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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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Cardiologic Issues in Breast Cancer Management

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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 Durand, Hunt, Pegram and Slamon 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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TABLE OF CONTENTS

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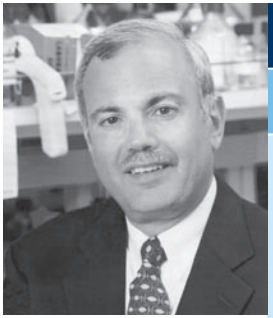


INTERVIEW

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 David Geffen School of Medicine at UCLA's Jonsson Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-11

Select Excerpts from the Interview

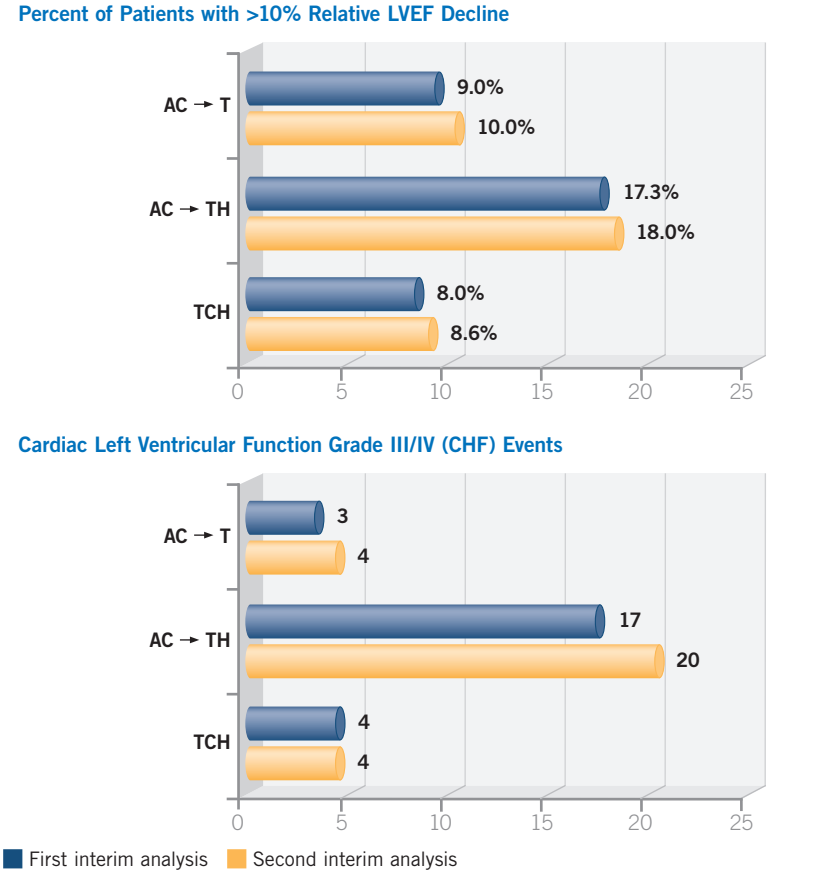
Track 3

DR LOVE: Can you summarize where we are currently in terms of cardiac safety and trastuzumab/chemotherapy?

DR SLAMON: The BCIRG 006 trial (Slamon 2006) had a nonanthracycline arm. The study demonstrated that cardiac dysfunction in patients who received trastuzumab and anthracyclines, even when trastuzumab was administered after the anthracycline, increased fourfold to fivefold (1.1).

This toxicity is certainly not short and transient, as people have been saying — a few weeks or months — it's clearly longer. If you factor in what also happens to these patients in the long term as they age — as we cure them, which is what we hope we do — and they accrue other health issues such as hypertension, obesity, diabetes and other cardiac insults, our concern is that the cardiac dysfunction will increase even further. Certainly, some of the SEER database analysis indicates that's the case with anthracycline therapy (Pinder 2007) — much more so than we previously thought. Among patients receiving trastuzumab, I'm worried that we will see the incidence go even higher.

1.1 Cardiac Events in BCIRG 006



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

Track 4

DR LOVE: Can you discuss TOPO II and how it relates to the treatment of HER2-positive disease?

DR SLAMON: Approximately eight percent of the world population of patients with breast cancer have coamplification of HER2 and TOPO II. It turns out that with these patients, you can use an anthracycline alone and obtain a trastuzumab-like benefit without using the trastuzumab, but that's for a small number of patients.

If you use trastuzumab without the anthracycline, you obtain the benefit that's been reported, and if you use a nonanthracycline chemotherapy, such as TCH,

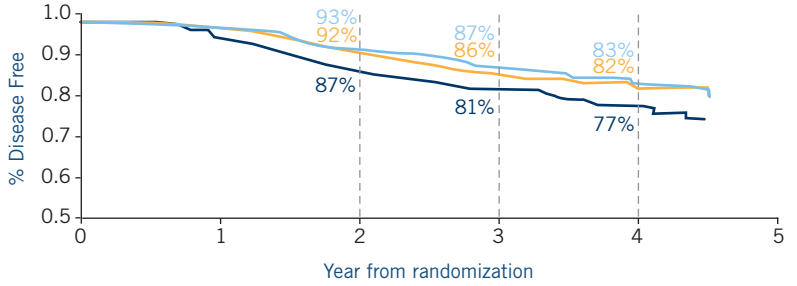
you obtain exactly the same benefit. The curves are identical — they overlap completely (Slamon 2006; [1.2]).

This indicates that 92 percent of women derive no benefit from anthracycline-based therapy in terms of an incremental improvement, but they derive all the toxicity — the cardiomyopathies, congestive heart failure, leukemia and myelodysplasia. So I don't believe these agents have a role in the adjuvant setting if you can use trastuzumab.

1.2

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**.

Track 5

DR LOVE: What about the issue of using anthracyclines for patients with HER2-negative tumors?

DR SLAMON: The clinical data seemed to indicate no benefit for the patients with HER2-negative disease, but we wanted to investigate a step further. So we asked how often TOPO II was amplified in patients from the BCIRG 005 trial (Press 2007), which included HER2-negative cases as determined by FISH.

Out of 1,800 cases analyzed, not a single case of TOPO II amplification was recorded. I believe that explains why the analyses from three decades of trials — randomized trials of more than 7,000 patients, conducted by four or five different groups — all showed no incremental benefit from anthracycline-based therapy compared to nonanthracycline-based therapy for the vast majority of patients.

DR LOVE: So what's your perspective on all this information?

DR SLAMON: We don't use anthracyclines in the adjuvant setting. The adjuvant regimen we use for our non-HER2-positive cases, based on the US Oncology data presented by Steve Jones, is TC (Jones 2006; [1.3]). I'm always asked if I would use TC even for node-positive disease. The answer is unequivocally yes. I don't believe — based on the data, which are significant and have been around for a while — that an incremental benefit to receiving anthracyclines occurs for these patients, so we don't use them.

1.3

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-/PR-	HR = 0.64 (95% CI: 0.38-1.04)			
ER+ or PR+	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%	
Neutropenic fever	5%	2.5%	0.07
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01

SOURCE: Jones SE et al. *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Track 8

DR LOVE: One of the biggest areas of controversy continues to be the management of HER2-positive, node-negative tumors, particularly smaller than one centimeter. Where are we right now in terms of data related to that decision?

DR SLAMON: Mike Press and Leslie Bernstein published data on HER2-positive tumors that were smaller than one centimeter (Press 1997; [1.4]). It turns out that the outcome data for those tumors indicate that those women have the same outcomes as women with node-positive tumors, so the recurrence rate at five years, and presumably out further, should be similar.

So the way we treat small tumors that are HER2-positive is to treat them as HER2-positive tumors. The argument we've made is that it isn't so much the size of the tumor or even the number of nodes, it's how the tumor is wired, and if it's wired as a HER2-positive tumor, it will behave badly and should be treated with trastuzumab-based therapy.

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

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

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

Track 10

DR LOVE: Can you discuss the BETH trial being launched by the CIRG and NSABP?

DR SLAMON: We're evaluating the combination of trastuzumab and bevacizumab because HER2 upregulates VEGF, which causes tumors to be more pro-angiogenic. The question is, if you combine bevacizumab and trastuzumab, what will you observe? Preclinically, remarkable efficacy was demonstrated — better than either drug alone.

In early clinical trials, in the first-line metastatic disease setting, we used only the two antibodies and achieved response rates of 52 percent and clinical benefits of 83 percent. Moving into the adjuvant setting with the NSABP, this proposed 2,700-patient trial will evaluate TCH with or without bevacizumab (1.5).

DR LOVE: What about the issue of cardiac safety using the combination of bevacizumab and trastuzumab?

DR SLAMON: One of the main reasons we built the regimen on a backbone of docetaxel/carboplatin is that we were worried that any added insult to the cardiovascular system could be problematic. We know that bevacizumab is associated with a hypertension rate of approximately 18 percent.

As the cardiologists have taught us — and we should have learned from basic cardiac physiology — an increased afterload can be one of the best predictors of inducing left ventricular dysfunction.

We'll be increasing afterload clinically in approximately one fifth of the patients and perhaps subclinically in an even higher number. We'll find out what the safety profile shows with TCH and TCHB. ■

1.5 BETH: Proposed NSABP/CIRG Trial of Adjuvant Monoclonal Therapy in Patients with HER2-Positive Early Breast Cancer

Target Accrual: 2,875

Eligibility

- Node-positive or high-risk node-negative early breast cancer
- HER2-positive by central testing

Stratification

- Number of positive nodes
- Hormone receptor status

SOURCE: Slamon D. The Art of Oncology Satellite Symposium at ECCO 14, Barcelona, Spain. September 26, 2007.

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365(9472):1687-717. **Abstract**

Hayes DF et al. **Circulating HER-2/erbB-2/c-neu (HER-2) extracellular domain as a prognostic factor in patients with metastatic breast cancer: Cancer and Leukemia Group B Study 8662.** *Clin Cancer Res* 2001;7(9):2703-11. **Abstract**

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**

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**.

Pinder MC et al. **Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer.** *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

Press MF et al. **Alteration of topoisomerase II-alpha gene in human breast cancer and its association with responsiveness to anthracycline-based chemotherapy.** *Proc ASCO* 2007;**Abstract 524**.

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

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

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

INTERVIEW

Sharon Hunt, MD

Dr Hunt is Professor of Cardiovascular Medicine and Medical Director of the Post-Cardiac Transplant Program at Stanford University Medical Center in Palo Alto, California.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the cardiac issues with trastuzumab?

DR HUNT: The cardiotoxicity documented with trastuzumab, particularly in the adjuvant trials, may be only the tip of the iceberg in terms of the natural history of that toxicity.

The five-year follow-up of the NSABP-B-31 trial was encouraging in that no burgeoning amount of cardiotoxicity occurred (Rastogi 2007; [2.1]). But doctors taking care of these women for the longer term need to be aware that having been through that course of trastuzumab, in addition to anthracyclines, may place women at higher risk for developing cardiac dysfunction later in life.

DR LOVE: You were one of the authors on a paper in the *Journal of Clinical Oncology*, "Trastuzumab-Related Cardiotoxicity: Calling into Question the

2.1 **NSABP-B-31: Five-Year Cumulative Incidence of Cardiac Events**

	Congestive heart failure		Cardiac deaths		Cardiac events (%)	
Years*	AC → T†	AC → TH	AC → T†	AC → TH	AC → T†	AC → TH
1	—	—	—	—	0.5	3.3
2	—	—	—	—	0.6	3.6
3	4	31	1	0	0.9	3.8
4	—	—	—	—	0.9	3.8
5	6	35	1	0	0.9	3.8

AC → T = AC → paclitaxel; AC → TH = AC → paclitaxel + trastuzumab

* Years post day 1 cycle 5

† Events among crossover patients censored

SOURCE: Rastogi P et al. *Proc ASCO* 2007;**Abstract LBA513**.

Concept of Reversibility" (Telli 2007; [2.3]). In the adjuvant setting with trastuzumab, how much of the cardiotoxicity is related to anthracycline/trastuzumab and how much to trastuzumab alone?

DR HUNT: In the data available so far, it appears that trastuzumab without anthracyclines has a much lower incidence of evident cardiotoxicity than the combination, at least at the three- and five-year follow-ups.

Whether that will continue to be the case as the natural history of the toxicity plays out, we obviously don't know. But for now it seems in the trials with the three- and five-year follow-up that it's the combination of the anthracycline and trastuzumab that leads to increased cardiotoxicity.

Track 3

DR LOVE: In your presentation at ASCO 2007, you showed a pie chart illustrating the reasons behind heart transplantation, and the anthracycline-related cardiomyopathy piece of the pie did not appear to be inconsequential (Hunt 2007).

DR HUNT: No, it was not inconsequential, although the absolute numbers were not large. Every year, the International Society for Heart and Lung Transplantation publishes data from a registry that has accrued over 100,000 heart transplants over the past 25 years. That pie chart documents the underlying cause of heart disease that led to the need for transplantation (2.2).

An approximately five percent section in that pie chart is listed as "other." The majority of that five percent is long-term anthracycline-related cardiotoxicity.

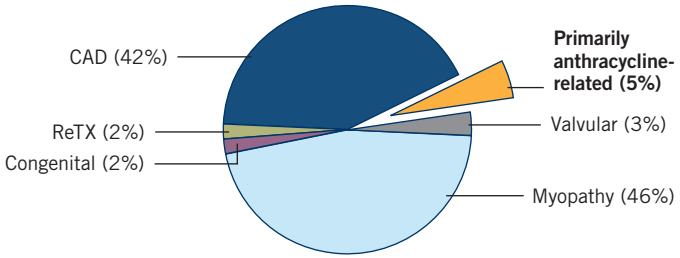
Five percent of 2,500 cases per year in the US is approximately 125 patients. That's not many patients, but again that's only the tip of the iceberg. The vast

majority of people who have advanced heart disease are not eligible for transplantation for a variety of reasons.

So that 125 is a representative number of patients who are dying of advanced anthracycline-related cardiotoxicities. We may find that a future population — five, 10 or 20 years from today — will have end-stage trastuzumab-related cardiotoxicities. We do not know that, but I believe we should watch for it.

2.2

Underlying Cause of Heart Disease in Adult Patients Who Have Undergone Heart Transplantation (1/2001-6/2005)



n = 12,234

CAD = coronary artery disease

ReTX = retransplantation

SOURCE: Hunt SA. Presentation. ASCO 2007. No abstract available

2.3

Trastuzumab-Related Cardiotoxicity: Calling into Question the Concept of Reversibility

"Focusing on severe symptomatic CHF does not tell the whole story. A substantial portion of patients treated with trastuzumab have experienced asymptomatic decrements in LVEF. Fourteen percent of patients in the NSABP B-31 trial had trastuzumab discontinued secondary to asymptomatic declines in LVEF, and 17% of patients in trial BCIRG 006 had a more than 10% relative LVEF decline from baseline, the majority of whom were asymptomatic.

Detailed cardiac data from NSABP B-31 was particularly striking in that significant proportions of patients, regardless of whether they were diagnosed with a cardiac event, symptomatic cardiac dysfunction, or an asymptomatic decrease in LVEF, had sustained decrements in LVEF to less than 50% on follow-up evaluations performed greater than 6 months after the onset of cardiotoxicity.

Follow-up data from BCIRG 006 patients who developed asymptomatic decrements in LVEF provides additional evidence supporting the persistence of cardiac dysfunction in a clinically significant proportion of patients."

SOURCE: Telli ML et al. *J Clin Oncol* 2007;25(23):3525-33. **Abstract**

Track 7

DR LOVE: What can be done for patients who are at a higher risk of developing heart failure, specifically women who've received adjuvant trastuzumab, particularly with an anthracycline? As these women age over five, 10 or 20 years, how can a medical oncologist, often the primary care provider, provide optimal cardiovascular support?

DR HUNT: It is important for the primary care physician and the oncologist to always have in the back of their minds the fact that the patient was exposed to a potential cardiotoxin, even if it was 20 years ago, and to be aware that any additional insults can lead to the development of heart failure in later life.

For instance, Dr Love, if you developed a little bit of hypertension, it might have no effect on you for many years if you didn't treat it, whereas a woman whose heart has been sensitized by this preexisting damage might be particularly sensitive to even small amounts of hypertension.

DR LOVE: What level of blood pressure would pique your attention in a patient like this?

DR HUNT: If a woman had undergone potentially cardiotoxic chemotherapy in the past, I wouldn't want her blood pressure to be over 120/80 mm Hg.

No guidelines on this exist, but with the analogous problem of diabetes, even the national organizations say that someone with diabetes should never have their blood pressure reach over 120 mm Hg.

They would allow you and me to reach 130 mm Hg before initiating therapy, but patients who are so much more prone to developing cardiac dysfunction should be monitored at lower levels.

Track 11

DR LOVE: Can you review the cardiac safety data in the adjuvant trastuzumab trials?

DR HUNT: There were four major trials (NSABP-B-31, NCCTG-N9831, HERA, BCIRG 006) and a smaller study from Finland (FinHER). The trials were all different clinical designs, but at the end of the day approximately four percent of patients at three years had developed overt cardiac toxicity (Telli 2007; [2.4]).

For subclinical cardiac toxicity, such as abnormalities on echocardiography, it was closer to 14 or 15 percent.

Some of those patients with either subclinical or clinical heart failure showed evidence of reversibility. In other words, over time and with treatment, ejection fractions and symptoms improved or totally resolved.

However, a significant fraction did not improve. It is not clear whether or not those conditions that seemed to resolve will stay resolved. That is why longer-term follow-up of these cohorts of women is essential. ■

2.4

Cardiotoxicity Data from Adjuvant Trastuzumab Trials

	Cardiac death and severe CHF	Symptomatic CHF	Decrease in LVEF
NSABP-B-31	C: 0.8% T: 4.1%	C: 1% T: 5.1%	T: 14%
NCCTG-N9831	C: 0.3% T: 3.5%	NA	T: 10.8%
HERA	C: 0.06% T: 0.6%	C: 0.2% T: 2.1%	C: 2.3% T: 7.4%
BCIRG 006	ACT: 0.3% ACTH: 1.6% TCH: 0.4%	NA	ACT: 9% ACTH: 17.3% TCH: 8%
FinHER	C: 3.4% T: 0%	NA	C: 6.0% T: 3.5%

ACT = doxorubicin, cyclophosphamide and docetaxel; ACTH = doxorubicin, cyclophosphamide, docetaxel and trastuzumab; C = control; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NA = not available; T = trastuzumab; TCH = docetaxel, carboplatin and trastuzumab

SOURCE: Telli ML et al. *J Clin Oncol* 2007;25(23):3525-33. **Abstract**

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Hooning MJ et al. **Long-term risk of cardiovascular disease in 10-year survivors of breast cancer.** *J Natl Cancer Inst* 2007;99(5):365-75. **Abstract**

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Ng R, Green MD. **Managing cardiotoxicity in anthracycline-treated breast cancers.** *Expert Opin Drug Saf* 2007;6(3):315-21. **Abstract**

Pinder MC et al. **Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer.** *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

Rastogi P et al. **Five year 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* 2007;**Abstract LBA513**.

Telli ML et al. **Trastuzumab-related cardiotoxicity: Calling into question the concept of reversibility.** *J Clin Oncol* 2007;25(23):3525-33. **Abstract**

Jean-Bernard Durand, MD and Mark D Pegram, MD

Tracks 1-52

(continued)

Tracks 1-52

Select Excerpts from the Discussion

Tracks 1-4

Case Discussion 1 (from the practice of William N Harwin, MD)

A 36-year-old African American woman who, at 32 weeks of gestation, underwent a lumpectomy with axillary dissection for a 2.7-cm, node-positive, ER-negative, PR-negative, HER2-positive infiltrating ductal carcinoma.

The patient developed preeclampsia, and delivery was induced. After delivering her baby, she enrolled in NCCTG-N9831 and was assigned to receive AC → paclitaxel → trastuzumab. Shortly after the completion of one year of trastuzumab, she developed dyspnea on exertion and her ejection fraction was 22 percent.

The cardiologist diagnosed a dilated cardiomyopathy, and she was treated with furosemide, digoxin, carvedilol and lisinopril. She is currently asymptomatic and has an ejection fraction of 50 percent while on the cardiac medications.

DR LOVE: This woman developed problems after completing treatment with trastuzumab. What do we know about the time course of trastuzumab- or anthracycline-related cardiotoxicity?

DR DURAND: We know that doxorubicin produces an acute, a subacute and a long-term cardiotoxicity. One factor that can be difficult to dissect with this particular patient is whether the decrease in ejection fraction is due to doxorubicin, one year after exposure, or to trastuzumab.

DR LOVE: Mark, how typical would it be for a patient to develop congestive heart failure within a month of completing trastuzumab?

DR PEGRAM: That's atypical. From NSABP-B-31, we have information about the time course of trastuzumab-related cardiotoxicity (3.1). It's important to note that in that trial about 6.5 percent of the patients never received trastuzumab because their ejection fraction declined after the four cycles of AC.

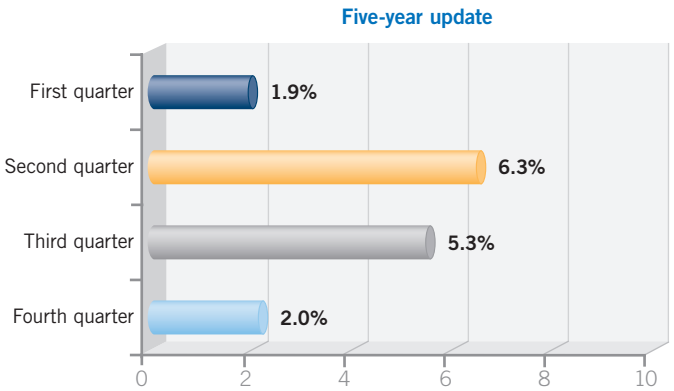
In the patients who received trastuzumab, a peak seems to have occurred in the incidence of trastuzumab-related cardiotoxicity in the second and third quarter of treatment, which then tapers off again in the fourth quarter (Rastogi 2007; [3.1]). So I would say that this presentation is somewhat atypical for patients with trastuzumab-related cardiotoxicity.

DR LOVE: This patient has been on cardiac medications for a couple of years. What about stopping the meds?

DR DURAND: At our national heart failure meeting, we presented data from our institution showing that when you withdraw ACE inhibitors and beta-

3.1

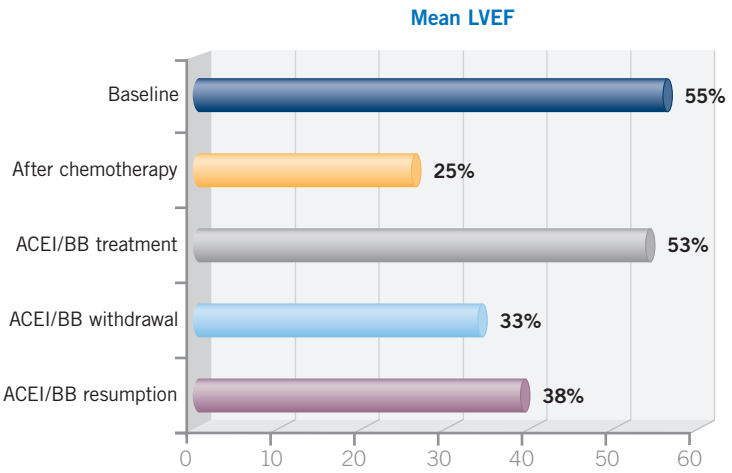
NSABP-B-31: Discontinuation of Trastuzumab Due to Asymptomatic or Symptomatic Cardiac Dysfunction by Treatment Quarter



SOURCE: Rastogi P et al. *Proc ASCO* 2007;**Abstract LBA513**.

3.2

Influence of ACE Inhibitor (ACEI) and Beta-Blocker* (BB) Therapy on Chemotherapy-Induced Cardiomyopathy



"These data suggest that patients should remain on aggressive doses of ACE inhibitors and carvedilol and that withdrawal of therapy may lead to severe cardiovascular events including death, especially in patients who have normalized left ventricular ejection fraction."

n = 8; * Carvedilol

SOURCE: Lenihan DJ et al. *J Card Fail* 2003;9(Suppl 5):77;**Abstract 281**.

blockers from patients who have anthracycline-related cardiomyopathy, their ejection fractions decline within 30 days (Lenihan 2003; [3.2]).

Tracks 8-10

DR LOVE: Mark, what is your opinion about the cardiac safety of docetaxel/carboplatin/trastuzumab (TCH) versus an anthracycline-based trastuzumab regimen?

DR PEGRAM: BCIRG 006 compared TCH to AC → docetaxel/trastuzumab (TH). TCH was significantly superior to the nontrastuzumab-containing control arm. Moreover, if you evaluate the outcome associated with TCH compared to AC → TH — even though that study design was not powered to test noninferiority between those two regimens — you see that the results are similar (Slamon 2006; [1.2, page 5]).

Because more than 1,000 patients are enrolled on each of those arms, it's likely that any difference between those arms must be trivial. So it's possible that these nonanthracycline-containing regimens with trastuzumab will be every bit as efficacious as anthracycline-based regimens with trastuzumab.

DR LOVE: If a healthy, 50- to 60-year-old patient without any cardiac risk factors asks, "What's the chance that TCH will cause a problem with my heart?" what do you say?

DR PEGRAM: You have to explain the nuances between clinically significant cardiac adverse events and asymptomatic declines in ejection fraction that might prompt one to hold trastuzumab for a month, repeat the echo and if the echo returns to normal, reintroduce trastuzumab. In terms of clinically significant cardiotoxicity, it's 0.4 percent in the TCH arm of BCIRG 006. All the other asymptomatic declines are largely reversible, and trastuzumab can be reintroduced during the course of the one year of treatment (Slamon 2006).

Track 16

DR LOVE: Can you update us on your work with the combination of trastuzumab and bevacizumab, particularly in terms of cardiac safety?

DR PEGRAM: We have completed enrollment of all 50 patients to the Phase II trastuzumab/bevacizumab trial, which was for patients with HER2-positive metastatic breast cancer in the first-line setting (Pegram 2006).

Early on in the trial, we had a patient who developed Grade IV congestive heart failure, so we conducted an audit of all the cardiac safety adverse events. We basically found a smattering of Grade I and II adverse events, none of which precluded the patients from continuing treatment on the study (3.3).

When you review the Grade I or II cardiac events more closely, you see that all of them were asymptomatic and some were judged to be Grade II because the ejection fraction was one point lower than the normal range.

3.3 Phase II Study of Trastuzumab and Bevacizumab as First-Line Therapy for 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 events by grade (number of patients)

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**.

Tracks 25-30

Case Discussion 2 (from the practice of Gracy Joshua, MD)

A 76-year-old woman underwent a mastectomy for a 2.1-cm, node-negative, ER-positive, PR-positive, HER2-negative infiltrating ductal carcinoma. She had a prior myocardial infarction and well-controlled hypertension and diabetes. Her ejection fraction as determined by MUGA scan was 50 percent. She was treated with four cycles of TC followed by anastrozole.

DR LOVE: Mark, this is an older patient with significant cardiac disease. What do we know about the safety and efficacy of adjuvant TC? Where do you think we are heading with nonanthracycline-containing regimens?

DR PEGRAM: Steve Jones has published data from US Oncology comparing four cycles of TC to four cycles of AC. The TC regimen compares favorably — it's slightly superior to four cycles of AC in terms of efficacy (Jones 2006; [1.3, page 6]). Without the anthracycline, one can anticipate an improved cardiac safety profile.

US Oncology has launched a new adjuvant trial for patients with HER2-negative, early-stage breast cancer, in which they'll compare six cycles of TC to six cycles of TAC — the so-called TC-TAC trial. The trial will directly test whether an anthracycline adds any benefit for patients with HER2-negative, early-stage breast cancer. I hope that will put this anthracycline question to rest for patients with HER2-negative disease.

DR LOVE: If a 65-year-old patient without any comorbidities asks, "What's the chance that I'm going to have a clinically significant cardiac problem over the next 20 years from four cycles of AC?" how would you answer?

DR DURAND: I'd tell her that initially the risk is two to four percent, but as far out as 20 years, I would tell her at least 10 percent, minimum.

DR PEGRAM: What struck me about the long-term follow-up data from MD Anderson (Pinder 2007) is that the incidence of cardiac abnormalities is higher after four cycles of AC than I would have thought considering long-term outcomes. The risk is significant, and it continues for a long time.

Tracks 42-44

Case Discussion 3 (from the practice of Carolyn B Hendricks, MD)

A 75-year-old woman who was treated with breast-conserving surgery and radiation therapy for Stage IIA, node-positive, hormone receptor-positive, HER2-positive breast cancer. She had a cardiac history, with medically controlled hypertension and hyperlipidemia. Her baseline ejection fraction declined from 86 percent to 40 to 45 percent after six weeks of trastuzumab.

DR LOVE: Would you consider lapatinib for this patient?

DR PEGRAM: Off study, it probably wouldn't be reimbursed. A new adjuvant study called ALTTO is being launched for women with HER2-positive, early-stage disease (3.4).

The trial has four arms — patients are randomly assigned to trastuzumab alone, lapatinib alone, the combination or the sequence of trastuzumab and lapatinib. In the meantime, off study, I probably wouldn't use lapatinib.

A considerable cardiac safety database is emerging for lapatinib-exposed patients. By all accounts, it appears to be associated with fewer cardiac adverse events than trastuzumab administered to similar patients.

3.4

Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial

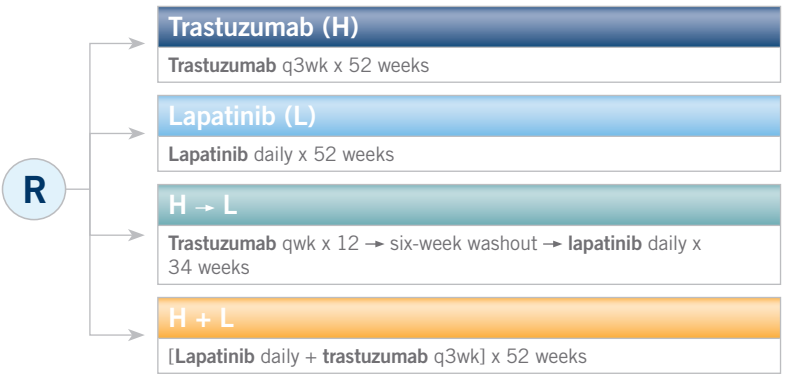
Protocol IDs: BIG 2-06, NCCTG-N063D, IBCSG 36-07; Target Accrual: 8,000

Eligibility

- HER2-positive breast cancer
- Prior treatment with at least four cycles of an approved anthracycline-based chemotherapy regimen

In STRATUM 1, patients will receive weekly paclitaxel together with the anti-HER2 targeted therapy following anthracycline-based (neo)adjuvant chemotherapy

STRATUM 2 will comprise patients who complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy



Study Contacts

Martine J Piccart-Gebhart, MD, PhD
Edith A Perez, MD

SOURCES: *Breast International Group Newsletter* Spring 2007;9(1); www.ibcsg.org; NCI Physician Data Query, December 2007.

Tracks 48-50

Case Discussion 4 (from the practice of Gracy Joshua, MD)

A 79-year-old woman who underwent lumpectomy and lymph node dissection for a 3-cm, node-positive, ER-positive, PR-positive, HER2-positive breast tumor. She has a history of diabetes, hypertension and hyperlipidemia. Her baseline ejection fraction was 83 percent. She received adjuvant AC followed by docetaxel/trastuzumab.

DR LOVE: What about the selection of adjuvant chemotherapy for a 79-year-old patient with diabetes, hypertension and hyperlipidemia?

DR PEGRAM: I wouldn't have recommended an anthracycline-based regimen for a 79-year-old. I would have chosen a nonanthracycline and something that minimizes exposure to chemotherapy. In similar cases, when I've chosen chemotherapy I've used four cycles of TC followed by trastuzumab, as in the HERA trial of sequential chemotherapy and trastuzumab (Smith 2007).

DR LOVE: Do you sequence trastuzumab after chemotherapy as a means of further protection for the heart?

DR PEGRAM: No, that's simply the way that data set was generated, and I follow that scheme. I have no doubt that you could administer TC along with trastuzumab safely. US Oncology is evaluating TC (docetaxel/cyclophosphamide) with trastuzumab. ■

SELECT PUBLICATIONS

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**

Lenihan DJ et al. **Withdrawal of ACE inhibitors and beta-blockers in cancer patients with congestive heart failure leads to severe cardiovascular adverse events.** *J Card Fail* 2003;9(Suppl 5):77;**Abstract 281**.

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**.

Pinder MC et al. **Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer.** *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

Rastogi P et al. **Five year 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* 2007;**Abstract LBA513**.

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

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In HERA, _____ percent of patients in the trastuzumab arm experienced a decrease in LVEF of at least 10 percent from baseline.**
   a. 2.3
   b. 4.4
   c. 7.4
   d. 10.5

2. **In NSABP-B-31, what was the five-year cumulative incidence of cardiac events in the AC → T paclitaxel/trastuzumab arm?**
   a. 0.9 percent
   b. 3.8 percent
   c. 5.9 percent
   d. 8.3 percent

3. **Compared to the three-year follow-up of NSABP-B-31, a significant increase in cumulative cardiac events occurred at five years.**
   a. True
   b. False

4. **In the second interim analysis of BCIRG 006, what percent of patients in the AC → TH arm developed a decrease of greater than 10 percent in LVEF?**
   a. 3.7
   b. 7.3
   c. 13.7
   d. 18.0

5. **Several important studies have shown that the benefits of anthracycline-based therapy are limited to patients with _____ disease.**
   a. Node-positive
   b. HER2-positive
   c. Both a and b
   d. None of the above

6. **The BETH trial will evaluate a trastuzumab regimen with or without _____ for patients with early breast cancer.**
   a. Bevacizumab
   b. Panitumumab
   c. Erlotinib
   d. Lapatinib

7. **Patients with HER2-positive tumors that are less than one centimeter in size should not be treated with trastuzumab.**
   a. True
   b. False

8. **Among patients who are receiving one year of adjuvant trastuzumab, the incidence of trastuzumab-related cardiotoxicity appears to peak in the second and third quarter of the year of treatment.**
   a. True
   b. False

9. **For patients who have anthracycline-related cardiomyopathy, the withdrawal of ACE inhibitors and beta-blockers does not affect their cardiac ejection fraction.**
   a. True
   b. False

10. **In BCIRG 006, the incidence of clinically significant cardiotoxicity associated with TCH is _____.**
    a. 40 percent
    b. 14 percent
    c. Four percent
    d. 0.4 percent

11. **The ALTTO trial will evaluate _____ as adjuvant therapy for women with HER2-positive, early breast cancer.**
    a. Trastuzumab
    b. Lapatinib
    c. Concurrent trastuzumab and lapatinib
    d. Sequential trastuzumab and lapatinib
    e. All of the above

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

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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
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Sharon Hunt, MD	5 4 3 2 1	5 4 3 2 1
Mark D Pegram, 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

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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