

Breast Cancer[®]

U P D A T E

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

EDITOR

Neil Love, MD

INTERVIEWS

Julie R Gralow, MD

Edith A Perez, MD

Daniel F Hayes, MD

**MIAMI BREAST CANCER CONFERENCE TUMOR PANEL:
MONOCLONAL ANTIBODIES IN THE MANAGEMENT OF
EARLY AND ADVANCED BREAST CANCER**

Joyce O'Shaughnessy, MD

George W Sledge Jr, MD

Eric P Winer, MD



Breast Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 5 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Gralow, Hayes, O'Shaughnessy, Perez, Sledge and Winer on the integration of emerging clinical research data into the management of breast cancer.

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Best of the best

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Julie R Gralow, MD

Associate Professor
Medical Oncology
University of Washington
and Fred Hutchinson Cancer
Research Center
Seattle, Washington

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Professor of Medicine
Mayo Medical School
Director, Cancer Clinical
Study Unit
Director, Breast Cancer Program
Division of Hematology and
Oncology, Mayo Clinic
Jacksonville, Florida

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Professor of Internal Medicine
Clinical Director
Breast Oncology Program
Division of Hematology/Oncology
Department of Internal Medicine
University of Michigan
Comprehensive Cancer Center
Ann Arbor, Michigan

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OF EARLY AND ADVANCED BREAST CANCER**

Joyce O'Shaughnessy, MD

Co-Director, Breast Cancer
Research Program
Baylor-Charles A Sammons
Cancer Center
US Oncology
Dallas, Texas

George W Sledge Jr, MD

Professor of Medicine
Ballve-Lantero Professor
of Oncology
Indiana University
Medical Center
Indianapolis, Indiana

Eric P Winer, MD

Director, Breast Oncology Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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UPCOMING EDUCATIONAL EVENTS

12th Annual Perspectives in Breast Cancer

October 6-7, 2006

Boston, Massachusetts

Event website: imedex.com/calendars/oncology.asp

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology

November 5-9, 2006

Philadelphia, Pennsylvania

Event website: astro.org

Chemotherapy Foundation Symposium XXIV Innovative Cancer Therapy for Tomorrow

November 8-11, 2006

New York, New York

Event website: mssm.edu/tcf

29th Annual San Antonio Breast Cancer Symposium

December 14-17, 2006

San Antonio, Texas

Event website: sabcs.org

Miami Breast Cancer Conference

February 21-24, 2007

Miami Beach, Florida

Event website: cancerconf.com

ASCO 2007 Annual Meeting

June 1-5, 2007

Chicago, Illinois

Event website: asco.org



EDITOR'S NOTE

Neil Love, MD

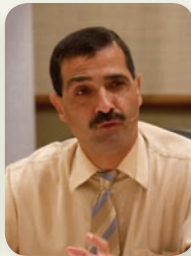
Best of the best

This issue of *Breast Cancer Update* includes contributions from four practicing medical oncologists who are frequent participants in our *Meet The Professors* audio series, in which highly astute and learned community docs present real cases to clinical investigators. Over the years, our CME group has searched for oncologists with a flair for education to assist in creating programs that interest their colleagues, perhaps the most highly informed subspecialists in contemporary medicine.

The *Breast Cancer Update* audio series usually focuses on interviews with breast cancer clinical investigators, but for the enclosed issue, we decided to infiltrate the program with our guerrilla oncology fighters, beginning with a case presentation by Dr David Dresdner, a medical oncologist from St Petersburg, Florida, who is among the elite and ever-growing band of practicing oncologists helping us shape the *MTP* series.

Dr D presents a quite scary case of a 60-year-old woman with a history of noninsulin-dependent diabetes who developed sudden and florid congestive heart failure shortly after receiving anthracycline chemotherapy in the form of dose-dense AC → paclitaxel, followed by radiation therapy to the breast.

Dr D's diagnosis, after comprehensive cardiologic and radiation oncology consultations, was anthracycline-related cardiomyopathy. The patient is currently doing well but continues to receive intensive pharmacologic cardio-



From left to right: Meet The Professors participants David M Dresdner, MD, Atif M Hussein, MD, William N Harwin, MD and Dennis A Lowenthal, MD

logic support.

I then queried clinical investigator Dr Julie Gralow about this case, and she concurred with Dr D's findings but noted the unusually early onset of CHF after anthracycline-based therapy. Our discussion then shifted to Dr Gralow's perspective on several related and intriguing presentations at the recent 2006 ASCO meeting in Atlanta on cardiac safety with adjuvant chemotherapy regimens containing anthracyclines.

MD Anderson's Dr Sharon Giordano presented SEER and Medicare data from more than 30,000 women who had full Medicare coverage for a year before and after their diagnosis of early-stage breast cancer. Extensive information on the diagnoses and treatments of these women was available from the Medicare database. The key event evaluated in this analysis was the clinical diagnosis of CHF as per Medicare coding. Mean follow-up was a little bit more than five years.

The data are complex but strongly suggest that the high baseline risk of CHF for older people is substantially increased with exposure to an anthracycline — with even greater risk in patients with comorbid conditions, including diabetes and hypertension (Figure 1). Given that these data were retrospective, it is difficult to estimate an absolute figure for the risk of clinical events in this patient population. However, selection bias in this analysis may mean that the adverse impact of anthracyclines could have been significantly underestimated.

Dr Lois Shepherd from the NCI Canada then discussed more data on our latest onco-acronym, "CRCD" (chemotherapy-related cardiac dysfunction). The patients in this prospective trial data set comparing CEF to CMF were considerably younger than those in the SEER-Medicare analysis, and the overall clinical risk of CHF was much closer to the one percent figure that is commonly described by oncologists to patients,

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COX Model: 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](#).

although asymptomatic drops in ejection fractions were much more common in patients receiving “E” (see figure 1.1, page 10). Another paper, by Dr Michele Halyard from an NCCTG adjuvant study, confirmed the apparent cardiac safety of using trastuzumab concurrently with radiation therapy to the breast and chest wall.

ASCO breast cancer program co-chair Cliff Hudis invited his colleague from Memorial Sloan-Kettering, cardiologist Dr Richard Steingart, to discuss these provocative papers. Dr Steingart had some unexpected and highly relevant thoughts, including the observation that “garden variety” CHF is usually a function of diastolic afterload related to hypertension, and therefore the ejection fraction is as likely to be normal as it is to be decreased. The bottom line is that there is much more to heart failure than measuring ejection fractions, and I, for one, walked out of this session deeply concerned that our previous sense of reassurance about the modest frequency of this toxicity may be seriously in error.

Dr Steingart’s comments, and the heightened awareness of the threat of treatment-related cardiac toxicity, highlight the potential clinical importance of several nonanthracycline-based chemotherapy regimens, including three discussed by Dr Galow that might be particularly appropriate for older patients with cardiovascular risk factors:

1. A taxane alone

CALGB-40101 is currently comparing four or six cycles of dose-dense paclitaxel to the same schedules of dose-dense AC. Of great interest is the lack of a nondose-dense control arm. In fact, all four arms seem somewhat experimental. The cardiologists are rooting for the taxanes to be equally or more effective at reducing recurrence, but no data are yet available.

2. Capecitabine

CALGB-49907 under the direction of Dr Hyman Muss is restricted to patients over age 65. This landmark study randomizes between dealer’s choice AC/CMF or capecitabine. Save your myocardium and hair, and lose the IV. Again, no data are available.

3. TC (docetaxel/cyclophosphamide)

As discussed at length on the last issue of this series by principal investigator Dr Stephen Jones, a US Oncology trial he presented at the last San Antonio meeting demonstrated that TC not only resulted in a third fewer relapses than AC but also less toxicity. This is all the more interesting in that Steve, Sid Salmon and a few other colleagues essentially invented AC, and it took three decades of clinical research to find something that might be better.

During my discussion with Dr Dresdner, he mentioned that he has used adjuvant TC about a half dozen times in his practice, mostly for patients with prior cardiac events. After the sobering experience he had with his dose-dense

patient, regimens like TC might be much more appealing for the large group of patients with diabetes, hypertension and other coexisting conditions.

Medical oncologists now wear many hats as they attempt to manage the side effects associated with new therapies. Aside from moonlighting as dermatologists charged with controlling rash induced by EGFR inhibitors and other cutaneously deforming agents, oncologists have been forced by these important ASCO data on anthracyclines, and the recent explosion of pressing cardiologic concerns in trials of adjuvant trastuzumab as discussed on this program by Dr Edith Perez, to add cardiology to their long list of clinical skills.

That's why it is so helpful to have our CME pulse on docs in practice. For example, in a premeeting telephone conference for our most recent MTP extravaganza, Dr Dresdner not only told me about his fascinating pulmonary edema nightmare but also of a 68-year-old man with breast cancer, with very symptomatic widespread bone metastases and a clear-cut response to fulvestrant. During the MTP recording session, Dr Gralow mentioned a similar case in her practice, and right then and there we had ourselves the beginning of a potentially important case series. (Send in your successes and failures with endocrine therapy of men with breast cancer, and put your rare male patients with mets on SWOG study S0511 evaluating the combination of goserelin and anastrozole.)

The other three community docs featured on this program are Dr Bill Harwin, my former U of Miami colleague who now leads a group of 40-plus medical oncologists in Southwest Florida, Dr Atif Hussein, director of the cancer program at Hollywood Memorial Hospital, and Dr Dennis Lowenthal, one of the many non-Floridians who jet down to South Florida to stump the professors. Dr Lowenthal is from "Joyzee."

Recently, Bill and Atif bravely volunteered for a superintense "mini-MTP" (three or four community docs and three faculty members) on renal cell cancer, a disease that used to be simple in that we didn't have a whole lot to offer and now suddenly seems complicated and highly interesting with maybe a unique susceptibility to anti-angiogenic therapy, whatever that is.

At the end of this session with a brilliant trio of renal investigators (Drs Ronald Bukowski, Nicholas Vogelzang and Janice Dutcher), Bill, Atif, Charles Henderson of Atlanta, Bill's colleague in progress Lowell Hart, and I were slack-jawed at how much great new stuff we had heard that afternoon.

The enthusiastic response our CME group has received to case-based sessions encouraged us to bring a bit of this into our *Update* series. For the last couple of years, we have used *Breast Cancer Update's* third audio CD to do some "Phase I-II" educational experimentation, and on this program we have included the edited proceedings of an "eat and learn" luncheon that took place at the 2006 Miami Breast Cancer Conference.

For this unique event, we adapted the Meet The Professors format and invited Bill, Atif and Dennis to present vexing cases from their practices that fit within the meeting's theme of Monoclonal Antibody Therapy for Breast

Cancer, a title that would have seemed like science fiction 10 years ago. The discussion was recorded in front of about 800 starving surgeons and med oncs who swallowed lasagna and choice content in large and sometimes audible gulps and dish clacks on the audio track.

Our faculty members Drs Joyce O'Shaughnessy, George Sledge and Eric Winer discuss what we do and don't know about monoclonal antibody therapy of breast cancer, not only that mysterious chameleon, bev, but also trastuzumab as adjuvant treatment of women with HER2-positive tumors.

Dr Lowenthal began the program by describing a 46-year-old woman with a triple-negative tumor that recurred in the chest wall and mediastinum less than three years after completing six cycles of adjuvant CAF.

Unable to obtain bevacizumab from the patient's insurer, Dr Lowenthal started paclitaxel alone, but after less than two months, the disease was progressing rapidly. At the time of the luncheon, the patient had just begun docetaxel, capecitabine and bevacizumab — a creative and perhaps controversial decision — but, on the other hand, this patient's situation was immediately life threatening.

Dr Harwin then presented another vexing metastatic case that demonstrates the many and varied communication skills required in medical oncology community practice. The patient is a 51-year-old woman Bill treated with bevacizumab and paclitaxel about 10 days after Kathy Miller presented the E2100 data on this regimen at ASCO in May 2005. The patient had extensive bulky liver metastases but experienced a dramatic tumor response to treatment.

At that point, the big bad world of reimbursement reared its unattractive head. Specifically, after paying the first tab, the patient's insurance company suddenly realized they were swallowing some serious charges and began questioning the use of bevacizumab.

Bill effectively described to these very interested bean counters the dramatic improvements in the patient's well-being and the rapid reduction in size of multiple 6- to 7-cm hepatic lesions seen on CT scan, and the payer became silent. Of some amusement was that when the insurer asked to be sent the ASCO abstract discussing the E2100 trial, Bill had nothing to send because the presentation was a late, late, late breaker that was abstract free.

To further challenge the faculty, the Miami luncheon then switched over to the very gratifying issue of adjuvant systemic therapy for patients with HER2-positive tumors. Dr Hussein presented a 44-year-old patient with a subcentimeter (0.8 centimeter) node-negative tumor that was ER-positive, PR-positive and HER2-positive.

Triple-positive, node-negative breast cancer is not uncommon and is perhaps the most controversial patient phenotype in the current management of early breast cancer. The cool thing about Atif's case is that the patient actually participated in BCIRG trial 006, which allowed for the inclusion of tiny

node-negative tumors because Dennis Slamon believes in biology.

This woman was randomly assigned to receive the supposedly noncardiotoxic TCH (docetaxel/carboplatin/trastuzumab) regimen but had her trastuzumab held briefly for a minor drop in ejection fraction that then returned to normal and stayed there.

Bill presented a 33-year-old mom with another “triple-positive,” node-negative tumor. The tumor size (1.7 centimeters) made chemotherapy and trastuzumab a given, but what had the satiated Miami crowd talking among themselves as they limped back into the afternoon session was the potential for new endocrine treatment options for this patient subset.

And so it goes. Sincere thanks to Atif, Bill, David, Dennis and the many other highly informed and thoughtful people in practice who keep CME people like me honest and set a superior standard of patient care for fellows in training to emulate.

— Neil Love, MD
NLove@ResearchToPractice.net
August 18, 2006

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Practicing Medical Oncologists Who Have Participated in Recent Meet The Professors Programs

Howard R Abel, MD Fort Lauderdale, FL	Lowell L Hart, MD, FACP Fort Myers, FL	Kenneth K Ng, MD Rockville Centre, NY
Mary Ann K Allison, MD Henderson, NV	Cheryl A Harth, MD Dallas, TX	William G Reeves, MD Youngstown, OH
Alan B Astrow, MD Brooklyn, NY	William N Harwin, MD Fort Myers, FL	Kert D Sabbath, MD Bethany, CT
Samuel N Bobrow, MD New Haven, CT	Charles A Henderson, MD Atlanta, GA	Michael A Schwartz, MD Miami Beach, FL
Patricia A De Fusco, MD Hartford, CT	Carolyn B Hendricks, MD Bethesda, MD	Leonard J Seigel, MD Fort Lauderdale, FL
Margaret A Deutsch, MD Raleigh, NC	Atif M Hussein, MD Hollywood, FL	Sheryl R Simon, MD Sewickley, PA
Leon H Dragon, MD Highland Park, IL	Sobha Kurian, MD Morgantown, WV	Mark A Taylor, MD Savannah, GA
David M Dresdner, MD St Petersburg, FL	Michel E Kuzur, MD Nashville, TN	Brenda L Towell, MD Austin, TX
Allan Freedman, MD Snellville, GA	Dennis A Lowenthal, MD Short Hills, NJ	Michael B Troner, MD Miami, FL
Roman A Gastesi, MD Fort Lauderdale, FL	Susan L Luedke, MD St Louis, MO	Jeffrey Vacirca, MD East Setauket, NY
Philip Glynn, MD Springfield, MA	Scott D Lunin, MD Pt Charlotte, FL	Paul L Weinstein, MD Stamford, CT
Stephen A Grabelsky, MD Boca Raton, FL	Noor M Merchant, MD Sebastian, FL	Richard S Zolkowitz, MD Norwalk, CT



INTERVIEW

Julie R Gralow, MD

Dr Gralow is Associate Professor of Medical Oncology at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington.

CD 1, Tracks 3-18

- | | | | |
|-----------------|--|-----------------|--|
| Track 3 | Cardiomyopathy associated with anthracycline-based chemotherapy | Track 11 | Monitoring and managing bone loss in patients on adjuvant aromatase inhibitors |
| Track 4 | Selection of an adjuvant chemotherapeutic regimen | Track 12 | Risk of fracture associated with aromatase inhibitors for patients with normal bone density |
| Track 5 | CALGB-49907: AC or CMF versus capecitabine for elderly patients | Track 13 | Tolerability and safety of aromatase inhibitors versus tamoxifen |
| Track 6 | Potential psychosocial benefits of adjuvant capecitabine | Track 14 | Efficacy and tolerability of lapatinib |
| Track 7 | Current barriers to completing clinical trials | Track 15 | Future directions in lapatinib clinical use and research |
| Track 8 | Efficacy and tolerability of docetaxel/cyclophosphamide (TC) versus AC | Track 16 | Time course for initiating therapy with letrozole following five years of adjuvant tamoxifen |
| Track 9 | Incidence of bone loss among patients with normal bone density in the ATAC trial | Track 17 | Duration of adjuvant therapy with an aromatase inhibitor |
| Track 10 | Selection of up-front adjuvant hormonal therapy | Track 18 | Importance of genomic profiling in the future of breast cancer management |

Select Excerpts from the Interview

CD 1, Track 3

► **DR LOVE:** What was your take on the data presented at the 2006 ASCO meeting on anthracycline-related cardiac toxicity?

► **DR GRALOW:** Lois Shepherd presented long-term follow-up data from the NCIC-CTG-MA5 trial comparing CEF versus CMF (Shepherd 2006). Clearly cardiomyopathy is real, and it occurs more often in patients who receive anthracycline-containing regimens (1.1).

The trials remind us that we need to consider toxicities when we're offering

1.1

Ten-Year Update of NCIC-CTG-MAS: Incidence of LVEF <50 Percent

Time	CEF		CMF		p-value
	N	<50%	N	<50%	
0	354	0	360	0	—
Six months	291	7%	296	4%	0.21
12 months	270	9%	286	4%	0.01
36 months	185	9%	172	5%	0.16
60 months	139	17%	144	2%	<0.001

SOURCE: Shepard LE et al. *Proc ASCO* 2006: [Abstract 522](#).

patients only a couple of percentage points improvement in survival. For patients at low risk, that small improvement has to be weighed against serious toxicities such as congestive heart failure and acute leukemia, even though they are rare.

► **DR LOVE:** How would you counsel a patient in the adjuvant setting regarding her risk of developing a doxorubicin-related cardiomyopathy, and has that changed since the ASCO meeting?

► **DR GRALOW:** For patients receiving four doses of doxorubicin at 60 mg/m², in the past I would have quoted a one percent or less chance of developing symptomatic cardiomyopathy. After ASCO, I would tell patients that with long-term follow-up, the risk could be as high as a couple of percentage points, even with the 240 mg/m² dose and especially when increasing doxorubicin to 360 mg/m², as they have done in some of the studies.

Clearly, hypertension and other risk factors for cardiac disease in general are risk factors for chemotherapy-related heart toxicity, and although everything was done correctly with Dr Dresdner's patient (1.2) in that the ejection fraction was checked before treatment, standard doses were used and the cumulative dose was quite low, this case illustrates that occasionally cardiomy-

1.2

Case Presentation: Acute Pulmonary Edema in a Patient Who Received Adjuvant Anthracycline-Based Chemotherapy (from the practice of David Dresdner, MD)

This is a 60-year-old woman with a history of diabetes who received dose-dense doxorubicin/cyclophosphamide, paclitaxel and anastrozole for ER-positive breast cancer with two positive nodes. The patient had no history of cardiac problems and experienced no problems while on chemotherapy. However, while on anastrozole after receiving radiation therapy, she developed pulmonary edema and heart failure. The patient's pretreatment ejection fraction was 58 percent, and it had dropped to 28 percent. She was treated medically, and 15 months later her ejection fraction had recovered to 50 percent.

SOURCE: *Breast Cancer Update* Audio Program Vol 5, Issue 5, 2006. **CD 1, Track 2.**

opathy can happen even in a patient who does not appear to be at high risk.

- ▶ **DR LOVE:** What do we know about the clinical course of anthracycline-related cardiomyopathy, particularly in the adjuvant setting?
- ▶ **DR GRALOW:** Asymptomatic drops in ejection fractions certainly do occur while patients are on therapy, but symptomatic congestive heart failure doesn't usually occur until after the chemotherapy is completed. It can be a couple of years later or even out to seven years. We do know from the trastuzumab trials that many drops in ejection fraction with AC prevented patients from receiving a taxane and trastuzumab.
- ▶ **DR LOVE:** In your practice, for which patients with HER2-negative disease receiving an anthracycline do you obtain pretreatment ejection fractions?
- ▶ **DR GRALOW:** In general, I always obtain an ejection fraction on patients over the age of 60. I don't routinely do so for younger patients with no known risk factors, although that is variable because I do discuss with patients the risk of cardiac toxicities, and some want to know their baseline measurement.

I don't generally repeat the ejection fraction for asymptomatic patients unless they are on trastuzumab.

CD 1, Track 4

▶ **DR LOVE:** How do you feel about a nonanthracycline-based regimen for patients with node-negative disease in the clinical setting?

▶ **DR GRALOW:** I would prefer not to have to give an anthracycline. The risk of myelodysplasia, acute leukemia and congestive heart failure with anthracyclines are all real concerns, especially for patients with node-negative disease who are receiving only a small benefit from chemotherapy.

I'm not a huge fan of CMF, although some of my colleagues still feel there is a time and place for this regimen. We have some nice ongoing studies investigating replacing anthracyclines, and many trials suggest that some better regimens exist for this group of patients as a whole.

A subpopulation that does just fine with CMF probably exists, but I also wonder if that's not a group that would also do just as well with endocrine therapy alone, especially with better endocrine therapy.

- ▶ **DR LOVE:** What adjuvant studies are currently evaluating nonanthracycline regimens?
- ▶ **DR GRALOW:** CALGB has a four-arm trial, 40101, examining AC versus paclitaxel for patients with only one to three positive nodes or node-negative disease (1.3).

The AC and paclitaxel are given every two weeks with growth factors for either four cycles or six cycles. That's an important study, evaluating whether we can give these patients only a taxane.

In the older population, Hy Muss is conducting the CALGB-49907 trial (1.4), which randomly assigns women older than age 65 to single-agent capecitabine versus AC or CMF, the physician's choice.

I believe these are both great studies that may prove that a single agent without a lot of CHF and leukemia risk is an appropriate substitute for standard chemotherapy regimens, especially for women in the lower-risk group.

1.3

Phase III Randomized Study of Two Different Schedules of Adjuvant Cyclophosphamide and Doxorubicin (AC) versus Paclitaxel in Operable Breast Cancer

Protocol IDs: CALGB-40101, NCT00041119
Target Accrual: 4,646 (Open)

Eligibility
Operable, invasive breast cancer
0-3 positive axillary lymph nodes



- AC q2wk x 4 cycles
- AC q2wk x 6 cycles
- Paclitaxel q2wk x 4 cycles
- Paclitaxel q2wk x 6 cycles

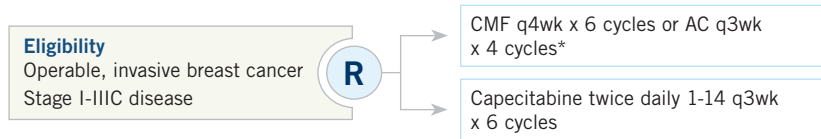
Study Contact:
Cancer and Leukemia Group B
Lawrence Shulman, MD
Tel: 866-790-4500

SOURCE: NCI Physician Data Query, July 2006.

- ▶ **DR LOVE:** What do you think CALGB-49907 will show with regard to toxicities and efficacy?
 - ▶ **DR GRALOW:** Initially the capecitabine was given at a full dose, and two early deaths occurred among the patients on capecitabine. One clearly looked like a DPD deficiency, and the other probably was the same, although it took a little longer for the symptoms to develop.
- At that point, some safeguards were added and we were allowed to reduce the dose. We have not had a problem with deaths or serious issues subsequently.
- The trial is designed to evaluate whether capecitabine is superior, and it has a real chance of showing that. Capecitabine as a single agent in the metastatic setting is a great drug, so it could win.
- In terms of the long-term toxicities, I expect the patients who receive AC will have some cardiac toxicity and potentially leukemia at some point in their lifetime. Even though this study involves an older population, we're living so long now that women who are 65 could live another three decades.

Phase III Adjuvant Study of Cyclophosphamide/Methotrexate/ Fluorouracil (CMF) or Cyclophosphamide/Doxorubicin (AC) versus Capecitabine in Elderly Women

Protocol IDs: CALGB-49907, CTSU, NCT00024102, CAN-NCIC-CALGB-49907, ECOG-CALGB-49907, SWOG-CALGB-49907
Target Accrual: 600-1,800 (Open)



* Patients on this arm with insufficient left ventricular ejection fraction (LVEF) are assigned to CMF. Patients with normal LVEF are assigned to either CMF or AC based on physician/patient choice.

Study Contacts:

Cancer and Leukemia Group B
Hyman Muss, MD
Tel: 800-358-1144

Southwest Oncology Group
Julie Gralow, MD
Email: pink@u.washington.edu

Eastern Cooperative Oncology Group
Antonio Wolff, MD
Tel: 410-614-4192

NCIC-Clinical Trials Group
Tamara Shenkier, MD
Tel: 800-663-3333

SOURCE: NCI Physician Data Query, July 2006.

CD 1, Track 6

▶ **DR LOVE:** If capecitabine proves to be at least equivalent to AC or CMF, will you use it for younger women or only for older patients?

▶ **DR GRALOW:** I'm much more likely to use a gentler chemotherapy regimen for older patients, and I use capecitabine for patients who have some comorbidities or a little lower performance status. Otherwise, I'm not sure I'm ready to make that leap for my younger patients without further data comparing it to an anthracycline/taxane combination, for example.

A group of women might exist who would prefer to avoid the side effects of standard chemotherapy, specifically someone who wants to keep working and doesn't want to lose her hair because she doesn't want people to know she's on treatment and doesn't want the lengthy appointments in the infusion room. It's an interesting option, and I'm optimistic that it will be a choice for some of our patients in the near future.

CD 1, Track 8

▶ **DR LOVE:** How do you feel about the docetaxel/cyclophosphamide (TC) data presented by Steve Jones at the San Antonio meeting in 2005 (Jones 2005)?

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 66 Months)

	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: 0.47-1.03)			
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	0.131

Hazard ratios < 1 indicate values in favor of TC.

“Based on this trial, TC should now be considered a standard nonanthracycline adjuvant regimen for operable breast cancer.”

Toxicities (Grades III/IV)	TC	AC	p-value
Neutropenia	59%	55%	NS
Neutropenic fever	6%	3%	0.03
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01
Congestive heart failure	0	0	NS

“TC was associated with more low-grade myalgias, arthralgias, edema and febrile neutropenia. AC was associated with significantly more nausea and vomiting.”

SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 40](#).

▶ **DR GRALOW:** That presentation was striking (1.5). The trial’s toxicity data showed that TC wasn’t substantially more toxic than AC (1.5). I’ve never prescribed TC, but if I were considering AC for a patient, TC would be a reasonable alternative. No survival advantage appeared that was significant, but a disease-free survival advantage was evident, and it was clinically relevant.



CD 1, Track 9

▶ **DR LOVE:** Can you discuss the five-year results regarding the effect of anastrozole on bone mineral density from the ATAC trial?

▶ **DR GRALOW:** The five-year bone density substudy of the ATAC trial was very interesting. The fracture rates on that trial were approximately 11 percent in the anastrozole arm and about 7.5 percent in the tamoxifen arm at 68 months of follow-up (Howell 2005).

However, we were trying to determine who should receive bisphosphonates up front and how often we should follow bone density studies. I believe the

ATAC data that Rob Coleman presented at ASCO showed that not everyone needs a DEXA scan every year or a bisphosphonate up front (Coleman 2006; [1.6]).

1.6

ATAC Substudy: Effect of Anastrozole and Tamoxifen on Bone Mineral Density (BMD)

Median percentage change in BMD from baseline to 1, 2 and 5 years

Year	Lumbar spine BMD		Total hip BMD	
	Anastrozole (n = 81)	Tamoxifen (n = 86)	Anastrozole (n = 81)	Tamoxifen (n = 86)
1 year	-2.2	1.4	-1.5	0.9
2 years	-4.0	2.1	-3.9	1.2
5 years	-6.1	2.8	-7.2	0.7


“For patients with data at baseline, 2, and 5 years, the rate of loss of lumbar spine BMD in the anastrozole group was significantly less from 2 to 5 years than from baseline to 2 years (mean difference in annual rate of change 0.0113, 95% CI 0.006, 0.017; $p = 0.0002$), but there was no evidence of slowing down in the loss of total hip BMD. Five patients with osteopenia at baseline developed osteoporosis on treatment with anastrozole (4) or tamoxifen (1). No patients with normal BMD at baseline became osteoporotic at 5 years.”

SOURCE: Coleman RE, on behalf of the ATAC Trialists’ Group. **Effect of anastrozole on bone mineral density: 5-year results from the ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial.** *Proc ASCO 2006*; [Abstract 511](#).

What was surprising to me but very reassuring was that none of the patients who started the ATAC trial with a normal bone mineral density — a T-score better than minus one — were osteoporotic after five years of treatment, although approximately 50 percent had become osteopenic.

We expect about a two to three percent bone loss during the five years simply based on aging, but in the tamoxifen arm, approximately 15 to 20 percent of the patients went from normal to osteopenic, and the rate was 50 percent for patients who received anastrozole.

Aging happens even to the best of us, but I believe these data show us that if the patient started with a normal bone mineral density, her chance of becoming osteoporotic after five years as a result of receiving an aromatase inhibitor in that study was zero.

 **CD 1, Track 16**

► **DR LOVE:** Can you discuss the updates on the endocrine switching trials presented at the 2006 ASCO meeting?

► **DR GRALOW:** The aromatase inhibitors continue to be an evolving story, with the first survival differences now being reported. The IES and ARNO 95

trials show a benefit to the patients who switched to an aromatase inhibitor (Coombes 2006; Kaufman 2006).

The question becomes whether priming occurs with tamoxifen or whether efficacy is improved because the two drugs are not totally cross reactive in terms of resistance.

► **DR LOVE:** Is it possible a more favorable group of patients with more endocrine-responsive tumors make it to two years?

► **DR GRALOW:** Yes. All of these are potential reasons for why we're seeing a survival advantage first in the switching trials rather than with up-front aromatase inhibitors.

We saw an update of the MA17 trial examining the patients who originally received a placebo after five years of tamoxifen as opposed to letrozole and then at about 30 months, when the study was unblinded, were offered letrozole (Robert 2006). Approximately two thirds of those patients chose letrozole, and they tended to be a higher-risk group.

Those patients had an average gap of 30 months without any endocrine therapy. Despite that and the fact that they were a good eight years out from their diagnosis, a reduction appeared across the board in every type of breast cancer recurrence — contralateral, in-breast and distant. It's impressive.

We saw the updated analysis for the MA17 trial at the San Antonio meeting in 2005 (Goss 2005), and at that point I began to at least offer patients the option of going back on an endocrine agent if they'd been off everything for a couple of years, especially if they were at high risk.

► **DR LOVE:** How long off tamoxifen or how long past her breast cancer diagnosis are you now willing to treat someone? If you saw a patient who was treated 10 years ago, would you discuss this option?

► **DR GRALOW:** Probably not. Although it might offer some benefit 10 years later, the duration off therapy in the MA17 trial was approximately 30 months, so I consider restarting endocrine therapy for patients up to three years off treatment. That's arbitrary, but you have to pick some time period. ■

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Coleman RE, on behalf of the ATAC Trialists' Group. **Effect of anastrozole on bone mineral density: 5-year results from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Proc ASCO* 2006;[Abstract 511](#).

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Jones SE et al. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005;23(24):5542-51. [Abstract](#)

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INTERVIEW

Edith A Perez, MD

Dr Perez is Professor of Medicine at the Mayo Medical School, Director of the Cancer Clinical Study Unit and Director of the Breast Cancer Program in the Division of Hematology and Oncology at Mayo Clinic in Jacksonville, Florida.

CD 1, Tracks 19-26 — CD 2, Tracks 1-14

CD 1

- Track 19 Introduction
- Track 20 Impact of adjuvant trastuzumab data on breast cancer management
- Track 21 Importance of waiting for definitive clinical trial data before using an untested therapy
- Track 22 Rationale for combined analysis of NCCTG-N9831 and NSABP-B-31 adjuvant trastuzumab trials
- Track 23 Design and results of NSABP-B-31 and NCCTG-N9831
- Track 24 Incidence of brain metastases in trials of adjuvant trastuzumab
- Track 25 Similarities and differences between the HERA trial and the combined NSABP/NCCTG analysis
- Track 26 Benefit of concurrent versus sequential administration of chemotherapy and trastuzumab observed in NCCTG-N9831

CD 2

- Track 1 BCIRG 006: Adjuvant trastuzumab with a nonanthracycline-containing regimen
- Track 2 Schedule of adjuvant trastuzumab following initial chemotherapy

- Track 3 Incidence of false-positive HER2 results with FISH testing
- Track 4 Potential correlations between cMYC overexpression and response to trastuzumab
- Track 5 Differences in eligibility criteria and definition of cardiac events among adjuvant trastuzumab trials
- Track 6 Incidence of cardiac toxicity with adjuvant chemotherapy and trastuzumab
- Track 7 Clinical use of adjuvant docetaxel/carboplatin/trastuzumab (TCH)
- Track 8 Dose-dense AC → paclitaxel in combination with adjuvant trastuzumab
- Track 9 Delayed adjuvant trastuzumab
- Track 10 Current role of adjuvant trastuzumab monotherapy
- Track 11 Adjuvant trastuzumab for patients with node-negative disease
- Track 12 Future NCCTG adjuvant trial for patients with HER2-positive disease
- Track 13 Potential benefit of combining lapatinib and trastuzumab
- Track 14 Role of trastuzumab in the management of ER-positive, HER2-positive disease

Select Excerpts from the Interview

CD 1, Track 23

► **DR LOVE:** Can you summarize the key findings from the combined analysis of NSABP-B-31 and NCCTG-N9831?

► **DR PEREZ:** With a median follow-up of two years, the data demonstrated a significant — not only statistical but clinical — improvement in disease-free, distant disease-free and overall survival for the patients who were assigned to receive concurrent paclitaxel/trastuzumab compared to those assigned to paclitaxel alone.

Another interesting aspect, which has been demonstrated in the other trastuzumab trials, is that the benefit of adding trastuzumab applied to all subgroups of patients with breast cancer. The benefit was irrespective of tumor size, nodal status or estrogen-receptor status (Romond 2005).

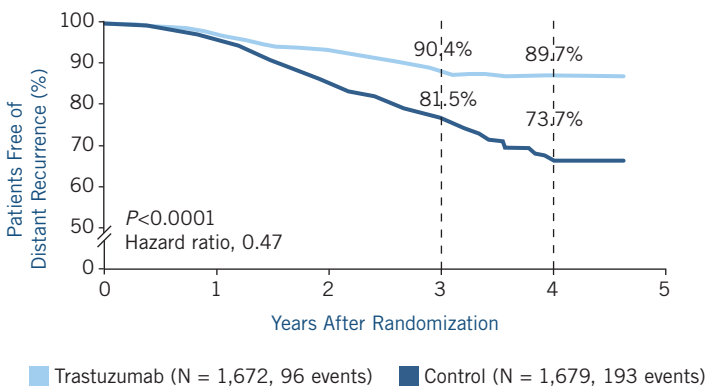
► **DR LOVE:** The distant disease-free survival curve from the combined analysis was very striking (2.1). What do you think this means?

► **DR PEREZ:** Dramatic — that’s the best word I can use — although not unexpected in terms of showing a difference. What’s unexpected is the magnitude of the difference. A clear benefit is irrefutable, even with this short median follow-up. This is important for patients and physicians because many times patients or physicians or regulatory agencies say, “In the adjuvant setting, you need to wait 10 or 20 years to make a decision about therapy based on the ultimate outcome.”

In these studies, even with the short median follow-up, the improvements in disease-free, overall and distant disease-free survival (2.2) are so dramatic that we cannot wait if we want to be ethical in our approach to patients. It is my

2.1

Distant Disease-Free Survival: Combined Analysis of NSABP-B-31 and NCCTG-N9831



Kaplan-Meier Estimates of Freedom from Distant Recurrence. The hazard ratios are for the comparison of the trastuzumab group with the control group.

SOURCE: With permission. Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. Copyright © 2005 Massachusetts Medical Society. All rights reserved. [Abstract](#)

belief that the difference in survival we have observed so far, which is already statistically significant, will increase in the future.

► **DR LOVE:** It was interesting that the distant disease-free survival curve looked flat at around 90 percent for the trastuzumab arm (2.1).

► **DR PEREZ:** Yes. One of the things we are looking at is the hazard ratio over time. It appears trastuzumab is working very quickly in terms of preventing relapses in these patients with this aggressive type of breast cancer. Their relapses are reaching a plateau, although we have to be careful because the follow-up is short. However, in the control arm, the relapses continue occurring at a higher rate.

2.2

Combined Analysis of NSABP-B-31 and NCCTG-N9831

“The addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide reduced the rates of recurrence by half among women with HER2-positive breast cancer. The absolute decreases in distant recurrence were 8.8 percentage points after three years and 15.9 percentage points after four years, although the latter value had a wide confidence interval (11.1 to 20.8 percentage points). The reduction was similar among women with hormone-receptor-negative tumors and women with hormone-receptor-positive tumors. No subgroups that did not appear to benefit from trastuzumab therapy were identified.... The addition of trastuzumab reduced the mortality rate by one third ($P = 0.015$). Among eligible patients who continued treatment after doxorubicin and cyclophosphamide and who were HER2-positive on central testing, the relative reduction in the mortality rate associated with trastuzumab was 39 percent ($P = 0.01$).”

SOURCE: Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. [Abstract](#)

CD 1, Track 25

► **DR LOVE:** Can you discuss the HERA trial?

► **DR PEREZ:** HERA is an important trial that is complementary to the studies we conducted in the United States. The HERA investigators conducted a three-arm trial in which trastuzumab was always administered sequentially to chemotherapy and radiation therapy.

The three arms included chemotherapy/radiation therapy as per standard of care, another arm that allowed trastuzumab for one year and another arm that allowed trastuzumab for two years. In that trial, trastuzumab was administered once every three weeks (Piccart-Gebhart 2005), whereas in our studies, we used it once per week (Romond 2005).

Some real issues related to HERA are important for clinical practice. Only about 26 percent of the patients in HERA received both anthracyclines and taxanes in the adjuvant setting (2.3). Therefore, the chemotherapy administered was quite different from the chemotherapy we administered in the US studies. About six percent of patients didn't even receive anthracyclines

(Piccart-Gebhart 2005; [2.3]). We need to continue following the curves, in terms of outcomes for the HERA trial.

I'm concerned that despite 32 percent of the patients enrolled in HERA having node-negative breast cancer, which would have led, in my opinion, to a better ultimate outcome for patients in the control arm, it appears that the patients in the control arm of the HERA trial did a little worse than the patients in the control arm of the US studies.

This may be a reflection of the differential outcomes for patients based on the country in which they were treated. It may also be that chemotherapy, especially the use of anthracyclines and taxanes, plays an important role in the setting of HER2-positive breast cancer. Seventy-four percent of the patients in HERA did not receive taxanes (Piccart-Gebhart 2005).

► **DR LOVE:** For those who did receive taxanes — and, of course, now we're getting into smaller numbers and subgroups — the effect of trastuzumab didn't seem to be as great.

► **DR PEREZ:** That's a very good point, which has been missed by many people. This is critically important, because NCCTG-N9831 did not show a dramatic benefit with the use of trastuzumab in a sequential fashion following chemotherapy (Perez 2005).

Our data are not that dissimilar from the data in the HERA study for the patients who received both anthracyclines and taxanes.

2.3

HERA Trial: Type of Adjuvant or Neoadjuvant Chemotherapy Used

	Trastuzumab for 1 year (n = 1,694)	Observation (n = 1,693)
No anthracycline	6.0%	6.1%
Anthracycline, no taxane	67.9%	68.3%
Anthracycline and taxanes	26.0%	25.6%

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

CD 1, Track 26

► **DR LOVE:** Can you review what NCCTG-N9831 showed in terms of concurrent versus sequential trastuzumab?

► **DR PEREZ:** Although we did not plan to conduct an analysis this early, we have approximately 25 percent of the events required to be firm about the statistical conclusions. We found, statistically, a better disease-free survival rate for patients who received trastuzumab concurrently with paclitaxel compared to those who received trastuzumab at the completion of paclitaxel (Perez 2005; [2.4]).

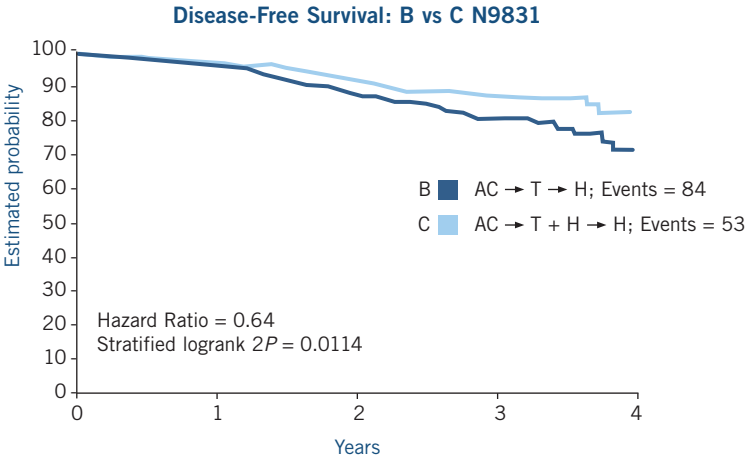
Based on our data and this important trend, we recommend that patients receive concurrent trastuzumab with a taxane as adjuvant therapy for HER2-positive breast cancer.

▶ **DR LOVE:** How can you make this conclusion with only a quarter of the events that you originally were targeting for this analysis?

▶ **DR PEREZ:** We still reached a nominal p -value for the difference between the concurrent and sequential arms. At this time, to be strict from the statistical standpoint, we have a strong trend showing that concurrent is better than sequential (Perez 2005; [2.4]). But again, it follows the data that exist both in preclinical models and the metastatic setting.

2.4

NCCTG-N9831: Disease-Free Survival for Concurrent versus Sequential Trastuzumab



Number of patients followed

B	842	501	285	162	20
C	840	520	285	178	17

SOURCE: With permission. Perez EA. **Further analysis of NCCTG-N9831.** Presentation. ASCO 2005. Late-Breaking Scientific Symposium. No abstract available

CD 2, Track 1

▶ **DR LOVE:** What are your thoughts about BCIRG trial 006?

▶ **DR PEREZ:** BCIRG 006 evaluated AC followed by docetaxel, AC followed by docetaxel with concurrent trastuzumab, and a third arm without an anthracycline — specifically the TCH regimen, a combination of docetaxel, carboplatin and trastuzumab. The results, as presented at the 2005 San Antonio Breast Cancer Symposium, demonstrated a better outcome for the two trastuzumab-containing arms compared to the control arm (Slamon 2005), which was

similar to what we saw in the other studies.

I see an important trend in benefit with AC followed by docetaxel/trastuzumab compared to TCH. Specifically, three-year disease-free survival was 86 percent for the patients who were assigned to AC followed by docetaxel/trastuzumab versus 80 percent for those assigned to TCH (Slamon 2005).

Based on the results from BCIRG 006, we can say that no statistical difference exists between AC followed by docetaxel/trastuzumab and TCH. However, this trend should be taken into consideration when counseling patients. At this time, I would not favor TCH over an anthracycline/taxane/trastuzumab regimen.

CD 2, Track 5

► **DR LOVE:** Can you summarize the cardiac risk associated with trastuzumab-containing regimens?

► **DR PEREZ:** The cardiac side effects associated with trastuzumab are minimal compared to its efficacy in terms of disease-free and overall survival. At the same time, we take cardiac risk very seriously, because we would like to administer therapies that have no side effects. However, we cannot forget the tremendous improvement in the lives of patients that we have achieved with the use of trastuzumab.

I would like people to remember that it is not appropriate to do cross-study comparisons related to cardiac toxicity. The eligibility, based on age, and the definition of cardiac toxicity varied between the different trials. So it is dangerously incorrect to put tables together comparing the cardiac toxicity in BCIRG 006, HERA, NCCTG-N9831 and NSABP-B-31.

For NSABP-B-31, NCCTG-N9831 (Romond 2005) and HERA (Piccart-Gebhart 2005), we did not have an upper age limit for enrollment. In BCIRG 006, patients had to be 70 years old or younger (Slamon 2005). In the FinHER trial, patients had to be younger than 66 years of age (Joensuu 2006).

If we look at the enrollment according to left ventricular ejection fraction (LVEF) in NSABP-B-31 and NCCTG-N9831, the baseline LVEF had to be above the lower limit of normal (Romond 2005) or above 50 percent, whereas in HERA it had to be greater than 55 percent (Piccart-Gebhart 2005).

Additionally, let's look at the definition of cardiac events. In the NCCTG-N9831 trial, NSABP-B-31 and BCIRG 006, if a patient developed one episode of decreased LVEF, that patient was counted in that group. In HERA, patients had to have a persistent decrease. So if the patient had only one decrease of LVEF, she was not counted in the group who developed decreases in LVEF.

Another important factor with HERA is that they divided patients with congestive heart failure into two groups — a mild and a severe group (Piccart-Gebhart 2005). When we reported our data from NCCTG-N9831, we

combined the mild and severe cases. It's going to be very important for us to compare apples to apples. We had a meeting with the cardiologists from HERA, NSABP-B-31 and BCIRG 006, and we're trying to come up with common definitions of cardiac toxicity.

CD 2, Track 6

► **DR LOVE:** What would you tell a patient who asks, “What is the chance I’m going to have a serious cardiac event with trastuzumab?”

► **DR PEREZ:** It’s about three percent. We’re finding out that this three-percent incidence appears to plateau. No differences appear between years two and three in terms of the incidence of cardiac toxicity (Tan-Chiu 2005). It’s specifically 3.5 percent in the AC followed by paclitaxel/trastuzumab arm of NCCTG-N9831. I believe most of the cardiac toxicity events are appearing quite early, but follow-up will be needed. The majority of these patients get better quickly.

► **DR LOVE:** What would you say about cardiac safety to a patient who’s considering TCH?

► **DR PEREZ:** In BCIRG 006, no statistical difference in cardiac toxicity appeared between TCH and AC followed by docetaxel/trastuzumab. I believe in terms of cardiac toxicity, either regimen is pretty safe. I would not favor one over another, based on the information presented by Dr Slamon at San Antonio (Slamon 2005). ■

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

Perez EA. **Advances in monoclonal antibody therapy for breast cancer: Further analysis of NCCTG-N9831.** Presentation. ASCO 2005. Late-Breaking Scientific Symposium. No abstract available

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INTERVIEW

Daniel F Hayes, MD

Dr Hayes is Professor of Internal Medicine and Clinical Director of the Breast Oncology Program of the Division of Hematology/Oncology in the Department of Internal Medicine at the University of Michigan Comprehensive Cancer Center in Ann Arbor, Michigan.

CD 2, Tracks 15-26 — CD 3, Tracks 1-6

CD 2

- Track 15 Introduction
- Track 16 Adjuvant chemotherapy for older patients
- Track 17 Benefit of adjuvant chemotherapy for patients with ER-positive disease
- Track 18 Potential biologic rationale for higher response rate to adjuvant chemotherapy in ER-negative versus ER-positive disease
- Track 19 Selection of an adjuvant chemotherapeutic regimen for patients with ER-positive, node-positive disease
- Track 20 Potential role of capecitabine in the adjuvant setting
- Track 21 Cardiac toxicity associated with AC
- Track 22 Clinical use of dose-dense AC in the adjuvant setting
- Track 23 Development of the *Oncotype* DX™ assay
- Track 24 ECOG-PACCT-1: Adjuvant hormonal therapy with or without chemotherapy based on the *Oncotype* DX recurrence score

Track 25 Utility of *Oncotype* DX for patients with HER2-positive disease

Track 26 Reliability of recurrence score in predicting benefit of adjuvant chemotherapy

CD 3

Track 1 Case discussion: A 51-year-old perimenopausal woman with ER-positive, PR-positive, node-negative disease

Track 2 Regaining ovarian function following chemotherapy-induced or biological amenorrhea

Track 3 Importance of monitoring estradiol in perimenopausal patients receiving adjuvant aromatase inhibitors

Track 4 Use of circulating tumor cells to predict outcome

Track 5 Potential benefit of switching therapies early based on presence of circulating tumor cells

Track 6 Future directions in the assessment of circulating tumor and endothelial cells

Select Excerpts from the Interview

CD 2, Track 16

▶ **DR LOVE:** Can you discuss your editorial in the *Journal of Clinical Oncology* about adjuvant chemotherapy for elderly women (Schott 2004)?

► **DR HAYES:** For older women, I believe the jury is out regarding the potential benefits of chemotherapy. The issue has two components. One is whether — for some mysterious reason — chemotherapy doesn't work as well in older women as in younger women. The second is whether the toxicities are greater for older women and, therefore, the benefit-to-toxicity ratio is smaller.

If you take it to its extreme — and we didn't put this in the editorial — another component is whether the number of life-years saved will be lower for older women and therefore not economically acceptable. An 80-year-old woman on average has another 10 years to live, but the number of life-years saved for her will be lower than for a 50-year-old woman for the same potential reduction in recurrences. Peter Ravdin has begun to build that into Adjuvant! Online. It's not something we normally talk to patients about, but I believe it is part of the equation.

CD 2, Track 17

► **DR LOVE:** Can you review CALGB-49907?

► **DR HAYES:** CALGB-49907 (1.4, see page 13) assumes that chemotherapy is beneficial. It is not a trial of chemotherapy versus none. The question is whether in this older age group one type of chemotherapy might be more acceptable by being less toxic. Patients either receive one of the standard regimens — AC or CMF — or capecitabine. A critical part of the study is to determine whether capecitabine is a more acceptable regimen.

I believe this goes back to some of the biology. We know older women are more likely to have ER-positive cancers. I'm increasingly convinced that patients with ER-positive cancers are less sensitive to chemotherapy in general, not to a specific agent. Additionally, they are more sensitive to hormonal therapies compared to patients with ER-negative disease.

We've seen data from the individual cooperative groups, especially CALGB, and Don Berry (Berry 2006). We've also seen a hint of that in the last Overview, in that the proportional reduction among patients with ER-positive disease is less than among those with ER-negative disease (EBCTCG 2005). Most women who have breast cancer in their sixties and seventies have ER-positive disease, and this is one reason chemotherapy may be less effective in that group.

CD 2, Track 22

► **DR LOVE:** Dose-dense AC → paclitaxel is the most common regimen used in the United States for patients with node-positive and high-risk node-negative disease. I find that many oncologists who use dose-dense therapy use dose-dense AC without paclitaxel off study. Do you do that?

► **DR HAYES:** Yes, we do. One reason is that we're using the same regimen across the board, which makes it safer for us. Second, I have not seen any

evidence that dose-dense AC results in more cardiac toxicity than nondose-dense AC. It's been a concern, but so far, CALGB hasn't seen it.

Third, although it does require growth factors, which increases the immediate costs of treatment and causes a few extra side effects, it's completed so much faster. You cut a whole month off the treatment. If you use four cycles of dose-dense AC, you're done in two months, which is terrific. At least, our patients say they like that.

Although the cost of the growth factors is elevated at the start, I'm convinced from the CALGB data that the lower number of hospital admissions required for neutropenia and fever outweigh it (Citron 2003).

Debate is ongoing about whether dose-dense therapy is better in terms of cancer outcomes. CALGB-9741 suggests it is. Another study published in the *JNCI* within the last year suggests that dose-dense FEC is not necessarily better (Venturini 2005).

CD 2, Track 23

► **DR LOVE:** Can you review where we are with the *Oncotype DX* assay and how it fits into clinical practice?

► **DR HAYES:** Genomic Health went to the NSABP and some other sources of data and examined the records of patients with node-negative, ER-positive disease who had received tamoxifen and had 10 or 15 years of follow-up. They developed an algorithm and applied it to a second data set, NSABP-B-14, and obtained exactly what they expected (Paik 2004).

It's very likely this test is accurate. However, I believe some caveats apply. These were older studies of older treatments, and the samples sat around for a while. For those reasons, the Intergroup is conducting a prospective study called TAILORx (3.1), in which women with ER-positive, node-negative disease will be profiled using the *Oncotype DX* assay.

If they have a low recurrence score, they will receive hormone therapy and be followed in a registry. If they have a high recurrence score, they will be invited to participate in chemotherapy trials within the Intergroup or be treated with chemotherapy off study and hormone therapy. If they have an intermediate recurrence score, for which we remain in enormous equipoise, they'll be randomly assigned to hormone therapy alone or chemotherapy and hormone therapy.

CD 2, Track 25

► **DR LOVE:** Do you think the *Oncotype DX* assay is useful for patients with HER2-positive tumors?

► **DR HAYES:** I don't know the answer to that because HER2 factors very heavily into *Oncotype*. One reason it might be useful is that I believe the

technical aspects of HER2 analysis in this country are very poor. I believe a lot of false-positive and false-negative results are presented, and that is true whether you test by FISH or immunohistochemistry.

Efforts are being made to standardize these tests. I expect you will see a lot of that in the next 12 months, both within the American Society of Clinical Oncology and the College of American Pathologists, because the stakes are high. Trastuzumab is an incredibly potent drug with an incredible price tag, both in terms of toxicities — the four to five percent risk of cardiac dysfunction in the short run and the potential long-term toxicities — and the actual dollar costs.

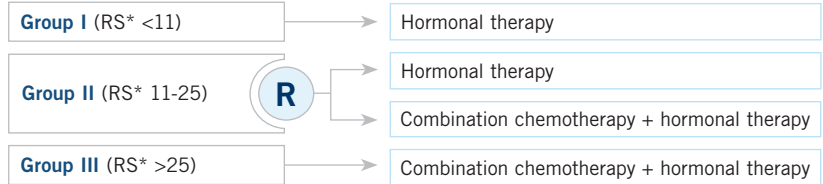
We need to standardize HER2 testing, and we will. The *Oncotype DX* assay might be a useful way to look at HER2 expression. Certainly it's built in.

3.1

TAILORx: Phase III Randomized Study of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Node-Negative Breast Cancer with Various Levels of Risk for Recurrence

Protocol IDs: ECOG-PACCT-1, TAILORx, NCT00310180
Target Accrual: 10,046 (Open)

Eligibility
Pre- or postmenopausal
ER-positive and/or PR-positive, HER2-negative breast cancer
Node-negative



* *Oncotype DX* recurrence score
Study Contact:
Eastern Cooperative Oncology Group
Joseph Sparano, MD
Tel: 718-920-4826

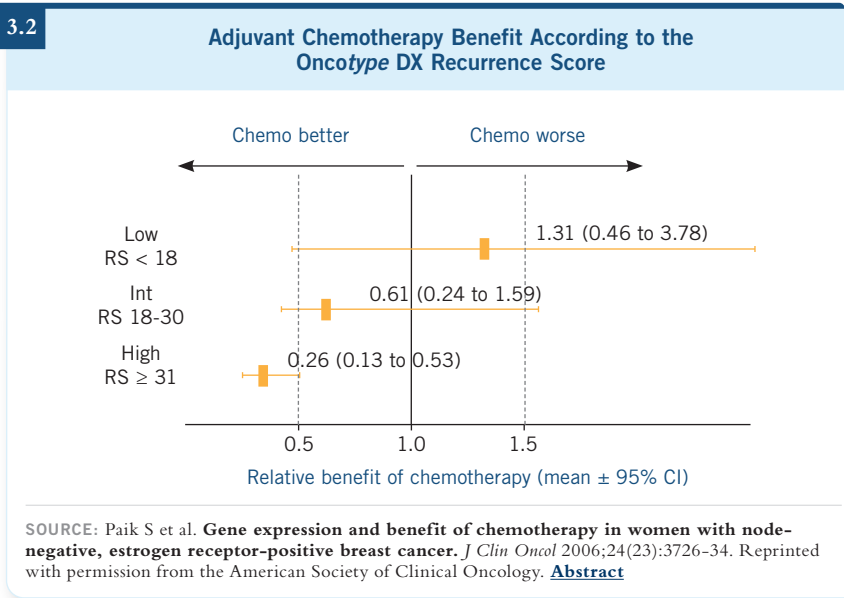
SOURCE: NCI Physician Data Query, July 2006.

 **CD 2, Track 26**

► **DR LOVE:** Patients with a high recurrence score show about a 75 percent relative reduction in the relapse rate associated with M → F or CMF. Do you feel comfortable enough with those findings to counsel patients with a high recurrence score?

► **DR HAYES:** Not quite. I'm pretty comfortable with the accuracy of the Oncotype DX assay relative to the benefit from tamoxifen, meaning that if you have ER-positive, node-negative disease and you receive tamoxifen, I believe the Oncotype DX assay provides an accurate outcome score. The predictive value of the Oncotype DX score for chemotherapy benefit, however, is based on a very small group of patients, and the confidence limits are enormous (3.2).

The patients with a high recurrence score tend to have lower ER levels. They're not ER-negative but show lower ER and higher HER2 levels. That's the group I would have guessed to have a higher proportional reduction from chemotherapy, and Oncotype DX suggests that's true. I expect the true reduction has yet to be precisely estimated, because the confidence limits are so large. We're talking of only about 200 patients from NSABP-B-20 (Paik 2006).



CD 3, Tracks 1-2

► **DR LOVE:** Oncologists in practice have many questions about the issue of endocrine therapy for the premenopausal woman who stops menstruating while on tamoxifen. Is it safe to switch those patients to an aromatase inhibitor?

► **DR HAYES:** I believe an important issue, which has been lost, is that all of the aromatase inhibitor studies enrolled women who were postmenopausal by virtue of not having a period for at least a year prior to enrollment. We have estrogen ablation studies ongoing for premenopausal women, such as SOFT,

TEXT and PERCHE. We don't know the answers from those studies yet.

I believe estrogen ablation is a more effective therapy than a SERM, but I also believe it's more toxic. I'm very supportive of those trials. We have enrolled 11 patients on SOFT. They're important studies, almost as much for the toxicity as for the outcomes.

The ovaries can go to sleep and wake back up again. Ian Smith at the Royal Marsden and I discussed this at a meeting. He went back and retrospectively reviewed his institution's experience with women who had received chemotherapy, became amenorrhic and were then placed on an aromatase inhibitor.

About one quarter of those patients had their ovarian function reemerge, either by virtue of developing menses or by having their estrogen levels increased (Smith 2006). ■

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Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. [Abstract](#)

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](#)

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Miami Breast Cancer Conference Tumor Panel: Monoclonal Antibodies in the Management of Early and Advanced Breast Cancer

CD 3, Tracks 7-25

- | | | | |
|-----------------|--|-----------------|--|
| Track 7 | Introduction | Track 17 | Use of capecitabine in the management of metastatic breast cancer |
| Track 8 | Case discussion: A 46-year-old woman with ER-negative, PR-negative, HER2-negative metastatic disease to the mediastinum and chest wall | Track 18 | Clinical use of bevacizumab in combination with other chemotherapeutic agents |
| Track 9 | Case discussion: A 51-year-old woman with ER-positive, HER2-negative metastatic disease to the liver | Track 19 | Case discussion: A 33-year-old woman with a 1.7-cm, ER-positive, PR-positive, HER2-positive, node-negative tumor |
| Track 10 | Counseling patients with metastatic breast cancer | Track 20 | Case discussion: A 44-year-old woman with a 0.8-cm, ER-positive, PR-positive, HER2-positive, node-negative tumor |
| Track 11 | Strategies to cope with metastatic disease | Track 21 | Quality control with HER2 testing |
| Track 12 | Selection of first-line therapy for patients with triple-negative metastatic disease | Track 22 | Selection of adjuvant therapy for premenopausal women with ER-positive, HER2-positive, node-negative disease |
| Track 13 | Side effects and tolerability of bevacizumab | Track 23 | Cardiac toxicity with adjuvant trastuzumab |
| Track 14 | Bevacizumab with paclitaxel as first-line therapy for metastatic disease | Track 24 | Cardiac monitoring for patients receiving adjuvant trastuzumab |
| Track 15 | Combination versus sequential single-agent chemotherapy | Track 25 | Adjuvant trastuzumab with chemotherapy for patients with node-negative disease |
| Track 16 | First-line therapy for patients with ER-positive metastatic disease | | |

Monoclonal Antibody Therapy in the Metastatic Setting

Case 1: Dr Lowenthal

46-year-old woman

4/02

T2N0 medullary cancer
ER-negative, PR-negative, HER2-negative
Lumpectomy/RT
CAF chemotherapy

9/05

Induration parasternal area
Bx + for recurrence
PET-CT
Mediastinal adenopathy
Parasternal mass
The patient is minimally symptomatic.

CD 3, Track 12

▶ **DR LOVE:** George, unfortunately Dr Lowenthal's patient's tumor doesn't have either ER or HER2 as a target. How would you think through the approach to chemotherapy in this situation?

▶ **DR SLEDGE:** The first issue that one considers for a patient with metastatic breast cancer is prior therapy. This patient has received prior anthracycline-based chemotherapy but not taxane-based chemotherapy. So we would certainly say that taxane-based therapy would be a standard of care for this patient.

I'll add another qualifier, which is that I'm not always sure we obtain correct "steroid" or HER2 receptor values. When you have a patient who has relapsed, you can almost always make a case for obtaining more tissue and retesting for ER, PR and HER2 because a small but fixed percentage of the time you'll find out that your pathologist didn't quite do it right in the past.

Let's assume this patient has triple-negative disease. In my clinic, based on the results of ECOG-E2100, we would likely recommend that she receive combination therapy with weekly paclitaxel and every two-week bevacizumab. ECOG-E2100 randomly assigned similar patients to receive chemotherapy alone — paclitaxel — or chemotherapy and bevacizumab (Miller 2005; [4.1]).

The results from ECOG-E2100 demonstrated that bevacizumab increased the median progression-free survival from about six months to about 11 months (Miller 2005; [4.1]). This five-month improvement is the largest improvement we've seen in a generation for progression-free survival among patients with metastatic breast cancer. It is, for instance, a larger absolute improvement than the one seen with trastuzumab in the trial comparing paclitaxel with or without trastuzumab as front-line therapy (Slamon 2001).

CD 3, Track 13

▶ **DR LOVE:** Eric, can you put into clinical context what you think the results from ECOG-E2100 mean in terms of patient care?

▶ **DR WINER:** The study was essentially open to women with HER2-negative disease, although it did include a handful of patients with HER2-positive disease who had received trastuzumab on a preoperative or adjuvant pilot study. Two thirds of the women in the study had ER-positive breast cancer and one third had ER-negative breast cancer (Miller 2005). Because most had HER2-negative disease, many had triple-negative disease like the patient in this case.

Apart from that, the study was relatively permissive. Most, but not all, of the patients had not received a taxane, like this woman. Of interest, although the group was small, the women who had received a taxane in the adjuvant setting appeared to derive every bit as much benefit from bevacizumab as those

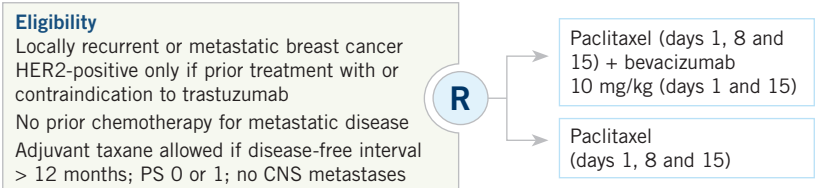
who hadn't (Miller 2005; [4.2]). Of course, the investigators looked for CNS disease because of concerns about bleeding. Hence, all the women on ECOG-E2100 had a negative scan of their brain.

I believe the real issue in terms of how one thinks about this patient is the sense that she's going to have more difficulty soon. She has triple-negative disease, and she's had a short disease-free interval. She's not terribly symptomatic, but at the same time, I would expect she would be more symptomatic in the short term.

The treatment options for somebody in this situation are relatively limited. I personally agree with George. For this patient, I would say it's a "slam-dunk" decision that she should receive bevacizumab and paclitaxel. Unless she's

4.1 **ECOG-E2100: Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy for Patients with Locally Recurrent or Metastatic Breast Cancer**

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
 Accrual: 680 (Closed)



	Paclitaxel + bevacizumab (n = 341)	Paclitaxel alone (n = 339)	Hazard ratio (95% CI)	p-value
Response rate				
All patients	29.9%	13.8%	—	<0.0001
Measurable disease	37.7%	16.0%	—	<0.0001
Progression-free survival	11.4 months	6.1 months	0.51 (0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months	0.84 (0.64-1.05)	0.12

CI = confidence interval

ECOG-E2100: Conclusions

"In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and more than doubles the objective response rate. Overall survival data are still premature, and longer follow-up will be needed to assess the true impact of this therapy... .

It's now time to move bevacizumab into the adjuvant setting and explore its role there. We'll also need to continue to develop methods to identify those patients who are most likely to benefit from VEGF targeted therapies."

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 3](#).

eligible for some trial that you want to pursue, that is the standard treatment for this woman.

CD 3, Track 14

► **DR LOVE:** If she was in visceral crisis and you were concerned that she might not survive if she didn't have a quick response, would you consider combination chemotherapy plus bevacizumab?

► **DR WINER:** I'm not sure that I would because I view bevacizumab plus paclitaxel as combination therapy. I don't know that adding another chemotherapy drug will do that much more. The paradox of the patient who's in visceral crisis and sicker is that although on the one hand one is sometimes tempted to add another drug — and sometimes I do that — this is also the patient for whom you're even more concerned about adding toxicities from drugs because she may become that much sicker as a result of the drugs.

► **DR LOVE:** Joyce, what would likely be your therapy for Dr Lowenthal's patient?

► **DR O'SHAUGHNESSY:** Outside of a clinical trial, I would treat her with weekly paclitaxel and bevacizumab. We happen to have a very interesting clinical trial that I'll mention. It is randomly assigning patients with triple-negative disease to irinotecan/carboplatin with or without weekly cetuximab, because about half of the patients with triple-negative disease have EGFR expression. We don't know if it's driving the cancer at all. This is a randomized Phase II trial to see if there's any signal that response rates or time to progression will be better in this group with cetuximab. So I would also talk to her about that clinical trial.

4.2

ECOG-E2100: Progression-Free Survival According to Prior Adjuvant Chemotherapy

Subgroup	Hazard ratio (95% confidence interval)
No adjuvant chemotherapy (n = 178)	0.60 (0.44-0.82)
Nontaxane-containing adjuvant chemotherapy (n = 234)	0.51 (0.39-0.67)
Taxane-containing adjuvant chemotherapy (n = 86)	0.38 (0.25-0.59)

ECOG-E2100: Effect of Paclitaxel/Bevacizumab in Patients Previously Treated with a Taxane

"Of note, patients who received previous adjuvant taxane therapy had the most striking improvement in their progression-free survival. This hazard ratio of 0.38 translates to an improvement in progression-free survival from just over four months to 12.4 months. The overall survival data for E2100 remained premature, with only 275 events reported."

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 3](#).

CD 3, Track 15

▶ **DR LOVE:** You have all said you'd use weekly paclitaxel and bevacizumab. What would your therapy have been a year ago?

▶ **DR WINER:** It might have been single-agent paclitaxel or capecitabine. It would have almost certainly been some single-agent chemotherapy. I don't believe the order in which we use these drugs makes a big difference. The reason I'd pick paclitaxel now is that it was used in ECOG-E2100, and I have no reason not to use paclitaxel for this patient.

▶ **DR SLEDGE:** I would have used a single-agent taxane — either paclitaxel on a weekly basis or docetaxel on an every three-week basis.

▶ **DR O'SHAUGHNESSY:** I tend to use combination therapy early on, and I probably would have used either paclitaxel or docetaxel in combination with capecitabine. I like the strategy of obtaining the highest possible response rate and trying to consolidate with some radiation therapy.

Stopping the taxane and continuing indefinitely with capecitabine is a strategy I use a lot. You administer about three to four months of the combination and then stop the taxane.

▶ **DR LOVE:** You've changed your paradigm pretty significantly.

▶ **DR O'SHAUGHNESSY:** Yes. The bevacizumab data, with the prolonged time to progression, are very intriguing. This patient, unfortunately, is at significant risk for brain metastases. It will be intriguing in ECOG-E2100 to see if any difference emerges, ultimately, in the development of brain metastases by inhibiting VEGF. I don't know the answer to that, but it would be terrific if that were the case.

▶ **DR LOVE:** Dr Lowenthal, can you follow up with this case?

▶ **DR LOWENTHAL:** In light of ECOG 2100, we would have liked to have started her on paclitaxel and bevacizumab, but appeals to her insurance company were repeatedly rejected.

We ultimately started her on single-agent paclitaxel, weekly, and she did well at first. A diminution in the tumor markers occurred, and there was a diminution in her palpable disease for about the first six to seven weeks, after which things slowly started to pick up again.

I restaged her a few days ago because her markers were going up and her performance level was slipping. A PET scan and a CAT scan showed that the disease was taking quite a leap. Her mediastinal nodal disease is now very extensive, and her chest wall lesion has doubled in size.

She has extensive bone metastases, which she did not have at the start of treatment. Because of the tempo of the disease, we bit the bullet and I switched her to docetaxel/capecitabine and bevacizumab.

Case 2: Dr Harwin

51-year-old woman

5/00

2 infiltrating lobular carcinomas total 3.3 cm
ER-positive, PR-positive, HER2-negative
MRM AND: 4 positive nodes
Treatment: AC → docetaxel, tamoxifen

5/05

Abnormal LFTs
CA27.29: 147
CT: multiple/large (6-7 cm)
liver metastases
Biopsy + for recurrence
The patient is asymptomatic.



CD 3, Track 16

► **DR LOVE:** Eric, how would you approach the therapy for Dr Harwin's patient?

► **DR WINER:** In the end, I would probably treat her the same as the prior patient, although I think about her a little differently. She's asymptomatic, but she has bulky liver disease. That would make me hesitant about using a hormonal agent, although she may have hormone-responsive disease. So I would start with some form of chemotherapy. Based on ECOG-E2100, I would probably start with bevacizumab and paclitaxel, since it worked equally well for ER-positive disease (Miller 2005; [4.3]).

I'm more optimistic about what's open to her in the future. If you told me she had two 2- or 3-cm lesions in her liver and normal liver function test results, I would have been quick to say, "Hold off the chemotherapy and use a hormonal agent."

► **DR LOVE:** George, how would you approach this woman?

► **DR SLEDGE:** Pretty much the same way as Eric would. I hear about visceral crisis a lot, but I don't see it much in my clinic. In fact, most of our patients with metastatic breast cancer do not fall into the category of visceral metastases.

Medicine is never going to be boiled down to simple rules. All of us, as physicians, when we're in a room with a patient, have a gestalt about the patient and our comfort level about whether the patient needs hormonal therapy or chemotherapy. This is a patient who I believe, as Eric has suggested, is right on the borderline.

► **DR LOVE:** Joyce, briefly, how would you treat this patient?

► **DR O'SHAUGHNESSY:** With this ER-positive biology that relapses in the bone and/or the liver — the primary sites of metastases — I'm extraordinarily impressed with the taxane/capecitabine combinations. We've done a lot of studies with either docetaxel/capecitabine or weekly paclitaxel/capecitabine. I have four patients with complete responses who are more than three years out, and they all have the same biology, exactly like this patient.

So I probably would not use bevacizumab for this patient because of my own experience with the taxane/capecitabine combinations. I'd be interested in using bevacizumab with her next round of therapy. It's an excellent agent, and it looks very promising, but with this particular biology, I'm extremely impressed with the taxane/capecitabine combinations.

4.3 **ECOG-E2100: Progression-Free Survival According to ER and PR Status**

Subgroup	Hazard ratio (95% confidence interval)
ER+, PR+ (n = 200)	0.39 (0.29-0.53)
ER+, PR- (n = 80)	0.86 (0.52-1.43)
ER-, PR- (n = 184)	0.47 (0.35-0.63)

SOURCE: Miller KD et al. San Antonio Breast Cancer Symposium 2005; [Abstract 3](#).

Case 3: Dr Harwin

33-year-old woman

1.7-cm, Grade III IDC, 11 negative nodes

ER-positive, PR-positive,
HER2-positive (FISH)

Case 4: Dr Hussein

44-year-old woman

0.8-cm, moderately differentiated IDC

ER-positive, PR-positive,
HER2-positive (FISH)

 **CD 3, Track 17**

▶ **DR HARWIN:** We ended up treating her with paclitaxel and bevacizumab. She had a very nice partial response. She received about nine or 10 cycles with very little toxicity except that she started to develop some neuropathy. Because of the neuropathy and the plateau in her response, I decided to stop the treatment and switched her to letrozole.

 **CD 3, Track 21**

▶ **DR LOVE:** George, accuracy in determining HER2 status is critical for both these patients. What do we know about false-negative and false-positive results with IHC and FISH for HER2 assessment?

▶ **DR SLEDGE:** I believe it's safe to say that immunohistochemistry (IHC) represents an art form, which is to say that we ask the pathologist to look under the microscope and determine if something is zero, 1+, 2+ or 3+. Variability occurs among pathologists and with the same pathologist from day to day.

It's reasonably likely that about 15 or 20 percent of the time the average pathologist just gets it wrong. Problems also arise related to fixation, which antibody is used, et cetera. Even in "good hands," a fair amount of inter-pathologist and intrapathologist variability occurs.

Fluorescence in situ hybridization (FISH), in theory, should overcome those

problems. When you do a FISH test, you have an internal control in the form of the chromosome 17-centromere marker. You should be able to count the number of centromeres and the number of HER2 in the cell and obtain a ratio that should be absolutely perfect.

Of course, in the real world, nothing is perfect. Indeed, emerging data suggest — because FISH has to be done fairly quickly and pathologists are not all equally well trained — that false-positive and false-negative results occur with FISH (Perez 2006). This is difficult for all of us, but I expect it will get better over time.

Today in my hospital, we tend to use FISH pretty much exclusively. I would not criticize someone if they had a patient with a result of 2+ by immunohistochemistry and then did a FISH test on that patient's tumor, or if they ignored FISH for a patient with a result of 3+ by IHC.

The tougher area includes those patients with a result of 0 and 1+, because we know from a fair number of studies that some of those patients have FISH-positive disease — about four and seven percent, respectively, in the largest database (Owens 2004; [4.4]).

Do you want to ignore seven percent of the patients with an IHC of 1+ when their lives might be saved by HER2 testing with FISH? I don't know the answer to that. Part of it is a cost-benefit analysis, and part of it is availability in your own hospital. In my hospital, however, we typically would use FISH.

4.4 Frequency of HER2 Gene Amplification According to HER2 Protein Expression in a Cohort of 6,556 Specimens from Impath Laboratories

IHC score	Percent of cases amplified
0	4.1
1+	7.4
2+	23.3
3+	91.7

SOURCE: Owens MA et al. *Clin Breast Cancer* 2004;5(1):63-9. [Abstract](#)

 **CD 3, Track 22**

▶ **DR LOVE:** Joyce, can you talk about whether to administer trastuzumab to a patient with node-negative disease, as in these cases, particularly the patient who has a 0.8-cm tumor?

▶ **DR O'SHAUGHNESSY:** We don't have good data sets to tell us how effective hormonal therapy alone (ie, tamoxifen) would be for this premenopausal woman. I don't feel comfortable using our overview analysis, in which we can show a 40 or 50 percent reduction in the risk of relapse with tamoxifen for all comers (EBCTCG 2005).

I don't know what those data are among patients with HER2-positive breast cancer. I expect the number would be lower. I believe HER2-driven breast

cancer is hormonally less sensitive. The same is true for chemotherapy. I don't know of a good data set that I can use to tell the woman, "Your benefits from chemotherapy are X with HER2-driven breast cancer."

Generally speaking, I multiply the risk by 1.5 in my head. So if an 8-mm, Grade II tumor — taking the HER2 status out of the equation — has about a 10 percent risk of systemic relapse, I usually multiply that by a 1.5 relative risk.

I'm starting at about a 15 percent risk of relapse, as far as I can possibly estimate. I don't know exactly how much benefit hormonal therapy or chemotherapy alone will provide this patient.

So I tend to look at the data and say that I don't see a lot of difference between an 8-mm tumor and a 10-mm tumor, which were allowed in BCIRG 006 and the HERA trial. Then I try to use the therapy to inhibit what is driving the cancer to minimize the risk part of the equation.

CD 3, Track 23

► **DR LOVE:** George, what would you say to a 33- or a 44-year-old woman about the risks associated with trastuzumab in terms of cardiac dysfunction or cardiac symptoms?

► **DR SLEDGE:** In the two large North American trials, in which we used doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab, the congestive heart failure rates overall were somewhere in the three to four percent range (Romond 2005). The questions that arise are, who are those three to four percent of women and can we use that information to guide our therapy?

Today, we're not sure. The NSABP database suggested that the women most likely to develop congestive heart failure were those who were older than age 50 and those with the lowest level of ejection fractions (50 to 55 percent) allowed to enroll in the trial. In NSABP-B-31, if you met those two criteria, you had roughly one chance in five of having a cardiac event (Tan-Chiu 2005; [4.5]), which is pretty significant.

I hasten to add that in NCCTG-N9831, an identical analysis was done and they did not come up with the same pattern (Perez 2005). When you run retrospective subset analyses of small subgroups in evolving trials, you can get very different results, although I don't find it particularly surprising that older people would have more heart dysfunction.

I believe you can say, "You have a three to four percent chance of developing congestive heart failure. There is a reasonable likelihood that if you develop it, it will improve, but probably not all patients will improve. Also, those that improve may need to be on chronic medication for CHF, perhaps for the rest of their life." That's very definitely part of the trade-off, particularly for a patient with an 8-mm tumor.

► **DR LOVE:** What about TCH?

► **DR SLEDGE:** There, of course, we run into a different issue. Is TCH as good as AC followed by TH? In the one trial we have, both regimens are better than not receiving a trastuzumab-containing regimen and the regimens are not statistically significantly different from each other with very early follow-up. The trend in that trial certainly favors AC → TH over TCH (Slamon 2005). So I personally tend to use TCH with patients for whom I have significant concerns about cardiac toxicity.

► **DR LOVE:** What would you say to the patient about the risk of cardiac toxicity with TCH?

► **DR SLEDGE:** It would be pretty trivial. A very small number of patients developed congestive heart failure in that arm of the trial (Slamon 2005).

4.5

NSABP-B-31: Incidence of Congestive Heart Failure (CHF) in Patients Receiving AC Followed by Paclitaxel/Trastuzumab

	Three-year cumulative incidence of CHF (95% CI)	
	≤49 years of age	≥50 years of age
Post-AC LVEF		
50%-54%	6.8% (2.3%-20.5%)	20.0% (11.1%-35.9%)
55%-64%	2.5% (1.0%-5.9%)	6.1% (3.4%-10.9%)
≥65%	1.1% (0.2%-8.0%)	1.5% (0.4%-6.1%)

CI = confidence interval

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

CD 3, Track 25

► **DR LOVE:** Dr Harwin, can we follow up on what happened to your patient (Case 3)?

► **DR HARWIN:** I started her on doxorubicin and cyclophosphamide with the plan to treat her with trastuzumab and a taxane concomitantly, like the patients in NCCTG-N9831. She has just started treatment.

► **DR LOVE:** Can you follow up on your patient, Dr Hussein (Case 4)?

► **DR HUSSEIN:** My patient qualified for BCIRG 006 because the trial allowed the enrollment of patients with node-negative disease. She was randomly assigned to receive docetaxel/carboplatin/trastuzumab (TCH). She received six cycles and a whole year of trastuzumab. She did well, but her ejection fraction dropped seven or eight points.

We stopped trastuzumab for a few weeks, and then we resumed it. She's now at six months after finishing the study, and her ejection fraction is back to baseline.

► **DR LOVE:** How did she tolerate the TCH?

► **DR HUSSEIN:** She did very well. She's an architect and was able to continue working full time. The carboplatin/docetaxel caused a moderate degree of fatigue, although her hemoglobin was normal. However, we got her through the treatment. ■

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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](#)

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. In CALGB adjuvant trial 49907, patients over age 65 are randomly assigned to single-agent _____ versus AC or CMF.
 - a. Docetaxel
 - b. Paclitaxel
 - c. Capecitabine
 - d. 5-FU
2. In the adjuvant trial comparing docetaxel/cyclophosphamide versus doxorubicin/cyclophosphamide, a disease-free survival advantage was seen with _____.
 - a. Docetaxel/cyclophosphamide
 - b. Doxorubicin/cyclophosphamide
3. The ATAC bone mineral density data presented by Coleman et al concluded that all patients receiving adjuvant aromatase inhibitors should undergo annual DEXA scans and receive bisphosphonates up front.
 - a. True
 - b. False
4. Patients on the MA17 trial who originally received a placebo after five years of tamoxifen and then received letrozole after the study was unblinded approximately 30 months later experienced a reduction in the rate of which of the following?
 - a. Contralateral recurrences
 - b. Ipsilateral recurrences
 - c. Distant recurrences
 - d. All of the above
5. TAILORx will include patients with a _____ recurrence score according to the Oncotype DX assay.
 - a. High
 - b. Intermediate
 - c. Low
 - d. All of the above
6. Which of the following is an advantage of dose-dense adjuvant therapy?
 - a. Therapy is completed more quickly
 - b. Less growth factor support is required
 - c. Both a and b
 - d. None of the above
7. The combined analysis of NSABP-B-31 and NCCTG-N9831 demonstrated a significant improvement in _____ for patients treated with adjuvant trastuzumab.
 - a. Disease-free survival
 - b. Distant disease-free survival
 - c. Overall survival
 - d. Both a and b
 - e. All of the above
8. According to an early, unplanned analysis of NCCTG-N9831, patients who received trastuzumab concurrent with paclitaxel had an improved disease-free survival rate compared to those who received trastuzumab at the completion of paclitaxel.
 - a. True
 - b. False
9. In BCIRG 006, no statistically significant difference appeared between AC followed by docetaxel/trastuzumab and TCH, but a trend for better three-year disease-free survival appeared with _____.
 - a. AC followed by docetaxel/trastuzumab
 - b. TCH
 - c. Neither
10. In ECOG-E2100, the addition of _____ to weekly paclitaxel improved the median progression-free survival of patients with metastatic breast cancer by five months.
 - a. Capecitabine
 - b. Bevacizumab
 - c. Cetuximab
 - d. Gemcitabine
11. Which of the following appear to be risk factors for trastuzumab-related CHF in NSABP-B-31?
 - a. Age over 50
 - b. Ejection fraction of 50 to 55 percent
 - c. Family history of CHF
 - d. Both a and b
 - e. All of the above

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GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Julie R Galow, MD	5 4 3 2 1	5 4 3 2 1
Edith A Perez, MD	5 4 3 2 1	5 4 3 2 1
Daniel F Hayes, MD	5 4 3 2 1	5 4 3 2 1
Joyce O'Shaughnessy, MD	5 4 3 2 1	5 4 3 2 1
George W Sledge Jr, MD	5 4 3 2 1	5 4 3 2 1
Eric P Winer, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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Writers	Lillian Sklaver Poltorack, PharmD Douglas Paley
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Web Master	John Ribeiro
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

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