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Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

Marc E Lippman, MD

C Kent Osborne, MD

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Charles E Geyer Jr, MD

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MIAMI BREAST CANCER CONFERENCE TUMOR PANEL DISCUSSION ON SYSTEMIC THERAPY OF METASTATIC DISEASE

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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 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 6 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Burstein, Geyer, Hayes, Henderson, Lippman, Osborne, Robertson, Smith, Vicini and Winer on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

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**

American Society of Breast Disease Annual Symposium
April 12-14, 2007
San Francisco, California
Event website: **asbd.org**

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

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

EDITOR'S NOTE

Neil Love, MD

Reality check

You are a tanned, fit, much-published clinical investigator specializing in prostate cancer. You just turned 60 and are in the peak of health. Yet within the span of two years, you have your prostate yanked out, a PSA recurrence and nine miserable months of pelvic radiation and combined androgen blockade. Your PSA becomes undetectable, but three years later it's back and doubling every three months, the strongest known predictor of prostate cancer death. You can go back on hormone therapy, but it's unlikely to provide long-term tumor control and you hated life as a chemical eunuch.

In 2000, when our CME group launched a prostate cancer audio series for urologists and radiation oncologists, Eastern Virginia Medical School urologist Dr Paul Schellhammer was one of the first investigators we invited to our offices in Miami for an interview. Paul agreed, hopped on a plane and spent a day as a visiting professor helping to bring us up to speed on the intricacies of this unique disease. However, his visit instantly became one of the most profound and deeply moving experiences of my career when he began our conversation by relating his recent travails as a prostate cancer patient.

Paul Schellhammer, MD

Since that time, Paul and I have caught up every year or so to update our national audience on his progress. During the most recent interview this summer, he related the excruciating dilemma described above, and to my surprise, rather than take the traditional route of androgen deprivation therapy, he had just entered a Phase II ECOG trial examining the role of lapatinib.

Lapatinib for prostate cancer? Why not? This agent has minimal toxicity (mainly skin rash) and perhaps Paul will be as fortunate as the women discussed by Dr Charles Geyer on this issue of *Breast Cancer Update*, who took a chance and entered a study randomly assigning patients with HER2-positive breast cancer progressing on trastuzumab after prior anthracycline and taxane therapy to capecitabine alone or with lapatinib.

The findings in this heavily pretreated population are very encouraging. On average, patients receiving the combination experienced more than a doubling in time to progression. I haven't heard much about an anti-HER2 approach to prostate cancer, but the point of this narrative is that both laypeople and highly informed patients like Paul Schellhammer are looking for innovation and the opportunity to perhaps be on the earliest wave of the next generation of targeted agents, just like the thousands of women who participated in the adjuvant trastuzumab trials hoping to avoid relapse.

Along the same train of thought, in this issue, Dr Marc Lippman talks about the translational approach to oncology that he has been enthusiastically championing for more than three decades. Marc has always loved pushing emotional buttons, particularly when he's right, and during this most recent interview, he issued forth the following fireworks:

> "It's thrilling and exciting to go to cancer meetings these days and see such a broad array of exciting activities, any one of which one could imagine having a specific transformative event on the disease. Whether or not you've spent your life doing angiogenesis or apoptosis or DNA repair or drug delivery, there's enough excitement and good work going on to imagine any of those approaches succeeding.
>
> In terms of barriers to moving forward, many are political and economic. We are still a disaster as a nation and as a world in putting patients on study. It's extraordinarily unfortunate that so few patients even to this date participate in trials. I'm deeply concerned about the substantial reduction in the federal budgets, despite the funding available from pharmaceutical companies. The major intellectual engine that drives cancer research is still academic in origin and then licensed or, in other ways, developed by the pharmaceutical industry.
>
> We're playing with fire right now to look at a flat or decreasing NIH budget, and that has ramifications not only in terms of actual investigations but also, what I see every day as Chairman of Medicine, in terms of decreased enthusiasm for an academic life. People don't want a life with this level of uncertainty, and I'm afraid we will lose a generation of the kinds of translational and clinical investigators that will be essential to driving this process forward. That would be a disgrace."
>
> ***— Marc E Lippman, MD***

It might just be time for cancer advocates to step in here. (Lance, are you out there?) The squeaky wheel gets the whatever. Putting the funding issue aside, there's another piece of the puzzle that truly has the potential to change the management of this disease, and that is the long-awaited NSABP-B-40 neoadjuvant trial (Figure 1), discussed by Dr Geyer on this program. Norm Wolmark and his NSABP warriors have been pushing this new-age approach to translational research through the morass of federal bureaucracy for more than three years, but finally it is about to happen.

The groundbreaking B-40 trial will generate answers years earlier and with fewer patients than adjuvant and neoadjuvant trials focusing on the traditional endpoints of disease-free and overall survival. The study will look primarily at pathologic complete response and tissue predictors of response to three different chemotherapy regimens alone or with bevacizumab. Cliff Hudis tells me that the CALGB and other Intergroup member groups are also shifting their emphasis toward neoadjuvant trials, particularly to identify active new agents quicker. Based on how patients like Paul Schellhammer view molecular targeted therapy, there is perhaps a rationale for optimism that trials like B-40 (and prior efforts such as Jenny Chang's neoadjuvant trastuzumab study in locally advanced disease) will significantly accelerate progress.

As more targets and targeted agents become available, we will also confront more complex acronyms for regimens. I like the sound of lapatinib with capecitabine: "Lapcap," "Lapacape" or the more concise "LC," and I will go on record with this prediction: In 2010, the most common adjuvant therapy for node-positive breast cancer patients with ER-positive, HER2-positive tumors will be dose-dense AC → nanoparticle paclitaxel/trastuzumab/capecitabine/lapatinib/aromatase inhibitor/fulvestrant ("ACATCLAF"), which at least sounds less threatening than R-HyperCVAD or PROMACE CYTOBOM. ■

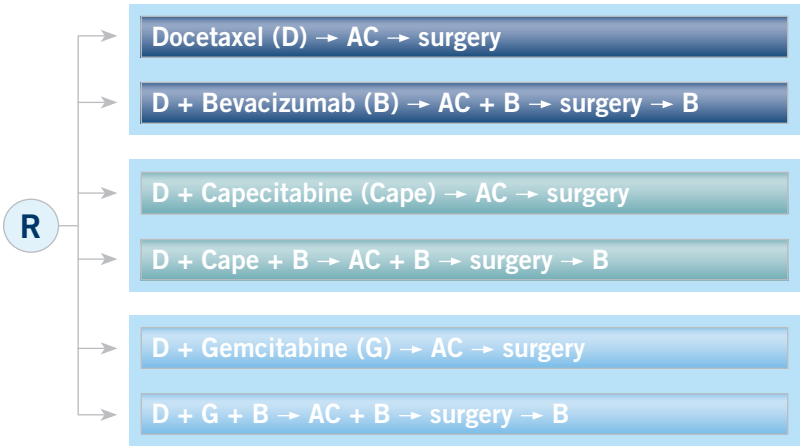
— Neil Love, MD
NLove@ResearchToPractice.net
October 12, 2006

1

Phase III Randomized Trial of Six Neoadjuvant Regimens for 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



SOURCE: NSABP Group Meeting, April 2006.

INTERVIEW

Marc E Lippman, MD

Dr Lippman is John G Searle Professor and Chair in the Department of Internal Medicine at the University of Michigan in Ann Arbor, Michigan.

Tracks 1-11

Select Excerpts from the Interview

Track 2

DR LOVE: Jenny Chang did some fascinating work with trastuzumab in the neoadjuvant setting showing that apoptosis was a big part of its antitumor effect (Mohsin 2005; [1.1]). Overall, what do we know about how trastuzumab works?

DR LIPPMAN: Some conflicting data exist on the mechanisms of action of trastuzumab. One thing that seems fairly certain is that it interferes with the signaling of the EGF receptor family on the cell surface.

Trastuzumab is an antibody to HER2. By interfering with that receptor, it blocks the intracellular signaling from that receptor, which is, in effect, a growth factor signal to the cell. Therefore, the cell is unable to continue its normal proliferative process and commonly undergoes apoptotic cell death.

1.1 **Neoadjuvant Trastuzumab Induces Apoptosis in Primary Breast Cancer**

"In conclusion, contrary to in vitro data, this prospective in vivo study demonstrates that trastuzumab induces apoptosis but does not affect cell proliferation as measured by Ki67 in the primary breast cancers of women receiving neoadjuvant treatment. This data suggests that trastuzumab would not likely antagonize the effects of chemotherapy on a cell kinetic basis, which might be of concern with other growth factor inhibitors, but would act coordinately to induce cell death."

SOURCE: Mohsin SK et al. *J Clin Oncol* 2005;23(11):2460-8. **Abstract**

Track 6

DR LOVE: What are your thoughts on the issue of response to chemotherapy based on estrogen-receptor status?

DR LIPPMAN: Almost 30 years ago, we published, in *The New England Journal of Medicine*, that patients with ER-negative disease responded more frequently to chemotherapy (Lippman 1978) than patients with ER-positive disease. Those data have been replicated in the meta-analyses conducted in England by Sir Richard Peto and his collaborators (EBCTCG 2005).

The clue as to why that occurs is obtained if you observe recurrence rates for women with breast cancer as a function of whether their disease is ER-positive or ER-negative. It is commonly said, but that doesn't necessarily make it the truth, that having ER-positive disease is a good prognostic factor. The data show — and this has now been shown several times — that early on, if your disease is ER-positive, your relapse rates are lower.

Over time, the patients with ER-negative disease who relapse at a higher rate initially stop relapsing, perhaps because most of the ones with bad prognoses have already died, whereas the patients with ER-positive disease continue to relapse, and those lines actually cross. At about 10 to 15 years, you're worse off having ER-positive than ER-negative disease.

Biologically, that probably means ER-positive tumors are growing more slowly. Therefore, the whole story of why chemotherapy works a little better is probably based on the fact that ER-negative tumors have a slightly higher cycling rate and are faster growing. A wealth of data suggests they're a little more sensitive to chemotherapy.

Tracks 7-8

DR LOVE: What was your impression of Dennis Slamon's presentation at the 2005 San Antonio Breast Cancer Symposium from the BCIRG 006 trial, specifically the data on TOPO II?

DR LIPPMAN: These were very exciting data, which I hope are substanti-

ated. It makes biological sense — TOPO II is a target for doxorubicin. That would potentially explain which subsets of patients gained particular advantage from the doxorubicin combinations compared to the platinum combinations (Slamon 2005; [1.2]).

I'm not ready to draw the conclusion that Professor Slamon seemed to want to draw, which is that in those patients who did not overexpress TOPO II, the use of a nondoxorubicin-containing combination was as efficacious (Slamon 2005).

That may be true, but I'm not there yet. I believe we need more analysis. Given the additional cardiac risks of using trastuzumab with doxorubicin, particularly in older women, it would be nice to have a less cardiotoxic regimen to use.

In that same regard, I found the data Soon Paik presented from the NSABP on cMYC overexpression (Kim 2005; [1.3]) extremely exciting and, once again, biologically plausible.

cMYC is an oncogene that is generally upregulated when cells are stimulated to grow; it is part of the growth response. When cMYC is overexpressed in tumors, it can transform other cells to become cancerous, and it is clearly overexpressed in about 20 to 25 percent of human breast cancer cases.

The question is, why is it that many patients with tumors that unquestionably overexpress HER2 do not respond to trastuzumab? Even in previously untreated patients, the response rates are only about 35 percent.

Dr Paik's data showed rather conclusively that only in those patients whose tumors coexpressed cMYC and HER2 was a response to trastuzumab seen (Kim 2005; [1.3]). Those data must be replicated, but if that is the case, this observation would be tremendously insightful. ■

1.2

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

	TOPO II amplified	TOPO II nonamplified
All patients (n = 744; n = 1,376)	57 (7.7%)	191 (13.9%)
AC → T (n = 227, n = 458)	23 (10.1%)	92 (20.1%)
AC → TH (n = 265, n = 472)	13 (4.9%)	45 (9.5%)
TCH (n = 252, n = 446)	21 (8.3%)	54 (12.1%)

"Coamplification of the TOPO II gene with HER2 may identify a subset of the HER2 amplified patients who might benefit from an anthracycline making it worth taking the risk of the cardiac dysfunction. Conversely, for 65 percent of the patients where there is no TOPO II amplification, they may be ideal candidates for an efficacious non-anthracycline containing regimen."

SOURCE: Slamon D et al, on behalf of the BCIRG 006 Investigators. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

1.3

NSABP-B-31: Efficacy of Adjuvant Trastuzumab According to the Presence of cMYC Amplification

	cMYC amplified (n = 471)	cMYC not amplified (n = 1,078)	Interaction *p*-value
Hazard ratio for recurrence	0.24	0.63	0.007
Hazard ratio for death	0.36	0.99	0.037

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

SELECT PUBLICATIONS

Burstein HJ. **The distinctive nature of HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1652-4. No abstract available

Buzdar AU. **Topoisomerase II alpha gene amplification and response to anthracycline-containing adjuvant chemotherapy in breast cancer.** *J Clin Oncol* 2006;24(16):2409-11. No abstract available

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13. **Abstract**

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

Kim C et al. **Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

Koziner B et al. **Pooled safety analysis of oblimersen alone or with fludarabine and cyclophosphamide in patients with advanced chronic lymphocytic leukemia.** *Proc ASCO* 2006;**Abstract 6611**.

Lippman ME et al. **The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer.** *N Engl J Med* 1978;298(22):1223-8. **Abstract**

Mohsin SK et al. **Neoadjuvant trastuzumab induces apoptosis in primary breast cancers.** *J Clin Oncol* 2005;23(11):2460-8. **Abstract**

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

Scandinavian Breast Group Trial 9401. **Topoisomerase II alpha gene amplification predicts favorable treatment response to tailored and dose-escalated anthracycline-based adjuvant chemotherapy in HER-2/neu-amplified breast cancer: Scandinavian Breast Group Trial 9401.** *J Clin Oncol* 2006;24(16):2428-36. **Abstract**

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

Villman K et al. **TOP2A and HER2 gene amplification as predictors of response to anthracycline treatment in breast cancer.** *Acta Oncol* 2006;45(5):590-6. **Abstract**

INTERVIEW

C Kent Osborne, MD

Dr Osborne is Director of the Cancer Center and Professor of Medicine and Molecular and Cellular Biology at Baylor College of Medicine in Houston, Texas.

Tracks 1-10

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss your current research interests?

DR OSBORNE: Right now, our main focus is to understand how tumors become resistant to hormone therapy. What we've discovered over the years is that a relationship exists between growth factor receptors and the estrogen receptor pathway (Osborne 2003).

In a sense, these pathways talk to each other and amplify the signals coming from each other. Data from our laboratory studies and from other laboratories are now beginning to be supported by results of clinical studies, which show that one of the ways tumors can become resistant — not only to tamoxifen but also to estrogen deprivation therapies like aromatase inhibitors — is through cross talk between growth factor pathways and estrogen receptors (Osborne 2005).

If that's the case, it might make sense to try and block both pathways simultaneously to get the maximum benefit. If you have a tumor, for instance, that

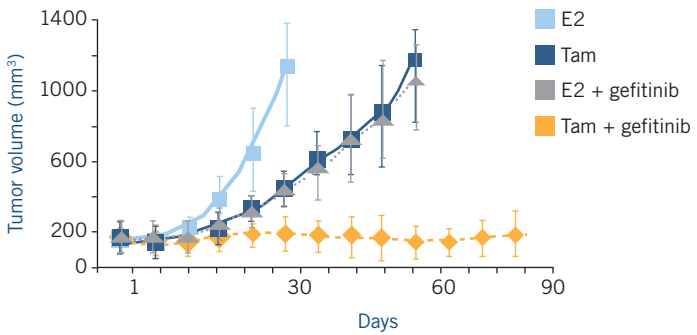
expresses estrogen receptor and overexpresses HER2, our data suggest that optimal therapeutic benefit requires targeting both receptors. You're not going to get a very good result by simply using trastuzumab to block HER2 and leaving the estrogen receptor wide open. Nor would you gain much ground by blocking the estrogen receptor and leaving HER2 wide open, because of the receptor cross talk.

Our group has been trying to see how we can best block those pathways, particularly the HER2 pathway. We found that although drugs like trastuzumab, gefitinib, and lapatinib block the HER2 and EGFR pathways, alone they don't do it optimally. Combinations of those therapies (Shou 2004; [2.1]) are needed to block what are called "heterodyne pairs" that form between different families of receptors.

If we block all the possible combinations, at least in preclinical mouse models for human breast cancer, we can frequently eradicate the tumors. These concepts are now starting to be tested in clinical trials in which we're using combinations of lapatinib and trastuzumab or gefitinib and trastuzumab and another drug that's being developed called pertuzumab.

2.1

Tumor Volume in Athymic Mice Bearing MCF-7/HER2-18 Tumors*



* Tumor growth was measured following treatment with estrogen (E2) or tamoxifen (Tam) with or without gefitinib.

SOURCE: Shou J et al. **Mechanisms of tamoxifen resistance: Increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer.** *J Natl Cancer Inst* 2004;96(12):926-35, by permission of Oxford University Press. **Abstract**

Track 4

DR LOVE: Can you comment on quality control in assays of estrogen receptor and HER2?

DR OSBORNE: I believe the assays for HER2 and ER are not very good in this country or around the world because they haven't been standardized, nor

validated against patients treated in specific ways. By and large only a couple of studies have done this. Many laboratories develop their own assays and use their own antibodies, thinking that their own technique is going to reproduce what others have published, and in fact it doesn't.

This problem is well documented, particularly in the NSABP-B-24 study that randomly assigned patients to tamoxifen or placebo. When the NSABP analyzed the ER assays done in the local hospitals (Allred 2002), we saw benefit from tamoxifen in patients with ER-negative disease (2.2), suggesting false negatives.

When those analyses were repeated in Craig Allred's laboratory, we saw no benefit from tamoxifen in ER-negative tumors determined by his assay and lots of benefit in tumors that were ER-positive. It turned out that 15 to 20 percent of the results were false negatives. That's a big problem when you consider this is potentially curative therapy for a patient with invasive breast cancer.

2.2

NSABP-B-24 Data: Clinical Comparison of ER-Negative Results from Outside and Central Labs

		Events/patients (%)			
Lab	N	Placebo	Tamoxifen	Relative risk	*p*-value
Outside lab ER-negative results	64	10/39 (26%)	3/25 (12%)	0.43 (↓57%)	0.20
Central lab ER-negative results	89	11/48 (23%)	11/41 (27%)	0.99 (↓1%)	0.98

SOURCE: Allred DC. Presentation. San Antonio Breast Cancer Symposium 2002;30. No abstract available

Track 6

DR LOVE: Could you summarize what was recently reported from the MA17 study?

DR OSBORNE: The interesting thing about what was presented was the falling hazard ratio during the five years of letrozole treatment, which excluded patients who were switched over after the data were analyzed. By the time the study was closed, a number of patients had already been on letrozole for five years — many of them less but some of them for five years.

What they found — and this is potentially very important — was that the hazard ratio or the benefit for letrozole seemed to increase the longer the patient was on the letrozole. Initially the hazard ratio was 0.6, which means that during the first couple of years of treatment with letrozole, the risk of recurrence was reduced by about 40 percent. By the fifth year, it was down to about 0.2 — a tremendous reduction in the risk of recurrence for the letrozole-treated patients (Ingle 2005; Goss 2005a; [2.3]).

2.3

Hazard Ratios of Disease Recurrence over Time for Patients on NCIC CTG MA17, Based on Events Prior to Trial Unblinding

Months after randomization	Hazard ratio: Letrozole versus placebo*
12	0.52 (0.40-0.64)
24	0.45 (0.33-0.56)
36	0.35 (0.21-0.48)
48	0.19 (0.04, 0.34)

* Hazard ratios less than one indicate values in favor of letrozole.

Conclusions: This analysis of the hazard ratios for disease recurrence over time between the letrozole and placebo arms of MA17 indicates that, at least out to 4 years, the longer patients are exposed to letrozole, the greater the benefit.

The increasing HR in the placebo group is of note and emphasizes the residual risk of recurrence that exists in women completing 5 years of tamoxifen. To further address the issue of duration of letrozole therapy, a rerandomization of all participants completing letrozole on MA17 to a further 5 years of treatment is underway.

SOURCE: Ingle JN et al. San Antonio Breast Cancer Symposium 2005;**Abstract 17**.

Track 7

DR LOVE: What are your thoughts about the Onco*type* DX assay?

DR OSBORNE: I believe the Onco*type* DX is well done — well standardized and well validated. It produces good results. For laboratories that don't perform a high volume of assays, where estrogen receptor and HER2 assays are not reliable, the Onco*type* DX would provide a much more reliable estrogen receptor test, because the estrogen receptor is such an important part of the generating signal.

So for institutions that don't measure these things very well, I believe they should use Onco*type* DX. In terms of trying to decide who has a worse prognosis and who might need to have adjuvant chemotherapy for a small, node-negative tumor, I believe the Onco*type* DX can be helpful.

Track 10

DR LOVE: What are your thoughts about *nab* paclitaxel?

DR OSBORNE: In some ways, I believe *nab* paclitaxel is a little safer (2.4) compared to the other taxanes. I'd be interested to see how it does, for example, combined with trastuzumab for HER2-positive disease or combined with other chemotherapy regimens to see if the hint that it might be better in the metastatic setting plays out in the adjuvant setting.

The attractive thing about it is that you don't have to administer premedica-

tion. For patients who are on this drug for a long period of time, that's a big advantage. Dexamethasone premedication can cause its own side effects. I haven't used *nab* paclitaxel all that often yet, but I like it and I'm anxious to see how it's going to be incorporated earlier in the management of the disease. ■

2.4

Phase III Randomized Trial Comparing *Nab* Paclitaxel to Paclitaxel as First-, Second-, Third- or Fourth-Line Therapy in Women with Metastatic Breast Cancer

	Nab paclitaxel (n = 229)	Paclitaxel (n = 225)	*p*-value
Complete response + partial response			
Investigator assessment			
Overall	33%	19%	0.001
First-line therapy	42%	27%	0.029
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
Overall	65 weeks	55.7 weeks	0.374
≥Second-line therapy	56.4 weeks	46.7 weeks	0.024
Neutropenia (Grade IV)	9%	22%	<0.001
Sensory neuropathy (Grade III)	10%	2%	<0.001
Hypersensitivity (any grade)	<1%	2%	Not reported

SOURCE: Gradhishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

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INTERVIEW

I Craig Henderson, MD

Dr Henderson is Adjunct Professor of Medicine at the University of California in San Francisco, California.

Tracks 1-11

Select Excerpts from the Interview

Track 3

DR LOVE: What is your opinion regarding recent data on the usefulness of TOPO II as a predictor of response to anthracyclines?

DR HENDERSON: The evidence is pretty clear that TOPO II makes sense scientifically. We began talking about it more than a decade ago. It's particularly interesting because TOPO II is on the same chromosome as HER2, and in the early papers we thought there was a correlation between the use of doxorubicin and HER2.

I don't believe that has really held up. Certainly, when Dan Hayes presented the data from CALGB-9344 at ASCO 2006 we didn't see a correlation between HER2 expression and doxorubicin dose (Hayes 2006).

DR LOVE: If a clinician had the results of a TOPO II assay for a patient,

should they be considered when deciding on therapy and whether an anthracycline is necessary?

DR HENDERSON: I believe anthracyclines are so powerful and so valuable in the treatment of breast cancer that I would be hesitant to leave out doxorubicin until we had compelling data that a particular group of patients received no benefit from it.

It's similar to the way we view estrogen receptor status and chemotherapy. We know that patients with ER-positive disease derive less benefit from chemotherapy than those with ER-negative breast cancer, but it's not an all-or-none phenomenon.

I believe the same principle applies here. When will you be comfortable enough to leave out a powerful drug? As good as the taxanes are — and I am enthusiastic about them — I don't believe they are any better than the anthracyclines in the treatment of breast cancer.

Track 4

DR LOVE: Speaking of taxanes, what is your opinion regarding *nab* paclitaxel?

DR HENDERSON: I am enthusiastic about *nab* paclitaxel. I have a bias in that I was very involved in the development of doxorubicin HCL liposome injection and it, like *nab* paclitaxel, has a delivery system that increases the amount of drug that actually reaches the tumor.

The issue of dose of chemotherapy has been a complicated one in cancer. When we examine dose in animal models, we clearly see a dose effect, and in leukemia we see an advantage with higher doses. Almost every oncologist has been taught as part of his or her earliest training that dose is a critical factor.

However, in most dose studies it's difficult to demonstrate that dose makes a lot of difference, high-dose chemotherapy in bone marrow transplant being a case in point. I believe the reason we have been unable to show that dose is so important is that we are examining the dose we administer rather than the dose that reaches the tumor.

With a delivery system, you change the distribution of drug so that less goes to the normal tissue and more — a higher dose — reaches the tumor itself. That's what happens with doxorubicin HCL liposome injection and *nab* paclitaxel. In both cases we can show that elegantly in preclinical models. Showing that in the human, of course, is more difficult because it's not so easy to biopsy a tumor and measure the drug level.

We know that we can administer higher doses. In CALGB-9342, which studied paclitaxel doses of 175 mg/m^2, 210 mg/m^2 and 250 mg/m^2 in patients with metastatic breast cancer, we saw no significant effect from escalating the paclitaxel dose (Winer 2004). However, there was some marginal effect from the higher doses and a suggestion of a longer time to tumor progression.

In fact, some of the analyses reached statistical significance as an endpoint. I believe with *nab* paclitaxel we are seeing that we can give higher doses and that patients tolerate higher doses.

In the preclinical models, mice tolerate higher doses of *nab* paclitaxel than paclitaxel delivered in Cremophor®. In addition, because of the way the albumin interacts with the paclitaxel, higher doses were delivered to the tumor.

I believe that's why they were able to show a significantly better outcome with *nab* paclitaxel. It's an interesting step forward.

Track 6

DR LOVE: What are your thoughts about Secreted Protein Acidic and Rich in Cysteine, known as SPARC, and how it may be related to the mechanism of action for *nab* paclitaxel?

DR HENDERSON: SPARC is an interesting observation. What's important about SPARC is that albumin appears to bind to it and SPARC is overexpressed in a number of different tumors (3.1). It's a protein that was first described 10 to 15 years ago. A lot of preclinical work has been conducted on this, and it's a story that makes sense.

You are dealing with a larger particle with *nab* paclitaxel, and a larger particle can go through the gaps that occur in tumor tissue because the vasculature is leaky, whereas the junctions between blood vessel cells in normal tissues are tighter and won't allow these big particles to go through.

That's one reason why a higher level of paclitaxel is delivered into the tumor with *nab* paclitaxel. A second reason is the binding to the albumin-binding sites in the vessels, which helps take a larger amount of the paclitaxel-bound albumin into the tumor.

3.1

Proposed Mechanism of Drug Delivery for *Nab* Paclitaxel

"*Nab*-Paclitaxel utilises the natural properties of albumin to reversibly bind paclitaxel, transport it across the endothelial cell and concentrate it in areas of tumour.

The proposed mechanism of drug delivery involves, in part, glycoprotein 60-mediated endothelial cell transcytosis of paclitaxel-bound albumin and accumulation in the area of tumour by albumin binding to SPARC (secreted protein, acidic and rich in cysteine).

Clinical studies have shown that *nab*-paclitaxel is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), with almost double the response rate, increased time to disease progression and increased survival in second-line patients."

SOURCE: Gradishar WJ. **Albumin-bound paclitaxel: A next-generation taxane.** *Expert Opin Pharmacother* 2006;7(8):1041-53. **Abstract**

Third, you have the binding to SPARC, an attraction to the tumor itself. All three of these reasons seem to explain why you get a better response to *nab* paclitaxel than you do to Cremophor-based paclitaxel.

DR LOVE: Is it possible to do an assay of SPARC, and could that, theoretically, be used to select therapies?

DR HENDERSON: Theoretically, I believe it could.

Track 7

DR LOVE: What do you think about the data on bevacizumab in colon, breast and lung cancer and particularly on the debate about why bevacizumab is working and whether it's delivering chemotherapy more effectively to tumor cells?

DR HENDERSON: It is an irony because intuitively you would think that bevacizumab would have exactly the opposite effect. In other words, we have always known that necrosis is one of the problems with delivering chemotherapy to the inside of the tumor. Tumors don't have a good vascular system, so there's not very much oxygen in there. Therefore, radiation therapy isn't as effective, and chemotherapy is less effective on this dying inner part of the tumor.

So you would think that an anti-angiogenesis agent, which kills these blood vessels, would be antagonistic rather than synergistic with chemotherapy. The effects we're seeing of increased activity of chemotherapy and bevacizumab in colon, breast, lung and renal cancer appear to be good evidence of synergy.

It is now necessary to go back to the laboratory with the understanding that these agents are working differently than hypothesized.

The preclinical data obviously suggest that, in the face of bevacizumab, there is less chaos. In other words, the vasculature is less chaotic and more effective and therefore can deliver more drug (3.2).

3.2

Normalization of Tumor Vasculature: An Emerging Concept in Anti-angiogenic Therapy

"Solid tumors require blood vessels for growth, and many new cancer therapies are directed against the tumor vasculature. The widely held view is that these antiangiogenic therapies should destroy the tumor vasculature, thereby depriving the tumor of oxygen and nutrients...

Emerging evidence support[s] an alternative hypothesis — that certain antiangiogenic agents can also transiently "normalize" the abnormal structure and function of tumor vasculature to make it more efficient for oxygen and drug delivery. Drugs that induce vascular normalization can alleviate hypoxia and increase the efficacy of conventional therapies if both are carefully scheduled."

SOURCE: Jain RK. *Science* 2005;307(5706):58-62. **Abstract**

Track 11

DR LOVE: Currently CALGB trial 40101 (3.3) in patients with node-negative disease is evaluating dose-dense AC without a taxane, and many clinicians who have used dose-dense AC followed by paclitaxel also use dose-dense AC because patients seem to get through the AC more easily. How do you feel about using off-protocol dose-dense AC in clinical practice?

DR HENDERSON: I see that happening even in my own clinic. I started a couple of patients in the last few weeks on dose-dense adjuvant chemotherapy and discussed it with some of my colleagues, and in fact, they are doing this in the university setting. In CALGB-9741, which compared sequential doxorubicin, paclitaxel and cyclophosphamide versus concurrent AC followed by paclitaxel at 14- and 21-day intervals, we can't separate which is the critical factor — the AC or the taxane (Hudis 2005). We will have to wait and see what the science says. ■

3.3

CALGB-40101: Phase III Randomized Study of Two Different Schedules of Adjuvant Cyclophosphamide and Doxorubicin versus Paclitaxel

Target Accrual: 4,646 within 29 months
Current Accrual: 2,437 (7/28/06)
Date Activated: May 15, 2002

Eligibility

Zero to three positive lymph nodes or high-risk node-negative to warrant chemotherapy

HER2-positive, negative or unknown

Any estrogen or progesterone receptor status

No locally advanced or inflammatory disease

R

AC x 4*
Doxorubicin + cyclophosphamide q2wk x 4

AC x 6*
Doxorubicin + cyclophosphamide q2wk x 6

Paclitaxel x 4*
Paclitaxel q2wk x 4

Paclitaxel x 6*
Paclitaxel q2wk x 6

- Primary endpoint: Disease-free survival (DFS)
- Secondary endpoints: Survival, local control, distant recurrence-free interval, toxicity, menopause induction, myelosuppression in MDR1 haplotypes, DFS in MDR1 haplotypes, correlation of polymorphisms with DFS and toxicity

* Growth factor support: Filgrastim or sargramostim recommended days 3-10 of each cycle. Pegfilgrastim may be substituted and should be given 24 to 36 hours after the administration of chemotherapy.

Study Contact:
Cancer and Leukemia Group B
Lawrence Shulman, MD, Protocol Chair

SOURCE: Cancer and Leukemia Group B Protocol.

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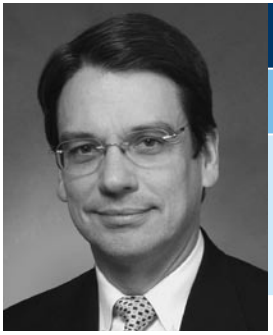


INTERVIEW

Charles E Geyer Jr, MD

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

Tracks 1-15

Track 1	Introduction
Track 2	Phase III randomized trial of capecitabine with or without lapatinib in women with previously treated, HER2-positive, metastatic breast cancer
Track 3	Mechanism of action of lapatinib
Track 4	Results of the Phase III randomized trial of capecitabine with or without lapatinib
Track 5	Clinical use of lapatinib
Track 6	Trials evaluating adjuvant or neoadjuvant lapatinib
Track 7	Planned NSABP neoadjuvant trial in women with HER2-positive disease
Track 8	Planned NSABP adjuvant trial in women with HER2-positive disease
Track 9	Clinical use of adjuvant trastuzumab in older women or women with cardiac risk factors
Track 10	Trial of trastuzumab/docetaxel with or without carboplatin in women with metastatic disease
Track 11	Cardiac monitoring of patients treated with trastuzumab
Track 12	NSABP-B-40: Neoadjuvant bevacizumab trial
Track 13	NSABP-B-38: Adjuvant TAC versus dose-dense chemotherapy
Track 14	Duration of adjuvant aromatase inhibitor therapy
Track 15	Clinical use of the Onco*type* DX assay

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: Can you discuss the design of the trial you presented at ASCO 2006 evaluating capecitabine in combination with lapatinib?

DR GEYER: It was a Phase III randomized trial comparing capecitabine alone to capecitabine in combination with lapatinib — a dual EGFR and HER2 tyrosine kinase inhibitor — in patients with progressive metastatic HER2-positive breast cancer. All the women had received previous therapy with an anthracycline and a taxane in either the adjuvant or metastatic setting. They also received trastuzumab in the metastatic setting (Geyer 2006).

Patients had to have tumors with IHC 3+ or amplification by FISH to be

eligible, and they had to have a normal ejection fraction, measurable disease and a reasonably good performance status (ECOG 0 or 1) even though they were pretreated.

The patients were randomly assigned to capecitabine at a total dose of 2,500 mg/m^2 per day or capecitabine at 2,000 mg/m^2 per day with lapatinib at 1,250 mg per day. Lapatinib was administered on a continuous basis and capecitabine on days one through 14 every 21 days (Geyer 2006).

The study was set up originally to look for an improvement in median time to progression from three months to 4.5 months. Because the group was pretreated and had HER2-positive disease, it was thought that those receiving capecitabine would probably have a median time to progression of about three months, and a 4.5-month median time to progression was felt to be a reasonable improvement. Overall survival was also evaluated.

The original sample size was 528 patients, but like all large Phase III studies it included an interim monitoring plan. The final evaluation for time to progression was supposed to occur with 266 events, and the interim analysis would occur at 133 events. Because this was an open-label trial, a blinded independent review committee (IRC) was to read all the films.

As of November 15, 2005, 114 events were recorded and 321 patients were enrolled. The 321 patients' films were reviewed, and the IRC determined that 114 events met the criteria for the study. It went to the Independent Data Monitoring Committee (IDMC), where it was determined that the study had crossed the O'Brien-Fleming boundaries for early reporting by a wide margin (Geyer 2006).

The capecitabine-alone group did better than anticipated. Instead of three months, the median time to progression was about 4.5 months. The group receiving capecitabine and lapatinib had a median time to progression of about 8.5 months. The median time to progression was nearly doubled (Geyer 2006; [4.1]).

Also, the overall response rate was improved from roughly 14 to 22 percent (4.1). Clearly it was an active regimen. The IDMC assessed the safety data and found minimal Grade IV toxicities (Geyer 2006).

It was a well-tolerated regimen, which is surprising because concern had been raised about significant synergy in terms of toxicity, but this did not arise. Based on the efficacy and the safety, the IDMC made the recommendation that the accrual be closed, the results announced and the patients who were still receiving capecitabine alone be offered lapatinib (Geyer 2006).

DR LOVE: If lapatinib were available and you were to see a patient who has progressed on trastuzumab, how would you treat that patient?

DR GEYER: I think a patient who meets the eligibility criteria of the trial certainly should be offered lapatinib, when it becomes available.

4.1

Phase III Randomized Trial of Capecitabine with or without Lapatinib in Women with Previously Treated, HER2-Positive Metastatic Breast Cancer

	Lapatinib + capecitabine (n = 160)	Capecitabine alone (n = 161)	Hazard ratio (95% CI)	*p*-value*
Median time to progression	36.9 wks	19.7 wks	0.51 (0.35-0.74)	0.00016*
Median progression-free survival	36.9 wks	17.9 wks	0.48 (0.33-0.70)	0.000045*
Overall response rate	22.5%	14.3%	—	0.113†

* Log-rank, one sided; † Fisher exact, two sided

SOURCE: Geyer CE et al. Presentation. *Proc ASCO* 2006. No abstract available

Track 7

DR LOVE: At what stage is the NSABP right now in terms of neoadjuvant trials for patients with HER2-positive disease?

DR GEYER: We are currently working on a straightforward concept evaluating trastuzumab versus lapatinib versus the combination using an AC followed by weekly paclitaxel template as neoadjuvant therapy. All the patients will receive that basic chemotherapy regimen, and the HER2 blockade will start with paclitaxel.

Then the patients will have surgery to determine the pathologic complete response rate. After surgery, all the patients will receive trastuzumab for one year. They will be receiving standard therapy with trastuzumab, but we will obtain baseline tissue and do the correlative work to see if we can determine which patients might do better with each of the drugs individually or in combination.

Track 8

DR LOVE: What about the adjuvant trials for patients with HER2-positive disease? Is the NSABP still thinking about adding bevacizumab to trastuzumab?

DR GEYER: We are committed to collaborating with Dennis Slamon and the BCIRG jointly on that concept. We have been waiting for their pilot data evaluating the combination of bevacizumab and trastuzumab as front-line therapy for patients with HER2-positive disease.

The trial is progressing well, and from what they have been able to share, it looks as if this is something we definitely will be pursuing.

DR LOVE: What do we know about the potential synergy between bevacizumab and trastuzumab?

DR GEYER: When patients' tumors have HER2 amplification, a high percentage — about three quarters of the patients — also have upregulation of VEGF. Those patients do not do well when treated with chemotherapy alone; they have a strikingly poor outcome.

The assumption is that something is mechanistically driving the cancer, and if you shut down both of those pathways, you will improve outcomes. Preclinical models look very strong, and they were the justification for taking this into a clinical trial.

Track 9

DR LOVE: Where are we in terms of cardiac safety with trastuzumab, particularly for the patient who may be older or has risk factors for heart disease?

DR GEYER: The exciting thing about the adjuvant trastuzumab data has been that no matter how you use it, patients derive a substantial benefit. Small differences probably occur among the different ways of using it, which we can't definitively address because the trials weren't designed that way, but it's clear that trastuzumab is the most important element of therapy for a patient with HER2-positive breast cancer.

The fact that a woman doesn't meet the eligibility criteria of the original trials doesn't mean that she shouldn't receive trastuzumab. I believe she should receive the safest regimen. TCH (docetaxel/carboplatin/trastuzumab) certainly has low cardiac toxicity, but TCH is not a gentler regimen for an elderly woman. It is a fairly rigorous program in and of itself, though the cardiac toxicity is less.

I believe the weekly carboplatin/paclitaxel/trastuzumab that we use for metastatic disease is active and well tolerated. Those are the substitutions I believe would be reasonable to consider for an elderly patient, if you felt you needed to use chemotherapy.

Can you use only trastuzumab or hormone therapy? I'm sure you can. You have to use your clinical judgment. Trastuzumab is active without chemotherapy; there is no question about that. If I were going to use trastuzumab, I would like to use some kind of chemotherapy, maybe just four cycles á la the HERA trial (Piccart-Gebhart 2005).

Track 11

DR LOVE: What do you think is a reasonable way to monitor cardiac function in a patient receiving trastuzumab?

DR GEYER: For me, the precedent for cardiac monitoring has been set by the adjuvant trials. The plan was a reasonable one: Check imaging halfway through the chemotherapy, check it at the end of chemotherapy and then

check it three months later. It made sense for the trial, and I believe it makes sense for the clinic.

In NSABP-B-31 and NCCTG-N9831, we stopped the drug in a significant number of patients — about 15 percent of the patients had asymptomatic declines in LVEF (Romond 2005). We don't know that we would have seen a higher rate of clinical heart failure if we had continued to treat them, but it's a reasonable assumption.

Track 12

DR LOVE: Can you update us on the NSABP neoadjuvant study for patients with HER2-negative disease?

DR GEYER: That is NSABP-B-40 (Figure 1), which was originally going to be a three-arm study evaluating sequential AC followed by either docetaxel alone, docetaxel with capecitabine or docetaxel with gemcitabine. We were about to open the trial but decided to modify it to incorporate bevacizumab. With that, we reconfigured the study to move the taxane ahead of the AC, which is the reversal of the usual order.

Our thinking was twofold. First, the data for bevacizumab in breast cancer were with a taxane. Hence we wanted to administer the two together as much as possible. Second, the possibility of increased cardiac toxicity for the anthracyclines with bevacizumab has been a concern.

More and more, it's looking as if that isn't going to be an issue, but because we have to stop bevacizumab a couple of cycles before surgery, it also makes sense from that perspective.

Track 13

DR LOVE: Can you review the randomization for NSABP-B-38? How are people regarding that study in view of the data that have been reported for patients with ER-positive tumors?

DR GEYER: The trial has three arms (4.2). In a sense, we have two control groups. We have the docetaxel control arm using the TAC regimen from the BCIRG study (Martin 2005). Our paclitaxel control arm is the dose-dense regimen (Citron 2003). The third arm adds gemcitabine to the dose-dense paclitaxel portion of the regimen.

The improvement with dose-dense therapy seemed to be largely confined to the patients with ER-negative disease. Does that mean dose-dense therapy isn't right for a patient with ER-positive disease? My view is that dose-dense therapy isn't less effective than every three-week therapy.

Clearly the big step is among patients with ER-negative disease, but it still has advantages in that the therapy is finished sooner. We still consider it a viable option.

In terms of adjuvant chemotherapy for patients with node-positive disease, about all you can say is that they probably should receive an anthracycline, cyclophosphamide and a taxane. The recipes are all over the place. This does allow a lot of flexibility for physicians and patients to make selections for off-protocol therapy.

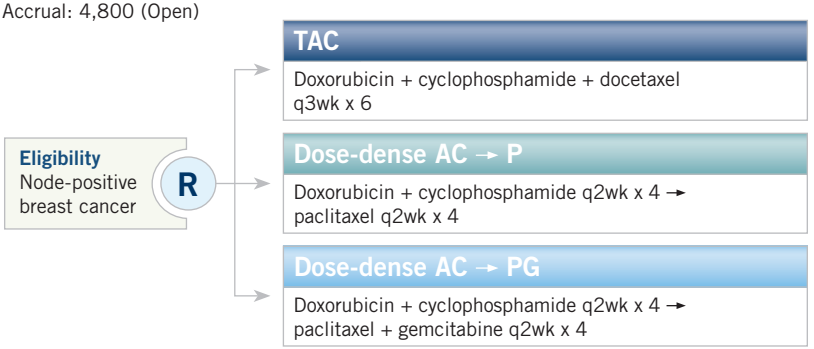
When you have an active protocol that is evaluating an optimal docetaxel regimen, an optimal paclitaxel regimen and a possible improvement, you have no reason to reconfigure that study.

I believe the dose-dense arm is a very reasonable treatment for patients with ER-positive, node-positive disease. ■

4.2

Phase III Randomized Trial of Three Different Adjuvant Chemotherapy Regimens

Protocol IDs: NSABP-B-38, CTSU
Accrual: 4,800 (Open)



Patients with ER-positive and/or PR-positive disease receive hormonal therapy.

SOURCE: NCI Physician Data Query, September 2006.

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INTERVIEW

Frank A Vicini, MD

Dr Vicini is Chief of Oncology Services in Oncology Services Administration at William Beaumont Hospital in Royal Oak, Michigan.

Tracks 1-9

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Can you discuss the evolution of partial breast irradiation (PBI)?

DR VICINI: PBI started in the early 1990s with the goal of reducing the treatment time from six and a half weeks to less than four or five days. The initial technique used was brachytherapy, which consisted of the placement of temporary catheters or needles in the breast.

The early experience with brachytherapy was good, and we now have 10-year data showing that the results are roughly equivalent to what one could expect with six weeks of whole breast radiation therapy. The reason why brachytherapy has not been adopted as widely as perhaps we would like is that the technique of brachytherapy is difficult both to teach and to learn.

Approximately five years ago the MammoSite balloon catheter was introduced, which requires only one catheter to be placed at the time of surgery or shortly thereafter. With the MammoSite you're able to deliver the same radiation as with multiple needles in the same short time period.

DR LOVE: Can you talk about the design and eligibility of the NSABP-B-39 trial comparing whole breast versus partial breast irradiation (5.1)?

DR VICINI: To understand the rationale for this Phase III trial, you have to understand that when we began using partial breast irradiation, we selected patients carefully — patients with very small tumors, clear margins and negative lymph nodes. We were trying to determine whether this technique was as efficacious as whole breast irradiation, but we selected only patients at low risk and, indeed, the five- and 10-year results with these low-risk cases have been good (5.2).

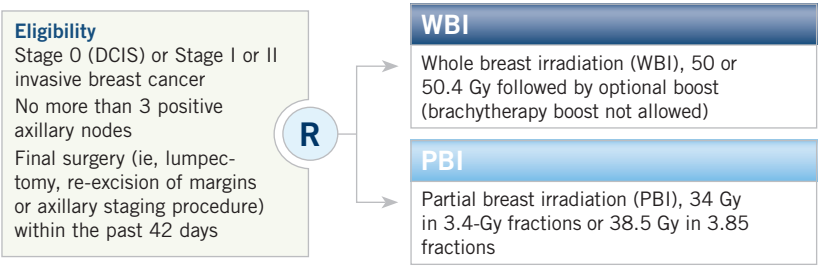
However, with the NSABP-B-39 trial, the eligibility criteria have been loosened significantly. We are treating patients with up to three positive lymph nodes and tumors up to three centimeters. We're including multiple types of histologies, not just infiltrating ductal carcinomas. The B-39 trial has been designed to test whether partial breast irradiation could be used for patients at a slightly higher risk or whether it should be restricted to patients with a lower risk. The three partial breast irradiation techniques used in the trial are brachytherapy with the traditional multiple needles, the MammoSite balloon catheter and 3-D conformal external beam radiation therapy.

If a patient is interested in participating in the trial, we first do a prerandomization CT scan. The radiation oncologist, with assistance from the surgeon, will look at the lumpectomy cavity on the CT scan to determine whether a patient is

5.1

Phase III Study Comparing Adjuvant Whole Breast versus Partial Breast Irradiation

Protocol IDs: NSABP-B-39, NCT00103181, RTOG-0413, SWOG-NSABP-B-39
Target Accrual: 3,000 (Open)



Study Contacts:

National Surgical Adjuvant Breast and Bowel Project
Frank Vicini, MD
Tel: 248-551-1219

Southwest Oncology Group
Lori Pierce, MD
Tel: 734-936-7810

Radiation Therapy Oncology Group
Julia White, MD
Tel: 414-805-4462

SOURCE: NCI Physician Data Query, September 2006.

a candidate for partial breast irradiation and then, specifically, which partial breast irradiation technique that patient is qualified for from a technical standpoint.

If the patient qualifies for one of the techniques, we let her know; if she agrees to that technique, the patient is then randomly assigned to either whole breast irradiation therapy or that particular partial breast irradiation therapy. If the patient is a candidate for all three partial breast irradiation techniques, then she tells us which one she wants and the randomization is between whole breast irradiation and the technique she's chosen.

DR LOVE: If a patient is eligible for all three techniques, what do you advise her in terms of quality of life and side effects when comparing these three?

DR VICINI: First, we indicate to the patient that we have one technique that's not invasive, whereas the other two techniques are invasive — one being less invasive, meaning only one catheter, and the other one requiring multiple catheters. We then tell the patient that we have the longest follow-up and the greatest number of patients treated with the brachytherapy technique. ■

5.2

Five-Year Actuarial Treatment Outcomes from Matched-Pair Analysis of Patients Treated with Whole Breast versus Limited-Field Radiation Therapy

Outcome	Whole breast % (95% CI)	Limited-field % (95% CI)	*p*-value
Ipsilateral recurrence	1 (0-2.4)	1 (0-2.8)	0.65
Regional failure*	1 (0-1.5)	1 (0.1-2.1)	0.54
Distant metastasis	5 (2.2-8.4)	3 (0.5-5.9)	0.17
Disease-free survival	91 (86.5-94.7)	87 (81.5-92.1)	0.30
Overall survival	93 (89.7-96.7)	87 (82.1-92.7)	0.23
Cause-specific survival	97 (95.0-99.8)	97 (93.8-99.9)	0.34
Contralateral breast failure	4 (1.0-6.4)	1 (0-2.4)	0.03

* Regional failure = recurrence of cancer in a regional nodal site before or simultaneously with the diagnosis of local recurrence or distant metastasis

SOURCE: Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-10. **Abstract**

SELECT PUBLICATIONS

Bovi JA et al. **Comparison of three partial breast irradiation techniques: Treatment effectiveness based upon biological models.** *Int J Radiat Oncol Biol* 2005;63(2 Suppl 1);**Abstract 1061**.

Vicini FA, Arthur DW. **Breast brachytherapy: North American experience.** *Semin Radiat Oncol* 2005;15(2):108-15. **Abstract**

Vicini FA et al. **First analysis of patient demographics, technical reproducibility, cosmesis, and early toxicity: Results of the American Society of Breast Surgeons MammoSite breast brachytherapy trial.** *Cancer* 2005;104(6):1138-48. **Abstract**

Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-10. **Abstract**

PANEL DISCUSSION

Miami Breast Cancer Conference Tumor Panel on Systemic Therapy of Metastatic Disease

Tracks 1-19

Select Excerpts from the Meeting

Tracks 6-8

DR LOVE: Eric, what are the treatment options for a 55-year-old woman with ER-negative, PR-negative, HER2-negative breast cancer who develops rapidly progressive, symptomatic, visceral metastases 15 months following adjuvant dose-dense AC → paclitaxel?

DR WINER: We have single-agent versus combination chemotherapy. In terms of single-agent chemotherapy, given that she received a taxane 15 months ago, I'm not terribly enthusiastic about using a taxane again. Of the various single-agent choices, probably capecitabine is the one for which we have the most data. It has also been specifically evaluated in patients with disease that is refractory to an anthracycline and a taxane. Vinorelbine or gemcitabine would

also be reasonable choices, although I'm not entirely sure of their activity in this situation.

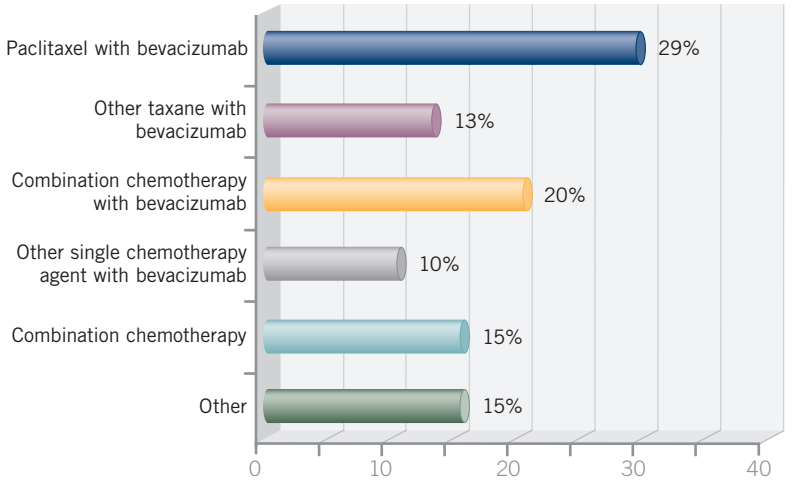
We have a number of combination therapy options. In the study conducted by Joyce O'Shaughnessy that evaluated docetaxel with or without capecitabine for women with metastatic breast cancer, the combination showed improvements in response rate, time to progression and overall survival. The patients were all docetaxel naïve, and they weren't crossed over on a regular basis to capecitabine if they had received docetaxel alone (O'Shaughnessy 2002).

The trial comparing paclitaxel with or without gemcitabine also demonstrated a small survival benefit for the combination. It included no crossover, and all the patients were taxane naïve (Albain 2004). Given the fact that this particular patient had received a taxane just a little more than a year ago, it's hard to become enthusiastic about either of these particular combinations.

Capecitabine/vinorelbine is a combination regimen that has been used fairly extensively in clinical trials (Ghosn 2006; Nole 2006). My understanding is that it's used somewhat more frequently in Europe than in the United States, and I'm not aware of any Phase III trials evaluating it. It certainly uses two active drugs that this patient has not previously seen. If I had no other options and a sense that I might not have the opportunity to use a second regimen, this might be a regimen I would consider.

6.1

Miami Breast Cancer Conference Poll Question: Fifteen Months After Completing Dose-Dense AC → Paclitaxel for an ER-Negative, PR-Negative, HER2-Negative IDC, A 55-Year-Old Woman Develops Rapidly Progressive and Very Symptomatic Metastases to the Liver, Lungs and Bones. Which Regimen Generally Might You Recommend?



SOURCE: Miami Breast Cancer Conference Tumor Panel, Participant Polling, February 2006, Miami, Florida.

That brings me to bevacizumab and the results from the ECOG-E2100 study, presented by Kathy Miller at ASCO 2005 (Miller 2005a) and the 2005 San Antonio Breast Cancer Symposium (Miller 2005b). ECOG-E2100 included patients who had not received prior chemotherapy for metastatic breast cancer. They were randomly assigned to receive weekly paclitaxel with or without bevacizumab (6.2). Technically, this patient probably would have been eligible for ECOG-E2100 because it excluded patients who had received a taxane within a year but not those who had received a taxane within 15 months.

The addition of bevacizumab to paclitaxel essentially doubled the response rate — the increase was a little more than that if one considers only the patients who had measurable disease. Importantly, progression-free survival showed approximately a five-month improvement, which was highly statistically significant, with the addition of bevacizumab to paclitaxel (Miller 2005b; [6.2]).

In terms of overall survival, when the data were initially presented at ASCO 2005, they suggested a preliminary survival advantage (Miller 2005a). When presented at San Antonio, the advantage was numeric, although it was not

6.2

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-MAC3, NCCTG-E2100, NSABP-E2100
Accrual: 715 (Closed)

Eligibility
Locally recurrent or metastatic breast cancer
HER2-positive only if prior treatment with or contraindication to trastuzumab
No prior chemotherapy for metastatic disease
Adjuvant taxanes allowed if disease-free interval > 12 months; PS 0 or 1; no CNS metastases

R

Paclitaxel + bevacizumab
Paclitaxel days 1, 8 and 15 + bevacizumab 10 mg/kg days 1 and 15

Paclitaxel
Paclitaxel days 1, 8 and 15

	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

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

considered statistically significant (Miller 2005b). I believe it must be followed over time to determine whether the addition of bevacizumab does, in fact, improve survival.

At the 2005 San Antonio Breast Cancer Symposium, the ECOG investigators presented the benefit in progression-free survival with bevacizumab across different subgroups. It appears that bevacizumab was active in virtually all subgroups. If you specifically consider the patients who had ER-negative and PR-negative disease, you see a clear improvement in progression-free survival within that subgroup (Miller 2005b).

It's important to keep in mind the prior study of bevacizumab for women with breast cancer. That trial was also conducted by Kathy Miller and evaluated capecitabine with or without bevacizumab. That trial demonstrated a small improvement in response rate but no improvement in progression-free or overall survival (Miller 2005c).

One might ask why those results were so different from the ones from ECOG-E2100. It's possible this was a chance finding, although I believe that's unlikely. It's possible that it's the use of paclitaxel instead of capecitabine. Preclinical work suggests synergy between the taxanes and bevacizumab. However, in colorectal cancer, bevacizumab has been combined successfully with 5-FU.

Importantly, there were differences in the patient populations. In the capecitabine trial, the majority of the patients had received prior chemotherapy for metastatic disease. Almost all the patients had received some form of prior chemotherapy and an anthracycline and taxane. The study populations were also somewhat different in terms of HER2 status and whether they had received trastuzumab (Miller 2005b, 2005c).

This patient falls somewhere in between those enrolled in ECOG-E2100 and the group of patients in the capecitabine trial. I personally would consider bevacizumab, but I'm not enthusiastic about using it with paclitaxel, despite the fact that that was the regimen used in ECOG-E2100 and she would have been eligible for the trial.

Other options I would tend to consider include bevacizumab with vinorelbine or, perhaps, a taxane/platinum combination. Given the negative trial with capecitabine, I'd probably take that off the list.

We conducted a study led by Hal Burstein evaluating bevacizumab and vinorelbine in 56 patients, which demonstrated a modest degree of activity and an acceptable side-effect profile (Burstein 2002). For this patient, I probably would use bevacizumab with some other chemotherapy drug. I fully recognize that others might want to be purists and say, "This patient was eligible for ECOG-E2100, and I'm going to use paclitaxel." I don't believe that is wrong.

If I expected an opportunity for a second agent and I were not going to use bevacizumab, I'd use single-agent capecitabine. Finally, if I felt compelled to use combination therapy — and this may be a situation in which, particularly

if you choose not to use bevacizumab, you might choose to do that, given the extent of the patient's disease and her symptoms — I would use a two-drug regimen with drugs she's never received before.

Track 14

DR LOVE: Which endocrine therapy would you recommend for a postmenopausal patient with ER-positive, PR-positive, HER2-negative breast cancer who relapses while receiving adjuvant anastrozole?

DR ROBERTSON: We have no randomized, controlled data on endocrine therapies for metastatic breast cancer following an adjuvant aromatase inhibitor. In fact, we have very little Phase II data. So we're going to have to take data from other situations and apply them.

Exemestane, a steroidal aromatase inhibitor, shows approximately a 30 percent clinical benefit rate following a nonsteroidal aromatase inhibitor (Carlini 2002). Fulvestrant shows a similar clinical benefit rate of around 30 percent following an aromatase inhibitor (Perey 2004). The numbers in these Phase II sequence studies, however, are pretty small, and the hormonal therapy was used as third-line therapy.

Another option would be to continue the anastrozole and start fulvestrant. The basis for that is preclinical data that were published in *The Journal of Biological Chemistry* by Dr Martin (Martin 2003). If you grow cells in estrogen-deprived media, they become more sensitive to low levels of estrogen. People assume that perhaps, in patients who've been treated with an aromatase inhibitor over a long period of time, this is what happens. It's one of the potential mechanisms of resistance to aromatase inhibitors.

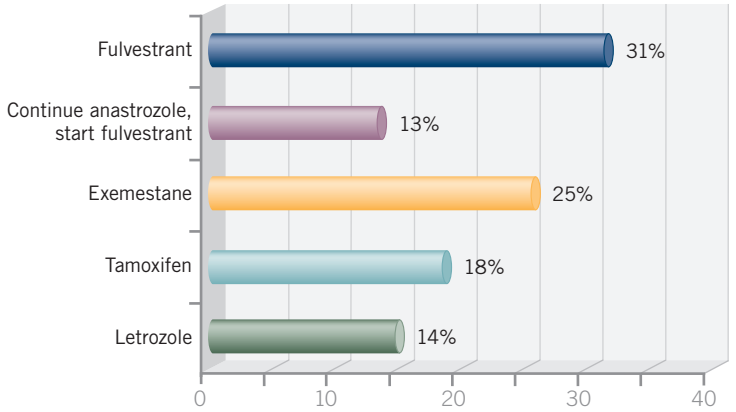
If you take cells that have been estrogen deprived for a long time and administer increasing doses of fulvestrant, then you can inhibit cell growth. The hypothesis is that when you have relapse on an aromatase inhibitor and the tumor becomes sensitive to these very low levels of estradiol, if you simply use fulvestrant and stop the aromatase inhibitor, then you increase estradiol again, which might compete with fulvestrant. Therefore, perhaps it may be better to keep the estradiol level low and bring in fulvestrant.

It's a great theory, which is being tested at the moment in an ongoing trial in the United Kingdom called the SoFEA study (6.4). We have no data, and we're probably not going to have a lot of clinical data in the next year or two.

The other option is tamoxifen. Again, we have no good randomized data. We have Phase II data from a first-line study of an aromatase inhibitor versus tamoxifen. From the patients who received the aromatase inhibitor, data were collected for those who went on to receive tamoxifen. A clinical benefit rate of approximately 50 percent appeared among patients with advanced breast cancer who received tamoxifen as second-line therapy following an aromatase inhibitor (Thürlimann 2004).

6.3

Miami Breast Cancer Conference Poll Question: The Patient Is a 57-Year-Old Postmenopausal Woman Who Was on Adjuvant Anastrozole for Four Years for an ER-Positive, HER2-Negative Tumor. She Now Has Bone and Lung Metastases, with Minimal Symptoms. What Would Your Likely First-Line Endocrine Therapy Be?



SOURCE: Miami Breast Cancer Conference Tumor Panel, Participant Polling, February 2006, Miami, Florida.

6.4

Phase III Trial of Fulvestrant with or without Concomitant Anastrozole versus Exemestane Following Progression on Nonsteroidal Aromatase Inhibitors

Protocol ID: ISRCTN44195747, SoFEA, NCT00253422
Target Accrual: 750

Eligibility
Postmenopausal women with ER-positive and/or PR-positive metastatic breast cancer that has progressed during endocrine therapy with a nonsteroidal aromatase inhibitor

R

Fulvestrant + anastrozole
Fulvestrant d1, d15, d29 then qm + anastrozole qd

Fulvestrant + placebo
Fulvestrant d1, d15, d29 then qm + placebo qd

Exemestane
Exemestane daily

Study Contact:
Stephen Johnston, MD, Protocol Chair
Tel: 44-20-7808-2745
Institute of Cancer Research-UK

SOURCES: National Cancer Research Network Trials Portfolio. Available at http://controlled-trials.com/isrctn/trial/%7c/o/44195747.html. Accessed April 15, 2006; NCI Physician Data Query, May 2006.

I personally would like to use a different mechanism of action, and I'd use an antiestrogen. I believe the clinical benefit rate with tamoxifen following an aromatase inhibitor as first-line therapy is high. Also, this tumor is HER2-negative.

If you believe breast cancer is less responsive if it's HER2-positive, then that would be another reason to be comfortable with tamoxifen. If I weren't going to use tamoxifen, then I would select another antiestrogen. My second choice would be fulvestrant.

Tracks 15-16

DR LOVE: If you were going to use fulvestrant, would you use a loading dose?

DR ROBERTSON: It takes about three to four months to reach a steady state with fulvestrant. However, if you administer 250 mg on days one, 14 and 28, and then repeat it every 28 days, you achieve a steady state much faster.

The question is, should you administer an extra dose at day 14? I have to say, "Not usually." I have used it for certain patients when I may have one chance at endocrine therapy.

If you're coming back to fulvestrant after chemotherapy, usually this is for patients with visceral disease. Even then, it's a small minority of cases. If they have nothing left to try, and they have ER-positive disease, I would use a loading dose. Normally, I would use 250 mg every 28 days.

DR LOVE: Kent, do you utilize that strategy?

DR OSBORNE: Yes, I have with some patients — the issue is how fast you need to reach therapeutic levels. I may take that approach in a patient who has more aggressive disease and the therapeutic levels need to be reached faster. However, in a patient with bone-only indolent disease, I'd probably utilize the once-a-month schedule.

Tracks 17-18

DR LOVE: Ian, can you talk about your general algorithm for the sequencing of hormonal agents for the postmenopausal patient with metastatic disease?

DR SMITH: We don't really have an algorithm. I would be inclined to use fulvestrant with estrogen deprivation. In other words, I would continue an aromatase inhibitor because I can't see any reason why it would be worse than fulvestrant alone. Until the trial results are reported, that would be the option I'd choose.

DR LOVE: Dan, can you talk about how you decide between fulvestrant, tamoxifen, and anastrozole for postmenopausal patients?

DR HAYES: With my own patients, I say, "Would you rather have an injection or take a pill?" If they'd rather have an injection, then I suggest fulvestrant. I do use the loading dose.

If they would rather take a pill, I suggest tamoxifen. I believe there's a reason, theoretically, that either one of them would be likely to work.

Surprisingly, in my practice it's 50-50. I always guess wrong what people will choose to do. So it's nice to have a couple of options. ■

SELECT PUBLICATIONS

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;**Abstract 510**.

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

Carlini P et al. **Exemestane (EXE) is an effective 3rd-line hormonal therapy for postmenopausal metastatic breast cancer (MBC) patients (pts) pretreated with 3rd generation non steroidal aromatase inhibitors (nSAI).** *Ann Oncol* 2002;13(Suppl 5):48. **Abstract**

Ghosn M et al. **Phase II trial of capecitabine and vinorelbine as first-line chemotherapy for metastatic breast cancer patients.** *Anticancer Res* 2006;26(3B):2451-6. **Abstract**

Martin LA et al. **Enhanced estrogen receptor (ER) alpha, ERBB2, and MAPK signal transduction pathways operate during the adaptation of MCF-7 cells to long term estrogen deprivation.** *J Biol Chem* 2003;278(33):30458-68. **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 2005a. No abstract available

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial conducted by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005c;23(4):792-9. **Abstract**

Nole F et al. **Capecitabine/vinorelbine: An effective and well-tolerated regimen for women with pretreated advanced-stage breast cancer.** *Clin Breast Cancer* 2006;6(6):518-24. **Abstract**

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

Perey L et al. **Fulvestrant (Faslodex™) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and aromatase inhibitors: Update of a phase II SAKK trial.** *Breast Cancer Res Treat* 2004;88(Suppl 1):236;**Abstract 6048**.

Thürlimann B et al. **Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: Results of the double-blind cross-over SAKK trial 21/95 — A sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial.** *Breast Cancer Res Treat* 2004;85(3):247-54. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patients whose tumors coexpress cMYC and HER2 may have a _____ chance of responding to trastuzumab.**
   a. Greater
   b. Lesser
   c. Comparable
   d. None of the above

2. **At a five-year follow up, the hazard ratio for recurrence among patients who received letrozole during MA17 had fallen from 0.60 to approximately _____.**
   a. 0.20
   b. 0.30
   c. 0.40
   d. 0.50

3. **In a group of women with previously treated, HER2-positive metastatic breast cancer, the addition of lapatinib to _____ nearly doubled the median time to progression.**
   a. Doxorubicin
   b. Paclitaxel
   c. Docetaxel
   d. Capecitabine
   e. Gemcitabine

4. **NSABP-B-40 will incorporate which of the following biologic agents in the neoadjuvant treatment of women with HER2-negative breast cancer?**
   a. Trastuzumab
   b. Lapatinib
   c. Bevacizumab
   d. Erlotinib
   e. Cetuximab

5. **NSABP-B-38 is comparing adjuvant therapy with TAC to dose-dense chemotherapy.**
   a. True
   b. False

6. **The Phase III NSABP-B-39 trial randomly assigns patients to conventional whole breast radiation therapy versus partial breast irradiation, using which of the following partial breast irradiation techniques?**
   a. Interstitial brachytherapy
   b. MammoSite
   c. 3-D conformal external beam radiation
   d. All of the above

7. **ECOG-E2100 demonstrated a statistically significant improvement in _____ when bevacizumab was added to paclitaxel as first-line therapy for metastatic breast cancer.**
   a. Response rate
   b. Progression-free survival
   c. Overall survival
   d. Both a and b
   e. All of the above

8. **Which of the following are being evaluated in the SoFEA trial?**
   a. Fulvestrant with placebo
   b. Fulvestrant with anastrozole
   c. Exemestane
   d. Both a and b
   e. All of the above

9. **In the Phase III study comparing AC with or without sequential paclitaxel, CALGB-9344, there was _____ between HER2 expression and doxorubicin dose.**
   a. No correlation
   b. A significant correlation

10. **Clinical trials have demonstrated increased activity when chemotherapy has been combined with bevacizumab in the treatment of breast, colon, lung and renal cancers.**
    a. True
    b. False

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

EVALUATION FORM

Breast Cancer Update — Issue 6, 2006

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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
Harold J Burstein, MD, PhD	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
Daniel F Hayes, MD	5 4 3 2 1	5 4 3 2 1
I Craig Henderson, MD	5 4 3 2 1	5 4 3 2 1
Marc E Lippman, MD	5 4 3 2 1	5 4 3 2 1
C Kent Osborne, MD	5 4 3 2 1	5 4 3 2 1
John F R Robertson, MB, ChB, BSc, MD	5 4 3 2 1	5 4 3 2 1
Ian E Smith, MD	5 4 3 2 1	5 4 3 2 1
Frank A Vicini, 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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Breast Cancer Update — Issue 6, 2006

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