient will be the HER2-directed therapy. That treatment will have the greatest impact in terms of proportional reduction and relative odds of recurrence.

The hazard ratio across the board for all of the adjuvant trastuzumab trials (Joensuu 2006; Piccart-Gebhart 2005; Romond 2005; Slamon 2006; Smith 2007) is approximately one half, and that's above and beyond chemotherapy (3.2).

DR LEYLAND-JONES: We're dealing with an unknown here. Martine Piccart made a beautiful presentation at the Istanbul meeting last October, in which she was asking what we do with tumors smaller than one centimeter. She showed this beautiful blue slide with two words written on it: "Nobody knows." So we are projecting here using the metastatic data from the TAnDEM trial (Mackey 2006).

Whether we did the right thing or not, I do not know, but if you do consider those metastatic data — trastuzumab alone in metastatic disease — you see the times to progression are between three to four months. With the chemotherapy and trastuzumab, the times to progression — whether it's a taxane or vinorelbine — are 10 to 12 months.

3.1

Summary of the TAnDEM Clinical Trial Results: Anastrozole with or without Trastuzumab as First-Line Therapy

"Given the trial results that we have, in the context of the data that we possessed prior to this trial, we can very safely conclude that trastuzumab added to anastrozole does significantly improve progression free survival in women with HER2 and hormone receptor-positive metastatic breast cancer.

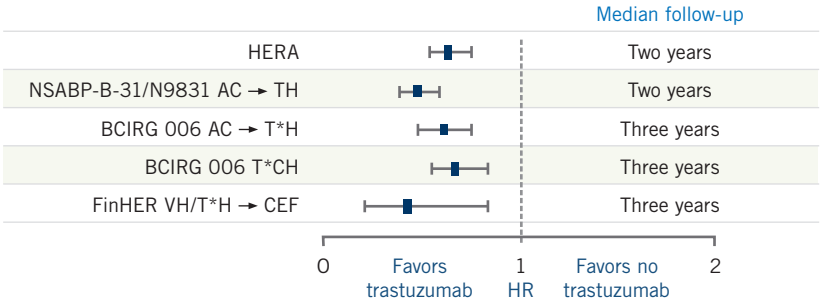
Interestingly, there were 15% of patients receiving the combination therapy who did not experience progression for at least two years. And at least for this population, the approach of anastrozole plus trastuzumab appears to be able to delay the requirement for chemotherapy for a considerable period.

Although 70% of patients did crossover to trastuzumab after progression, we are nonetheless seeing a numerical improvement in the overall survival, and in general, the combination of anastrozole plus trastuzumab was very manageable and there were no unexpected or new adverse events."

SOURCE: Mackey JR. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

This is a lot of your synergy data, Mark. I would agree with you completely that the major benefit was from the trastuzumab. However, there would seem to be, if you project from metastatic data, distinct synergy from trastuzumab and the chemotherapy together. Now we are worried about administering trastuzumab alone in the adjuvant setting because we have no data for it.

3.2 **Hazard Ratios for Disease-Free Survival with Trastuzumab**



H = trastuzumab; T = paclitaxel; T* = docetaxel; V = vinorelbine

SOURCES: Smith I et al. *Lancet* 2007;369(9555):29-36. **Abstract**; Slamon D et al. *Proc SABCS* 2006;**Abstract 52**; Joensuu H et al. *N Engl J Med* 2006;354(8):809-20. **Abstract**; Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Tracks 5-9

Case Discussion 2

A 53-year-old woman with a mammographically detected T1, ER-positive (30 percent), PR-negative, HER2-amplified (FISH+), Grade III, node-negative tumor, with a 0.4-cm focus of invasion and a component of DCIS but with clear surgical margins (Dr Pegram)

DR PEGRAM: For this patient, I simulated as best I could what might be the relative risk reduction with cytotoxic therapy and with endocrine therapy alone and concluded that the single most important component of her adjuvant therapy would arguably be trastuzumab. After evaluating simulations using Adjuvant! Online and evaluating the utility of chemotherapy for these small tumors with ER-positive disease, we decided that chemotherapy would not be a good choice.

For this woman, we used endocrine therapy in combination with trastuzumab. We used tamoxifen because she was 53 years old and early perimenopausal.

DR LOVE: Are there any situations in which either of you would use ovarian suppression and an aromatase inhibitor off protocol for a premenopausal patient with HER2-positive disease?

DR LEYLAND-JONES: We have used it once for a HER2-positive tumor in a patient who had high-grade disease. In the vast majority of our cases, we're administering tamoxifen and ovarian suppression.

DR PEGRAM: I must plead guilty and admit I have done it.

For patients with 10 or more positive lymph nodes, what are you going to do? You want to maximize, biologically, the probability of response. I am impressed that, in adjuvant cohorts, aromatase inhibitors are somewhat better than tamoxifen for postmenopausal patients.

So if you simulate a postmenopausal state in a premenopausal woman, either biochemically or with surgical ovarian ablation, then you should be able to capture that same small but significant advantage of the aromatase inhibitors over tamoxifen, even in premenopausal patients, theoretically.

DR LEYLAND-JONES: I agree with Mark, and I believe the combination of ovarian ablation and aromatase inhibitors will be used increasingly, Neil.

DR LOVE: Mark, we should point out that your openness to using trastuzumab in the adjuvant setting without chemotherapy is not something that we see in a lot of clinical investigators and oncologists in practice. Everybody says, "Well, you want to at least stick a taxane in there." In fairness, we should say that your approach is a little unusual.

DR PEGRAM: Sure, and I don't suggest that everybody should jump to use this approach. However, in terms of enthusiasm for the approach, a rising swell of clinical investigators want to tackle this question in a clinical trial.

Tracks 10-11

Case Discussion 3

A 60-year-old woman with a 5.0-cm, ER-positive (90 percent), PR-positive (10 percent), HER2-amplified (FISH+) inflammatory breast tumor with eight positive nodes, hypertension, an LVEF of 43 percent and renal failure treated with dialysis (Dr Leyland-Jones)

DR PEGRAM: Obviously, patients like this woman were excluded from the adjuvant trastuzumab studies, as they probably should have been. However, we have to understand that her risk of recurrence and death is so high that if you don't maximize efficacy at this point, she will succumb to her disease.

I would still be inclined to consider a trastuzumab-based adjuvant scheme, pray that her heart will be okay and follow her closely. This comes up occasionally in metastatic breast cancer, too, and at some point the patient's breast cancer will be as or more life threatening than the risk of cardiomyopathy associated with the trastuzumab. When that boundary is crossed, then trastuzumab becomes a therapeutic option.

Chemotherapy also has to be on the table in this case. I would try it, but I would bail out in the event of any toxicity. Weekly taxanes are particularly well tolerated. I would have to read the literature on hemodialysis and paclitaxel.

I don't know what effect it has on the pharmacology of paclitaxel. Anthracyclines are off the table in this case because of the low ejection fraction.

DR LEYLAND-JONES: Would you administer taxanes and trastuzumab concurrently?

DR PEGRAM: Yes, I would probably try weekly paclitaxel/trastuzumab.

DR LOVE: What do we know about the cardiac safety of a taxane and trastuzumab, without any prior anthracycline, compared to nothing?

DR PEGRAM: We have the data from several randomized clinical trials in which paclitaxel/trastuzumab has been one of the treatment arms.

The Robert study compared paclitaxel/trastuzumab to paclitaxel/carboplatin/trastuzumab (Robert 2006). That's in the metastatic setting, but at least we have the safety data. Paclitaxel/trastuzumab used alone has no real impact on ejection fraction.

We also have the pivotal trial data in metastatic disease (Slamon 2001). I will not say there was no impact on cardiac functioning. Anecdotes exist of depressed ejection fractions in patients who were treated even with single-agent trastuzumab. So you're not going to say it has no impact, but the risk is low.

In the BCIRG 006 cohort — which did not receive paclitaxel but rather docetaxel/carboplatin and trastuzumab — the risk of clinical congestive heart failure or Grade III/IV cardiotoxicity was extremely low.

It's disconcerting that this patient is starting out with known cardiac disease, but it's more disconcerting that she has such a high risk of recurrence and will probably die from breast cancer if you don't attempt adjuvant therapy in order to gain distant disease control.

DR LOVE: Brian, how did you think this case through, and what did you do?

DR LEYLAND-JONES: This was made easy for us, Neil, because she refused to undergo any kind of intravenous or systemic therapy. She had a psychiatric history, and the consensus of the group at tumor board was to treat her with an aromatase inhibitor alone.

I must admit that the risk of recurrence here is extremely high, and I would have leaned in Mark's direction. I would probably have gone back to the cardiologist and asked whether, if we'd played around with the cardiac protective medications and an ACE inhibitor, we could have kicked the LVEF up a bit more.

The weekly paclitaxel and trastuzumab would probably be the optimal therapeutic index. The other option would have been an aromatase inhibitor with trastuzumab, as we discussed in the previous case.

Tracks 12-14

Case Discussion 4

A 49-year-old premenopausal woman in excellent health who presented with a 9.0-cm, ER-negative, PR-negative, HER2-amplified (FISH+), invasive tumor, with a palpable left axillary lymphadenopathy. Staging evaluation with CT scans of the chest, abdomen and pelvis, bone scans and serum markers were negative (Dr Pegram)

DR LEYLAND-JONES: Generally, we administer neoadjuvant therapy, with something like the Buzdar regimen by which we administer all the chemotherapy up front (Buzdar 2005). Our own leaning is more toward administering something like AC → TH or FEC → TH for four cycles of each.

DR LOVE: Are you administering the trastuzumab during the anthracycline, as Buzdar did?

DR LEYLAND-JONES: We're not at this moment, but my understanding is that a publication from Buzdar will appear fairly soon, in which the safety of that regimen is confirmed (Buzdar 2007; [3.3]).

DR LOVE: For patients who have residual tumor and positive nodes, what do you do postoperatively?

DR LEYLAND-JONES: We continue the trastuzumab for a full year, without any other type of chemotherapy.

DR LOVE: Mark, what did you do in this situation?

DR PEGRAM: We administered docetaxel/carboplatin and trastuzumab. This was, at least in part, based on a collaboration we've had with Judith Hurley in Miami, who published a paper in the *JCO* last year showing that in a cohort of similar patients with large primary tumors, she obtained a respectable pathologic complete response rate with TCH (Hurley 2006).

The pathologic complete response rate was approximately 26 percent, which compares favorably to any other cytotoxic induction for locally advanced disease.

Considering she achieved that in a cohort of patients with a massive median tumor size, we thought that was impressive and had no hesitation recommending the regimen off protocol to this patient.

DR LOVE: What happened when she was treated?

DR PEGRAM: She had a fantastic clinical response. She literally had no palpable disease by the time she finished her cytotoxic induction regimen, but on histopathology she still had multiple residual, small areas of invasive disease in the area of the primary and multiple, small metastases by H&E stain in the axillary lymph nodes.

DR LOVE: Postoperatively, she received trastuzumab alone?

DR PEGRAM: She received trastuzumab with concurrent chest wall radiation therapy. You're always uncertain with these neoadjuvant cases that don't show pathologic complete responses whether or not to administer additional cytotoxic therapy later on.

In the absence of data, it's difficult to recommend that, although emotionally we all want to believe it will help. We wound up not administering any additional cytotoxic therapy.

3.3

Cardiac Safety of Neoadjuvant Therapy with Paclitaxel Followed by FEC and Concurrent Trastuzumab in HER2-Positive, Operable Breast Cancer

"Patients who were followed up clinically and had a subsequent cardiac evaluation after completion of trastuzumab-based therapy have maintained their cardiac function in the same range, and no patients have developed clinically apparent congestive heart failure. These findings provide further evidence that trastuzumab and anthracycline-based combinations may be reasonably safe when used as in this protocol.

Whereas some of the trastuzumab-treated patients have a decrease in their ejection fraction, these decreases have not progressed to clinical heart failure.

This is in keeping with the concept that trastuzumab therapy is associated with type II treatment-related cardiac dysfunction that may be reversible and mechanistically or prognostically different than cardiotoxicity associated with anthracyclines."

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

Tracks 15-21

Case Discussion 5

A 31-year-old woman with two small children who presented with a large, red right breast, matted axillary lymph nodes, bone pain and a tender liver. She was diagnosed with a Grade III, ER-negative, PR-negative, HER2-positive inflammatory ductal carcinoma. CT scan of the brain revealed a mottled cortical destruction of the bone with dural thickening and lytic lesions of the skull. Bone scan was diffusely positive in multiple areas. CT scan of the liver revealed multiple lesions. Skin biopsy showed dermal lymphatic invasion. CEA was 54, and CA 15-3 was 311 (Dr Leyland-Jones)

DR PEGRAM: This is first-line metastatic breast cancer, so I'm going to consider trastuzumab-based regimens because the patient's cardiac status is okay.

She would be a candidate for a cytotoxic therapy in combination with trastuzumab. If she's young and otherwise healthy, she could probably even consider combination cytotoxics along with the trastuzumab, such as TCH, but I don't feel strongly with metastatic disease about combinations versus single agents or about which agents are used, as long as it's trastuzumab based.

I suspect that a 31-year-old woman will likely see multiple cytotoxics over time. It is just a matter of trying to maximize the probability of obtaining control of her disease up front and then palliation thereafter. Of course, this would be used in combination with a bisphosphonate for her bone metastases.

DR LOVE: Brian, how did you approach this patient?

DR LEYLAND-JONES: She was treated with carboplatin/paclitaxel and trastuzumab with pamidronate.

DR LOVE: What do you think your second-line therapy will be?

DR LEYLAND-JONES: We will probably follow the Chuck Geyer data (Geyer 2006; [3.4]) and recommend capecitabine/lapatinib.

DR LOVE: How would you decide between that and keeping the trastuzumab going and adding another chemotherapeutic agent?

DR LEYLAND-JONES: A big controversy existed about continuing trastuzumab on progression. It seemed people would say, "Well, if the patient had a good, prolonged response to first-line therapy, I might be more likely to continue the trastuzumab." Will that now go totally out the window, and will people simply go to second-line lapatinib?

DR PEGRAM: A strong sentiment will probably emerge to change classes of inhibitors. The lessons learned from other targeted therapy approaches — the estrogen receptor — are that by changing the strategy of therapeutic targeting, you might capture additional responses, albeit with perhaps somewhat lower frequency and not as long a duration, but nevertheless resulting in tangible clinical benefit.

This issue of trastuzumab duration in the metastatic setting has never been put to rest in a randomized clinical trial, which is unfortunate because once the

3.4

Lapatinib and Capecitabine for HER2-Positive Advanced Breast Cancer: Efficacy Endpoints in the Intention-to-Treat Population

Endpoint	Lapatinib and capecitabine (N = 163)	Capecitabine alone (N = 161)	Hazard ratio (95% CI)	*p*-value
Median TTP	8.4 months	4.4 months	0.49 (0.34-0.71)	<0.001
Median PFS	8.4 months	4.1 months	0.47 (0.33-0.67)	<0.001
Overall response Complete response Partial response	22% <1% 21%	14% 0% 14%		0.09
Clinical benefit	27%	18%		
Death	22%	22%		

TTP = time to progression; PFS = progression-free survival

SOURCE: Geyer CE et al. *N Engl J Med* 2006;355(26):2733-43. **Abstract**

tyrosine kinase inhibitors are available in the community, that question will probably become impossible to address.

Tracks 22-23

Case Discussion 6

A healthy, active 67-year-old woman who was treated three years ago with AC followed by docetaxel for an ER-negative, PR-negative, HER2-amplified (FISH+), node-positive breast tumor and now presents with asymptomatic, biopsy-proven lung and liver metastases (Dr Pegram)

DR LOVE: How did you manage this patient, Mark?

DR PEGRAM: We used weekly low-dose paclitaxel/carboplatin/trastuzumab, and she did well for a number of months but eventually had disease progression. She was still fit and without symptoms. Her blood counts were fine, and she had no problems in terms of ejection fraction. Her progression was detected initially with a rise in tumor marker values. The CA27-29 was doubling and she had a new hepatic metastasis, which again was not associated with any biochemical liver dysfunction.

DR LOVE: Brian, what would you be thinking at this point?

DR LEYLAND-JONES: Most of my colleagues would use either vinorelbine and trastuzumab or capecitabine and trastuzumab at this point, although without any question, soon we will be moving on to capecitabine/lapatinib.

DR LOVE: What did you do, Mark?

DR PEGRAM: She received vinorelbine and continued trastuzumab in the absence of supporting data, but that's what we elected to do because she had had a several-month time to progression while on the weekly low-dose TCH and had no contraindications to continuation of the trastuzumab at this point.

She was on that for only about two to three months and then she once again experienced disease progression, indicated by a rise in tumor markers. That prompted reimaging studies, and disease progression was found in the lung and the liver, with new lesions and a substantial increase in the size of her existing lesions.

Surprisingly, she was still asymptomatic. She had a mild transaminase elevation, but it was less than 1.5 times the upper limit of normal — not too severe.

She developed complications with her port, with an infection followed by a thrombosis. Ultimately, the port had to come out, so we did not have great IV access. The question at that time was whether to continue intravenous therapy with further trastuzumab-based salvage chemotherapy or not. She chose not to receive further trastuzumab, and we treated her with single-agent capecitabine. Her disease was stable on that for a period and then subsequently progressed. ■

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Bacus SS et al. **Inhibition of ErbB1/2 by small molecule tyrosine kinase inhibitors, but not trastuzumab, affects metabolic pathways: Implications to cardiac toxicity.** San Antonio Breast Cancer Symposium 2006;**Abstract 304**.

Buzdar AU et al. **Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen.** *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

Cristofanilli M et al. **A phase II combination study of lapatinib and paclitaxel as a neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer (IBC).** San Antonio Breast Cancer Symposium 2006;**Abstract 1**.

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43. **Abstract**

Hurley J et al. **Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer.** *J Clin Oncol* 2006;24(12):1831-8. **Abstract**

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Konecny GE et al. **Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells.** *Cancer Res* 2006;66(3):1630-9. **Abstract**

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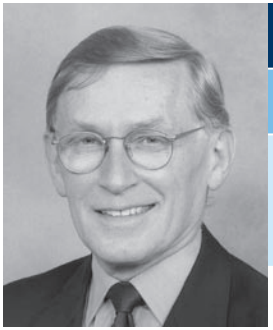
Robert N et al. **Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2006;24(18):2786-92. **Abstract**

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**.

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **Abstract**

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**



INTERVIEW

Anthony Howell, MD

Dr Howell is Professor of Medical Oncology at the Christie Hospital NHS Trust at the University of Manchester in Manchester, England.

Tracks 1-12

Track 1

DR LOVE: Would you discuss the bone data from the ATAC trial presented at the 2006 ASCO meeting?

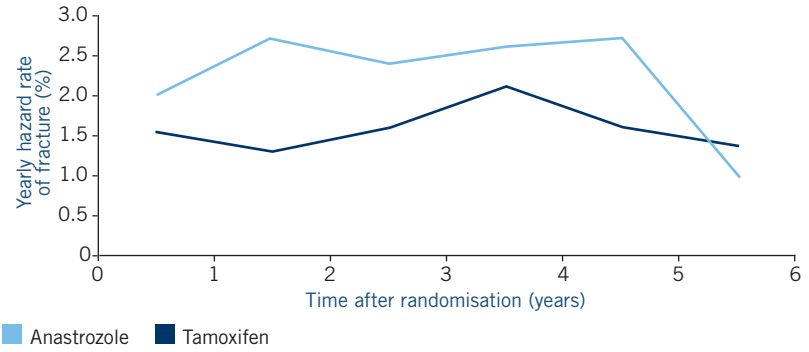
DR HOWELL: The bone data (Coleman 2006; ATAC 2006; [4.1]) are important because these are the first five-year data on the aromatase inhibitors, and they show a marked loss on anastrozole compared to tamoxifen over the five years in ATAC — a seven to eight percent loss over the five years in the lumbar spine, but this levels off slightly after two years. In the hip, it goes straight to eight percent.

It does appear that we are able to prevent bone loss with the bisphosphonates, but the important clinical point from the analysis was that if they started with a normal bone density, none of those women became osteoporotic over the five years. If the patient starts with osteopenia, you need to follow her carefully.

DR LOVE: What do we know right now about how effective bisphosphonates are in preventing this bone loss?

DR HOWELL: We're beginning to get quite a lot of data. The most important data remain those from the Austrian study, which was published in the *Journal of Clinical Oncology* (Gnant 2007). They show that zoledronic acid at four milligrams administered every six months completely abrogated the bone loss from goserelin with either tamoxifen or anastrozole. This was presented at San Antonio two years ago by Michael Gnant (Gnant 2004).

4.1 **ATAC Trial: Yearly Hazard Rate of Fractures During and After Treatment**



Frequency of first fracture before recurrence by treatment group
Data calculated by Kaplan-Meier estimates

SOURCE: Reprinted from The Lancet Oncology, Vol 7, Buzdar A et al, **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial**, 633-43, Copyright 2006, with permission from Elsevier. **Abstract**

Track 3

DR LOVE: Can you describe the initial results of the EFECT study for postmenopausal patients with hormone receptor-positive metastatic disease (Gradishar 2006; [2.1])?

DR HOWELL: The trial compared fulvestrant to exemestane after failure on a previous nonsteroidal aromatase inhibitor as second- or third-line therapy in advanced disease, and patients could enroll after having received an aromatase inhibitor as adjuvant therapy.

The response rate and clinical benefit were identical between the two arms, with approximately a 20 percent response rate in each arm (2.1). At the moment, from that trial, no difference is evident between fulvestrant and exemestane with regard to time to progression. So if you want to use a simple treatment, you can administer exemestane. Otherwise, you can administer the fulvestrant injections.

Three other studies evaluating fulvestrant are important: SoFEA, SWOG-S0226 and FACT. The FACT and the SWOG studies are evaluating the combination of anastrozole and fulvestrant versus anastrozole alone after failure of a SERM such as tamoxifen, and these studies are crucially important.

The SoFEA trial is different. It's a three-arm study: exemestane versus fulvestrant versus fulvestrant with anastrozole. That trial will provide another indication of whether fulvestrant is better than exemestane and whether the combination is better than a single agent. That trial is trying to examine whether maintaining a low estrogen environment is beneficial for the effectiveness of fulvestrant.

Track 4

DR LOVE: Can you discuss the mechanism of action of fulvestrant and the aromatase inhibitors, what you think would happen with the two in combination and how that might be different combining a SERM like tamoxifen with an aromatase inhibitor?

DR HOWELL: The major difference between tamoxifen and fulvestrant is thought to be what happens when the SERM or the SERD binds the estrogen receptor. When tamoxifen binds the receptor, it goes to the estrogen response element (ERE) of the appropriate genes.

Tamoxifen can inhibit the gene activity, but the estrogen receptor can also be activated by growth factors through phosphorylation of activating factor one (AF-1). The SERD causes downregulation of the receptor, which is degraded, and growth factors can't act through phosphorylating AF-1.

With the combination, the aromatase inhibitor keeps estrogen low and inhibits it from going to the ERE. If estrogen reaches the ERE, fulvestrant causes degradation of the estrogen receptor, so presumably growth factor activity can't occur via AF-1 and phosphorylation. The combination works in Angela Brody's animal models, but it will be another year before we see the results of these trials and find out whether it works in women with breast cancer.

DR LOVE: I guess the key issue is that fulvestrant is a competitive inhibitor of estradiol. So you can increase the dose of fulvestrant or remove the ligand.

DR HOWELL: Exactly. That is the rationale behind the SoFEA trial. You're maintaining a low estrogen level in that trial, so you reduce the estrogen level or you increase the dose or, possibly, both.

Track 7

DR LOVE: Can you discuss where we are with the IBIS-1 and Royal Marsden studies?

DR HOWELL: The data on long-term preventive effects of tamoxifen are clearly important. Four prevention trials are under way, but only two of them will be

able to provide good long-term data that are uncontaminated by women who were on the control arm receiving treatment, as occurred in NSABP-P-1.

Clearly NSABP-P-1 is an important study with large numbers, and within a relatively short period of treatment, patients had a 50 percent reduction in the risk of developing breast cancer.

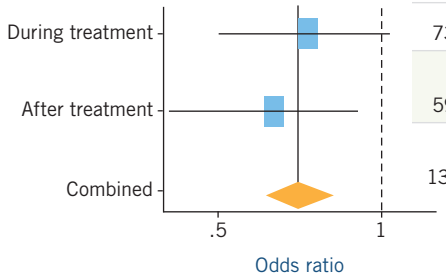
Two studies (Cuzick 2006; Powles 2006) reported at San Antonio asked the question, what happens when you stop treatment? Would you see a carry-over effect or not? The answer is that you do see a carryover effect, which is absolutely fascinating. In the IBIS-1 study, 7,000 women remained blinded after stopping five years of treatment, and the data presented by Jack Cuzick demonstrated a 30 to 40 percent reduction continued after 10 years (4.2) — and the toxicity goes down (Cuzick 2006).

The problem of endometrial cancer goes away, and the deep vein thrombosis goes away (Sestak 2006). So you're left with a net benefit in the end. Therefore, let's reconsider the view that we have on tamoxifen and reconsider this drug as a preventative agent.

The data are supported by the Royal Marsden trial, which Trevor Powles presented (Powles 2006). It was a randomized trial of eight years of tamoxifen versus placebo. He's shown a 50 percent reduction beyond stopping tamoxifen, which is clearly another carryover effect. So we have two trials showing a carryover effect, which is important for prevention.

4.2

Long-Term Efficacy of Tamoxifen for Chemoprevention in IBIS-1: Incidence of Invasive ER-Positive Breast Cancer During and After Treatment (Median Follow-Up = 95.6 Months)



	Placebo	Tamoxifen	OR (95% CI)
During treatment	73	54	0.74 (0.51-1.07)
After treatment	59	33	0.56 (0.35-0.87)
Combined	132	87	0.66 (0.50-0.87)

SOURCES: Cuzick J et al. *J Natl Cancer Inst* 2007;99(4):272-82. **Abstract**; Cuzick J et al. San Antonio Breast Cancer Symposium 2006;**Abstract 34**.

Track 8

DR LOVE: Can you discuss the IBIS-2 and MAP-3 trials?

DR HOWELL: IBIS-2 and MAP-3 are logical trials to conduct. IBIS-2 evaluates anastrozole versus placebo, and MAP-3 compares exemestane to placebo in postmenopausal women at increased risk of developing breast cancer. Both trials are recruiting reasonably well. IBIS-2 needs 6,000 women, and MAP-3 needs about 4,500 to 5,000 women.

The important data presented at the San Antonio meeting from the point of view of IBIS-2 are on cognitive function. I was particularly worried that a decline in cognitive function would appear with anastrozole, and we've shown in more than 200 patients that after six months there's absolutely no difference in cognitive function, and these women underwent 10 carefully controlled cognitive function tests (Jenkins 2006). I find this reassuring. The patients will receive up to five years of follow-up. They'll undergo another test at two years and another at five years. ■

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Cuzick J et al. **Long-term results of tamoxifen prophylaxis for breast cancer — 96-month follow-up of the randomized IBIS-I trial.** *J Natl Cancer Inst* 2007;99(4):272-82. **Abstract**

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Gnant MF et al. **Zoledronic acid effectively prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: A report from the Austrian Breast and Colorectal Cancer Study Group.** *J Clin Oncol* 2007;25(7):820-8. **Abstract**

Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen — Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

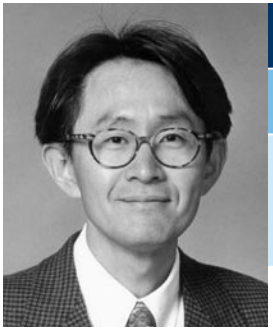
Gradishar W et al. **Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: First results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

Howell A et al. **Analysis of fracture risk factors from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial: 5-year data.** *Proc ASCO* 2006;**Abstract 563**.

Jenkins V et al. **Preliminary results from the IBIS II (prevention) cognitive sub-protocol.** San Antonio Breast Cancer Symposium 2006;**Abstract 5076**.

Powles TJ et al. **20 year follow-up of the Royal Marsden tamoxifen breast cancer prevention trial.** San Antonio Breast Cancer Symposium 2006;**Abstract 51**.

Sestak I et al. **Comparison of side-effect profiles during active treatment versus follow-up in the IBIS-I tamoxifen prevention study.** San Antonio Breast Cancer Symposium 2006;**Abstract 1051**.



INTERVIEW

Soonmyung Paik, MD

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

Tracks 1-12

Track 1	Identification of predictive markers for adjuvant trastuzumab
Track 2	ASCO/College of American Pathologists recommendations for quality control of HER2 assessment
Track 3	Quality control in the assessment of hormone receptor status
Track 4	Quantitative analysis of ER and PR by Onco*type* DX association with prognosis and prediction of tamoxifen benefit
Track 5	Background for the evaluation of HER2 and cMYC coamplification
Track 6	Impact of HER2 and cMYC coamplification on benefit from trastuzumab
Track 7	Utility of the Onco*type* DX assay for patients with HER2-positive and node-positive disease
Track 8	Development of a tumor gene assay for recurrence risk in colon cancer
Track 9	Evaluation of the Onco*type* DX assay in the TAILORx trial
Track 10	Quantitative analysis of ER and HER2 via RNA methodologies
Track 11	NSABP-B-40 correlative tissue studies: Predictors of pathologic complete response
Track 12	Impact of chemotherapy on hormone receptor-positive disease

Tracks 3-4

DR LOVE: Can you discuss your work on NSABP trial B-31 evaluating tissue predictors of outcome in HER2-positive disease?

DR PAIK: We are interested in learning whether we can identify prognostic factors or predictive markers for benefit from trastuzumab. Although patients in NSABP-B-31 derived a significant benefit from trastuzumab, their four-year recurrence rate was still about 15 percent, so they were not completely cured.

We had to design a next-generation trial in which we could add more agents, such as bevacizumab, but we didn't want to administer additional treatment to everybody, so we had to generate the prognostic model for trastuzumab-treated patients. We were trying to uncover many markers.

DR LOVE: What specific markers are you evaluating?

DR PAIK: Obvious candidates such as HER2 gene copy or expression level by immunohistochemistry in addition to some other molecules, such as PTEN (Fujita 2006), are described as important in a HER2 receptor signaling pathway.

DR LOVE: What have you learned about gene copy number and response to trastuzumab?

DR PAIK: That's interesting biology. As trastuzumab is targeted to HER2, one would expect that the HER2 level should be a direct predictor of degree of benefit from trastuzumab in the adjuvant setting. But when we assessed the degree of benefit by HER2 gene amplification level, it was not directly predictive (Shak 2006). Because of the way eligibility was set up in the B-31 trial, about 10 percent of the patients overall turned out to have a normal gene copy number — no amplification.

DR LOVE: In other words, 10 percent of the patients essentially had HER2-negative disease? Were there enough patients or events to document any impact of trastuzumab on HER2-negative disease?

DR PAIK: It's a small number. In that small number of patients with normal-copy HER2, a trend to benefit did appear. That was surprising, and when we conducted an interaction test or a test for impact of benefit across all categories of gene amplification, we didn't find any significance. So it appears as though the HER2 gene copy is not a good predictor of degree of benefit.

DR LOVE: Can you discuss the new ASCO/CAP guideline for HER2 testing?

DR PAIK: The new guideline adopted by ASCO and CAP (Wolff 2007), published in the *Journal of Clinical Oncology*, states that if the FISH ratio is between 1.8 and 2.2, a result that would be regarded as equivocal, patients should be tested again or tested with HER2 IHC.

DR LOVE: What else that was new came out in that guideline?

DR PAIK: That is the bottom line — essentially it recommends strict quality control for the laboratories that conduct testing for HER2.

Track 5

DR LOVE Do you think the situation with ER testing is any better than that with HER2?

DR PAIK: No, ER testing I believe is much worse off.

DR LOVE: Do you see CAP, ASCO and other major entities focusing on ER testing?

DR PAIK: Yes. I do believe the next target will be ER assay standardization. For HER2, we had two competing assays that we could always use to compare data, and besides, the expression level of HER2 is somewhat bimodal in distribution because of amplification. The ER is not like that — it's more continuous.

The current-generation immunohistochemical assay that pathology labs use incorporates an amplification method for the signal to generate color in the slide, and this biases the assay as too sensitive at the low level of estrogen receptor. So it will be a fairly difficult effort.

Tracks 7-8

DR LOVE: Can you review the data on cMYC in the B-31 adjuvant trastuzumab study?

DR PAIK: A benefit in relapse rate was still evident among the patients with cMYC-nonamplified disease, but it was much attenuated. Analysis of the interaction between cMYC amplification and benefit from trastuzumab (Kim 2005) demonstrates an extremely strong p-value ($p < 0.001$). I wondered why cMYC turned out to be the predictor. It turns out that I was relatively uninformed about cMYC biology.

When I began to read the literature about cMYC, I realized that our results make a lot of sense. The cMYC gene is a transcription factor, and it essentially regulates a lot of genes, including those relating to cell proliferation and also cell death. It's crazy that the same molecule regulates both cell proliferation and cell death — it's almost like an inherent biological defense the cells have against cancer.

The genes that are important in the body are always dual regulators, and cMYC is one of them. Because it has this dual capability of inducing both proliferation and cell death, when this molecule becomes abnormal (deregulated expression due to gene amplification or mutation and so on) the cells go through cell death, so they cannot become cancer cells.

The only way cancer cells can develop is when they can bypass survivor factors that inhibit the apoptotic signal.

My theory is that HER2 is one of the survivor factors. In those cells that have gene amplification of both HER2 and cMYC, which is a small subset of breast cancer patients (about six percent), HER2 is not the oncogene in that situation — cMYC is the oncogene. HER2 helps cMYC to become the oncogene by suppressing the cell death signal. In that setting, because of the high survivor signal coming from HER2, the cells are inherent and resistant to chemotherapy.

DR LOVE: So chemotherapy is part of the equation here too?

DR PAIK: Right. If you administer trastuzumab in this situation, the survivor signal coming from HER2 goes away, and it leaves the strong cMYC to induce cell death, especially in combination with chemotherapy, and causes a massive cell suicide.

DR LOVE: That's interesting. We've always had this question about how much of the effect of trastuzumab is related to synergy with chemotherapy. We know as a single agent trastuzumab has significant activity. Does your model make sense in terms of the effect of trastuzumab without chemotherapy?

DR PAIK: We know of two possible ways to interpret these data. One interpretation is that the trastuzumab obviously causes immune-related cell death, too, so the reason that cMYC-negative patients also gain some benefit in disease-free survival might be the fact that immune killing occurs in addition to the chemotherapy killing.

The other possibility is that in the cMYC-nonamplified group, trastuzumab is simply causing growth inhibition, not cell death. That's why you see a continued failure even on trastuzumab if you view the Kaplan-Meier plot in the cMYC-nonamplified group, but if you evaluate the cMYC-amplified cohort, you see almost no failure after two years (5.1).

So for the patient with cMYC amplification, the mechanism of trastuzumab varies mainly with chemotherapy, and apoptosis occurs. In cMYC-negative disease, trastuzumab simply inhibits growth.

Using that hypothesis, the prediction is that for cMYC-positive disease, you might not have to administer trastuzumab for one year. Perhaps you only need to administer it together with chemotherapy. For patients with cMYC-negative disease, you have to administer trastuzumab essentially forever.

5.1

Efficacy of Chemotherapy with or without Trastuzumab (H) in cMYC-Nonamplified and cMYC-Amplified Patients with Operable HER2-Positive Breast Cancer: Analysis of NSABP-B-31

	cMYC-nonamplified (N = 1,078)			cMYC-amplified (N = 471)			Interaction *p*-value
	Chemo	Chemo + H	HR	Chemo	Chemo + H	HR	
Recurrence	15.2%	10.2%	0.63	21.8%	5.5%	0.24	0.007
Death	5.2%	5.4%	0.99	9.8%	3.4%	0.36	0.037

"While patients with co-amplification of cMYC and HER2 had worse outcome when treated with chemotherapy alone, addition of trastuzumab reversed this trend, achieving 4 year recurrence free survival of over 90%. Although these data contradict our a priori hypothesis, they are consistent with pre-clinical models that suggest that the pro-apoptotic function of dysregulated cMYC needs to be counterbalanced by an anti-apoptotic signal by another activated oncogene in order for such cells to develop into cancer.

Amplified HER2 may provide such anti-apoptotic signaling that is reduced by treatment with trastuzumab, resulting in triggering of apoptosis. These data suggest that indirect targeting of dysregulated cMYC may be possible if co-operating oncogenes providing anti-apoptotic signals are identified."

SOURCE: Kim C et al. San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

Track 9

DR LOVE: Can you update us on the status of your research on Onco*type* DX?

DR PAIK: Two interesting issues were raised by many people regarding the Onco*type* DX assay. Our data showed that if patients had HER2 amplification, they were usually categorized as being at high or intermediate risk and none of them were at low risk.

Steve Shak has screened approximately 10,000 patients so far and has found some patients have HER2 amplification but are still at low risk (Shak 2006). So he believes they still must be tested, but my bias considering the NSABP-B-14 data is that they don't need to be tested.

Because of those data, some people are arguing that if you take out the patients with HER2 amplification, then the Onco*type* DX assay will not be as strong a prognosticator for patients with HER2-negative disease. We did assess the HER2-negative subset in B-14, and it worked exactly as it did for the overall cohort.

The other issue is that everybody wants to find out whether the Onco*type* DX assay can be used for patients with node-positive disease. For that, we are eagerly waiting for Kathy Albain's SWOG study (SWOG-S8814A-ICSC) to learn whether it is also predictive of benefits of chemotherapy for patients with node-positive disease. ■

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Fujita T et al. **PTEN activity could be a predictive marker of trastuzumab efficacy in the treatment of ErbB2-overexpressing breast cancer.** *Br J Cancer* 2006;94(2):247-52. **Abstract**

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Paik S. **Molecular profiling of breast cancer.** *Curr Opin Obstet Gynecol* 2006;18(1):59-63. **Abstract**

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Paik S et al. **Technology insight: Application of molecular techniques to formalin-fixed paraffin-embedded tissues from breast cancer.** *Nat Clin Pract Oncol* 2005;2(5):246-54. **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. **Abstract**

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

Shak S et al. **Relationship between proliferation genes and expression of hormone and growth factor receptors: Quantitative RT-PCR in 10,618 breast cancers.** San Antonio Breast Cancer Symposium 2006;**Abstract 6111**.

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. **In the second interim analysis of BCIRG 006, no statistically significant difference appeared in disease-free survival between AC → TH and TCH in the overall population or in the population with amplification of TOPO II.**
   a. True
   b. False

2. **A joint analysis of NSABP-B-31 and NCCTG-N9831 showed that the addition of trastuzumab to adjuvant taxane-based therapy was associated with a _____ percent relative risk reduction in recurrence rate at four years.**
   a. 12
   b. 25
   c. 33
   d. 52

3. **According to new HER2 testing guidelines by ASCO and the College of American Pathologists (CAP), a FISH ratio of _____ is considered equivocal and reason to retest for HER2 status.**
   a. Less than 1.8
   b. Greater than 2.2
   c. From 1.8 to 2.2
   d. None of the above

4. **Analysis of the NSABP-B-31 adjuvant trastuzumab trial revealed that patients with tumors with coamplification of cMYC and HER2 who were treated with chemotherapy and trastuzumab had a four-year recurrence-free survival rate of approximately _____ percent.**
   a. 50
   b. 60
   c. 70
   d. 90

5. **The addition of lapatinib to capecitabine resulted in a significant improvement in time to progression compared to capecitabine alone among patients with HER2-positive metastatic breast cancer that had progressed on treatment regimens including an anthracycline, a taxane and trastuzumab.**
   a. True
   b. False

6. **The TAnDEM trial failed to demonstrate an advantage in progression-free survival when trastuzumab was added to anastrozole for patients with ER-positive, HER2-positive, metastatic disease.**
   a. True
   b. False

7. **In the ATAC trial, no patient who had normal bone mineral density at baseline developed osteoporosis after receiving five years of adjuvant anastrozole.**
   a. True
   b. False

8. **An Austrian study for premenopausal breast cancer patients receiving goserelin and either tamoxifen or anastrozole demonstrated that the addition of zoledronic acid completely abrogated bone loss.**
   a. True
   b. False

9. **The EFECT study demonstrated no difference in time to progression or response rate among postmenopausal patients with metastatic disease who received fulvestrant or exemestane after disease progression on a nonsteroidal aromatase inhibitor.**
   a. True
   b. False

10. **Early assessment in the IBIS-2 chemoprevention trial demonstrated significantly worse cognitive functioning in patients receiving anastrozole compared to those receiving placebo.**
    a. True
    b. False

11. **ECOG trial E5103 will evaluate bevacizumab in combination with _____ in patients with node-positive or high-risk node-negative, HER2-negative breast cancer.**
    a. AC alone
    b. AC → paclitaxel
    c. AC → docetaxel
    d. TCH

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

EVALUATION FORM

Breast Cancer Update — Issue 3, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this Evaluation Form. A certificate of completion will be issued upon receipt of your completed Post-test and Evaluation Form.

Please answer the following questions by circling the appropriate rating:

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

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 neoadjuvant, adjuvant 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
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . . . . 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
Eric P Winer, MD	5 4 3 2 1	5 4 3 2 1
Aman U Buzdar, MD	5 4 3 2 1	5 4 3 2 1
Brian Leyland-Jones, MD, PhD	5 4 3 2 1	5 4 3 2 1
Mark D Pegram, MD	5 4 3 2 1	5 4 3 2 1
Anthony Howell, MD	5 4 3 2 1	5 4 3 2 1
Soonmyung Paik, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 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

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 3, 2007

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

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

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

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To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation 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 Evaluation online at www.BreastCancerUpdate.com/CME.

BCU307

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