BCU | 2008 VOL 7 | ISSUE 1

Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

Larry Norton, MD

John Mackey, MD

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ROUNDTABLE DISCUSSION: SCHWARTZ CENTER ROUNDS — PSYCHOSOCIAL ISSUES IN BREAST ONCOLOGY

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CME Certified

Breast Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician 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, hematologists and hematology-oncology fellows with 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 findings into management strategies in the neoadjuvant, adjuvant and metastatic settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Describe the key clinical and pathologic risk factors that influence clinician selection of the medical and surgical management of early breast cancer.
- Identify existing data and emerging research focusing on the optimal duration and sequence of adjuvant endocrine therapy in the management of the postmenopausal patient with ER-positive breast cancer, and apply this evidence to routine patient care decisions.
- Describe and implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for early and advanced HER2-positive breast cancer.
- Evaluate the practical application of currently available tissue-based genomic assays to assist with therapeutic decision-making in the management of early breast cancer and, when applicable, use these in the selection of individualized treatment regimens.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense or alternative novel scheduling and the contributory roles of taxanes and anthracyclines, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate the emerging data for novel biologic and molecular-targeted therapies with clinical activity in breast cancer, and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- Explore the challenging practice of integrating psychosocial support, optimal patient-physician communication strategies and evidence-based clinical decision-making into comprehensive oncology care.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 1 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Burris, Carey, Geyer, Mackey, Norton, Winer and Wolff on the integration of emerging clinical research data into the management of breast cancer.

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This program is supported by educational grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline, Roche Laboratories Inc and Sanofi-Aventis.

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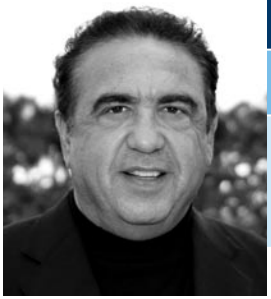


EDITOR'S NOTE

Neil Love, MD

Another perspective on metastatic breast cancer

January 7, 2008

You are a previously healthy 55-year-old woman who was diagnosed several years ago with a 2.1-cm, ER-positive, PR-positive, HER2-negative breast tumor with one positive node. After receiving dose-dense AC → paclitaxel, you began treatment with an aromatase inhibitor and have taken the small white pill daily without complications. Your life has been super busy balancing work, family and a full social calendar, and you barely have time to think about cancer, but for a few days just before every follow-up visit with your oncologist, you lie awake at night fearing what could be.

For the past few weeks, you've had a persistent backache, and on Christmas Day, you woke up with sore ribs. The NSAID you were taking is no longer effective, and the pain has been bothersome enough to make you pull out an old bottle of oxycodone. Instead of going out on the town as planned, you rang in the New Year with a quiet dinner at home with your family, trying not to think about your appointment for a bone scan in a couple of days and a return visit to see your oncologist.

Today, the news you've dreaded is delivered by your compassionate but crestfallen doctor. The bone scan shows multiple suspicious lesions and a CAT scan revealed masses in your liver as well. A subsequent biopsy confirms recurrence. The oncologist expresses concern about the extensive nature of the liver involvement and wishes to begin chemotherapy with the hope of seeing a response, which might then be followed by endocrine treatment. Specifically, a combination of *nab* paclitaxel and bevacizumab is recommended, and treatment is initiated the Friday of Super Bowl weekend. Previously, when you received adjuvant chemo, there was some numbness and tingling toward the end of the paclitaxel, but when treatment was stopped, this resolved as your hair regrew. The chemo premeds during adjuvant therapy made you agitated and sleepless, and you are grateful that now, with the *nab,* you can get some rest.

March 11, 2008

Within a few weeks of beginning therapy, the bone pain abates, and although you feel better physically, your soul is crushed. Your teenage children are withdrawn and tense, and you can see the anguish in your spouse's eyes as he does everything possible to reassure your kids, reminding them of the oncolo-

gist's vision of metastatic breast cancer as a "chronic disease." Everyone seems cautiously optimistic but also completely uncertain about what to expect next.

The repeat CAT scan — a terrifying experience — reveals major shrinkage of the liver lesions. You receive the news with tearful gratitude, but in spite of your healthcare background, you don't ask to see the images. Several months pass, and numbness returns in your fingers, followed by paresthesias in your feet. You attend your daughter's high school graduation and wonder if you will be around to watch your other daughter receive her diploma in the same auditorium next year.

July 22, 2008

The *nab* paclitaxel is stopped because the neuropathy has worsened, but the bevacizumab is continued. You are back at work, and every other Friday you leave early for your oncologist's office for the bevacizumab infusion, which causes no noticeable side effects. Every other visit you also receive fulvestrant and zoledronate.

For some years you've had mild hypertension, and it gets a bit worse on the bevacizumab. With a few changes to your regular medication, your blood pressure is quickly controlled and you joke about how you wished your cancer responded that well. In August, you join your family on a vacation and wonder if this is the last time you will truly feel well and be able to travel. You have a nice autumn, and things seem to be falling into a consistent pattern.

December 15, 2008

Thanksgiving takes on a new meaning this year, but only a few days after an emotional and festive family gathering, the bone pain returns. A new bone scan and abdominal CT show more osseous and hepatic lesions. You feel apathetic about Christmas for the first time, and after another subdued New Year's Eve, you begin a series of sequential systemic therapies that have modest or no major benefits.

June 2, 2009

You attend your younger daughter's graduation, knowing that things are not going well. You begin painful discussions with your husband about a living will, and you enter a Phase I trial of a novel targeted agent, which results in a skin rash and disease progression. On two occasions, you receive radiation therapy to painful bony areas, which slowly results in symptom relief only to be followed by new areas of discomfort.

November 24, 2009

Your oncologist — an extraordinary, compassionate, open physician — tells you and your spouse that further systemic therapy is likely to cause more problems than benefit. A nurse from hospice visits and describes their services. Your family is at your side constantly, and you view yourself from a distance, not really believing what is happening. On New Year's Eve, you realize this will be the last time you watch the ball descend in Times Square.

March 14, 2010

A little more than two years after the first diagnosis of metastatic breast cancer, your life ends.

The above vignette is written by a clinician/educator and not a patient. I could never presume to understand such an experience from the outside. The main purpose of this fictitious scenario is to put a human face on clinical research data.

This case scenario demonstrates a number of key issues, including the following:

1. The personal side of the risk-benefit equation in the treatment of metastatic breast cancer is very different from the numbers and graphics we see in clinical trial reports.

The 26-month duration of survival in this case matches the outcome of one of the most important breast cancer clinical trials of the last decade, ECOG-E2100, an Eastern Cooperative Oncology Group study that compared paclitaxel alone or with bevacizumab (Figure 1). As in this case, the median time to progression for patients receiving the combination was 11+ months or, in real terms for this patient, most of 2008 (Figure 2).

Based on the ECOG data, had bevacizumab not been used, this hypothetical woman who began treatment in January would have experienced a return of bone pain and progressive disease not in December but in July, about 5 months earlier. Of course, one could argue that the lack of a placebo control in the E2100 study might mean that the PFS advantage really does not exist, but I don't know one major breast cancer clinical investigator who questions this

1

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

Stratification factors

- Disease-free interval
  - ≤24 months
  - >24 months
- Number of metastatic sites
  - <3
  - ≥3
- Adjuvant chemotherapy
  - Yes
  - No
- ER status
  - ER-positive
  - ER-negative
  - Unknown

R

Arm A

Paclitaxel: 90 mg/m^2 IV infusion over 1 hour every week for 3 weeks followed by 1 week of rest
Bevacizumab: 10 mg/kg after **paclitaxel** treatment on weeks 1 and 3 of every cycle

Arm B

Paclitaxel: 90 mg/m^2 IV infusion over 1 hour every week for 3 weeks followed by 1 week of rest

SOURCE: NCI Physician Data Query, December 2007.

2

ECOG-E2100: Patient Age Demographics, Tumor Baseline Characteristics and Efficacy Data

	Paclitaxel (n = 326)	Paclitaxel/bevacizumab (n = 347)
Age (mean)	55 years (27-85)	56 years (29-84)
Sites of involvement		
Viscera	87.1%	79.5%
Bone-only	7.7%	10.4%
ER/PR status		
ER-positive	62.9%	59.9%
PR-positive	45.1%	44.7%
HER2 status by FISH or IHC 3+		
Negative	89.9%	92.5%
Positive	0.9%	1.4%
Not evaluated	9.2%	6.1%
Efficacy		
Progression-free survival	5.9 months	11.8 months
	HR = 0.60, $p < 0.001$	
Overall survival	25.2 months	26.7 months
	HR = 0.88, $p = 0.16$	
One-year survival	73.4%	81.2%
	$p < 0.01$	
Objective response rate	21.2%	36.9%
	$p < 0.001$	

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry

SOURCE: Miller K et al. *N Engl J Med* 2007;357:2666-76. **Abstract**

advantage, and our Patterns of Care surveys consistently demonstrate support from researchers and docs in practice for these cooperative group data. Also based on the E2100 findings, the date of death might have been a couple of months earlier had bev not been utilized, but this assumption is far less certain, and this trial is not different than many other recent studies in metastatic breast cancer (MBC) demonstrating PFS but not survival benefits, perhaps because the downstream events make survival benefits more difficult to document.

Of course, bev is not without its toxicities, and we might have also inserted an arterial event in this case history, although one wonders whether the risk might be lower in a "healthy" 55-year-old woman.

I am not a politician, regulatory expert or economist, but there are also important questions about the cost of healthcare in this case scenario, not

restricted solely to bevacizumab but also relating to *nab* paclitaxel, which may be less toxic and more effective than its Cremophor®-based cousin.

Many other such "costly" agents and regimens exist in contemporary oncology, and a number of vocal investigators and healthcare pundits have expressed legitimate and deep concerns about this trend.

I wonder how these individuals and regulatory bodies would have viewed the E2100 results with the five-month median delay in progression had the therapy in question been an inexpensive elemental agent like calcium or magnesium. Smarter and more experienced people than me can weigh in on the way data, agents and their cost should be carried into practice, but I would ask with all humility, if you were this patient in this first-line situation, what treatment would you want?

2. MBC is a devastating disease.

Another issue this case raises is the disappointing reality of our current treatment tools for MBC. Every day, medical oncologists are asked to do the impossible by providing reassurance to people with incurable and largely uncontrollable clinical situations. It is natural to stretch the truth a bit and talk about MBC as a chronic disease, but despite the fact that thousands of women live many comfortable years with this illness, in toto — as reflected in the E2100 data and in the case scenario — many or most people succumb to MBC within a couple of years, and if reading the above narrative was as painful for you as writing it was for me, we can both begin to understand the apocalyptic nature of this illness and, for that matter, every fatal case of cancer.

Can laboratory and clinical research truly make MBC a chronic controllable disease with minimal morbidity and mortality? After listening to hundreds of investigators day and night for many years, and thinking through these comments critically, my conclusion is a resounding, "Probably!" If a patient in the above scenario can remain asymptomatic with minimal objective signs of tumor growth for one year, can we extend that to 40 years and allow "aging" in the form of cardiovascular and cerebrovascular disease to be the eventual cause of death?

The tragedy of cases like this one is that the dream of eliminating the morbidity and mortality of MBC is not likely to happen in our lifetime unless dramatic changes are made to the cancer research infrastructure. Again, no politics here — I am just a humble reporter of the obvious. See the excerpt below from the interview with Dr Larry Norton in this issue of *Breast Cancer Update* for more details. ■

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
January 4, 2008

"There is no doubt in my mind that cancer can be eliminated — not just breast cancer, but all cancers, and not a hundred percent eliminated because you always have biologic aberrations — but largely eliminated.

I've seen rapid changes in childhood leukemia, Hodgkin's disease, and testicular carcinoma. We've all seen this within the memories of practicing oncologists. My expectation is that advances can occur even more quickly now because we're learning so much more about the biology of life and so much more about the biology of cancer.

So the issue is not, 'Can we dramatically reduce the incidence, morbidity and mortality of cancer?' The question is how fast can we do it, and the big problem in that regard is not just innovative science, which is important, and it's not just more basic science and more translational science and more clinical science, but that the cancer war is grossly inadequately funded.

If you add together everything that Americans spend on cancer research in this country, and I'm talking about all segments of our society — government, industry and philanthropy — it's between $11 or $12 billion, about two thirds of the $16 billion the tobacco industry spends on advertising and one sixth of the $68 billion Americans spend on soft drinks annually. The entire National Cancer Institute budget for cooperative group trials is under $158 million. If we really want to get rid of cancer, we know what to do. We just have to do it.

We are going to make progress, but at a very slow rate because we don't have enough money to get everybody into clinical trials. We don't have enough money to do the biological assays that need to be done and to answer the critically important questions. We have not yet done the experiment of adequately funding the entire operation.

One message that shocks audiences when I give talks is that the NCI budget is a dollar and a quarter per American per month. Is that how frightened of cancer we are, that we're willing to put just a dollar and a quarter per month into the kitty to defeat cancer? If that really measures how frightened we are of cancer, then we have to really go back and look carefully about what the actual risks are. Most people estimate their risk of developing cancer in the single digits, and don't realize that a third to a half of us are going to die of this disease.

I'd like to see more people act on a rational assessment of what their risks are and risks of the people they love, and if they did that, I think that most would find that they would rather put more than a dollar and a quarter per month into the enterprise."

— Larry Norton, MD

SELECT PUBLICATIONS

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005. No abstract available

INTERVIEW

Larry Norton, MD

Dr Norton is Deputy Physician-in-Chief at Memorial Hospital for Breast Cancer Programs and Norna S Sarofim Chair in Clinical Oncology at Memorial Sloan-Kettering Cancer Center in New York, New York.

CD 1, Tracks 1-17

Select Excerpts from the Interview

CD 1, Tracks 2-3

DR LOVE: Can you comment on the recent paper published in *The New England Journal of Medicine* that examined the benefit of paclitaxel in various subgroups of patients, based on estrogen receptor (ER) and HER2 status?

DR NORTON: Dan Hayes was the first author of this interesting paper that retrospectively examined data from CALGB-9344, the trial that tested dosing of adjuvant doxorubicin in combination with cyclophosphamide and the addition of paclitaxel or not for women with node-positive breast cancer (Hayes 2007).

His team found that the benefits of paclitaxel were observed in all patients with HER2-overexpressed disease and in all patients with ER-negative disease. However, patients with HER2-nonoverexpressed disease and ER-positive disease did not seem to benefit from paclitaxel.

I'm a coauthor of that paper, and we stated clearly that these data are hypothesis generating. Any time you examine study data retrospectively, you can always find subsets in which all the difference is observed and differences that you do not observe in that subset. It's critical that before we use these data to make decisions for individual patients, we examine other data sets and challenge the academic community, which has relevant data from other data sets.

Another issue complicating this analysis is defining HER2 positivity. We have a great deal of uncertainty in measuring HER2 because both IHC and FISH require an experienced pathologist and are dependent on the method of fixation and the handling of the tissue. We desperately need better means of finding out which cancers are HER2 driven so that we can properly understand the meaning of HER2 in this particular setting.

Even measurement of the estrogen receptor is something we haven't determined with great authority, and methodological issues must be addressed. More critically, what does ER-positive mean? Is the cancer a luminal A type? Is it a luminal B type? We don't necessarily know that by analyzing the estrogen receptor status, and subsets of these cases may be driving the whole observation.

An enormous amount of work has to be done in terms of understanding the fundamental biology of the cancer and, as a practicing clinician, I want to know these answers for my patients tomorrow, not in 10 years. We need to complete this work quickly, and we have to obtain the answers for practicing oncologists as fast as we can.

However, until we have those answers, the authors of the Hayes paper agree that it's premature to deny paclitaxel to a patient with HER2-negative, ER-positive disease because we can't say with certainty that these patients don't

1.1

Interaction Between HER2, Estrogen Receptor Status and Response to Paclitaxel in Node-Positive Breast Cancer

"In an exploratory analysis, we observed an apparent three-way interaction among HER2 positivity, estrogen-receptor negativity, and a benefit from paclitaxel. We found no benefit of paclitaxel in patients with HER2-negative, estrogen receptor–positive breast cancer.... This subgroup represents more than half the patients with node-positive breast cancer who participated in the CALGB 9344 trial and who would, under most current circumstances, receive a taxane with or after cyclophosphamide plus an anthracycline. Our studies suggest that such patients could avoid the toxic effects associated with adjuvant paclitaxel when given after doxorubicin plus cyclophosphamide. Our results require validation before adoption into clinical practice, however."

SOURCE: Hayes DF et al. *N Engl J Med* 2007;357(15):1496-506. **Abstract**

benefit — simply that they didn't seem to benefit in our retrospective analysis of our own data (1.1).

CD 1, Track 6

DR LOVE: Dennis Slamon feels that currently, anthracyclines do not have a role in the adjuvant treatment of breast cancer. In clinical trials, the incremental benefit of adjuvant anthracyclines is observed in patients with HER2-positive, but not HER2-negative, disease, and in the BCIRG 006 trial, TCH was as beneficial as AC → TH (Slamon 2006). What are your thoughts on that?

DR NORTON: We all have extensive experience treating patients with anthracyclines for metastatic breast cancer, and we know they're active. I don't know why they would be active in Stage IV disease but not in early breast cancer. This is something we need to examine carefully.

For the sake of discussion, let's assume there is a subset of patients who do not benefit from anthracyclines. How do we select those patients? The measurement of HER2 is not absolute at the present time. If you are using topoisomerase (TOPO) IIA as a manner of delineating who will benefit, the FISH probe for that is broad. You are not simply evaluating TOPO II but rather that whole region of the gene, and you do not know exactly what you are measuring.

In the CIRG experience, it was simply a subset of patients who were examined, and the studies are early in terms of the number of events, so you're considering a subset of a subset (Press 2005). The results are provocative, but they must be examined carefully.

I believe the biochemical analysis of those specimens is a meritorious area of research, and it's certainly hypothesis generating, but in terms of clinical extrapolation at this point, I don't believe we're ready to say to any patient that she will not benefit from anthracycline therapy.

DR LOVE: A paper from MD Anderson published in the *Journal of Clinical Oncology* reported a high risk of congestive heart failure among women aged 66 to 70 who received an anthracycline-based regimen in the adjuvant setting (Pinder 2007; [1.2]). Can you comment on those data?

DR NORTON: Remember, the patients receiving anthracyclines live longer, so they will be at risk for basic cardiac problems longer, and that must be factored in. The patients who relapse and die of metastatic disease we won't see in the long term to observe the cardiac toxicity.

Many aspects of this situation must be analyzed before we decide that regimens that have clearly been associated with the declining mortality from breast cancer — which is apparent in national SEER statistics — are not meritorious. We need to be careful about what we say and how we analyze and present the data.

1.2

Cox Proportional Hazards Model for Association Between Anthracyclines and Subsequent Congestive Heart Failure (CHF) in Older Women Treated for Stage I to III Breast Cancer*

Variable	Hazard ratio	95% CI
Age 66-70 years		
Received adjuvant nonanthracycline	1.00	Reference
Received adjuvant anthracycline	1.26	1.12 to 1.42
Received no adjuvant therapy	0.90	0.86 to 0.99
Age 71-80 years		
Received adjuvant nonanthracycline	1.00	Reference
Received adjuvant anthracycline	1.01	0.90 to 1.13
Received no adjuvant therapy	0.92	0.86 to 0.99
Received anthracycline >1 year after diagnosis		
No	1.00	Reference
Yes	1.53	1.34-1.53

* Adjusted for Charlson Comorbidity Index

CI = confidence interval

"In this large, observational data set, we found that women aged 66 to 70 years treated with adjuvant anthracycline chemotherapy had a statistically significant increase in the risk of being diagnosed with CHF. At 5 years of follow-up, we observed absolute differences of 1% and 4.6% respectively in rates of CHF between anthracycline-treated women in this age group and those who received other adjuvant chemotherapy or no chemotherapy. After 10 years, the increased risk of CHF in anthracycline-treated patients was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when comparing anthracycline-treated patients to the other or no adjuvant chemotherapy groups, respectively....

A previous analysis using the SEER-Medicare data set showed no difference in breast cancer outcomes for older women treated with anthracycline versus nonanthracycline chemotherapy. Given the incidence of breast cancer in this age group, the growth of this segment of our population, and the increased life expectancy of women in this age group, informed decisions about adjuvant therapy are essential. Our findings underscore the need for prospective studies in older women, with careful monitoring and longer follow-up to quantify the risk of CHF and to define chemotherapy regimens with the best therapeutic ratio for this group."

[Citations omitted]

SOURCE: Pinder MC et al. *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

CD 1, Track 7

DR LOVE: It's my understanding that, within a few months, Onco*type* DX assay results will include a quantitative ER measurement and that they are working on HER2 also. Do you feel this strategy will affect quality control of these measurements?

DR NORTON: I hope that everyone working on the biochemical analysis of cancer will give a lot of attention to hormone-responsive genes. The fact that the Onco*type* DX assay can take a population of patients with ER-positive disease, analyze a family of genes rather than ER alone and categorize them by risk and whether they will benefit from adjuvant chemotherapy is extremely instructive.

We are learning from the Onco*type* DX assay, MammaPrint® and experimental assays that, although ER status correlates with the biochemical characteristics of the cancer, it doesn't define the biochemical characteristics of the cancer, and we need to define those in a much more meaningful way. Quantitative ER results may be closer to defining the biochemical characteristics of the cancer.

Anyone who has used the Onco*type* DX assay can tell you that cancer that appears to be hormone responsive and benign on the basis of IHC, when analyzed by Onco*type* DX can surprise you and fall into a high-risk category that would benefit from chemotherapy.

CD 1, Tracks 12-13

DR LOVE: Can you provide an update on your work evaluating the dose and schedule of capecitabine and combining it with bevacizumab?

DR NORTON: Many of us have been using capecitabine for a long time to treat metastatic breast cancer and are impressed with the activity of the agent, but we are also impressed with the toxicity when administered for 14 days followed by a break for seven days. In many series and in many people's experience, up to one third of patients stop receiving this agent not because of disease progression but because of toxicity, particularly because of hand-foot syndrome.

We initiated some animal experiments in which we examined the impact of capecitabine administered for 14 days on the perturbation of the tumor growth curves. We found that the maximum perturbation occurs at approximately a week of treatment and that the impact during the second week was dramatically reduced, but its toxicity was not.

Based on this information, we designed a regimen in a mouse experimental model evaluating seven days on and seven days off (Theodoulou 2007). We found we can increase the dose of capecitabine almost twofold compared to what we can deliver safely with a schedule of 14 days on, seven days off — and lo and behold, this resulted in increased tumor regression and more than doubled the survival benefit.

We then designed experimental models combining capecitabine with bevacizumab, and in the HER2-positive setting we also added trastuzumab, and these results have been published in abstract form (Traina 2007). The combination of all three drugs is profoundly effective, with not only significant inhibi-

tion of tumor growth or regression, but also improvement of survival of the animals with HER2-positive, ER-negative disease (1.3). The experiments with capecitabine and bevacizumab in the HER2-negative setting are still ongoing.

The important point to emphasize here is that achieving a proper dosing schedule of capecitabine enables us to combine it with biological agents and optimize the capecitabine effect without compromising the effect of the biological agent.

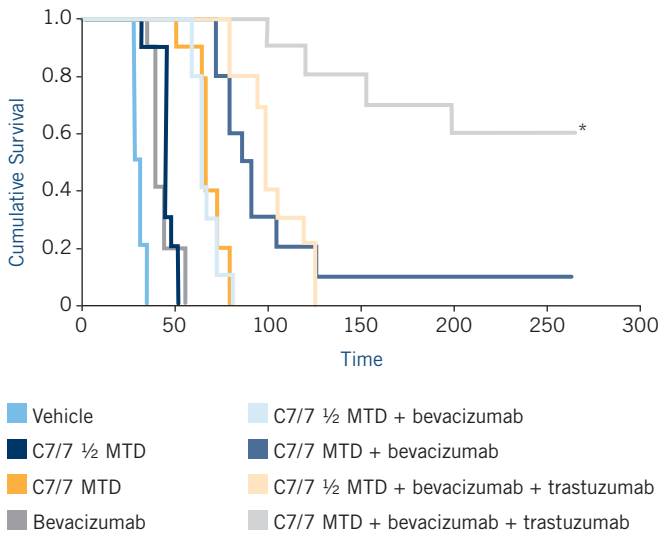
DR LOVE: What did your dose-escalation study show?

DR NORTON: We completed the Phase I-II trial and have determined that a fixed dose of 2,000 milligrams BID for seven days is a well-tolerated regimen (Theodoulou 2007). Indeed, many patients tolerated a higher dose — 2,000 milligrams/2,500 milligrams in one day for seven days — and that is delivering much more capecitabine than you can safely deliver on a 14-day schedule. Even 1,000 mg/m^2 for 14 days causes inordinate toxicity, for the most part, and patients require dose modifications (Yap 2007).

DR LOVE: At ASCO 2007, George Sledge presented data from the XCaliBr trial, which evaluated capecitabine with bevacizumab as front-line therapy for metastatic breast cancer. What were your thoughts on the data (1.4)?

1.3

Kaplan-Meier Cumulative Survival Estimate for Capecitabine, Seven Days On, Seven Days Off (C7/7), and Bevacizumab with or without Trastuzumab in Female Mice



* Follow-up ongoing for C7/7 MTD + bevacizumab + trastuzumab
MTD = maximum tolerated dose

SOURCE: With permission from Traina TA et al. *Proc ASCO* 2007;**Abstract 1049**.

DR NORTON: Until we combine bevacizumab and capecitabine at the optimum dose and schedule for capecitabine, we won't know how effective that combination is. In preclinical, experimental animal models, the combination is effective, and I see no reason to believe that it won't be effective in people. ■

1.4

XCaliBr: Efficacy of Capecitabine with Bevacizumab as First-Line Therapy in Metastatic Breast Cancer

Efficacy (median follow-up = 12.9 months)

Parameter	ITT (n = 106)	ER-negative (n = 49)	ER-positive (n = 57)
Median TTP (95% CI)	5.7 mos (4.9-8.4)	4.0 mos (3.0-4.9)	8.9 mos (7.5-13.6)
Median OS (95% CI)	16.0+ mos (12.9-*)	7.5 mos (5.6-16)	16.6+ mos (15.1-*)
ORR (CR + PR)	38%	27%	47%

* Not yet reached

ER-positive versus ER-negative, p <0.001 for all endpoints

SOURCE: Sledge G et al. *Proc ASCO* 2007;**Abstract 1013**.

SELECT PUBLICATIONS

Albain K et al. **Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen (ER) and/or progesterone (PgR) receptor-positive breast cancer: Mature outcomes and new biologic correlates on Phase III Intergroup trial 0100 (SWOG-8814).** *Breast Cancer Res Treat* 2004;88(Suppl 1):A-37. **Abstract**

Hayes DF et al. **HER2 and response to paclitaxel in node-positive breast cancer.** *N Engl J Med* 2007;357(15):1496-506. **Abstract**

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

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

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

Sledge G et al. **Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer.** *Proc ASCO* 2007;**Abstract 1013**.

Theodoulou M et al. **Phase I study of a novel capecitabine schedule based on Norton-Simon mathematical modeling.** *Proc ASCO* 2007;**Abstract 1045**.

Traina TA et al. **Preclinical testing of a novel regimen of capecitabine (C) in combination with bevacizumab (B) and trastuzumab (T) in a breast cancer xenograft model.** *Proc ASCO* 2007;**Abstract 1049**.

Yap YS et al. **Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer — How low can you go?** *The Breast* 2007;16(4):420-4. **Abstract**

INTERVIEW

John Mackey, MD

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

CD 1, Tracks 18-24 — CD 2, Tracks 1-7

CD 1

Track 18	Cancer International Research Group (CIRG)
Track 19	NSABP/CIRG "BETH" adjuvant trial of chemotherapy/ trastuzumab with or without bevacizumab in HER2-positive early breast cancer
Track 20	Cardiac safety and TCH/ bevacizumab
Track 21	Cardiac monitoring and management of bevacizumab-related hypertension on BETH
Track 22	Assessment of trastuzumab-associated cardiovascular risk
Track 23	Clinical use of adjuvant TCH versus AC → TH
Track 24	Cardiovascular effects of adjuvant therapy for breast cancer: Multiple-hit hypothesis

CD 2

Track 1	Multifactor decline in cardiovascular fitness among breast cancer survivors
Track 2	START: Exercise for breast cancer patients receiving adjuvant chemotherapy
Track 3	Long-term risk of congestive heart failure after anthracycline-containing adjuvant therapy
Track 4	Questioning the role of adjuvant anthracyclines
Track 5	Clinical use of docetaxel/ cyclophosphamide adjuvant chemotherapy
Track 6	Aromatase inhibitors and cardiovascular health
Track 7	CIRG clinical trial strategy focusing on validated molecular targets

Select Excerpts from the Interview

CD 1, Track 18

DR LOVE: What are some of the new trials being conducted by the Cancer International Research Group?

DR MACKEY: The most exciting trial that we're conducting is the BETH trial (2.1), a collaborative effort between the NSABP and CIRG that is evaluating bevacizumab in combination with trastuzumab in the adjuvant setting for HER2-positive breast cancer. We proposed the idea because Dennis Slamon's laboratory found evidence of a profound synergistic interaction between those two drugs. In Phase I and then Phase II trials, they demonstrated tremendous

efficacy with the two agents in advanced breast cancer (Pegram 2006; [2.2]). It was only logical to move it into the adjuvant setting.

In the BETH trial design, we require that all tumors be submitted for central analysis prior to randomization to ensure true HER2 positivity. We will also examine a number of molecular markers, and we hope to tease out the subpopulation of patients who particularly benefit from the combination of trastuzumab and bevacizumab.

2.1

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

Target Accrual: 2,875

Eligibility

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

Stratification

- Number of positive nodes
- Hormone receptor status

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

2.2

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

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

Select drug-related adverse events by grade (number of patients)

Adverse event	Grade I	Grade II	Grade III	Grade IV
Cardiac event*	7	5	0	1
Shortness of breath/exacerbation	0	1	0	0
Tachycardia	2	0	0	0
Hypertension	2	6	7	0

* According to NCI-CTC (v.2) criteria

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

CD 1, Tracks 19, 22

DR LOVE: What do we know about the cardiac safety associated with combining bevacizumab and trastuzumab?

DR MACKEY: At present, we don't have a lot of experience with bevacizumab in combination with agents that have been associated with cardiotoxicity. When I look at the literature, my take is that bevacizumab causes minimal direct cardiotoxicity. It does have cardiovascular side effects. I believe a slight increase occurs in bleeding and clotting, and a substantial proportion of patients develop hypertension.

Trastuzumab, when used either with or after anthracyclines, clearly carries a cardiotoxicity signal. At present we have four years of follow-up on the adjuvant trastuzumab trials, so we don't know whether the additional cardiotoxicity associated with trastuzumab following an anthracycline will be a big clinical problem in the future.

We've done some work in CIRG with the nonanthracycline adjuvant regimen of TCH (docetaxel, carboplatin and trastuzumab). Six cycles of TCH were administered in the adjuvant setting in BCIRG 006, and the rate of heart failure was low. Only four patients out of a thousand developed congestive heart failure (Slamon 2006; [2.3]). TCH appears to be an effective and fortunately noncardiotoxic adjuvant regimen, and we're using it as the backbone for the BETH trial (2.1).

If you take a strictly scientific view, for a woman with early-stage breast cancer that's HER2 driven, the absolute benefits are statistically identical from TCH and AC → TH. TCH is just as good in terms of efficacy. But a statistically significant benefit is evident in terms of the safety profile of TCH compared to an anthracycline/taxane backbone (Slamon 2006; [2.3]). When I view the data, I say, "We have two treatments that are equivalent and one is safer — end of discussion."

DR LOVE: In what situations, if any, are you using anthracyclines in adjuvant therapy for women with HER2-positive breast cancer?

DR MACKEY: Currently in my practice, I'm not.

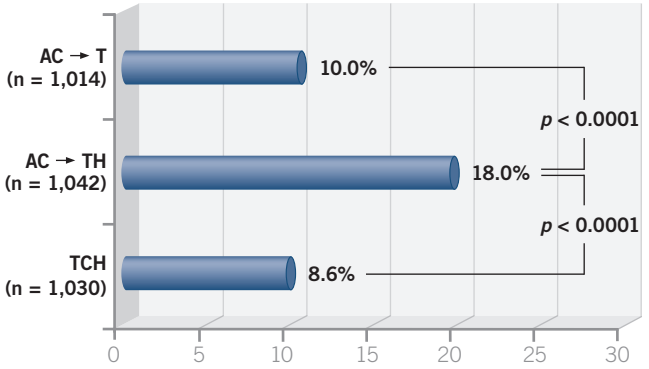
CD 2, Tracks 3-4

DR LOVE: What do you think about the available data on the long-term safety of anthracyclines?

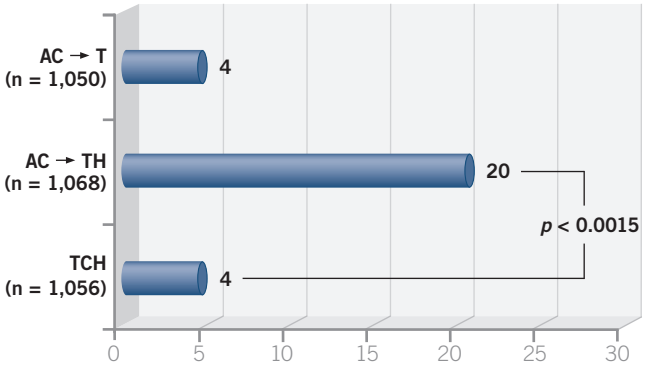
DR MACKEY: As breast cancer oncologists, we've been so concerned about curing the disease that we haven't thoroughly evaluated the collateral damage. So we don't have a lot of good long-term data on how people fare after adjuvant therapy with respect to cardiovascular morbidity. One of the best studies followed women treated with the MA5 regimen, which was an aggres-

2.3 **Cardiac Events in the Second Interim Analysis of BCIRG 006**

Percent of Patients with >10% Relative LVEF Decline



Left Ventricular Function Grade III/IV (Congestive Heart Failure) Events



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

sive epirubicin combination. At five years, 25 percent of the women on the study had substantial drops in LVEF (Shepherd 2006).

I believe one of the best data sets to address the issue comes from the SEER-Medicare database of women older than age 65 who received adjuvant therapy. Women who received CMF-like chemotherapy didn't experience much incremental cardiotoxicity compared to age-matched controls, but among the women who received anthracyclines, an excess rate of CHF emerged (Pinder 2007; [1.2, page 12]). We're concerned that a real problem exists, and it's not well described because we haven't been aware.

DR LOVE: What are your thoughts about the hypothesis that anthracyclines have no role in the adjuvant treatment of breast cancer, regardless of HER2 status?

DR MACKEY: It has merit. If you consider all the trials comparing a nonanthracycline- to an anthracycline-based adjuvant regimen, the incremental benefit of the anthracyclines seems to be entirely confined to the population with HER2-positive disease. This was before adjuvant trastuzumab. The anthracyclines seemed to be benefiting only the women with HER2-positive disease.

DR LOVE: In the past, CIRG did a lot of work with adjuvant TAC, which includes an anthracycline. In which situations are you using adjuvant anthracyclines right now for HER2-negative disease?

DR MACKEY: We compared TAC to a standard anthracycline regimen, FAC. TAC provided a benefit in HER2-positive, HER2-negative, ER-positive and ER-negative disease. There wasn't a subgroup that didn't benefit (Martin 2005). So we adopted TAC as our standard regimen here in Edmonton, Alberta. Now we have to ask, do we need the anthracycline?

The strict scientific answer is that we don't have prospective randomized trials to tell us whether you can drop the anthracycline in a regimen like TAC for a patient with HER2-negative disease. A trial is being launched, however, that is the brainchild of Steve Jones and US Oncology — it's called the TC-TAC trial. The study will compare TAC to TC (docetaxel/cyclophosphamide) for patients with HER2-negative disease, with the intent to show that you can drop the anthracycline and obtain equivalent efficacy and less toxicity with TC.

CD 2, Track 4

DR LOVE: In your own practice outside of a clinical trial setting, how do you handle decisions about whether to use an anthracycline for patients with HER2-negative disease?

DR MACKEY: My preference and what I discuss with patients is that we proceed with TC. I'm not administering anthracyclines to patients with HER2-negative disease unless the patient is adamant that she wants one of the older regimens. It's clear that TC has achieved a survival advantage over AC (Jones 2007c; [2.4]), which is exciting because this population is unselected and includes patients with HER2-positive disease who did not receive trastuzumab. So in a sense this trial was stacked against the TC regimen, but TC is still outperforming AC

2.4 **Adjuvant Trial Comparing Four Cycles of TC (Docetaxel/Cyclophosphamide) to Four Cycles of AC (Doxorubicin/Cyclophosphamide) for Women with Node-Negative or Node-Positive Early Breast Cancer: Six-Year Follow-Up Data**

	TC (n = 506)	AC (n = 510)	*p*-value
Overall disease-free survival	85%	79%	0.018
Overall survival	88%	84%	0.045

SOURCE: Jones S et al. San Antonio Breast Cancer Symposium 2007c;**Abstract 12**.

in terms of safety and efficacy. With the survival advantage, I simply don't see where the anthracyclines fit into the treatment of HER2-negative disease.

DR LOVE: What if the patient had five positive nodes?

DR MACKEY: I would administer six cycles of TC.

DR LOVE: What about a new TCH using cyclophosphamide, instead of carboplatin, with docetaxel and trastuzumab? US Oncology will evaluate this regimen in an adjuvant clinical trial for patients with HER2-positive, early breast cancer (2.5).

DR MACKEY: It's a perfectly reasonable approach. TC is good chemotherapy, and trastuzumab is good biological therapy. Whether it really matters what the chemotherapy backbone is in terms of efficacy is not clear to me. However, there is a lot to be said for the nonanthracycline backbone in terms of toxicity (Slamon 2006; [2.3]). ■

2.5

Phase II Trial of Adjuvant TC (Docetaxel/Cyclophosphamide) with Trastuzumab for Patients with HER2-Positive, Early-Stage Breast Cancer

Protocol IDs: US Oncology 06038, NCT00493649
Target Accrual: 260
Start Date: June 2007

Eligibility

- Stage I to IIIA, HER2-positive disease
- None of the following: myocardial infarction within six months of trial enrollment, NYHA Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmia, clinically significant pericardial disease or electrocardiographic evidence of acute ischemic change
- No abnormal baseline MUGA or ECHO (less than 50 percent or less than the institutional lower limit of normal)

Treatment → **Docetaxel/cyclophosphamide + trastuzumab**

Principal Investigator

US Oncology
Stephen E Jones
Tel: 832-348-5915

SOURCES: www.clinicaltrials.gov; www.usoncology.com

SELECT PUBLICATIONS

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial.** *Lancet Oncol* 2007;[Epub ahead of print]. **Abstract**

Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. **Abstract**

Buzdar A et al; Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006;7(8):633-43. **Abstract**

Coates AS et al. **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98.** *J Clin Oncol* 2007;25(5):486-92. **Abstract**

Courneya KS et al. **Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial.** *J Clin Oncol* 2007;25(28):4396-404. **Abstract**

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

Jones LW et al. **Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor-positive operable breast cancer.** *Oncologist* 2007a;12(10):1156-64. **Abstract**

Jones LW et al. **Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab.** *Cancer Epidemiol Biomarkers Prev* 2007b;16(5):1026-31. **Abstract**

Jones LW et al. **Early breast cancer therapy and cardiovascular injury.** *J Am Coll Cardiol* 2007c;50(15):1435-41. **Abstract**

Jones S et al. **Extended follow-up and analysis by age of the US Oncology adjuvant trial 9735: Docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well tolerated in women 65 or older.** San Antonio Breast Cancer Symposium 2007;**Abstract 12**.

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

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Mouridsen H et al. **Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: Safety analysis of BIG 1-98 trial.** *J Clin Oncol* 2007;25(36):5715-22. **Abstract**

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

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

Rasmussen BB et al, for the BIG 1-98 Collaborative and International Breast Cancer Study Groups. **Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: Supplementary results from the BIG 1-98 randomised trial.** *Lancet Oncol* 2007;[Epub ahead of print]. **Abstract**

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

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

Viale G et al. **Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98.** *J Clin Oncol* 2007;25(25):3846-52. **Abstract**

INTERVIEW

Charles E Geyer Jr, MD

Dr Geyer is Director of Medical Affairs of the National Surgical Adjuvant Breast and Bowel Project and is Vice-Chair of the Department of Human Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania.

CD 2, Tracks 8-20 — CD 3, Tracks 1-4

CD 2

Track 8 NSABP trial concept: Adjuvant sunitinib for patients with residual disease after neoadjuvant chemotherapy

Track 9 Cooperative group investigations of (neo)adjuvant bevacizumab

Track 10 NSABP-B-42: Extended adjuvant letrozole for postmenopausal patients with hormone receptor-positive breast cancer

Track 11 Clinical use of adjuvant aromatase inhibitor therapy beyond five years

Track 12 NSABP-B-35: Anastrozole versus tamoxifen for postmenopausal patients with hormone receptor-positive DCIS

Track 13 US Oncology trial of adjuvant TC versus TAC for patients with HER2-negative breast cancer

Track 14 Relationship between biomarker status and benefit from adjuvant taxanes

Track 15 Rationale for the BETH trial: Adjuvant chemotherapy/ trastuzumab with or without bevacizumab

Track 16 ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) study

Track 17 Mechanism of action of lapatinib

Track 18 Lapatinib with capecitabine for patients with HER2-positive advanced breast cancer

Track 19 Treatment after relapse on adjuvant trastuzumab

Track 20 Identification of biomarkers predictive of response to lapatinib

CD 3

Track 1 Lapatinib-associated cardiac effects

Track 2 Efficacy of lapatinib for brain metastases

Track 3 Optimizing the oral administration of lapatinib and capecitabine

Track 4 NSABP-B-41: Neoadjuvant AC followed by paclitaxel and trastuzumab, lapatinib or the combination for patients with operable HER2-positive breast cancer

Select Excerpts from the Interview

CD 2, Track 9

DR LOVE: What are some of the new areas of research that the NSABP is considering?

DR GEYER: We have a trial in development designed to investigate therapies for patients who have been through standard neoadjuvant chemotherapy regimens but have residual disease at the time of surgery. We know from the NSABP-B-27 study and others that, whereas the patients who achieve a complete pathologic response (pCR) do well, those with residual disease don't do as well and are actually at high risk (Bear 2006; Mamounas 2005).

Clearly some patients do have substantial residual disease after therapy. Their risk of recurrence is increased, and they don't derive benefit from additional chemotherapy. So what we have proposed is a two-arm trial comparing a treatment with an oral VEGF inhibitor, sunitinib, to placebo to determine whether treating patients with "micrometastatic disease" with a therapy targeted specifically at VEGF with platelet-derived growth factor receptor (PDGFR) improves outcomes and lowers the risk for recurrence. Our plan is to administer the therapy for a year.

DR LOVE: How do you think it will go taking patients out to a year on sunitinib? From what I have seen in renal cell carcinoma (RCC), sunitinib is not necessarily easy to tolerate.

DR GEYER: That has been a concern, but these targeted therapies have been administered for a year in initial trials, so we thought it would be reasonable to plan for a year. We will learn if side effects are sufficient that patients are discontinuing the medication. But our expectations are that patients will complete the year of therapy.

DR LOVE: What is known about sunitinib as breast cancer treatment?

DR GEYER: The data that led to its approval in RCC indicate that sunitinib effectively targets VEGF. Kathy Miller has evaluated it as a single agent for patients with previously treated breast cancer, and the data showed a response rate of 11 percent and an overall clinical benefit rate of 16 percent, which is respectable for single-agent therapy in pretreated patient populations, indicating that it does have activity in breast cancer (Miller 2005a).

CD 2, Track 10

DR LOVE: What's your take on the NSABP-B-40 neoadjuvant study with bevacizumab and the ECOG-E5103 adjuvant study evaluating chemotherapy with or without bevacizumab for patients with HER2-negative tumors?

DR GEYER: The results of the ECOG-E2100 trial in the metastatic setting were compelling (Miller 2005b), and they justified moving bevacizumab into adjuvant and neoadjuvant trials. I believe the ECOG adjuvant trial is a well designed study that will answer a number of questions regarding whether the addition of bevacizumab to chemotherapy improves outcomes and, if so, whether duration is a critical component.

NSABP-B-40 is one of the more complex trials that we have attempted to complete (3.1). Initially it was more of a pure chemotherapy trial investigating

whether or not adding antimetabolites to sequential AC/docetaxel would improve pCR rates.

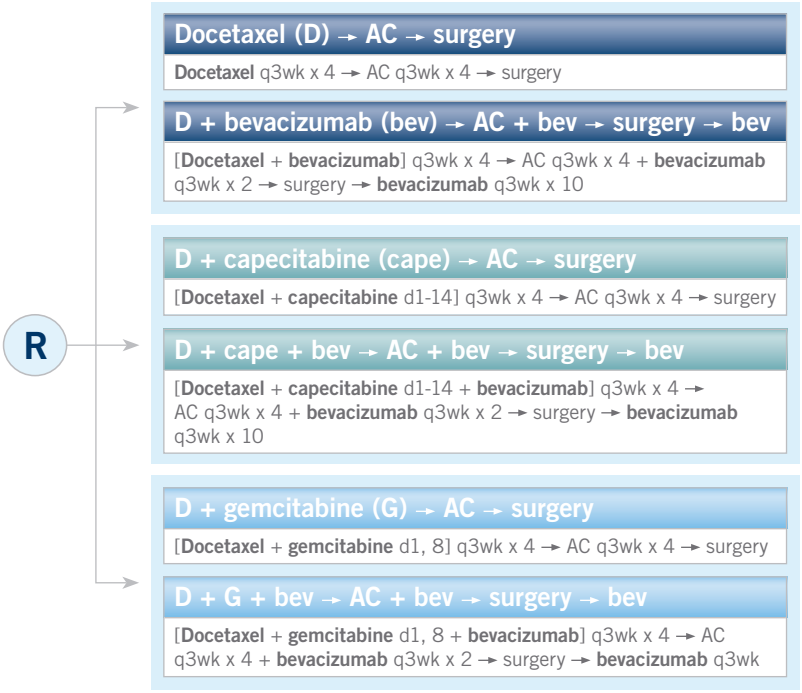
As the protocol was being developed, the data from the E2100 trial became available and a decision was made to ask a second question. So it is, in essence, a three-by-two study, in which half of the patients in each chemotherapy arm also receive bevacizumab and half of the patients do not.

The NSABP is also interested in collecting specimens from patients who do not achieve pCR to possibly understand evolving resistance mechanisms in addition to the up-front potential predictors for pCR. It's a complicated and challenging study, and we believe it will be a gold mine of information when the study is finished.

3.1

Phase III Randomized Trial of Six Neoadjuvant Regimens in Patients with Palpable and Operable HER2-Negative Breast Cancer

Protocol ID: NSABP-B-40
Target Accrual: 1,200



Eligibility

- Tumor ≥2 cm
- HER2-negative breast cancer

Patients with ER-positive and/or PR-positive disease receive a minimum of five years of hormonal therapy.

SOURCE: NCI Physician Data Query, December 2007.

CD 2, Tracks 11-12

DR LOVE: What is the current status of NSABP-B-42?

DR GEYER: B-42 is a trial for postmenopausal women with hormone receptor-positive breast cancer who have completed a standard five-year duration of hormonal therapy either entirely consisting of an aromatase inhibitor or up to three years of tamoxifen followed by an aromatase inhibitor (3.2). The randomization is to either letrozole or placebo and the accrual to date is at 489 out of a sample size of 3,840.

DR LOVE: I know your first choice is to put a patient on the study, but if that can't be done, how do you approach the decision to stop or continue at five years (3.3)?

DR GEYER: We try to get some sense of the patients' residual risk. We infer that based on their baseline risk from their disease at presentation — a larger tumor, a larger number of nodes and so on indicate a higher risk for recurrence initially.

The assumption is that the relative reduction is fixed, so the residual risk beyond five years is higher. So if I have a patient with a large number of positive nodes, I will discuss with that patient the uncertainties regarding benefits of additional therapy, toxicities and so on. I believe that you also have to assess how the patient is tolerating the aromatase inhibitor.

3.2

NSABP-B-42: A Phase III Trial to Determine Improvement in Disease-Free Survival with Adjuvant Letrozole Following Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI

Eligibility

- Postmenopausal
- No later than six months after completion of five years of hormonal therapy
- ER-positive and/or PR-positive
- Invasive breast cancer

R

- Letrozole daily x 5y
- Placebo daily x 5y

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Survival, recurrence-free interval, distant recurrence-free interval, osteoporotic fracture rate, arterial thrombosis

Target Accrual: 3,840 over 5.25 years

Current Accrual: 554 (12/10/07)

Date Activated: August 14, 2006

Study Contact

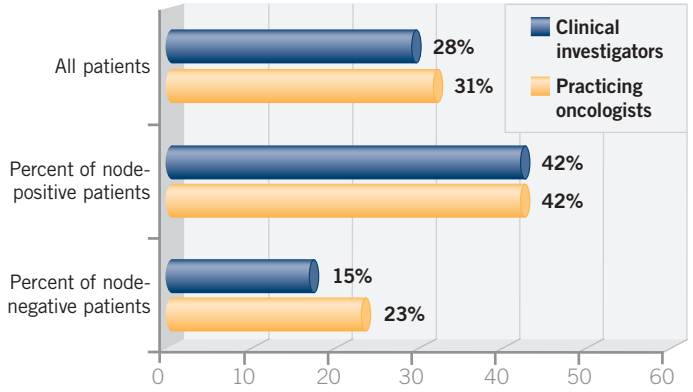
National Surgical Adjuvant Breast and Bowel Project
Eleftherios P Mamounas, MD, MPH
Protocol Chair

SOURCES: NSABP-B-42 Protocol, July 2006; www.nsabp.pitt.edu.

3.3

Patients Treated with Extended Adjuvant Aromatase Inhibitors: A National Patterns of Care Survey

For approximately what percent of your patients who complete five years of an AI do you continue the AI? (Mean)



SOURCE: *Patterns of Care in Medical Oncology* 2007;4(2). Available at: www.PatternsOfCare.com

CD 2, Track 16

DR LOVE: What are your thoughts about the BETH trial (2.1)?

DR GEYER: The statistical design for BETH is chemotherapy with trastuzumab with or without bevacizumab, and the protocol basically provides for two chemotherapy regimens. One is the TCH regimen that was used in the BCIRG 006 trial (Slamon 2006). The other regimen uses docetaxel at 100 mg/m^2 every three weeks times three cycles followed by FEC with the epirubicin at 90 mg/m^2. Patients on the docetaxel/FEC regimen receive the targeted therapy with the docetaxel. It is suspended during the FEC and then resumed after the FEC. Obviously the targeted therapy with TCH begins concurrently with the chemotherapy in both arms. All patients entered through the CIRG and NSABP will receive TC.

The idea of the two arms and the TCH justification arrive from the current results that Dr Slamon presented at the 2006 San Antonio meeting showing that outcomes with TCH versus AC → TH were statistically indistinguishable (3.4). The confidence intervals overlapped tremendously, and no statistically discernible difference in efficacy is apparent at this point, with a substantial number of events already reported.

The other compelling part of the 006 trial relates to the cardiac toxicity issue. All the trials with trastuzumab following anthracyclines have shown a low tolerable rate of cardiac dysfunction, but clearly the lowest cardiotoxicity rates of any of the trials were seen on the TCH arm. So I believe the TCH is

showing efficacy on a similar magnitude to the anthracycline and does have a more favorable safety profile.

CD 2, Track 17

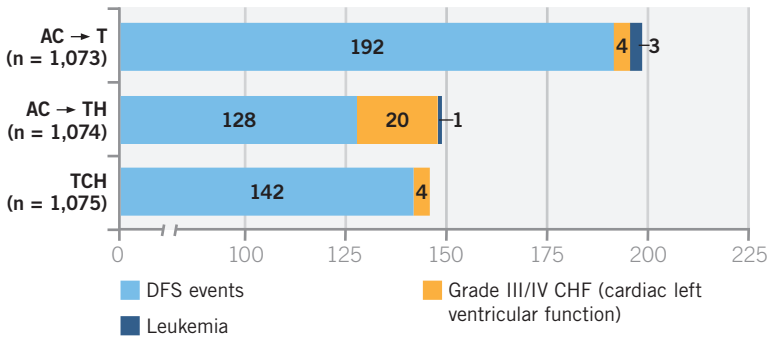
DR LOVE: Let's talk about the other major research strategy, embodied in the so-called ALTTO trial evaluating chemotherapy with trastuzumab, lapatinib or the combination of the two. Can you talk about the eligibility and design of that study?

DR GEYER: ALTTO is a particularly large trial of adjuvant or neoadjuvant targeted treatment for women with HER2-positive, operable breast cancer. Investigators can choose from a number of recommended anthracycline regimens, and if a patient's ejection fraction is 50 percent or higher, that patient can enter the trial and be randomly assigned to one of four targeted therapy options.

DR LOVE: What clinical research information do we have on the combination of trastuzumab and lapatinib?

3.4

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



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

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

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

DR GEYER: A Phase I dose-finding study showed that fatigue is the dose-limiting toxicity. With the standard dose of trastuzumab, the lapatinib has to be reduced to 1,000 mg/day from 1,500 mg/day. So the lapatinib dose must be adjusted according to the partner with which you're administering it.

CD 2, Track 19

DR LOVE: Can you review what we know from the clinical studies of lapatinib?

DR GEYER: A study that I was involved with, the lapatinib/capecitabine versus capecitabine alone study, crossed an early reporting boundary on the first interim analysis and so had accrual closed early (Geyer 2006). The data that we presented at the last ASCO meeting were an update of the efficacy data. That represents about four and a half additional months to what was in the manuscript in *The New England Journal of Medicine* (Geyer 2006). So the numbers have changed a little, but the overall findings are the same.

The hazard ratio for time to progression was 0.57, and the median time to progression was 4.3 for capecitabine to 6.2 months for the combination, so the data held for the initial publication.

DR LOVE: What did you observe in terms of side effects and toxicity in that study?

DR GEYER: The important thing to remember about the trial is that the comparator arm was capecitabine at 2,500 mg/m^2, and that is a dose that most practicing oncologists no longer use to begin therapy. I believe most of us are starting at 2,000 mg/m^2 or perhaps a little less. The only significant difference between the toxicity of the lapatinib/capecitabine and that dose of capecitabine was an increase in the rate of diarrhea from 40 percent to 60 percent, but the bulk of that increase was in the Grade I/Grade II range. So this dose did not substantially increase the toxicity that we see with 2,500 mg/m^2.

About the same number of patients — approximately 13 percent — discontinued therapy due to side effects on both arms. Overall, it was impressive that lapatinib didn't notably increase the toxicity, but this is a regimen that must be monitored and doses modified, or patients can experience substantial toxicity.

CD 3, Track 4

DR LOVE: Can you discuss the NSABP-B-41 neoadjuvant trial (3.5)?

DR GEYER: In this neoadjuvant trial, we use AC followed by weekly paclitaxel along with trastuzumab or lapatinib or the combination using pCR as a primary endpoint. After surgery, everyone completes the year of targeted therapy with trastuzumab.

Lapatinib clearly has a different mechanism of action than trastuzumab. My hope is that patients responding to trastuzumab will be different from patients

responding to lapatinib and to the combination of the two. I believe that it is important to see these trials completed, to collect the tissue and to find out whether there are fundamental differences among these women that can be identified before we begin therapy.

Then we can choose the correct drug from day one. That is why I believe the neoadjuvant studies are of particular importance here — to provide us with that kind of information. ■

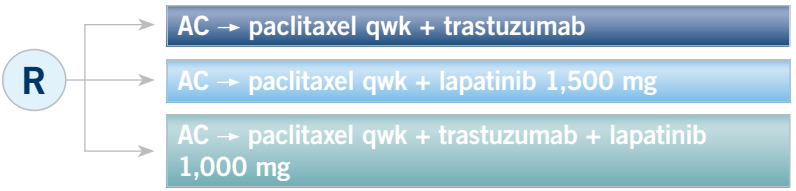
3.5

A Phase III Trial of Neoadjuvant Therapy for Patients with Palpable and Operable HER2-Positive Breast Cancer

Protocol ID: NSABP-B-41
Target Accrual: 522 Start Date: July 2007

Eligibility

HER2-positive, invasive breast cancer diagnosed with core needle biopsy with palpable breast mass ≥ 2.0 centimeters



Postoperative therapy for all patients: Trastuzumab 6 mg/kg q3wk to one year after the first dose of preoperative trastuzumab or lapatinib

Rationale for Lapatinib in NSABP-B-41: Mechanisms of Action and Resistance

"Since resistance to trastuzumab eventually results in progressive disease in the metastatic setting and contributes to recurrence following adjuvant trastuzumab-based therapy, it is important to develop agents other than trastuzumab that target HER2 signaling through different mechanisms of action. Lapatinib, an oral, small molecule, dual tyrosine kinase inhibitor of HER2 and EGFR, has demonstrated non-cross resistance with trastuzumab in preclinical studies and activity in women with HER2-positive, metastatic breast cancer progressing on trastuzumab. Trastuzumab blocks the downstream signaling of HER2 by binding to the extracellular domain of the receptor. Potential mechanisms of resistance to HER2 include: cleavage of the extracellular domain of HER2 which results in a potent oncogenic receptor (p95HER2) that is less responsive to trastuzumab; abnormal PTEN function; and heterodimerization with EGFR, with continued activation through the heterodimer by EGFR activation in spite of interruption of HER2 signaling. Lapatinib binds to the intracellular domains of HER2 and EGFR at the ATP-binding sites and prevents phosphorylation and activation of downstream signaling pathways. Because of this different mechanism of action, lapatinib may be effective in trastuzumab-resistant disease."

SOURCES: www.nsabp.pitt.edu/B-41.asp; www.clinicaltrials.gov; NSABP-B-41 Protocol Document, version June 12, 2007.

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Valabrega G et al. **Trastuzumab: Mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer.** *Ann Oncol* 2007;18(6):977-84. **Abstract**

ROUNDTABLE DISCUSSION

Schwartz Center Rounds

CD 3, Tracks 5-25

"It has been a harrowing experience for me and for my family. And yet, the ordeal has been punctuated by moments of exquisite compassion. I have been the recipient of an extraordinary array of human and humane responses to my plight. These acts of kindness — the simple human touch from my caregivers — have made the unbearable bearable."

— Kenneth B Schwartz

Shortly before his death from lung cancer at age 40 in September of 1995, Kenneth B Schwartz established an organization dedicated to strengthening the relationship between patients and caregivers in the changing healthcare system. Ken viewed the Center as a

vehicle to advance the ideas, hopes, and concerns that he expressed in his article, "A Patient's Story," published on July 16, 1995, in *The Boston Globe Magazine*....

During his ten-month ordeal, Mr Schwartz came to realize that what matters most when a medical issue arises — whether for ourselves or a loved one — is the "human connection" between patients and healthcare professionals. This special Roundtable discussion is dedicated to the Schwartz Center, a multidisciplinary forum in which caregivers discuss difficult emotional and social issues that arise in caring for patients. More than 26,000 clinicians at 129 sites in 26 states participate in these interactive discussions and share their experiences, thoughts and feelings on a variety of topics.

SOURCE: **www.theschwartzcenter.org**

Select Excerpts from the Discussion

CD 3, Tracks 5-25

Cases Discussed

- **DR WINER:** A young, single woman with metastatic breast cancer who has very limited social support wishes to adopt a child
- **DR BURRIS:** A 47-year-old woman with metastatic breast cancer is involved in a custody dispute for her 10- and 12-year-old children
- **DR CAREY:** A 54-year-old professional woman and mother of young children becomes depressed after completion of adjuvant chemotherapy for high-risk breast cancer
- **DR WOLFF:** A woman in her midthirties develops inflammatory breast cancer with bony metastases immediately after the birth of her first child

End-of-Life and Hospice Care

DR CAREY: I introduce the hospice discussion early. Each time we make a decision on active therapy versus symptom management, I remind patients that their condition isn't curable and that when they're tired of treatment, we can move on to simply managing their symptoms. I don't want it to be a surprise when I suggest that maybe it's time to stop active treatment.

DR BURRIS: Every Monday, after the weekend call, a little confrontation arises in our group because some clinicians can't talk to their patients about hospice. I have some colleagues whose patients are on hospice for 1.5 days. Hospice should be a six-week experience at a minimum, and it's meant to be up to six months or longer.

DR WOLFF: The national average for the amount of time patients are in hospice is approximately three days.

It takes five minutes to say, "Your cancer has progressed. Let's change treatment." It takes an hour to say, "Your cancer has progressed. Maybe it is time to stop doing treatment."

Sometimes we have not had those conversations until that moment. We can start conversations earlier about how far we may go, but that's easier said than done.

DR WINER: We need to discuss, set and recalibrate expectations with the patient along the way. That requires spending a good deal of time on many different occasions talking to our patients about where they are in their trajectory.

Organizing an Approach to End-of-Life Decision-Making

"Physicians can organize their approach to helping patients to make critical end-of-life decisions by assessing the patient's current physical symptoms and psychological and spiritual needs, assessing family and social support systems, estimating and communicating prognosis, and asking the patient to define his or her end-of-life goals. The optimal timing for this discussion is during a routine outpatient visit for a patient with any chronic life-limiting disease. The patient should have an opportunity to learn from the physician the future expected disease course, potential treatment options, and together with the physician, define specific goals of care prior to an acute medical crisis.

... not every crisis or possible intervention can be anticipated and discussed before the event. However, beginning the conversation can develop the physician's understanding of the patient's preferences, reassure the patient that the physician is open to discussing end-of-life care, and begin what may be a slow process toward acceptance of a terminal diagnosis."

[Citations omitted]

SOURCE: Weissman DE. *JAMA* 2004;292(14):1738-43. **Abstract**

Coping with Burnout in Oncology

DR BURRIS: I have witnessed some colleagues lately who made me think, "I don't want to end up practicing oncology like that." They make business relationships with patients and quit having the personal interaction. Some become guarded. I believe the oncologists who handle their practices in a healthy fashion appreciate how short life is and the need to take advantage of what you can while you're here.

DR WINER: I work out religiously — for my brain, not my body. Work creeps into my life at many hours of the day and night, but I also really enjoy what I do. It helps to have colleagues to talk to who deal with the same problems. If you wall yourself off from patients, then I believe you burn out. Dealing with some of these challenging issues and getting to know patients help protect you because you feel that you're doing the best job you can.

DR WOLFF: One of the key issues in taking care of myself is to try to enjoy

what I do. In many cases, we are helping people survive. In other cases, we are not, but we are helping them and their families cope with a difficult situation. Diversity in my work also helps, as does having a balanced life in terms of exercise, physical activity and time with my family.

Effect of Exercise After Completed Treatment for Early Breast Cancer

"Individuals treated for cancer often experience higher levels of emotional distress than the general population. Previous research has shown that exercise can have an ameliorating effect on these problems. This 12-month prospective longitudinal study investigated mood, quality of life, cancer-related symptoms, and exercise behavior of 69 women who had completed treatment for Stage 0-2 breast cancer. We studied the natural progression of exercise participation after cancer treatment....

Results indicated that women did not increase their exercise participation over time and that overall mean minutes of exercise participation were below recommended levels. Baseline demographic predictors of exercise participation included younger age, having a spouse or partner, increased time since diagnosis, higher social support, and higher depression. Exercise participation was associated with improved physical functioning, but not overall mood or cancer-related symptoms."

SOURCE: Pinto BM et al. *Psychooncology* 2002;11(5):389-400. **Abstract**

Qualitative Study of Children's Perceptions of the Mother's Breast Cancer

"This study builds on previous work by interviewing children aged 6-18 years old as well as mothers recently diagnosed with breast cancer. We found that even very young children were often aware of cancer as a disease before their mother's disease was diagnosed, but that this awareness was often skewed.... Many children associated the word cancer with death. Children who knew (of) someone else with cancer could mistakenly assume that their mother's experience would be the same.

Parents are often unaware how much their children know and, often reeling from the diagnosis themselves, may not be in the best position to decide what and how to tell them. Our results suggest that many parents would benefit from preparation to tell their children and consider the ways children at different developmental stages might react."

SOURCE: Forrest G et al. *BMJ* 2006;332(7548):998-1003. **Abstract**

Impact of a Parent's Cancer Diagnosis on Young Children

DR WINER: How kids fare depends on how the parents cope with their experiences. I often tell people this is why they need to obtain help and support for themselves. The better shape they are in psychologically, the better the kids will adjust to these difficult situations. One good reason to try to get their act together emotionally and psychologically is that their kids will do much better, not only while they're sick but years afterwards. When secrets are held in the family and communication is poor, the kids feel it and everything falls apart.

DR CAREY: Many of our patients don't have their young children participate actively in their care, and I generally advocate against that. I believe the pediatric oncologists are much more thoughtful about these issues, and they have found that children fare much better with honesty. What children invent in their heads, if you try to protect them, is worse than the reality. In general, they tend to feel better if they're participants in the process. In my own clinical experience, when the parents do include the children, the function of the family seems to be better overall.

Psychosocial Issues in the Postadjuvant Period

DR CAREY: Among patients completing adjuvant therapy, subclinical and clinical depression are far more common than we have recognized. Data from the psychiatric literature suggest that a form of post-traumatic stress disorder occurs in many patients. However, it has not been established how aggressive we need to be in diagnosing and treating this condition. I know a psychologist who works with many of my patients and is especially attuned to these issues. Often my patients see her for a few months after completing adjuvant therapy.

DR BURRIS: Some patients don't want to think about their cancer, but a substantial proportion of patients would just as soon come in every month and ask, "What can I do now?" Without a magic prevention pill, diet and exercise seem to be solid with regard to enhancing immune system functioning.

DR CAREY: I have patients who engage in exercise and lifestyle modifications, but I advise them that I don't know that it will affect their breast cancer recurrence risk and that they are not in charge of whether their disease comes back.

DR WINER: The syndrome of falling apart or having a hard time at the end of adjuvant treatment should not be viewed as the exception. It happens with the

A Medical Oncologist's Perspective on Contributors to Stress and Burnout

"Over the past eight years, I have led discussions and had private conversations about stress and burnout with oncologists of all stripes. Several common themes have emerged with regard to what it is that stresses and burns out oncologists and what helps them the most. At the top of the burnout list are time issues: not enough time with patients, time with family, or time for relaxation. Oncologists are overcommitted and overscheduled, inundated with paperwork, phone calls, and anxiety over never seeming to know enough.

Physical, mental, and psychological weariness are enormous. Sleep is interrupted by calls, worries, children, and family issues. The afternoon waiting room is filled with apprehensive patients newly diagnosed, or waiting for news of restaging, all of them nice people, many of them friends. Telling one person their cancer has progressed despite all the hard work they and their family have done hits you hard. Telling several in succession can decimate you. You may begin to protect yourself by withdrawing, becoming cynical, jaded. Sartre's existential nausea may creep in. You begin to wonder if you have accomplished anything."

SOURCE: Lyckholm L. *Oncology (Williston Park)* 2007;21(2):269. No abstract available

majority of patients and is the result of transitioning to a time when they're receiving less support from us, seeing us less frequently, no longer focused on completing treatment. Their personal problems, put aside during therapy, can come crashing back when treatment is completed. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The proposed BETH trial by CIRG and NSABP will evaluate the combination of chemotherapy/trastuzumab with _____ for women with HER2-positive, early breast cancer.**
   a. Lapatinib
   b. Bevacizumab
   c. Erlotinib
   d. Cetuximab
   e. None of the above
2. **In BCIRG 006, the incidence of heart failure was _____ with TCH compared to AC → TH.**
   a. Lower
   b. Higher
   c. The same
3. **START randomly assigned women with early-stage breast cancer who were about to begin chemotherapy to _____.**
   a. Usual care
   b. Aerobic exercise
   c. Resistance exercise
   d. Dietary fat reduction
   e. a, b and c
   f. All of the above
4. **The TC-TAC trial will determine whether anthracyclines are a necessary component of adjuvant chemotherapy regimens for women with HER2-negative, early breast cancer.**
   a. True
   b. False
5. **A significant _____ survival advantage was reported with TC over AC as adjuvant therapy for early breast cancer.**
   a. Disease-free
   b. Overall
   c. Both a and b
   d. None of the above
6. **US Oncology will evaluate trastuzumab in combination with docetaxel/cyclophosphamide for women with HER2-positive, early breast cancer.**
   a. True
   b. False
7. **In ECOG-E2100, the primary site of metastases was limited to the bone.**
   a. True
   b. False
8. **NSABP-B-42 is a Phase III trial to determine improvement in _____ with adjuvant letrozole following completion of five years of hormonal therapy.**
   a. Time to progression
   b. Disease-free survival
   c. Overall survival
9. **_____ is a small-molecule tyrosine kinase inhibitor that binds by interfering with the phosphorylation sites of the tyrosine kinase residues in EGFR and HER2.**
   a. Lapatinib
   b. Trastuzumab
   c. Letrozole
10. **Pinder and colleagues reported a higher risk of congestive heart failure among women aged _____ who received an anthracycline-based regimen in the adjuvant setting.**
    a. 66 to 70
    b. 71 to 80
    c. 81 to 90
11. **In ECOG-E2100, published in *The New England Journal of Medicine*, the addition of bevacizumab to paclitaxel as first-line therapy for patients with metastatic breast cancer resulted in a significant improvement in _____.**
    a. Progression-free survival
    b. Overall survival
    c. Objective response rate
    d. Both a and c
    e. a, b and c
12. **In an exploratory analysis of CALGB-9344 published in *The New England Journal of Medicine* by Dr Hayes and colleagues, a three-way interaction was observed among HER2 positivity, estrogen receptor negativity and benefit from _____.**
    a. AC chemotherapy
    b. Trastuzumab
    c. Paclitaxel

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

EVALUATION FORM

Breast Cancer Update — Issue 1, 2008

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment, and incorporate these findings into management strategies in the neoadjuvant, adjuvant and metastatic 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
- Describe the key clinical and pathologic risk factors that influence clinician selection of the medical and surgical management of early breast cancer. . . . . 5 4 3 2 1 N/A
- Identify existing data and emerging research focusing on the optimal duration and sequence of adjuvant endocrine therapy in the management of the postmenopausal patient with ER-positive breast cancer, and apply this evidence to routine patient care decisions. . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for early and advanced HER2-positive breast cancer. . . . . 5 4 3 2 1 N/A
- Evaluate the practical application of currently available tissue-based genomic assays to assist with therapeutic decision-making in the management of early breast cancer and, when applicable, use these in the selection of individualized treatment regimens. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense or alternative novel scheduling and the contributory roles of taxanes and anthracyclines, and explain the absolute risks and benefits of these regimens to patients. . . 5 4 3 2 1 N/A
- Evaluate the emerging data for novel biologic and molecular-targeted therapies with clinical activity in breast cancer, and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . . . . 5 4 3 2 1 N/A
- Explore the challenging practice of integrating psychosocial support, optimal patient-physician communication strategies and evidence-based clinical decision-making into comprehensive oncology care. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Howard A Burris III, MD	5 4 3 2 1	5 4 3 2 1
Lisa A Carey, MD	5 4 3 2 1	5 4 3 2 1
Charles E Geyer Jr, MD	5 4 3 2 1	5 4 3 2 1
John Mackey, MD	5 4 3 2 1	5 4 3 2 1
Larry Norton, 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
Antonio C Wolff, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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

☐ Audio CDs ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 1, 2008

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

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Telephone: ..... Fax: .....

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Research To Practice designates this educational activity for a maximum of 4.25 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

Signature: ..... Date: .....

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

BCU108

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

Breast Cancer® UPDATE

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Breast Cancer®

U P D A T E

This program is supported by educational grants from
Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology,
Genomic Health Inc, GlaxoSmithKline, Roche Laboratories Inc and Sanofi-Aventis.

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Last review date: January 2008
Release date: January 2008
Expiration date: January 2009
Estimated time to complete: 4.25 hours