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Cardiologic Issues in Breast Cancer Management

Proceedings and Interviews from a Closed Roundtable Meeting of Clinical Investigators and Practicing Oncologists

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And a case-based roundtable discussion featuring the faculty and practicing oncologists

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Cardiologic Issues in Breast Cancer Management
A Continuing Medical Education Audio Program

STATEMENT OF NEED/TARGET AUDIENCE

Improvements in survival of patients with breast cancer require increased attention to the trade-offs between the benefits of commonly utilized, effective therapies and the iatrogenic effects of those treatments, including the increasingly recognized potential cardiotoxic side effects. Understanding of treatment-associated cardiotoxicity will allow physicians to more effectively counsel patients about treatment options and to more effectively manage treatment-related adverse events. To bridge the gap between research and patient care, this activity uses one-on-one discussions with leading oncology investigators and case discussions with community oncologists and 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

- Understand the pathophysiologic mechanisms, risks and the nature of cardiotoxicity associated with anthracyclines, trastuzumab and other biologic agents in order to assist patients with breast cancer in treatment decision-making.
- Develop a clinical algorithm for monitoring cardiac functioning in patients receiving anthracyclines, trastuzumab and other biologic agents, and develop an approach to managing treatment-induced cardiotoxicity while providing optimally effective cancer treatment.
- Identify the relative advantages and disadvantages of MUGA and echocardiography for monitoring left ventricular ejection fraction (LVEF).
- Develop awareness of the intraindividual and interobserver variability in the assessment of LVEF in order to evaluate the relevance of changes to individual patient care.
- Evaluate the relative advantages and disadvantages of anthracycline- and nonanthracycline-containing regimens in order to counsel patients with HER2-positive and HER2-negative disease about potential treatment options with less cardiac risk.
- Recognize the importance of cardiology-oncology collaboration in the care of patients with cardiac risk factors, particularly those receiving potentially cardiotoxic adjuvant therapy, in order to mitigate risk of congestive heart failure.

PURPOSE OF THIS CME ACTIVITY

The purpose of this program is to support these global objectives by offering the perspectives of Drs Steingart, Slamon and Burstein on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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Research To Practice designates this educational activity for a maximum of 4.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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UPCOMING EDUCATIONAL EVENTS

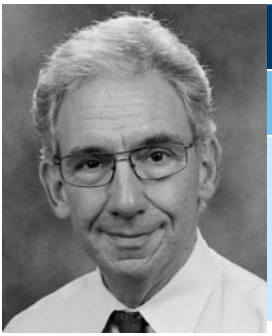
NCCN 12th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care
March 14-18, 2007
Hollywood, Florida
Event website: **www.nccn.org**

Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions
March 26-27, 2007
Bethesda, Maryland
Event website: **http://ctep.cancer.gov/bcmeeting**

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **www.aacr.org**

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

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



INTERVIEW

Richard M Steingart, MD

Dr Steingart is Chief of Cardiology Service at the Memorial-Sloan Kettering Cancer Center, Professor of Medicine at Weill Medical College of Cornell University and President of the Society of Geriatric Cardiology in New York, New York.

CD 1, Tracks 1-14

Select Excerpts from the Interview

CD 1, Tracks 2-3

DR LOVE: Can you provide an overview of anthracycline-related cardiotoxicity?

DR STEINGART: There are acute, subacute and long-term anthracycline-associated cardiotoxicities. The acute toxicity may be associated with arrhythmias and chest pain. It looks like an inflammatory response and occurs within hours or days of the administration of an anthracycline. The subacute toxicity is described as heart failure at a month or more thereafter.

Long-term toxicity occurs when individuals who have received an anthracycline and are not suspected of having any cardiac reaction end up with

heart failure years later. Whether those are separate entities or simply clinical manifestations of the fundamental toxicity showing themselves at different time points in the disease is unclear in my mind.

I conceptualize the events as part of the same entity. It is a matter of how sensitive the patient is to the drug and whether there's a substrate for it to manifest clinically. I don't know that there's any fundamentally different pathophysiologic basis behind those three arbitrarily defined stages.

DR LOVE: What do we know about its molecular pathogenesis?

DR STEINGART: It seems to be related to the requirement for elemental iron and dangerous free-radical oxygen species that cause fundamental mitochondrial damage to the myocyte. That is the premise behind dexrazoxane, which has been advocated as a means of ameliorating the cardiotoxicity. If you remove iron from the environment where anthracyclines are working, you can alleviate some of the cardiotoxicity through production of fewer free radicals, less damage to the mitochondria, less myocardial cell death and less fibrosis.

CD 1, Track 4

DR LOVE: Can you summarize the studies evaluating anthracycline-related cardiotoxicity that were presented at ASCO 2006?

DR STEINGART: Dr Giordano from MD Anderson used the SEER-Medicare database to consider women older than 65 years of age who had received an adjuvant anthracycline and were followed long term. It is exciting to have five- and 10-year data for women with breast cancer (Giordano 2006; [1.1]).

The goal of the study was to determine whether anthracyclines were associated with long-term congestive heart failure in two distinct age groups — 66 to 70 years old and over 70 years old. They divided the elderly into those age groups because they found an interaction between age and chemotherapy (Giordano 2006).

For women aged 66 to 70 years, those receiving an adjuvant anthracycline compared to those receiving an adjuvant nonanthracycline or no adjuvant chemotherapy had a higher rate of clinical congestive heart failure. At 10 years, more than 40 percent of the women between 66 and 70 years of age who received an adjuvant anthracycline had a clinical diagnosis of congestive heart failure (Giordano 2006; [1.1]).

Patients older than 70 years of age also had a very high incidence of congestive heart failure, but it didn't matter whether they received an anthracycline or a nonanthracycline-containing regimen or no chemotherapy (Giordano 2006).

A remarkably high incidence of clinical congestive heart failure was diagnosed in the Medicare database. Cofactors associated with congestive heart failure included hypertension, diabetes and coronary artery disease (Giordano 2006; [1.2]).

1.1

SEER-Medicare Database: Rates of Congestive Heart Failure in Women 66 to 70 Years of Age According to Adjuvant Chemotherapy Received for Breast Cancer

	Five years	Ten years
Adjuvant anthracycline (n = 898)	19%	47%
Adjuvant nonanthracycline (n = 1,008)	14%	33%
No adjuvant chemotherapy (n = 6,939)	12%	28%

SOURCE: Giordano SH et al. *Proc ASCO* 2006;**Abstract 521**.

DR LOVE: It was counter-intuitive that the difference wasn't seen in the women older than 70 years of age. Do you think this might have been related to the background incidence of CHF or maybe selection bias?

DR STEINGART: The authors speculated it was the result of selection bias. Patients older than 70 years of age who received an anthracycline were so carefully screened that they were materially different from the patients who did not receive an anthracycline — they were healthier.

Whatever increase in the incidence of cardiomyopathy there may have been from the anthracycline in that group was offset by other risk factors in the patients who did not receive anthracyclines (Giordano 2006).

1.2

SEER-Medicare Database: Previous Diagnoses Significantly Associated with Risk of Congestive Heart Failure

	Hazard of CHF
Hypertension	HR 1.47 (1.40-1.55)
Diabetes	HR 1.65 (1.56-1.75)
CAD	HR 1.60 (1.41-1.82)
PVD	HR 1.33 (1.25-1.42)

CAD = coronary artery disease; PVD = peripheral vascular disease

"Among patients age 66-70 years, those treated with anthracyclines had a 38% higher risk of developing heart failure than those treated with non-anthracycline chemotherapy regimens. Among women age 71-90 years, there was no significant difference in risk among the three cohorts. ...

We then performed a second analysis that removed the comorbidity score and included specific comorbidities of interest. In this model, previous diagnoses of hypertension, diabetes, coronary artery disease, and peripheral vascular disease were all significantly associated with the risk of congestive heart failure."

SOURCE: Giordano SH et al. *Proc ASCO* 2006;**Abstract 521**.

CD 1, Tracks 5-6

DR LOVE: Can you discuss the correlation between a decline in ejection fraction and congestive heart failure?

DR STEINGART: We spend a great deal of time monitoring the ejection fraction when we administer chemotherapeutic agents. Declines in ejection

fraction with anthracyclines are associated with adverse outcomes, mortality and the development of clinical congestive heart failure.

When you start getting into the older age groups, however, declines in ejection fraction and heart failure are different concepts. Most of the heart failure in women older than 65 years of age occurs in the presence of a normal ejection fraction.

DR LOVE: Is that specific to women?

DR STEINGART: It's specific to women in the sense that most of the heart failure in women older than 65 years of age is the consequence of hypertension. In men, it's a consequence of a mixture of hypertension and coronary artery disease.

Older men are more likely than younger men to develop heart failure with a normal ejection fraction. However, there is still a slight preponderance of heart failure with a depressed ejection fraction because coronary artery disease is still the driving force in heart failure in older men.

In women, however, the driving force for congestive heart failure is far and away hypertension. Those women present with concentric left ventricular hypertrophy, normal-sized cardiac cavities, thick walls, inability to fill the ventricle properly and backward heart failure, pulmonary congestion, edema and exercise intolerance.

If one carefully examines the literature, one sees that anthracyclines not only affect the ejection fraction, but they also affect the diastolic properties of the left ventricle.

As women age, they may develop hypertension, coronary disease or diabetes. The coalescence of those factors with anthracycline toxicity can produce the clinical entity of congestive heart failure.

That is an important diagnosis because recent data from the Mayo Clinic and Canada, published in *The New England Journal of Medicine*, show that the prognosis of congestive heart failure with a normal ejection fraction is the same as that of congestive heart failure with a depressed ejection fraction (Bhatia 2006; Owan 2006).

CD 1, Track 7

DR LOVE: What are the chances that a 55-year-old woman without any comorbidities will develop heart failure over the next 20 years as a result of four cycles of AC?

DR STEINGART: I can't answer that question. The data I described from the SEER-Medicare database were with women who started adjuvant treatment at 65 years of age or older (Giordano 2006). What happens to the 55-year-old who receives treatment and lives to 65 or 75 years of age is unclear. I don't believe it's unreasonable, however, to extrapolate from the data with women older than 65 years of age.

DR LOVE: Based on Patterns of Care surveys we have conducted, the most common answer an oncologist in this country will provide to this question is one or two percent. Do you think that is correct?

DR STEINGART: The excess risk due to doxorubicin — at 240 mg/m^2 — is somewhere between one and four percent, in the shorter term, over three to five years. However, if you obtain a biopsy from these women and do careful measurements of left ventricular function, you will find abnormalities of cardiac structure and function in the majority of them.

Then you add to that the rising incidence of hypertension over the next five to 20 years, which goes as high as 75 to 85 percent of women by the time they reach the age of 85. The probability of excess risk of developing congestive heart failure is dramatically higher than simply one or two percent.

DR LOVE: What about in a 65-year-old woman without any comorbidities?

DR STEINGART: For 65-year-old patients, the data are better. If they received an anthracycline, probably 30 to 40 percent will have a clinical diagnosis of congestive heart failure over the next 10 to 20 years.

CD 1, Tracks 10-11

DR LOVE: What are the mechanisms involved with trastuzumab-related cardiotoxicity?

DR STEINGART: Trastuzumab appears to work by blocking cell-repair pathways when it blocks the HER2 receptor. It appears to turn off a mechanism that is designed to prevent programmed cell death. Trastuzumab is not a primary cardiotoxin, like an anthracycline. However, if a cell is already in the process of distress, trastuzumab will accelerate cell death or prevent recovery of normal cellular function because it blocks reparative pathways.

NSABP-B-31 was thoughtfully constructed to assess potential cardiac toxicity. In that trial, when the ejection fraction fell according to prespecified parameters, trastuzumab was stopped and cardiac monitoring was continued. In the vast majority of patients, left ventricular function returned to normal (Tan-Chiu 2005; [1.3]), which supports the hypothesis of cellular repair.

Michael Ewer produced biopsy data for women with depressed ejection fractions who had received an anthracycline and trastuzumab. No obvious changes were evident by light microscopy (Ewer 2005).

More recent data do show abnormalities on electron microscopy with trastuzumab, but those abnormalities have been characterized as what is generally associated with reversible cardiomyopathy (Guarneri 2006).

Those studies include few biopsies, and the data are early. Researchers have not been able to discover a permanent, structural lesion in the cell that has become dysfunctional as a consequence of trastuzumab. The hope is that function will improve on the withdrawal of trastuzumab.

In the combined analysis of NSABP-B-31 and NCCTG-N9831, approximately 18 percent of the women with normal ejection fractions following the anthracycline phase of their treatment discontinued trastuzumab because they either had clinical congestive heart failure or their ejection fraction fell beyond a prespecified parameter (Romond 2005).

DR LOVE: What do we know about the reintroduction of trastuzumab in patients whose ejection fraction dropped within the normal range?

DR STEINGART: We don't know a lot about the reintroduction of trastuzumab from the randomized trials. We do know about it from our clinic's experience and a publication in the *Journal of Clinical Oncology* (Ewer 2005; [1.4]). For the most part, in the metastatic breast cancer setting, where there's greater experience, the vast majority of women tolerated the reintroduction of trastuzumab with or without treatment for left ventricular systolic dysfunction with beta blockers, ACE inhibitors or angiotensin receptor blockers (Ewer 2005; [1.4]).

1.3

NSABP-B-31: Cardiac Dysfunction Associated with Adjuvant Trastuzumab

"Another important consideration is reversibility of CD [cardiac dysfunction]. The CHF associated with trastuzumab seemed to be responsive to cessation of therapy and management, and LVEF generally recovered to nearly normal levels over time. These findings suggest that CD associated with trastuzumab is qualitatively different than anthracycline cardiotoxicity."

SOURCE: Tan-Chiu E et al. *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

1.4

Reversibility of Trastuzumab-Related Cardiotoxicity

"The principal findings of our observational study indicate that patients who experience cardiotoxicity while receiving trastuzumab therapy generally recover their cardiac function when trastuzumab is discontinued. This improvement usually occurs over a period of months (mean time, 1.5 months) after withdrawal of the agent. ...Additionally, patients who experienced a benefit with trastuzumab and demonstrated a resolution or improvement of cardiotoxicity could, with acceptable risk, be re-treated with trastuzumab while receiving protective CHF medications and undergoing close cardiac function monitoring by multiple-gated acquisition scans or echocardiography techniques."

SOURCE: Ewer MS et al. *J Clin Oncol* 2005;23(31):7820-6. **Abstract**

CD 1, Track 12

DR LOVE: What about the use of trastuzumab or an anthracycline for patients with prior cardiac events but normal ejection fractions?

DR STEINGART: In the world of cardiology, there's very little published experience with that issue. It is a key question. If there's no significant valvular

disease in a patient who has had a small infarct or some other insult, the tolerability of the toxicity will be the same as long as the ejection fraction is within the normal range of 55 percent or higher. I would imagine that trastuzumab or an anthracycline could be tolerated under those circumstances.

DR LOVE: Is trastuzumab absolutely contraindicated in a patient with HER2-positive, metastatic breast cancer who has cardiomyopathy or cardiac problems?

DR STEINGART: Absolutely not. It's a negotiation on a patient-by-patient basis. We clearly continue to recommend using trastuzumab in the palliative care setting for patients with ejection fractions in the 40s or compensated congestive heart failure. One of the challenges of being a cardiologist or an oncologist is striking the proper balance with those patients.

If the patient has bone pain, a pleural effusion or symptomatic abnormalities from the metastatic cancer that may be relieved by trastuzumab, we're no longer talking about differences in survival under those circumstances. We're talking about improving the quality of life. Trading the possibility of congestive heart failure for an improvement in the quality of life from the metastatic breast cancer is well worth a discussion between the patient and the oncologist. ■

SELECT PUBLICATIONS

Bhatia RS et al. **Outcome of heart failure with preserved ejection fraction in a population-based study.** *N Engl J Med* 2006;355(3):260-9. **Abstract**

Ewer MS et al. **Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment.** *J Clin Oncol* 2005;23(31):7820-6. **Abstract**

Giordano SH et al. **Congestive heart failure (CHF) in older women treated with anthracycline (A) chemotherapy (C)**. *Proc ASCO* 2006;**Abstract 521**.

Guarneri V et al. **Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: The MD Anderson Cancer Center experience**. *J Clin Oncol* 2006;24(25):4107-15. **Abstract**

McArthur HL et al. **A population-based study of adjuvant trastuzumab-mediated cardiotoxicity among early stage HER-2+ breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 2098**.

Owan TE et al. **Trends in prevalence and outcome of heart failure with preserved ejection fraction**. *N Engl J Med* 2006;355(3):251-9. **Abstract**

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

Routledge HC et al. **Monitoring the introduction of new drugs — Herceptin to cardiotoxicity.** *Clin Med* 2006;6(5):478-81. **Abstract**

Shepherd LE et al. **Left ventricular function following adjuvant chemotherapy for breast cancer: The NCIC CTG MA5 experience.** *Proc ASCO* 2006;**Abstract 522**.

Sledge GW et al. **Adjuvant trastuzumab: Long-term results of E2198.** San Antonio Breast Cancer Symposium 2006;**Abstract 2075**.

Smith KL et al. **Cardiac dysfunction associated with trastuzumab.** *Expert Opin Drug Saf* 2006;5(5):619-29. **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**

Harold J Burstein, MD, PhD, Dennis J Slamon, MD, PhD, Richard M Steingart, MD

CD 1, Tracks 15-28 — CD 2, Tracks 1-15 — CD 3, Tracks 1-2

CD 1

Track 15 Introduction

Track 16 Case discussion: A 60-year-old woman with a node-positive, HER2-positive tumor

Track 17 Intraindividual variability in LVEF

Track 18 Selection of adjuvant chemotherapy regimen to combine with trastuzumab

Track 19 Cardiac safety of dose-dense AC → paclitaxel/trastuzumab

Track 20 Intraindividual and intraobserver variability of MUGA and ECHO

Track 21 Duration of concurrent chemotherapy/trastuzumab with dose-dense regimens

Track 22 Utility of protocol-defined guidelines for discontinuing trastuzumab due to decreases in LVEF

Track 23 Optimal duration of adjuvant trastuzumab

Track 24 Clinical decision-making based on surveillance of LVEF

Track 25 Case discussion: A 59-year-old woman with HER2-positive, node-negative breast cancer

Track 26 Case discussion: A 54-year-old woman with strongly ER-positive, PR-positive, HER2-negative breast cancer and cardiomyopathy

Track 27 Prognosis of idiopathic dilated cardiomyopathy

Track 28 Selection of adjuvant systemic therapy for a patient with significant cardiac disease

CD 2

Track 1 SEER analysis of long-term cardiotoxicity in women treated with anthracyclines

Track 2 Adjuvant chemotherapy for patients with small, node-negative, HER2-negative tumors

Track 3 Long-term risk of congestive heart failure with adjuvant AC

Track 4 Effect of lifestyle and hormonal changes on cardiac risk

Track 5 Case discussion: A 59-year-old woman with an ER-positive, PR-negative, HER2-positive, node-negative tumor

Track 6 Selection of adjuvant systemic therapy for a patient with aortic valve disease

Track 7 Case follow-up: Treatment with AC followed by paclitaxel/trastuzumab

Track 8 Cardiac effects of lapatinib and clinical use in patients unable to continue trastuzumab

Track 9 Case discussion: A 52-year-old woman with a 4-cm, ER-negative, PR-negative, HER2-positive, node-positive tumor

Track 10 Acute respiratory syndrome in patients with pulmonary metastases treated with trastuzumab

Track 11 Use of trastuzumab in patients with cardiomyopathy and HER2-positive metastatic disease

Track 12 Treatment after progression on trastuzumab: Continue, switch or combine with lapatinib?

Track 13 Participation in adjuvant clinical trials randomly assigning patients to lapatinib without trastuzumab

Track 14 Selection of hormonal therapy for patients with ER-positive, PR-positive, HER2-positive disease

Track 15 Longer versus shorter duration of adjuvant trastuzumab

CD 3

Track 1 Hypertension associated with anti-angiogenic agents

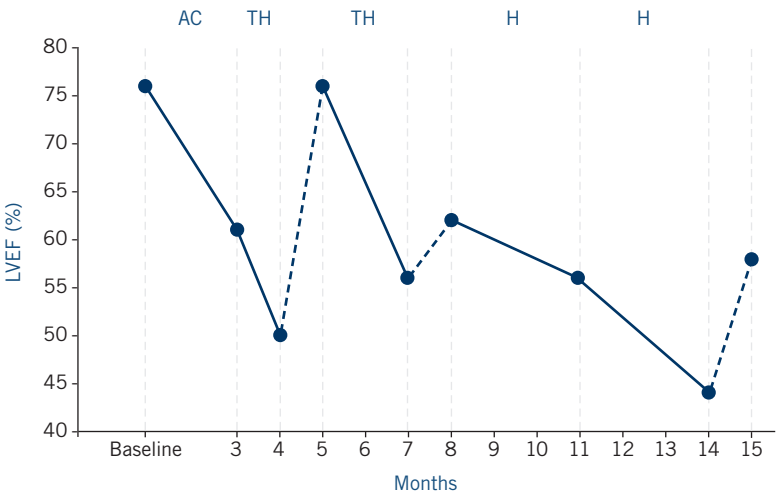
Track 2 Unforeseen adverse cardiac effects of biologic agents

CD 1, Tracks 16-17

Case Discussion 1

A 60-year-old, otherwise-healthy woman with a 1.1-cm, ER-negative, PR-negative, HER2-positive, node-positive invasive breast cancer who had multiple changes in LVEF during adjuvant AC → paclitaxel/trastuzumab (from the practice of Richard Zelkowitz, MD)

Changes in LVEF from Baseline Through Treatment with AC → Paclitaxel and Trastuzumab



AC = doxorubicin/cyclophosphamide; T = paclitaxel; H = trastuzumab

SOURCE: CD 1, Track 16.

DR LOVE: Hal, how often do you see significant changes in the ejection fraction in patients treated with trastuzumab?

DR BURSTEIN: I have found, especially with an LVEF greater than 70 percent, that there's a lot of noise and it is a hyperdynamic number. I wonder whether these drops from 76 to 61 percent are real events. However, dropping below 50 percent seems more real and would be worrisome, especially if it were linked to symptoms and obvious changes on an echocardiogram.

DR LOVE: Dr Steingart, can you talk about the variation in ejection fraction, particularly within the normal range?

DR STEINGART: We have discovered that when the ejection fraction is 70 percent or higher, there is enormous variability from one measurement to

the next. If you measure serial ejection fractions, a 15-unit ejection fraction change is not unusual.

At a very high ejection fraction in a normal-sized heart, you're talking about an end-systolic dimension that is literally a pixel on the computer matrix. Any variation in the detection of the edge around that one pixel will make it grow from one to three or four pixels.

With very small end-systolic volumes in a healthy heart, minor variations in your edge detection ability can produce dramatic changes in the ejection fraction. So, in practice, we are skeptical about these fluctuations within the normal range.

CD 1, Track 18

DR LOVE: Dennis, what chemo/trastuzumab regimen would you have used with this patient?

DR SLAMON: I believe you can go with either of the BCIRG 006 trastuzumab regimens, and patients should be aware of the differences in efficacy and toxicity between the regimens.

In addition, although we don't have data, I believe docetaxel/cyclophosphamide, the regimen Steve Jones evaluated (Jones SE 2006), would be equally efficacious because the taxane is the same and cyclophosphamide has additive and synergistic interactions with trastuzumab.

DR LOVE: I believe US Oncology is planning to study docetaxel/cyclophosphamide with trastuzumab. Would you be comfortable using it right now?

DR SLAMON: My sense is that the chemotherapy platform you build trastuzumab on is much less important than using trastuzumab and using it for an optimum period of time, which has yet to be determined. For a HER2-driven tumor, that is the critical factor.

DR LOVE: Why would you use docetaxel as opposed to paclitaxel?

DR SLAMON: The cardiotoxicity data we're seeing from all the trials show less cardiotoxicity in the one trial using docetaxel (Slamon 2005) compared to all the trials using paclitaxel (Romond 2005; Piccart-Gebhart 2005). Everyone who's observed the data from all those different groups is saying the same thing — the only difference was the taxane.

DR BURSTEIN: My most common trastuzumab-based regimen remains AC followed by paclitaxel, which is similar to the regimen used in the Intergroup study (Romond 2005). We participated in that trial and treated a lot of patients with every three-week AC times four followed by weekly paclitaxel times 12.

DR LOVE: Do you agree with Dennis's comment that there seems to be less cardiotoxicity with the docetaxel regimens than with paclitaxel regimens?

DR BURSTEIN: The incidence of symptomatic cardiac events in the AC → docetaxel/trastuzumab arm of BCIRG 006 was a little more than two percent (Slamon 2005). In NSABP-B-31, the absolute incidence of congestive heart failure symptomatology with AC → paclitaxel/trastuzumab was about four percent compared to 0.8 percent for the chemotherapy regimen alone (Tan-Chiu 2005).

I don't know whether that means there is more or less cardiotoxicity. These patient groups were different. For any number of reasons, it is easy to imagine that they had different preexisting criteria. It's always tricky to compare across trials.

CD 1, Track 19

DR LOVE: Dr Steingart, what do we know about the cardiac safety of dose-dense AC → paclitaxel/trastuzumab?

DR STEINGART: We were involved with a recent study of dose-dense AC → paclitaxel/trastuzumab (Dang 2006a; [2.1]) that utilized stopping endpoints that were similar to those in the NSABP-B-31 study. The rate of holding the drug regimen was extremely low, so the dose-dense regimen with trastuzumab, from a cardiac perspective, in the short term, seemed to be well tolerated.

DR LOVE: Dennis, is there any theoretical reason to be concerned about closer spacing of the doxorubicin with the dose-dense regimen?

DR SLAMON: I can't imagine there would be any theoretical reason to be concerned. It's clear that the HER2 protein serves a protective function against stress in the heart. When you have trastuzumab on board, you're inhibiting that pathway. You're inhibiting the pathogenic part of the pathway with regard to breast cancer, but it appears you're also inhibiting the positive effects of the HER2 protein in the heart.

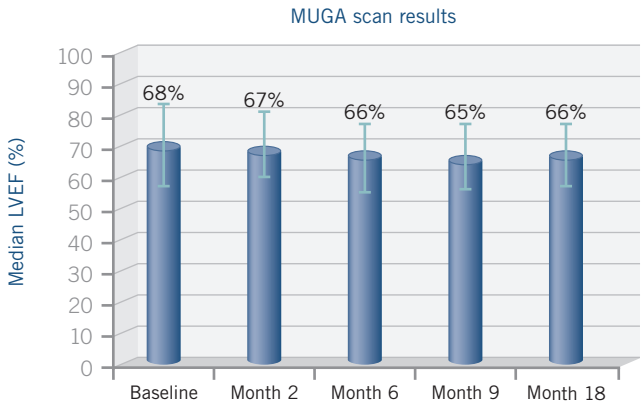
CD 1, Track 21

DR LOVE: Hal, according to our Patterns of Care studies, in patients with HER2-negative, node-positive disease, the most common adjuvant regimen used is dose-dense AC → paclitaxel. Is that your general approach for these patients?

DR BURSTEIN: We frequently recommend that regimen for patients with HER2-negative disease. The Memorial group has reported on dose-dense AC → paclitaxel with trastuzumab in HER2-positive disease, and the data look encouraging. However, it is a relatively small feasibility study with approximately 70 patients (Dang 2006a; [2.1]). The study is too underpowered to make strong conclusions about how the safety compares. It's certainly encouraging that it looks good.

2.1

Mature Cardiac Monitoring Results of Dose-Dense AC Followed by Paclitaxel with Trastuzumab in HER2-Positive Breast Cancer



- <1% (1/70) of patients had a protocol-defined cardiac event.
- 4% (3/70) of patients stopped trastuzumab as a result of asymptomatic LVEF decline, which recovered for all patients.

SOURCE: Dang C et al. Poster. San Antonio Breast Cancer Symposium 2006a;**Abstract 2101**.

It's not clear that dose-dense AC → paclitaxel is necessarily better than the other ways AC → paclitaxel was administered in the larger trials for HER2-positive disease. The only thing that still gives me pause is that you limit your concurrent chemotherapy/trastuzumab exposure to eight weeks with the dose-dense regimen.

However, we don't know if that would be any different from the 12 weeks used in NSABP-B-31, NCCTG-N9831 or BCIRG 006 (Romond 2005; Slamon 2005). This is a theoretical concern, which isn't totally trivial because the duration of concurrent therapy might be important.

We need to be candid with patients and say, "These limited data support the regimen in terms of its feasibility." It is a shorter course of chemotherapy, which is appealing to many patients. It's not something that we routinely offer outside of a clinical trial.

CD 1, Track 22

DR LOVE: Dr Steingart, oncologists are trying to follow the adjuvant trastuzumab trial guidelines in terms of monitoring ejection fractions. Are there times when the trial guidelines can be stretched?

DR STEINGART: I don't fully understand the rationale for the guidelines, particularly with the change in ejection fraction within the normal range.

I don't understand why one would think a 78 percent ejection fraction that drops to 63 or 62 percent would be a physiologically important change.

I can understand when you start fluctuating near the lower limit of normal, where the room for error is less. If I were consulting on a patient in clinical practice and her ejection fraction went from 78 percent to 62 or 63 percent, assuming there weren't other pathological indicators on the study, I would not advise the oncologist to stop therapy.

DR LOVE: Dennis, do you agree?

DR SLAMON: I agree that we don't know what those drops mean. I disagree when some of that information is interpreted to say that there's no problem.

A definite signal is coming out of the trials that a loss of left ventricular function occurs when these two drugs are used together. It is either clinical or subclinical, but there's a significant loss of left ventricular function.

We learned this from the 13,000 women in the adjuvant trastuzumab trials, whose median age was 49 years old. The median age of patients with breast cancer is 62 to 63 years. So the trials included younger women, and we're seeing a signal. They have not yet accrued their other life events that could affect cardiac function.

If this is a real signal and it's sustained, it may be a problem. If it's not and they all recover, then "no harm, no foul." The efficacy data are incredible, but the efficacy has to be weighed against the toxicity. Trastuzumab has no bigger advocate than me, but I've tried to be cautious about saying that there's no issue when there are subclinical losses above the lower limits of normal.

DR LOVE: When you make that decision, how do you factor in the risk of recurrence — for example, a patient with 10 versus zero positive nodes?

DR SLAMON: A HER2-positive tumor is a HER2-positive tumor. To me — and I may be in the minority — the number of nodes is irrelevant. The data demonstrate that node-negative disease that is HER2-positive behaves as if it is node-positive disease, even if the tumor is smaller than 1.5 centimeters.

When I see a patient with a HER2-positive tumor, even when it is 0.5 centimeters, the argument I make is, "This is a HER2-driven tumor. We would recommend trastuzumab-based therapy."

CD 1, Track 23

DR LOVE: Hal, people have pointed out what they thought was a blip up in the recurrence rate in the HERA study after trastuzumab was stopped at a year. Do you think that's real?

DR BURSTEIN: I don't know. The worry has been that chronic suppression is necessary and if you withdraw trastuzumab, you might put the patient in greater jeopardy for recurrence.

As a practical matter, the trials had to start somewhere. Most of the large cooperative group trials administered one year of therapy. The HERA trial had a randomization to one versus two years (Piccart-Gebhart 2005; Smith 2007).

A challenge in interpreting that literature, when it finally matures, is that they did not administer chemotherapy concurrently with trastuzumab in the HERA trial. I remain concerned that that may be a less optimal way to utilize trastuzumab.

Although there may be some advantage for a second year, it will not be clear that the advantage would be the same if you used chemotherapy and trastuzumab concurrently. This is something that will have to be teased out once the more mature data become available. For the moment, outside of a clinical trial, I use one year of trastuzumab.

DR SLAMON: I believe Hal's point is well made; those data definitely need to be teased out. There's one other big problem with the HERA trial. It's a wonderful trial showing that if you use trastuzumab after chemotherapy, you will still have a clinical benefit.

What is factored out of the HERA trial, however, which few people mention, is that the randomization occurred after patients finished their surgery, chemotherapy and radiation. That could have taken close to 10 months (Piccart-Gebhart 2005; Smith 2007).

In the US cooperative group trials and the BCIRG trial, a number of recurrences occurred early in the patients with HER2-positive disease. In the HERA trial, those patients never went onto the trial. So it's a favorably selected group in the sense that the worst cases were factored out.

The hazard ratio in HERA is 0.54 (Piccart-Gebhart 2005; Smith 2007), which is a little worse than the hazard ratio we're seeing in the concurrent trials of around 0.47 to 0.49 (Slamon 2005; Romond 2005). Whether that's real when comparing across trials is another question.

CD 1, Track 24

DR LOVE: Hal, should oncologists be following the adjuvant trastuzumab protocols, in terms of when to monitor ejection fractions and when to stop and start trastuzumab?

DR BURSTEIN: It's a tough situation because there is a black-box warning about cardiotoxicity with the use of trastuzumab. Clearly, these patients merit cardiac surveillance. It seems as if borderline ejection fraction at baseline, age and perhaps preexisting hypertension stand out as predictors of trastuzumab-related cardiomyopathy (Tan-Chiu 2005).

The patients still require surveillance, irrespective of those risk factors. My practicing algorithm is to check cardiac function at baseline, after the anthracycline-based chemotherapy, after three to four months of the taxane/trastuzumab combination and at some point again. It must be said that these

safeguards were put in place when we did not know the clinical efficacy of trastuzumab.

The challenge arises in cases with a high-risk breast tumor in which you are trying to bring important therapy to bear on the patient's disease. When you are trying to combat these reductions in ejection fraction of unknown clinical significance, it's tough to be a clinician because there aren't hard and fast rules. The rules in the trials were based on not knowing that trastuzumab was going to be a lifesaving drug for women.

CD 1, Tracks 26-27

Case Discussion 2

A 54-year-old woman with a 1.6-cm, low-grade, ER-positive, PR-positive, HER2-negative breast cancer and a micrometastasis (greater than 0.2 mm but less than 2 mm) in one lymph node. She had a history of well-controlled hypertension and idiopathic cardiomyopathy with an LVEF of about 40 percent following aggressive medical management (from the practice of Bonni Gearhart, MD).

SOURCE: CD 1, Track 26.

DR LOVE: Dr Steingart, can you talk about idiopathic cardiomyopathy? What's the long-term prognosis, and what do we know about the interaction between it and cardiotoxic agents, such as anthracyclines?

DR STEINGART: We don't know much about idiopathic dilated cardiomyopathy. The therapy involves attempting to exclude known causes, such as alcohol use, hypothyroidism, hyperthyroidism, tachycardia or coronary artery disease. It's a diagnosis of exclusion.

Because this patient became clinical Class I without further symptoms, her outlook is favorable and is related to the ejection fraction. However, the overall survival of such an individual is not normal.

If one were to biopsy such a heart postmortem, there would be a great deal of fibrosis. The ventricle would be abnormal, and I have concerns about adding a cardiotoxic agent.

I would have a long discussion with the oncologist about the importance of the drug. I believe with this degree of compensation, it wouldn't take much to further worsen the left ventricular function and make this patient symptomatic again.

This could further accelerate the progression to clinical congestive heart failure, which has an adverse prognosis. I would have substantial reservations about using cardiotoxic chemotherapy in such a patient.

DR LOVE: Hal, how would you think through this case?

DR BURSTEIN: Even without the history of the cardiomyopathy, you could easily convince yourself to just use hormone therapy for this patient. It's a low-grade tumor, she's postmenopausal and her general prognosis is good. The marginal benefits of adjuvant chemotherapy in a postmenopausal woman with hormone receptor-positive breast cancer are modest.

With Peter Ravdin's Adjuvant! Online, you could estimate the benefit of chemotherapy to be an improvement of a few percentage points in the 10-year disease-free survival. If you really wanted to refine the estimate, you could obtain an Onco*type* DX™ assay to quantify the risk.

Given the cardiomyopathy history and what we heard from Dr Steingart about the frailty of these patients, this woman is much more likely to die of her heart disease in the next decade than from her breast cancer, although one would have to look at formal models.

I would be loath to use chemotherapy in this patient, even nonanthracycline-based regimens. Don't rock this boat. This patient is barely compensated on four cardiac drugs, and you should quit while you're ahead with the hormone treatment.

CD 1, Track 28

DR LOVE: Dennis, what are your thoughts about nonanthracycline-containing alternatives? What about the docetaxel/cyclophosphamide (TC) regimen Steve Jones presented at the 2005 San Antonio Breast Cancer Symposium?

DR SLAMON: Steve Jones's US Oncology data, comparing TC to anthracycline-based therapy, are impressive (Jones SE 2006; [2.2]). It's a large study, and the data are robust. I believe US Oncology will conduct an even larger repeat study. I find it a very attractive regimen.

In the case that was just presented, I agree with Hal. An argument would arise as to whether the patient should receive any chemotherapy given the nature of her tumor, the biologic markers and the fact that it's low-grade, postmenopausal disease. If I were inclined to use chemotherapy, I would not want to administer anything that threatened any minimal cardiac insult.

DR LOVE: Can you follow up on what happened with the patient?

DR GEARHART: Although she had low-grade and fairly small disease, we also recognized that she had at least whatever lymph node burden can be interpreted from the micrometastasis. We elected to treat her with a nonanthracycline-containing regimen, and we chose docetaxel over paclitaxel, thinking perhaps we'd slice off another smidgen of cardiac toxicity. She was treated with Steve Jones's TC regimen followed by hormonal therapy.

She actually flew through her TC. We monitored her ejection fraction throughout. She's now about one year postchemotherapy and continues to have an ejection fraction of about 45 percent and is asymptomatic.

2.2

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 5.5 Years)

	TC (n = 506)	AC (n = 510)	Hazard ratio	*p*-value
Five-year disease-free survival	86%	80%	0.67	0.015
ER-negative/PR-negative	HR = 0.64 (95% CI: 0.38-1.04)			
ER-positive or PR-positive	HR = 0.71 (95% CI: 0.47-1.08)			
Node-positive	HR = 0.67 (95% CI: 0.45-0.98)			
Node-negative	HR = 0.73 (95% CI: 0.42-1.27)			
Five-year overall survival	90%	87%	0.76	0.13

Hazard ratios < 1 indicate values in favor of TC.

"We conclude that our study has established a new standard nonanthracycline regimen, TC, for the adjuvant treatment of early-stage breast cancer."

Toxicities (Grades III/IV)	TC	AC	*p*-value
Neutropenia	61%	55%	NR
Neutropenic fever	5%	2.5%	0.07
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01

"AC was associated with significantly more nausea and vomiting (all grades as well as grades 3 and 4), but TC had more low-grade edema, myalgia, and arthralgia secondary to the use of docetaxel."

NR = not reported

SOURCE: Jones SE et al. *J Clin Oncol* 2006;24:5381-7. **Abstract**

DR LOVE: Dennis, can you comment on the issue of anthracycline cardiotoxicity in the absence of trastuzumab?

DR SLAMON: The issue of cardiac dysfunction with anthracycline-based regimens — until the HER2 era — was either enormously underappreciated or now we're overestimating it. It's one of those two extremes, but I'm not sure which.

I was taught in medical school not to worry until you reached more than 450 mg/m^2 of doxorubicin. With the regimens consisting of six cycles at 60 mg/m^2, we're at a cumulative dose of 360 mg/m^2. When we used four cycles of AC followed by four cycles of T, we were at a cumulative dose of 240 mg/m^2. No one ever thought to consider cardiotoxicity.

When we conducted the registrational trial for trastuzumab, we weren't measuring cardiac dysfunction. No signal came out of the Phase I or Phase II trials. It was during the Phase III trial that women started to say, "Things are going great, except I can't walk upstairs and I become short of breath, which has never happened to me before."

We started to look, and we saw this signal. We then planned the adjuvant trastuzumab trials, where everything was followed closely. When we started to follow closely, we found women developing left ventricular dysfunction, some of it significant, at 150 to 180 mg/m^2 of doxorubicin.

This is a cardiotoxic drug beyond our traditional thinking. Doxorubicin does bad things to the heart that are independent of the other long-term effects.

CD 2, Tracks 1-2

DR LOVE: Hal, you have a 60- to 65-year-old patient for whom you're recommending either AC alone or dose-dense AC → paclitaxel. She will receive four doses of doxorubicin at 60 mg/m^2, and she asks, "What are the chances over the next 20 years, by taking this as opposed to a nonanthracycline regimen, that I'm going to run into a problem with my heart?"

DR BURSTEIN: I usually tell patients that less than one percent will have clinically significant heart failure through at least a decade of follow-up. As we're learning from the SEER-Medicare data set (Giordano 2006; [1.2]) and the long-term follow-up of some of the original Milan adjuvant trials, there is a much larger fraction of women who may have late disease or subclinical changes in LVEF.

In the overview analysis, survival at any given time was usually governed by whether the breast cancer recurred. The incidence of excessive deaths from cardiac causes in chemotherapy-treated patients was surprisingly low (EBCTCG 2005). We have a conundrum: Many asymptomatic changes occur, and as women live longer, they seem to be in jeopardy for more late heart failure.

Anthracyclines are undergoing a fascinating revision in the breast cancer literature. Everybody who published articles 15 years ago saying anthracyclines were better than nonanthracycline-based chemotherapy is now publishing papers saying that not everybody needs anthracyclines. We oversold it in the first place.

I believe we will see less use of the anthracyclines, not because of concerns over cardiotoxicity — which are real but fortunately rare — but because we will discover that most women don't need anthracycline-based chemotherapy.

If you consider many of the major trials that evaluated various doses of anthracyclines, such as MA5 (Levine 2005) and CALGB-8541 (Budman 1998), in the aggregate, anthracyclines clearly helped and that is supported by the overview (EBCTCG 2005).

In many of the retrospective analyses, anthracyclines were most critical in patients with HER2-positive breast cancer (Pritchard 2006). In patients with HER2-negative breast cancer, it's been hard, for a decade, to see that you actually needed anthracycline-based chemotherapy compared to nonanthracycline-based chemotherapy.

Because those were unplanned, retrospective analyses, those data were not readily accepted. Now we're coming full circle and there's more questioning

about whether these patients need chemotherapy and if they do, whether they really need anthracycline-based chemotherapy.

Paradoxically, the women who need anthracycline-based chemotherapy are those with HER2-positive disease. We're going to need the mature data from BCIRG 006 to tease out, within that subgroup, who needs the anthracycline in combination with trastuzumab. For the moment, anthracyclines are the mainstay for HER2-positive disease. I believe we should, as part of this reassessment, be thinking through which breast tumors need anthracycline chemotherapy. It isn't clear to me that most women do.

DR LOVE: What is your usual regimen for patients with small, HER2-negative, node-negative disease?

DR BURSTEIN: I usually use AC if they're going to receive chemotherapy.

DR LOVE: What were your thoughts about the data, which showed fewer recurrences with adjuvant TC?

DR BURSTEIN: It's a provocative study, and I congratulate Steve Jones and the US Oncology Group for that trial (Jones SE 2006; [2.2]). We have so many studies with AC as the backbone — it's the whole corpus of the NSABP work.

This doesn't mean that everybody needs it, but it is the backbone of our historical experience in the past 15 or 20 years of chemotherapy. Before giving it up for a well-done but ultimately medium-sized randomized trial, it's worth looking for confirmatory data. If you want a nonanthracycline-based regimen, you can always use CMF.

DR SLAMON: I disagree with Hal that anthracyclines are undergoing a significant revision. At some of the centers like his that is the case, but the vast majority of people feel that if a patient has breast cancer, you "cannot not" use anthracycline-based therapy. And I disagree with that.

The data from US Oncology and Steve Jones are compelling. I agree they need to be reproduced, but I suspect that will happen. We've been using a drug that has a lot of problems because we were used to using it. These one-size-fits-all approaches for the disease are just wrong.

CD 2, Track 3

DR LOVE: Dennis, what do you say to a woman who's about to receive four cycles of AC in terms of her long-term excess risk of cardiac toxicity? Is it one percent or 40 percent?

DR SLAMON: I don't believe for a moment it's one percent. We're using old data sets to make current calls, and women are living into their eighth and ninth decades. The presentation at ASCO was remarkable and long overdue (Giordano 2006). It was a high-water mark in terms of our understanding of the downside effects of what we're doing.

I don't believe the risk is one percent. It's much higher. The possibility of study bias and the fact that these women were followed closely are real, but usually study bias with such large numbers as were examined in the SEER-Medicare database (Giordano 2006; [1.1]) does not result in such a dramatic difference. So I'd have to believe that the signal is, at least in part, real. It's not just because the women were followed more closely.

CD 2, Tracks 5-6

Case Discussion 3

A 59-year-old woman with a 2.2-cm, Grade III, ER-positive, PR-negative, HER2-positive invasive ductal carcinoma and a micrometastasis (5 mm) in one lymph node. She had been treated 36 years earlier with mantle radiation therapy and MOPP for Hodgkin's disease. Subsequently, she developed aortic stenosis and aortic insufficiency. Her LVEF seven months prior to her breast cancer diagnosis was 65 to 75 percent. She also had hyperglycemia and hyperlipidemia controlled by diet and medication (from the practice of Patricia De Fusco, MD).

SOURCE: CD 2, Track 5.

DR LOVE: Dr Steingart, what is the relationship between aortic stenosis and mantle radiation?

DR STEINGART: A nice series of studies from Stanford evaluated the long-term effects associated with mantle radiation in patients with Hodgkin's disease (Heidenreich 2003). Aortic regurgitation is usually the lesion, but mixed aortic stenosis and regurgitation is possible.

She is in the age group where it's conceivable that she has a congenital bicuspid valve having nothing to do with the therapy. But I believe there's enough evidence to say that mantle radiation therapy does predispose to aortic valve disease.

DR LOVE: What about the use of an anthracycline or trastuzumab?

DR STEINGART: The ejection fraction is 65 to 75 percent, her dimensions are normal and she's not symptomatic. I might put her on a treadmill and gauge her physiologic response to exercise to convince myself that she had a normal exercise tolerance. If she did, I would — with one hand on the brake — say it would be reasonable to administer chemotherapy. I would be concerned that she would be predisposed to heart failure.

DR BURSTEIN: She has HER2-overexpressing disease. All of us feel that trastuzumab is an important treatment for women in this situation. If the cardiologist clears her for any therapy, I would consider a nonanthracycline- and trastuzumab-based regimen.

DR LOVE: Which specific chemotherapy regimen would you have used with trastuzumab?

DR BURSTEIN: The timing of this patient's diagnosis was somewhere between the ASCO 2005 presentation of three adjuvant trastuzumab trials and Dennis's presentation of the BCIRG 006 data at the 2005 San Antonio Breast Cancer Symposium. In fall 2005, you had the HERA data. In HERA, some women received nonanthracycline-based regimens, and trastuzumab was safely administered after chemotherapy (Piccart-Gebhart 2005; Smith 2007).

You could have considered a CMF-type of program followed by trastuzumab. Nowadays, I believe we would use something like the TCH program Dennis and his colleagues put together.

DR LOVE: Dennis, what would you do with this patient?

DR SLAMON: I would use a nonanthracycline-based regimen, based on what I've heard. Her chances of doing well would be as good as with an anthracycline-based regimen without compromising cardiac function.

DR LOVE: Richard, are you comfortable treating her with trastuzumab?

DR STEINGART: The hearts of people with aortic stenosis/aortic regurgitation are stressed and fibrotic. If the pathophysiologic mechanism of trastuzumab involves interfering with repair mechanisms — these hearts are constantly stressed and being repaired. I don't have systematic data, but I do have anecdotal experience in patients with valvular heart disease who have received trastuzumab with dramatically abnormal ventricular responses.

CD 2, Track 7

DR LOVE: Dr De Fusco, what treatment did the patient receive?

DR DE FUSCO: Being that it was August 2005, not December 2005, and I had the cardiologist's assurance that she could tolerate it, we proceeded with AC. We used dose-dense AC, and she did have some complications of dehydration and fatigue. She became a little anemic and received growth factor support. She had some hypotension and tachycardia in her third and fourth cycles.

At the completion of AC, her ejection fraction was 60 percent by ECHO, and she had some lower-extremity edema. She also had tachycardia. The aortic valve area was the same.

DR LOVE: Dr Steingart, are you still comfortable going ahead with trastuzumab?

DR STEINGART: No. I would obtain a BNP (B-type natriuretic peptide). I would start wondering why this woman had tachycardia and would look for occult congestive heart failure, despite the normal ejection fraction.

DR LOVE: Dr De Fusco, what happened?

DR DE FUSCO: This woman wanted to be as aggressive as possible. So she went ahead with paclitaxel in January. I didn't start trastuzumab until the third dose of paclitaxel because I wanted her to be further out from the AC.

She was using diuretics, and in March she started developing some increasing dyspnea and intermittent wheezing. Her eleventh dose of trastuzumab was administered in April. I talked about stopping trastuzumab and couldn't get the patient to agree as long as the cardiologist was working with her and treating her.

An ECHO in April showed an ejection fraction of 45 percent. She was admitted in May for a cardiac catheterization, and she had 20 percent obstruction of the left circumflex and the left anterior descending (LAD) artery. Her aortic valve area had now dropped. Her ejection fraction had also decreased to 35 percent.

It was urgently planned that she have an aortic valve replacement. She then had a cardiac arrest in the hospital. She came out of it with minimal neurologic defect, other than some amnesia for the event. She underwent aortic valve replacement with reconstruction of the aortic route.

Her ECHO in June showed an LVEF of 55 percent, and she had ongoing problems with pleural effusions. In September, the ECHO showed an ejection fraction of 65 percent. She said, "Can't I have more trastuzumab?" I said, "No."

CD 2, Tracks 9-11

Case Discussion 4

The patient is a 52-year-old woman with a 4-cm, ER-negative, PR-negative, HER2-positive breast cancer. She had a pretreatment MUGA of 60.2 percent and a clinical complete response to five cycles of neoadjuvant AC administered every three weeks with pegfilgrastim. This was followed by lumpectomy and axillary dissection.

The pathology revealed a 1-cm residual tumor and two positive lymph nodes. She was treated with one dose of trastuzumab and paclitaxel and developed shortness of breath, dyspnea on exertion and an ejection fraction of less than 20 percent (from the practice of Barbara Fallon, MD).

SOURCE: CD 2, Track 9.

DR LOVE: Dennis, have you seen patients develop acute heart failure after one dose of trastuzumab?

DR SLAMON: No.

DR LOVE: Hal?

DR BURSTEIN: I haven't seen that. It's coincidental that it occurred right after the trastuzumab with paclitaxel, but it would not be inconsistent with anthra-

cycline-induced cardiomyopathy, which usually occurs in the first four to 12 weeks after anthracycline exposure.

DR LOVE: Dr Steingart, do you have any comment on what was happening with this patient from a cardiology point of view?

DR STEINGART: From time to time we see this dramatic change in the ejection fraction, not with trastuzumab, but with other highly effective cancer therapies. In other circumstances, I believe the cause of the severe left ventricular dysfunction is multifactorial and relates to cytokines.

We see it with huge increases in white counts, effective debulking therapies in ovarian cancer and tumor lysis syndromes. I'm told it's a sign of an effective antitumor agent. It is conceivable that it is an effect of tissue factors influencing left ventricular function and not necessarily a direct toxic effect of the drug on the heart.

We work very hard in the metastatic setting to support the oncologist in the continued use of trastuzumab with particular attention to symptomatic status and quality-of-life issues. We balance heart failure risk and effectiveness of trastuzumab. In the metastatic setting, the thresholds are different for withholding trastuzumab. ■

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Smith I et al. **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**

Smith KL et al. **Cardiac dysfunction associated with trastuzumab.** *Expert Opin Drug Saf* 2006;5(5):619-29. **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

Dennis J Slamon, MD, PhD

Dr Slamon is Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical/Translational Research at the Jonsson Comprehensive Cancer Center of the David Geffen School of Medicine at UCLA in Los Angeles, California.

CD 3, Tracks 3-20

Select Excerpts from the Interview

CD 3, Tracks 4-5

DR LOVE: Can you discuss the impact of "holding" trastuzumab due to anthracycline-associated declines in LVEF?

DR SLAMON: In the adjuvant trastuzumab trials, we frequently saw patients with HER2-positive disease who were treated with AC but never received the

taxane/trastuzumab therapy because they had declines in their LVEF, yet those are not scored as a toxicity.

It's a greater negative when that happens than when other things happen because now you're denying a potentially active drug to a woman who might benefit from it because you forced the agenda with the anthracycline. That happens between three and five percent of the time in all the studies that were examined, and it's more frequent in older patients. The problem is that once physicians see the LVEF drop, they're reluctant to go ahead and take the risk.

DR LOVE: What do we know about the long-term effects and reversibility of cardiotoxicity associated with trastuzumab and anthracyclines?

DR SLAMON: Since the release of the data presented at ASCO in 2005, I believe oncologists are becoming increasingly aware that the cardiac toxicities might continue for longer than previously believed. The assumption had been that once we stop trastuzumab, the cardiac problems reversed in a matter of a couple of weeks or months. However, the data — at least the BCIRG 006 data — show that it is longer lasting. We now know that a year and a half later, those subclinical LVEF declines seem to be maintained at some level.

We previously thought that the patients with clinical congestive heart failure improved with treatment. However, at least two thirds of them require continued treatment. That means you can treat their congestive heart failure, but it doesn't mean you've made that heart better. I believe these definitions must be more carefully stated when some of these data are presented.

We thought the cardiac problems did not occur until after a certain large cumulative dose of anthracyclines. However, as we're carefully measuring the ejection fractions in the trastuzumab trials, we're seeing them much earlier than anyone previously thought.

At doses of 150 mg/m^2 and higher, you begin to see this issue "raise its head." Those doses were always thought to have a safe cardiac profile. As we examine this more carefully, we are seeing that left ventricular dysfunction is not just the noise of the MUGA scan or the ECHO but real left ventricular dysfunction at very low doses of doxorubicin. It is a potential long-term problem.

CD 3, Track 7

DR LOVE: Data will be presented at the 2006 San Antonio Breast Cancer Symposium from the trial combining bevacizumab and trastuzumab in the adjuvant setting. Can you discuss that study (Pegram 2006; [3.1])?

DR SLAMON: Mark Pegram will be presenting that trial (Pegram 2006), and we're excited about the data we're seeing with bevacizumab and trastuzumab. The challenge will be how to administer that combination safely.

We're guaranteed to cause hypertension in 15 to 20 percent of the women on standard-dose bevacizumab, and most of us believe we are already at the wall regarding cardiac dysfunction with the combination of trastuzumab and

doxorubicin. So the question is, if we administer bevacizumab on that same backbone, will we offset any increased benefits by increasing the toxicity? That's a concern we have at this point.

DR LOVE: Have any cardiac studies evaluated the combination of bevacizumab, trastuzumab and doxorubicin?

DR SLAMON: Studies have been conducted with bevacizumab and doxorubicin, and there's a cardiac signal there, but it's weak, but we all know about the signal seen when combining trastuzumab and doxorubicin.

The question is whether we will potentiate that significantly when we begin with the cardiac insult of doxorubicin and increase LVEF in some percentage of the patients by causing the hypertension and then blocking the HER2 protective effect on the heart. We won't know that until we see data from a clinical trial.

DR LOVE: Do we have any data on the cardiac effects of just bevacizumab with trastuzumab?

DR SLAMON: They're being generated. In our pilot trial of bevacizumab and trastuzumab, we saw an increased incidence of cardiac dysfunction. In the first 29 cases examined, there were two clinical congestive failures, one of which required ICU hospitalization and pressers. Also, we're seeing a large number of patients with Class I or II dysfunction. It's a first-line metastatic trial, and these patients have received doxorubicin in the past.

We believe just the two biologic agents can be administered safely. The question in the adjuvant setting will be, what happens if you add doxorubicin? Docetaxel/carboplatin/trastuzumab (TCH) is in play because it gives us a noncardiotoxic regimen if the efficacy of bevacizumab and trastuzumab is significant and warrants that that should be used next.

We're considering a study that evaluates some variation of AC → TH as the new standard control arm versus AC → THB versus TCHB, if we're not using TOPO II amplification.

If we use TOPO II amplification, an alternative design would be that patients who have TOPO II-amplified disease would receive AC → TH versus AC → THB, and patients who have non-TOPO II-amplified disease would receive TCH versus TCHB. That's assuming the BCIRG 006 data continue to show that the benefit accrued with an anthracycline is, for the large part, restricted to the TOPO II data (Press 2005; Slamon 2005). Either of these study designs would answer whether you can safely administer trastuzumab and bevacizumab together.

DR LOVE: What's the next step?

DR SLAMON: The NSABP approached the BCIRG about collaborating on the next generation of trastuzumab trials. We have an enormous amount of respect for the NSABP, so we are considering it, assuming we can arrive at a common design that we both feel comfortable with. A major meeting of the two groups will be held at the San Antonio meeting to discuss this.

3.1

Phase II Study of Trastuzumab and Bevacizumab as First-Line Therapy of HER2-Amplified Breast Cancer (N = 37): Interim Efficacy and Safety Data

	Number of patients	Percent
Complete response	1	2.7
Partial response	19	51.4
Stable disease	11	29.7
Progressive disease	6	16.2

Select drug-related adverse event by grade				
Adverse event	Grade I	Grade II	Grade III	Grade IV
Cardiac event (NCI-CTC)	7	5	0	1
Shortness of breath/exacerbation	0	1	0	0
Tachycardia	2	0	0	0
Hypertension	2	6	7	0

SOURCE: Pegram M et al. San Antonio Breast Cancer Symposium 2006;**Abstract 301**.

CD 3, Track 9

DR LOVE: How do you think the efficacy data for adjuvant trastuzumab will hold up over time?

DR SLAMON: We don't yet know if the 50 percent reduction in the event rate for the patients who received adjuvant trastuzumab will hold up longitudinally. The other studies will not be able to answer that question because they allowed patients to cross over to trastuzumab, but BCIRG 006 will provide that answer because we had very few crossovers.

DR LOVE: Why weren't there many crossovers in the BCIRG trial?

DR SLAMON: When it became evident that the adjuvant studies were positive, patients in the control groups on HERA and the US trials were offered trastuzumab. A number of those patients then received trastuzumab.

On the other hand, our trial accrued quickly, and in less than three years, we had enrolled all 3,222 patients. We were waiting for our data to mature when the two US groups combined theirs. Our patients were far out from their adjuvant chemotherapy, and only a handful of patients in the BCIRG 006 trial crossed over. So this 3,000+ patient study will tell us how those hazard ratios stand up over time.

CD 3, Tracks 10, 12

DR LOVE: How do you feel about using trastuzumab in patients with lower-risk, node-negative disease?

DR SLAMON: The HERA and the BCIRG trials were the only two that enrolled patients with node-negative disease. The HERA trial shows an equivalent benefit for patients with node-negative and node-positive disease. The data for the patients with node-negative disease in the BCIRG trial, which was 30 percent of the patients, will be released at the San Antonio Breast Cancer Symposium this year (Slamon 2006; [3.2]).

DR LOVE: Are there any cases of HER2-positive, node-negative breast cancer in which you would not use adjuvant trastuzumab?

DR SLAMON: The only type of case where I would consider not using trastuzumab — and it's a judgment call — is DCIS with an area of microinvasion. If there's a frank, invasive carcinoma that's HER2-positive, I don't care about the size. That tumor, in my opinion, is a HER2-driven tumor and should be treated accordingly.

DR LOVE: In that situation, does it matter to you whether the tumor is ER-positive or ER-negative?

DR SLAMON: No.

3.2

BCIRG 006: Efficacy of Trastuzumab in Patients with Node-Negative Disease

Disease-free survival (vs AC → T)	HR (95% CI)	*p*-value
AC → TH (n = 310)	0.32 (0.17-0.62)	0.0007
TCH (n = 309)	0.47 (0.26-0.83)	0.0096
Overall survival (vs AC → T)		
AC → TH (n = 309)	0.16 (0.04-0.73)	0.018
TCH (n = 307)	0.42 (0.15-1.2)	0.106

SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

CD 3, Track 13

DR LOVE: From a cardiac perspective, is docetaxel safer than paclitaxel in a trastuzumab-based regimen?

DR SLAMON: The data from the trastuzumab adjuvant trials and clinical experience clearly indicate that docetaxel may be less cardiotoxic than paclitaxel. Both taxanes have similar mechanisms of action but different toxicity profiles.

As for the cardiac issue, data indicate that docetaxel may be less cardiotoxic, although much of that comes from cross-trial comparison. The fact that we saw this big difference and that the adjuvant trastuzumab trials were conducted almost simultaneously with similar criteria for monitoring cardiac function in identical groups of women made us start to consider that docetaxel is a less cardiotoxic drug.

In the *Journal of Clinical Oncology* publication of the NSABP-B-31 data, the incidence of cardiac dysfunction of any type was 34 percent among the patients who received an anthracycline with trastuzumab (Tan-Chiu 2005; [3.3]). One third of the patients are developing some signal, disproportionate to what you see in the nontrastuzumab-containing arm, where it's closer to 12 or 13 percent.

The rate of cardiac dysfunction in our study was 17 percent of the patients, so again it was about half. It's remarkable how these numbers have stayed consistent. In clinical cardiotoxicity, the difference is about twofold. In subclinical cardiotoxicity, it's also twofold. So this isn't just noise. I believe it's a real signal that we're getting from the clinical data sets.

DR LOVE: Do you think this is relevant only when trastuzumab is on board or in general?

DR SLAMON: I believe it's particularly relevant when trastuzumab is on board, but that tends to make us believe that docetaxel is a less cardiotoxic agent.

This audio program on cardiac issues is timely because of the important messages that have come out recently, which have been a wake-up call for oncologists (3.4). We came to realize that treatment doesn't only involve getting patients through their neutropenia and fevers and then they get better.

Patients are incurring some longer-term damage that we need to be aware of, so as we introduce the new, targeted therapies — such as the small-molecule tyrosine kinase inhibitors like sorafenib or sunitinib — we realize we may be potentiating cardiac dysfunction when we begin with these cardiac-injuring drugs.

3.3

Cardiac Dysfunction (CD) in the Adjuvant Trastuzumab Trials

"Trastuzumab has been evaluated in the adjuvant setting using less cardiotoxic regimens than those in (NSABP) B-31. Recent data from NCCTG N9831 indicated delaying administration of trastuzumab until completion of paclitaxel may result in lower rates of severe CD. However, an unplanned interim efficacy analysis of the N9831 data suggested that this approach may be less effective than concurrent administration.

Conversely, the Herceptin Adjuvant (HERA) trial, which compared trastuzumab to observation after completion of chemotherapy, resulted in little symptomatic CD and demonstrated improvement in disease-free survival comparable to the disease-free survival seen in B-31/N9831. Currently, Breast Cancer International Research Group Study 006 is evaluating trastuzumab administered concurrently with docetaxel and carboplatin. Toxicity data from this trial indicate minimal CD. If efficacy results are ultimately favorable, this study could support removal of anthracyclines from the chemotherapy regimen with which trastuzumab will be administered."

[Citations omitted]

SOURCE: Tan-Chiu E et al. *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

3.4

Cardiac Event Rates and Cardiac Monitoring in the Adjuvant Trastuzumab Trials

	NSABP-B-31[1]	NCCTG-N9831[1]	HERA[2]	BCIRG 006[3]
Cardiac event rates	AC → T: 0.8% AC → TH: 4.1%	AC → T: 0% AC → TH: 2.9%	Ch → observation: 0% Ch → T x 1y: 0.54%	AC → T*: 0.95% AC → T*H: 2.34% T*CH: 1.33%
Protocol-defined cardiac events	NYHA Class III or IV CHF or death from cardiac causes		NYHA Class III or IV CHF and ≥10% ↓ from baseline in LVEF to <50%	Grade III/IV CHF, cardiac ischemia/infarction and arrhythmias, or cardiac death
Test to assess LVEF	MUGA	MUGA or ECHO	MUGA or ECHO	NR
Frequency of assessment	Baseline, post-AC, 6, 9 and 18 months after randomization		Baseline, 3, 6, 12, 18, 24, 30, 36 and 60 months after randomization	NR

A = doxorubicin; C = cyclophosphamide; T = paclitaxel; T* = docetaxel; H = trastuzumab; Ch = chemotherapy; CHF = congestive heart failure; NR = not reported; NYHA = New York Heart Association

SOURCES: [1] Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**; [2] Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353(16):1659-72. **Abstract**; [3] Slamon D et al. Presentation. SABCS 2005;**Abstract 1**; [4] Slamon D et al. Presentation. SABCS 2006;**Abstract 52**.

CD 3, Track 14

DR LOVE: Trastuzumab monotherapy has been heavily debated in terms of clinical practice. Will this be evaluated in a clinical trial?

DR SLAMON: It absolutely should be studied. Clinicians use it in practice now in isolated cases of elderly patients with HER2-positive tumors who might not tolerate chemotherapy but are otherwise healthy.

The risk factors for cardiac dysfunction are hypertension, low baseline LVEF and age. They appear to be almost equal in their contribution, and they are cumulative.

So in patients who have all of those factors, the incidence of cardiac dysfunction is high. For some of the patients who have all of those factors but in particular hypertension and advanced age, the incidence of clinical congestive heart failure goes up to about 10 percent.

Everyone agrees that a one-in-10 risk of cardiac dysfunction in the adjuvant setting is unacceptable. We "dialed up" the efficacy nicely, and I believe we may be reaching the ceiling, and now it's time to consider "dialing back" on the toxicity.

DR LOVE: Do we have any idea of what we might be losing, in terms of antitumor effect, by not using chemotherapy?

DR SLAMON: No, I don't have any idea. We need a clinical trial of adjuvant trastuzumab monotherapy versus the standard approach. I believe that trial will be conducted, despite the fact that the regulators and the physicians who presume to speak for the patients say that patients absolutely will not accept taking trastuzumab without chemotherapy.

When you actually talk with large groups of patients and ask if they would be willing to take this risk and eliminate chemotherapy, the answer comes back resoundingly, "Yes." We believe that's a question worth asking and answering.

DR LOVE: Do you think such a trial will be conducted?

DR SLAMON: I hope so. In the BCIRG, we're talking about trying to do something along those lines. ■

SELECT PUBLICATIONS

Dang C et al. **Mature cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** San Antonio Breast Cancer Symposium 2006;**Abstract 2101**.

Geyer CE et al. **Update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC) → paclitaxel (T) vs AC → T with trastuzumab (H).** *Proc ASCO* 2006;**Abstract 581**.

Gupta AK et al. **Trastuzumab for all? A decision analysis examining tradeoffs between efficacy and cardiac toxicity of adjuvant therapy in HER2 positive breast cancer.** *Proc ASCO* 2006;**Abstract 6022**.

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

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

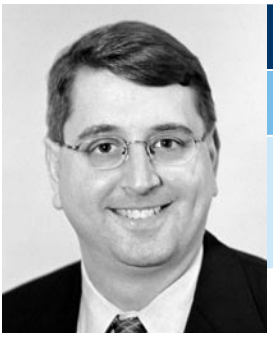
Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (Herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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

Slamon D et al. **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**.

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

Harold J Burstein, MD, PhD

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

CD 3, Tracks 21-29

Track 21 Introduction

Track 22 Background and first interim results of the BCIRG 006 adjuvant trastuzumab clinical trial

Track 23 Updated results of BCIRG 006

Track 24 Update of TOPO II as a predictor of benefit from anthracycline-containing chemotherapy in BCIRG 006

Track 25 Future role of anthracycline-containing chemotherapy regimens

Track 26 Relative cardiac safety of TCH compared to AC → TH

Track 27 Phase II study of trastuzumab with bevacizumab as first-line therapy for patients with HER2-positive disease

Track 28 Potentially beneficial and adverse synergy between trastuzumab and bevacizumab

Track 29 NSABP/BCIRG adjuvant trial for HER2-positive disease: TCH with or without bevacizumab

Editor's note:

A few weeks subsequent to the audio recording of the November 2006 interviews with Drs Steingart and Slamon and the Tumor Panel Discussion, Dr Slamon presented an updated analysis of BCIRG 006 at the San Antonio Breast Cancer Symposium. Dr Burstein was interviewed immediately after this presentation to discuss the findings.

Select Excerpts from the Interview

CD 3, Track 22

DR LOVE: First, by way of background, can you summarize the BCIRG 006 data originally reported at the San Antonio Breast Cancer Symposium in 2005 (Slamon 2005)?

DR BURSTEIN: BCIRG 006 was one of four or five major randomized trials evaluating adjuvant trastuzumab combined with chemotherapy for patients with HER2-positive breast cancer. In this trial, approximately 3,200 patients were randomly assigned to doxorubicin/cyclophosphamide followed by docetaxel (AC → T) or AC followed by docetaxel with trastuzumab

(AC → TH) or docetaxel, carboplatin and trastuzumab (TCH). Approximately 30 percent of the patients had node-negative disease, and all of the tumors were HER2-positive by FISH.

The BCIRG trial differed from some of the others in that it had a non-anthracycline-containing arm. The rationale for this arm was twofold. One reason was to determine whether cardiotoxicity, which had been seen in the metastatic setting, could be avoided during adjuvant therapy with trastuzumab. A second reason was to study one of the combinations of chemotherapy that had been shown in the laboratory to have dramatic synergy with trastuzumab, and they selected docetaxel with carboplatin.

When the data were originally presented at the San Antonio Breast Cancer Symposium in 2005, we saw that both the trastuzumab-based arms, AC → TH and TCH, were superior to the nontrastuzumab-containing arm, AC → T. That fit with the results from the other four major adjuvant trials (Joensuu 2005; Piccart-Gebhart 2005; Romond 2005).

The second finding was that the incidence of cardiac toxicity seemed to be lower in the TCH arm versus AC → TH. Although the differences were not statistically significant, approximately two and a half percent of patients in the AC → TH arm versus about one percent in the TCH arm experienced symptoms consistent with congestive heart failure. Also a greater fraction of patients receiving AC → TH had asymptomatic changes in LVEF (Slamon 2005).

A third finding, which was not statistically significant but was visually apparent when examining the Kaplan-Meier curves, was that AC → TH was superior to TCH in terms of efficacy. The difference was approximately four percent (Slamon 2005).

For those reasons, I and many other clinicians continued to favor an anthracycline- and taxane-based trastuzumab regimen, akin to what NSABP-B-31 and the North American Intergroup study (NCCTG-N9831) had shown. My preference was for the Intergroup regimen — four cycles of AC followed by 12 weeks of paclitaxel with trastuzumab. Having participated in the trial, we had experience with and extensive, well-documented safety information for that regimen.

CD 3, Track 23

DR LOVE: What did the second interim analysis of BCIRG 006 show as presented yesterday by Dr Slamon (Slamon 2006)?

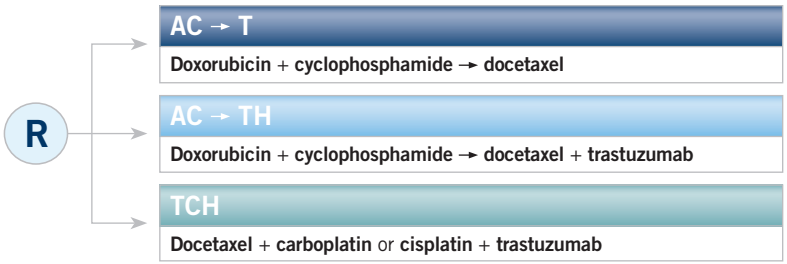
DR BURSTEIN: With approximately 12 more months of follow-up, the data had changed a bit. Whereas the basic findings were the same — that is, the trastuzumab-containing arms continued to outperform the nontrastuzumab-containing arm — the efficacy differences between AC → TH and TCH became less apparent (4.1, 4.2). In fact, the curves now track closely together, with only about a one percent difference separating them (Slamon 2006).

The updated analyses of cardiac function continue to show a lower risk of symptomatic congestive heart failure with the TCH regimen (Slamon 2006; [4.3, 4.4]). Also, with the longer follow-up, four cases of leukemia emerged among the roughly 2,100 women who received one of the anthracycline-based regimens. That's a low percentage in absolute terms, but it's consistent with prior reports of anthracycline-based regimens. In the 1,100 or so women who received the TCH regimen, no cases of leukemia have been reported (4.3).

I believe the BCIRG 006 data stand out as one of the highlights of the 2006 San Antonio Breast Cancer Symposium and will result in clinicians considering the TCH regimen much more often as an option for patients with HER2-positive, early-stage breast cancer. It seems to be as efficacious as the

4.1 **Phase III Study Comparing Doxorubicin/Cyclophosphamide → Docetaxel with or without Trastuzumab versus Docetaxel/Carboplatin/Trastuzumab**

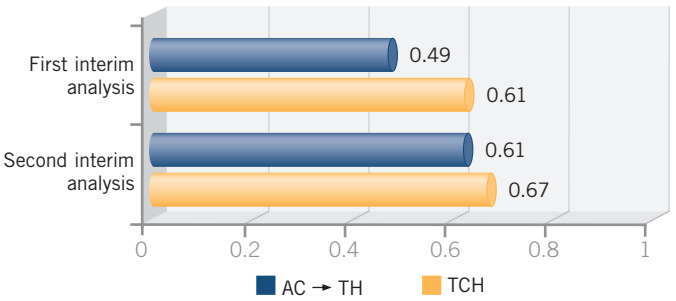
Protocol ID: BCIRG 006
Accrual: 3,222 (Closed)



Eligibility

- HER2-positive breast cancer
- Node-positive or high-risk node-negative

First and Second Interim Analysis: Disease-Free Survival Hazard Ratio versus AC → T



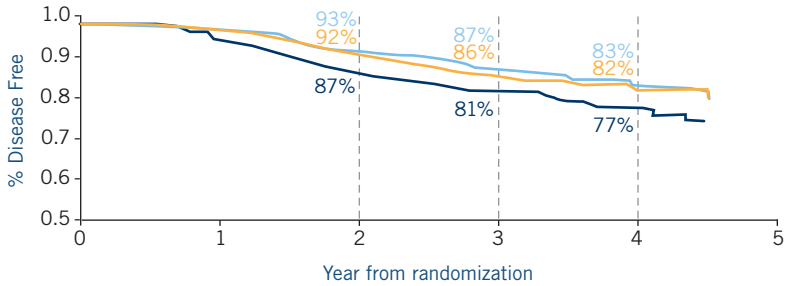
- First interim analysis (median follow-up = 23 months; *p*-value = 0.16)
- Second interim analysis (median follow-up = 36 months; *p*-value = 0.42)

SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006; **Abstract 52**.

4.2

Second Interim Analysis of Disease-Free Survival in Patients with HER2-Positive Early Breast Cancer Treated with Docetaxel, Carboplatin and Trastuzumab (TCH), or Doxorubicin and Cyclophosphamide (AC) Followed by Docetaxel (AC → T) or Docetaxel and Trastuzumab (AC → TH): BCIRG 006

	Patients	Events		
	1073	192	AC → T	
	1074	128	AC → TH	HR (AC → TH vs AC → T) = 0.61 [0.48;0.76] P < 0.0001
	1075	142	TCH	HR (TCH vs AC → T) = 0.67 [0.54;0.83] P = 0.0003



SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006;**Abstract 52**. With permission from CIRG, **www.bcirg.org**.

anthracycline-based regimens and to have a better toxicity profile with respect to certain rare, but serious, late complications (Slamon 2005).

CD 3, Track 24

DR LOVE: Would you summarize the TOPO II data from BCIRG 006?

DR BURSTEIN: The TOPO II issue, which has been discussed a lot since the BCIRG 006 data were presented in 2005, looks less relevant now with the 2006 data (Press 2005; Slamon 2006; [4.5, 4.6]).

The TOPO II gene is on human chromosome 17, not too far from the HER2/neu locus. In some cases of acquired HER2 gene amplification, you also have amplification of the TOPO II locus. TOPO II is a target of anthracyclines, and many people have suggested that TOPO II overexpression particularly identifies tumors that benefit from anthracyclines.

In the preliminary work from the BCIRG 006 trial that Dennis Slamon and Mike Press reported at the San Antonio meeting in 2005, they suggested that in TOPO II overexpressors, the anthracycline/trastuzumab (AC → TH) arm was superior to the nonanthracycline/trastuzumab (TCH) arm. For the majority of tumors in which the TOPO II is not amplified, however, TCH was more or less equivalent to AC → TH (Press 2005). If in the aggregate they're the same, it washes out the effects of the TOPO II test question. I believe

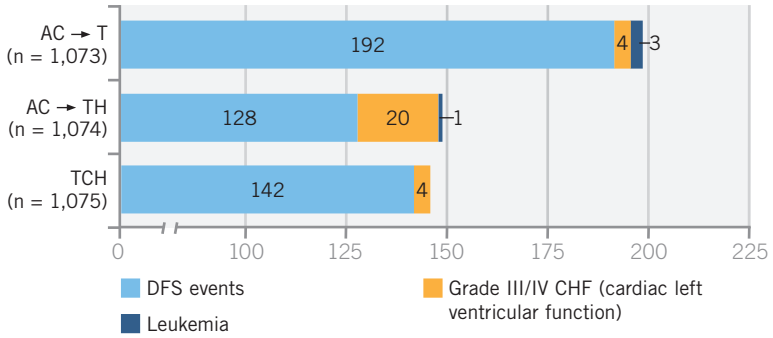
if clinicians decide that they can use a nonanthracycline/trastuzumab-based regimen, it doesn't matter whether they perform the TOPO II testing.

In the 35 percent of cases in which the tumor was both HER2-positive and TOPO II-positive, the curves all track similarly, which is a puzzle (Slamon 2006). I'm not sure I have a brilliant explanation for that. One thought would be that anthracyclines are important if the tumor is TOPO II-positive and perhaps those tumors have a greater resistance to trastuzumab, such that we don't see a huge additional benefit.

One thing to remember is that curves are not etched in marble, as Slamon's additional one-year follow-up data illustrate. Data evolve over time. The data presented in 2005 had a median follow-up of approximately two to two and a half years. Although I don't expect the fundamental conclusions will change in any major way, it is important to realize that as time goes by, you will see some evolution of the curves and in this trial that may be clinically relevant. Also, any time you have subsets of subsets and you're talking about a lower number of cases, then the curves are less stable.

4.3

BCIRG 006: Disease-Free Survival (DFS) Events and Critical Adverse Events at Second Interim Analysis



"Considering the published data just this month from the US Oncology trial that Steve Jones led that showed that docetaxel and cyclophosphamide outperforms significantly Adriamycin and cyclophosphamide for all breast cancers, and now the recent data we have from our update of BCIRG 006, that for HER2-positive malignancies, the difference in disease-free survival events and overall survival events in favor of the AC → TH are now exceeded by critical toxicities with regard to leukemias and congestive heart failure, the question becomes this: What is the role of anthracyclines in the adjuvant treatment of breast cancer?"

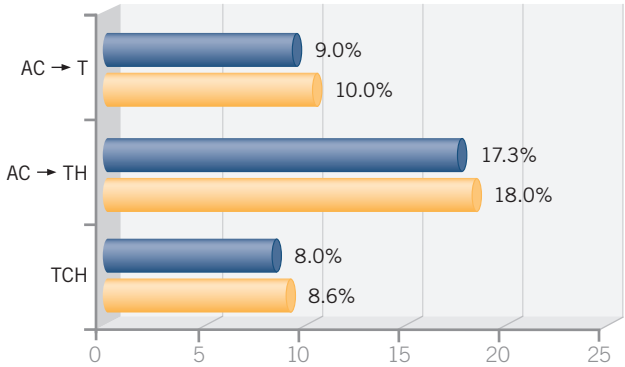
— Dennis J Slamon, MD, PhD
San Antonio, December 14, 2006

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

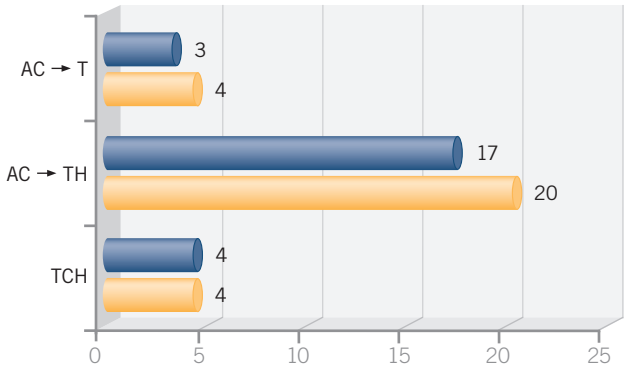
4.4

Cardiac Events in BCIRG 006

Percent of Patients with >10% Relative LVEF Decline



Cardiac Left Ventricular Function Grade III/IV (CHF) Events



SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

DR LOVE: What about the curves for the TOPO II–nonamplified tumors?

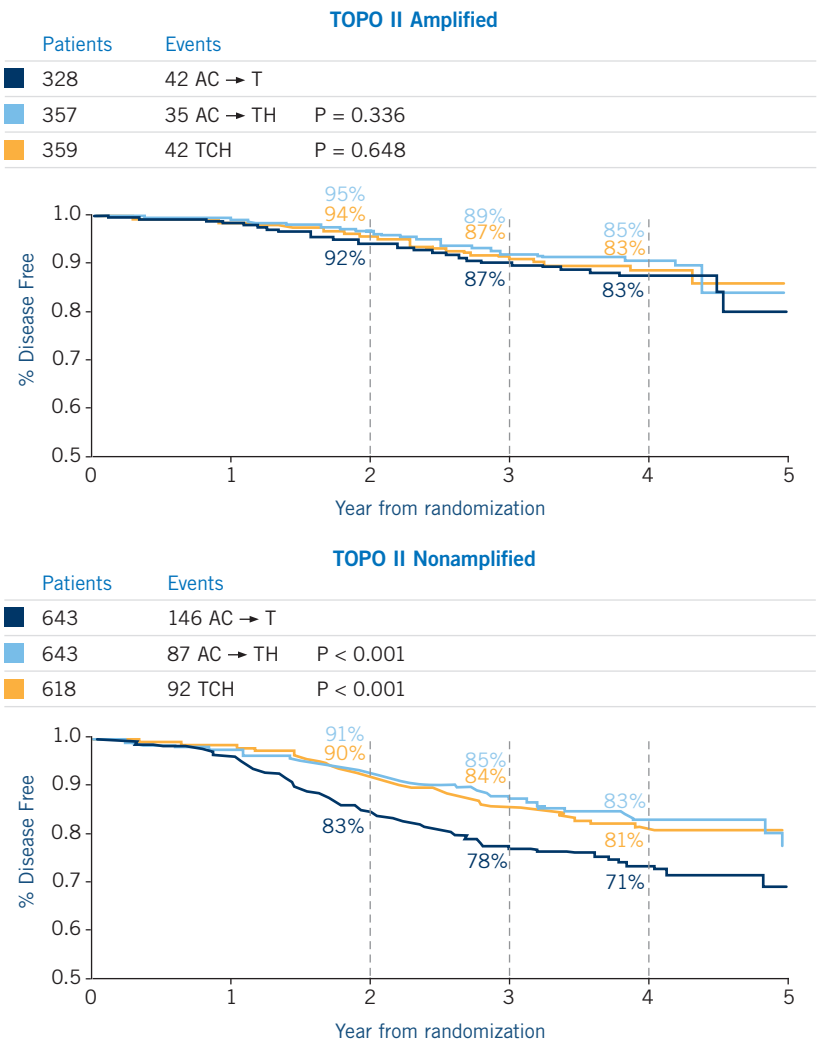
DR BURSTEIN: For those patients, the trastuzumab-based arms are superior to the nontrastuzumab arm. Visually, there's less difference between the two trastuzumab-based arms than there seemed to be a year ago (Slamon 2006; [4.5, 4.6]).

DR LOVE: I've talked to a number of clinicians who in a few difficult cases sent specimens to Mike Press at UCLA to test TOPO II this past year, but now, based on the new data, they don't plan to do that anymore. Does that seem logical?

DR BURSTEIN: I wasn't certain it was logical to begin with because the data were preliminary with short follow-up and reflected subsets of patients in a three-arm study, which is always dodgy. At this point, I believe there's even

4.5

Second Interim Analysis of Disease-Free Survival According to TOPO II Amplification During BCIRG 006 in Patients with HER2-Positive Early Breast Cancer



SOURCE: Slamon D et al. San Antonio Breast Cancer Symposium 2006;**Abstract 52**. With permission from CIRG, **www.bcirg.org**.

less rationale for testing. I assume clinicians will either continue to use AC → TH, because they'll say that's what they've always used and it's effective, or they'll increasingly switch to TCH. In either case, you don't need TOPO II testing to help you.

4.6

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

"When we looked at the disease-free survival for the cases with TOPO II gene coamplified at the first interim analysis, we saw that the AC → TH performed very well. We thought with more events and more follow-up that this would perhaps become statistically significant. However, what's happened, instead, is now all the arms look very much the same.

So if you have any target in the amplicon, you treat with a targeted therapy — AC → T or Herceptin, or Herceptin plus anthracycline. It's just that you're buying more toxicity with the AC → T arm, and certainly more with AC → TH."

— Dennis J Slamon, MD, PhD

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

CD 3, Track 25

DR LOVE: What do you see as the future role for anthracyclines?

DR BURSTEIN: In trying to determine the best chemotherapy foundation for trastuzumab in the adjuvant setting, we have compelling data for several strategies. Using TCH looks more viable than it did a year ago. In the BCIRG 006 trial, TCH seems to be as efficacious as AC → TH (4.3).

A lot of retrospective analyses, including updates of multiple trials presented at the 2006 San Antonio meeting, strongly suggest that the tumors that most benefit from anthracycline-based therapy are those that are HER2 amplified or TOPO II amplified (Gunnarsdottir 2006; Johnson 2006; O'Malley 2006). However, we now have a whole different treatment paradigm for them. The patients with HER2-positive disease all receive trastuzumab-based therapy, and in patients with HER2-negative disease, it's difficult to see much benefit from anthracycline-based regimens over nonanthracycline-based regimens.

Anthracyclines have been useful for many women for a long time, and they probably have contributed to much better outcomes for these women. However, because we increasingly have subsets of breast cancer for which we have different treatment programs — for example, patients with HER2-positive disease receive trastuzumab and patients with HER2-negative disease might not need as much chemotherapy or might need different flavors of chemotherapy — we increasingly have the flexibility of offering nonanthracycline-based regimens.

Many nonanthracycline-based regimens are available. In addition to CMF, we have taxane-based regimens, such as the docetaxel/cyclophosphamide regimen that the US Oncology group has put forward (Jones 2006), and others will continue to emerge. I believe this is something we should continue to explore vigorously in clinical trials because it might spare our patients some toxicity.

DR LOVE: To what extent are you using nonanthracycline-containing regimens for your patients with HER2-negative breast cancer?

DR BURSTEIN: I still frequently use four cycles of AC or AC followed by a taxane for non-HER2-positive disease. We have a lot of data suggesting that dose-dense AC followed by paclitaxel, as used in CALGB-9741, is a highly effective regimen for breast cancer, particularly for patients with ER-negative disease (Citron 2003). I have also used CMF in the adjuvant setting.

Studies have examined AC followed by paclitaxel on an every three-week schedule and suggest that it is an inferior regimen to other options (Burnell 2006). I believe every three-week anthracyclines are on their way out. Whether dose-densifying anthracycline-based regimens continues to be superior to nonanthracycline options such as CMF or TC is something that we need to explore.

CD 3, Track 26

DR LOVE: Dr Slamon feels that nonanthracycline-containing regimens, such as TCH, have a significantly better cardiac safety profile than the anthracycline-based regimens. Do you agree?

DR BURSTEIN: I only have the data Dr Slamon has presented, and the differences in the absolute incidence of cardiotoxicity are very small, approximately a percentage point (Slamon 2006). In addition, a slightly greater percentage of patients have an asymptomatic decline in ejection fraction with AC → TH, the significance of which is unknown.

I believe that the ultimate efficacy of the regimen is what should mostly dictate which treatment to use. If two regimens are equally efficacious, then you focus on convenience, side-effect profiles and late — but serious — consequences. With respect to those choices, TCH looks better today than it did a year ago because it's now equally efficacious and seems to have some advantages with respect to safety (Slamon 2006; [4.4]).

DR LOVE: Have you treated any patients with HER2-positive breast cancer with a nonanthracycline-containing regimen in the clinical setting?

DR BURSTEIN: Since the data were presented at ASCO, I have not because approximately 9,000 of the 10,000 women treated in the adjuvant trastuzumab randomized studies received anthracyclines and I believe that before everybody walks away from anthracyclines, we need ongoing follow-up of all these trials (Perez 2005; Joensuu 2005; Piccart-Gebhart 2005; Romond 2005; Slamon 2006; Smith 2007). I do believe that clinicians will use TCH more often.

We have been considering strategies for treating patients with HER2-positive breast cancer with nonanthracycline regimens. In early 2007, we'll be inaugurating a feasibility study for patients with Stage I breast cancer in which patients will receive 12 weeks of paclitaxel with trastuzumab. We have relatively few data on the benefits of trastuzumab for these women at lower risk. We believe that 12 weeks of a chemotherapy agent that's reasonably well tolerated, such as weekly paclitaxel, might be an effective treatment.

CD 3, Track 27

DR LOVE: Would you discuss the data from the Phase II trial of bevacizumab and trastuzumab in women with advanced HER2-positive breast cancer?

DR BURSTEIN: There is no reason to believe bevacizumab would work only in HER2-negative breast cancer. However, we have surprisingly few data for bevacizumab in HER2-positive breast cancer. That was a part of the motivation for Pegram's study at UCLA, and the other part was an interest in determining whether it would be safe and effective to pair these two humanized monoclonal antibodies — trastuzumab and bevacizumab — with one another.

When Dr Pegram presented the Phase I data for approximately a dozen patients, he showed that there did not seem to be pharmacokinetic interactions between bevacizumab and trastuzumab (Pegram 2004). He followed up on this by showing preliminary results from the open-label Phase II trial, where chemotherapy-naïve patients with HER2-positive breast cancer receive trastuzumab and bevacizumab in the metastatic setting (Pegram 2006).

Although the data presented were somewhat premature because they are still accruing patients, the response rate was dramatic — 54 percent — in the 37 assessable patients. That's interesting because it suggests that a nonchemotherapy regimen with potent biological agents could have substantial activity.

One concern is the safety of this combination, and it looks feasible. One case of symptomatic heart failure in these 37 patients was reported, but it's not clear if that's an artifact of single-agent trastuzumab, which can rarely cause congestive heart failure, or if there's some other signal.

About another dozen patients had asymptomatic changes in LVEF of unclear significance. In all, about 35 percent of the patients had asymptomatic changes in LVEF, which is a high number. It's higher than we saw in the AC → TH arm in the adjuvant trial. We need to determine in the metastatic setting whether that has long-term consequences.

This trial suggests that bevacizumab and trastuzumab can be combined safely, and it invites ongoing research with this doublet to see if that's a better way to treat HER2-positive disease. It may also generate interest in adjuvant trials. I suspect the next generation of adjuvant trials from some of the cooperative groups will evaluate chemotherapy with trastuzumab, with or without bevacizumab, in patients with HER2-positive breast cancer. ■

SELECT PUBLICATIONS

Burnell M et al. **A randomized trial of CEF versus dose dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: Results of an interim analysis.** San Antonio Breast Cancer Symposium 2006;**Abstract 53**.

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant**

treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Gunnarsdottir K et al. **CEF is superior to CMF for tumors with topoisomerase II gene alterations: A STEPP (subpopulation treatment effect pattern plot) analysis on Danish breast cancer cooperative group study 89D.** San Antonio Breast Cancer Symposium 2006;**Abstract 1023**.

Joensuu H et al. **Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: The FinHer Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 2**.

Johnson PH et al. **Nuclear staining of topoisomerase II (topo II) may predict response to anthracycline but not taxane-based neoadjuvant chemotherapy regimens.** San Antonio Breast Cancer Symposium 2006;**Abstract 1024**.

Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

O'Malley FP et al. **Topoisomerase II alpha protein overexpression has predictive utility in a randomized trial comparing CMF to CEF in premenopausal women with node positive breast cancer (NCIC CTG MA.5).** San Antonio Breast Cancer Symposium 2006;**Abstract 38**.

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**.

Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** *Breast Cancer Res Treat* 2004;88(Suppl 1):124;**Abstract 3039**.

Perez E et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;**Abstract 556**.

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

Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (Herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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 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**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following types of anthracycline-induced cardiotoxicity have been described?**
   a. Acute or subacute
   b. Chronic
   c. Late-onset
   d. All of the above
2. **A study published in *The New England Journal of Medicine* demonstrated that patients with congestive heart failure and depressed LVEF have a worse prognosis than those with normal LVEF.**
   a. True
   b. False
3. **Which of the following have been implicated as a mechanism of trastuzumab-associated cardiotoxicity?**
   a. Free radical production of mitochondrial damage to myocytes
   b. Myocardial cell death
   c. Blocking cell reparative pathways
   d. All of the above
4. **A retrospective, observational study reported by Ewer and colleagues in the *Journal of Clinical Oncology* indicated that patients who experience cardiotoxicity while receiving trastuzumab generally recover cardiac function when trastuzumab is discontinued.**
   a. True
   b. False
5. **In a study of dose-dense AC followed by paclitaxel and trastuzumab, which used the same stopping criteria for cardiac events as NSABP-B-31, what percentage of patients had to discontinue trastuzumab as a result of asymptomatic declines in LVEF?**
   a. Four percent
   b. 10 percent
   c. 20 percent
6. **According to an analysis of the SEER-Medicare database, approximately ____ of the women between 66 and 70 years of age with breast cancer who were treated with an adjuvant anthracycline-containing regimen developed CHF.**
   a. Five percent
   b. 10 percent
   c. 20 percent
   d. 40 percent
   e. 80 percent
7. **In the combined analysis of NSABP-B-31 and NCCTG-N9831, approximately ____ of the women with normal ejection fractions following the anthracycline phase of their treatment discontinued trastuzumab because they either had clinical congestive heart failure or their ejection fraction fell beyond a prespecified parameter.**
   a. Five percent
   b. 10 percent
   c. 20 percent
   d. 40 percent
   e. 80 percent
8. **In the HERA trial, patients did not begin treatment with trastuzumab until after completion of surgery, radiation therapy and chemotherapy.**
   a. True
   b. False
9. **In the US Oncology adjuvant trial, docetaxel/cyclophosphamide resulted in a(n) _____ improvement in five-year disease-free survival compared to AC chemotherapy.**
   a. One percent
   b. Six percent
   c. 11 percent
10. **In 2006, data from the second interim analysis of BCIRG 006 demonstrated approximately a ____ percent nonsignificant difference in disease-free survival for patients receiving AC → TH versus TCH.**
    a. One
    b. Five
    c. 10
    d. 12
11. **In the BCIRG 006 trial, four cases of leukemia were reported among patients who received anthracycline-based chemotherapy versus _____ cases among the patients who received TCH.**
    a. Zero
    b. Two
    c. Eight
    d. 10
12. **In 2006, data from the second interim analysis of BCIRG 006 demonstrated statistically significant improvements in disease-free survival for patients with coamplification of HER2 and TOPO II who received AC → T compared to those who received TCH.**
    a. True
    b. False

Post-test answer key: 1d, 2b, 3c, 4a, 5a, 6d, 7c, 8a, 9b, 10a, 11a, 12b

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GLOBAL LEARNING OBJECTIVES

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

- Understand the pathophysiologic mechanisms, risks and the nature of cardiotoxicity associated with anthracyclines, trastuzumab and other biologic agents in order to assist patients with breast cancer in treatment decision-making. . . . . 5 4 3 2 1 N/A
- Develop a clinical algorithm for monitoring cardiac functioning in patients receiving anthracyclines, trastuzumab and other biologic agents, and develop an approach to managing treatment-induced cardiotoxicity while providing optimally effective cancer treatment. . . . . 5 4 3 2 1 N/A
- Identify the relative advantages and disadvantages of MUGA and echocardiography for monitoring left ventricular ejection fraction (LVEF). . . . . 5 4 3 2 1 N/A
- Develop awareness of the intraindividual and interobserver variability in the assessment of LVEF in order to evaluate the relevance of changes to individual patient care. . . . . 5 4 3 2 1 N/A
- Evaluate the relative advantages and disadvantages of anthracycline- and nonanthracycline-containing regimens in order to counsel patients with HER2-positive and HER2-negative disease about potential treatment options with less cardiac risk. . . . . 5 4 3 2 1 N/A
- Recognize the importance of cardiology-oncology collaboration in the care of patients with cardiac risk factors, particularly those receiving potentially cardiotoxic adjuvant therapy, in order to mitigate risk of congestive heart failure. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Richard M Steingart, MD	5 4 3 2 1	5 4 3 2 1
Dennis J Slamon, MD, PhD	5 4 3 2 1	5 4 3 2 1
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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