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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

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TUMOR PANEL DISCUSSION

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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 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.

LEARNING OBJECTIVES

- 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.
- Select medical and surgical management regimens for early breast cancer based on key clinical and pathological risk factors.
- Assess existing data and emerging research on the optimal duration and sequence of adjuvant endocrine therapy for patients who are postmenopausal with ER-positive breast cancer, and apply this evidence to routine patient care decisions.
- Implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for patients with early and advanced HER2-positive breast cancer.
- Evaluate the utility of tissue-based genomic assays for therapeutic decision-making and, when applicable, use these in the selection of individualized treatment regimens for patients with early breast cancer.
- Review the emerging data on various adjuvant chemotherapy approaches, including modified doses and schedules and the use of taxanes, and explain the absolute risks and benefits of these regimens to patients.
- Appraise emerging data on 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, including patients with triple-negative tumors.
- Integrate psychosocial support, optimal patient-physician communication strategies and evidence-based clinical decision-making into a comprehensive approach to patient care.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 3 of *Breast Cancer Update* is to support the learning objectives by offering the perspectives of Drs Forbes, Gralow, Hayes, Perez, Robert, Robertson and Wolff on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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

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HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, review the monograph and complete the Post-test and Educational Assessment and Credit Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

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

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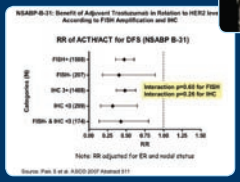

Review RTP's special multimedia presentation featuring Dr Soonmyung Paik discussing his and other work evaluating HER2 expression and its correlation with the impact of trastuzumab in the adjuvant setting. Watch or read Dr Paik's comments and hear related discussion on this topic from the most recent *Breast Cancer Update* Clinical Investigator Think Tank at www.BreastCancerUpdate.com/Video08Paik

CONTENT VALIDATION AND DISCLOSURES

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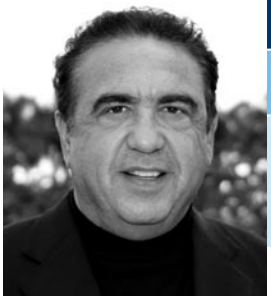


EDITOR'S NOTE

Neil Love, MD

Bev, BETH, BEATRICE and the next big moment in oncology research: NSABP-C-08

It's Saturday afternoon at the gym, and I climb on an ellipse machine with my iPhone (which doubles as an iPod) ready for another audio adventure. I pop in some earphones and take notice of the surrounding television monitors that are filled with sound bites from silly politicians with fabulous hair and beautiful clothes.

The weekend warriors around me have no idea of the extreme content about to be pumped into my cortex, and I hit "play" in iTunes to find Antonio Wolff presenting a case from his practice during our most recent breast cancer Think Tank. The patient, who is a mother of two teenage children, has rapidly progressive visceral metastases six months after receiving adjuvant dose-dense AC → T for a triple-negative tumor with one microscopic positive node.

Antonio's anguish quickly infects the other faculty members as he describes the crushing depression that engulfed his entire staff the day this woman showed up in a wheelchair with massive anasarca from advanced liver mets.

Hy Muss makes a gentle jibe that situations like this are "two cocktail" nights, and John Mackey notes that he always makes sure there are plenty of tissue boxes in his exam rooms, both for him and his patients.

Gliding along on my machine, I see the sweaty Zumba® class attendees filing out and wonder if any of these women will someday be in the same desperate situation as Dr Wolff's patient. As I continue to listen, Antonio describes how his patient's tumor responded dramatically to anti-angiogenic therapy in the form of bevacizumab and some recycled paclitaxel but now, six months later, the disease was again progressing, and he was unsure of his next move. Although investigators in other tumor types generally turn to breast cancer as the role model for clinical research and progress, cases like this one remind us that for all our new biologic options and chemo choices, metastatic breast cancer is usually far from chronic, and most patients do not survive five years.

The FDA recently approved the use of bevacizumab for patients with breast cancer, but let's be realistic: Bev for any metastatic solid tumor ain't no imatinib for CML, which is the reason that all eyes are on the adjuvant setting. In that regard, there is a sleeping giant in the spare bedroom who will soon wake up and let us know if this treatment strategy can save a few or maybe many of our

mothers, sisters, wives and daughters, and for that matter, our brothers, fathers, husbands and sons.

As is often the case, the NSABP holds the ticket, and the show is about to begin — specifically, the unfolding of results from NSABP trial C-08, comparing FOLFOX to FOLFOX/bev as adjuvant therapy for colon cancer. The international AVANT study also holds this answer, but C-08 is closer to reporting. As discussed by Mike O'Connell on our colon cancer series, the C-08 safety data will be presented at ASCO in June (adjuvant bev is relatively safe, at least in the short run) and the efficacy data will be reported no later than fall 2009, and possibly earlier, as the data monitoring committee continues to review the findings.

I can't convince any investigator in the fertile bev research fields of breast, colon, lung, renal and ovarian cancer and, yes folks, malignant glioma to hazard a guess about what we'll see in the adjuvant setting with this interesting agent. How about you?

NSABP-C-08 will eventually show that disease-free and overall survival comparing FOLFOX to FOLFOX/bev are:

a. The same

b. Better with FOLFOX alone

c. Better with FOLFOX/bev but only a minor advantage

d. Better with FOLFOX/bev as a major advantage

e. A "home run" for FOLFOX/bev with unprecedented improvements observed

You and I will guess "c" because we've seen it before and we think we understand the disease. In any event, for all the grandeur and "astonishment" at ASCO 2005 with the adjuvant trastuzumab data explosion, adjuvant bev trials like C-08 offer the opportunity to impact quantum numbers more people than the modest 20 to 25 percent of the breast cancer population (or maybe more according to Soon Paik) affected by adjuvant trastuzumab.

With the hope and expectation that bev works in the adjuvant setting, researchers around the world have launched a panoply of other studies. In breast cancer, this includes BETH, a combined effort of the CIRG and NSABP comparing TCH to TCH/bev in HER2-positive disease, and BEATRICE, a nouveau-style CIRG study of dealer's choice adjuvant chemo with or without bev in triple-negative breast cancer. ECOG also has trial 5103 in HER2-negative disease, evaluating adjuvant chemo alone or with bev, which complements their major adjuvant non-small cell lung cancer bev study (1505), and the list continues in other tumors.

The quiet before the C-08 storm takes me back to one of the most memorable interviews of our 20 years of querying investigators — in February 2005 with Dr Edith Perez. It is difficult to remember that at that point, adjuvant trastuzumab was still a faint glimmer in our minds. No one had any idea when these

trials would report, and the widespread feeling was that it would be years before there were answers.

In the interview, Dr Perez knocked my socks off by announcing that the NCI and the two US cooperative groups with major adjuvant trastuzumab trials "cooking in the oven" (NCCTG and NSABP) had just decided to speed up the timetable by combining data from the two studies into an unplanned efficacy analysis. I asked Dr Perez when this look-see would be performed and heard the shocking answer that the analysis was to be conducted during the following two months and presented at ASCO that May.

ASCO? Are you serious? We are going to find out about these studies now!

Within three weeks, we had published this interview "alert" hoping that docs would know that ASCO 2005 would be a very interesting event, and sure enough, on my birthday, April 26, the most stunning press release in oncology history documented the unprecedented effect of adjuvant T, and at ASCO, Edith was right up there on the podium as a presenter.

It is interesting to note that in 2005, when ASCO set up a last-minute "education session" chaired by George Sledge to present these landmark findings, not only were the NSABP, NCCTG and HERA trastuzumab trials presented but also on the docket was Kathy Miller reporting for the first time the findings from ECOG trial 2100 evaluating paclitaxel/bevacizumab in first-line metastatic disease. Almost three years later, this intervention has regulatory approval, and we will soon learn whether anti-angiogenesis (or however bev works) is effective as adjuvant therapy, at least in colon cancer.

Whatever the results of C-08, and the trials that will follow, these studies will profoundly affect the oncology landscape and lead to a series of important new challenges that will be quite different depending on what happens. If C-08 does a belly flop and shows no benefit with bev, how will accrual to the huge adjuvant trials in other tumors fare? And how will we feel as a society footing yet another substantial palliative care expense?

On the other hand, if C-08 shows trastuzumabian efficacy, will docs want to use adjuvant bev off study in other tumor types, and will we be able to complete accrual to trials in these tumors? We still will be spending a fortune to block VEGF, but this time with curative intent and, more importantly, there will be further proof that molecular targeted therapy — even if we aren't quite sure what the target is — may truly be able to help us move forward out of the current quagmire in every oncology office on the planet. ■

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
April 22, 2008

SELECT PUBLICATION

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

INTERVIEW

Daniel F Hayes, MD

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

Tracks 1-16

Select Excerpts from the Interview

Track 6

DR LOVE: Can you discuss the results from your paper in *The New England Journal of Medicine* evaluating the efficacy of taxanes based on HER2 status?

DR HAYES: I had the opportunity to work with the CALGB to prospectively collect tissue blocks from the patients enrolled in CALGB-9344, which evalu-

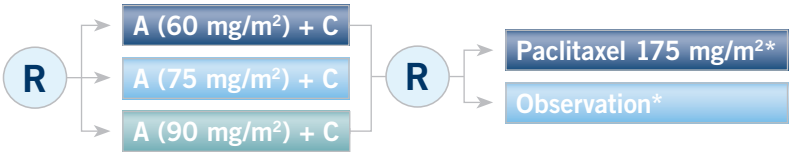
1.1

Phase III Randomized Study of Adjuvant Doxorubicin (A)/ Cyclophosphamide (C) Comparing Standard- versus Intermediate- versus High-Dose Doxorubicin, with or without Subsequent Paclitaxel, in Women with Node-Positive Breast Cancer

Protocol IDs: CALGB-9344, INT-0148
Accrual: 3,121 (Closed)

Eligibility

- Node-positive breast cancer



* Radiation therapy as indicated; tamoxifen 20 mg/day x 5y if ER-positive

SOURCES: Hayes DF et al. *Proc ASCO* 2006;**Abstract 510**; NCI Physician Data Query, April 2008.

ated AC with or without paclitaxel (1.1). We proposed that we might find a benefit with higher doses of doxorubicin for patients with HER2-positive disease. We didn't know what to propose for paclitaxel. Preclinical data suggested that HER2-positive cells were resistant to paclitaxel and docetaxel. That was one hypothesis, but at the time we wrote the protocol, some clinical data suggested the opposite.

DR LOVE: This study began in 1994 when HER2 assays were not being done. How did you obtain the data?

DR HAYES: Once CALGB-9344 was completed, we wrote a separate protocol to evaluate HER2 with three different assays and incorporate the ER data from the primary sites. We conducted the HER2 testing in investigational laboratories. Ann Thor performed HER2 analysis with CB11 staining. Don Weaver used the HercepTest™ at the University of Vermont, and Lynn Dressler performed the PathVysion® FISH analysis at the University of North Carolina. We did not retest the ER status, but we're doing that now.

Our first finding was that regardless of HER2 status, no consistent benefit was evident from higher doses of doxorubicin (Hayes 2007). The relative benefits of doxorubicin reach a plateau at about 60 mg/m^2. It doesn't matter if your disease is HER2-negative or HER2-positive — going above 60 mg/m^2 doesn't appear to bring additional benefit. It's bad news because I'd like to make progress, but it's good news because you can have a lot of toxicity at those higher levels of doxorubicin.

Regardless of which of the three assays we used, we determined that a substantial benefit occurred with the addition of paclitaxel for patients with HER2-positive disease, irrespective of ER status. If the patients had HER2-

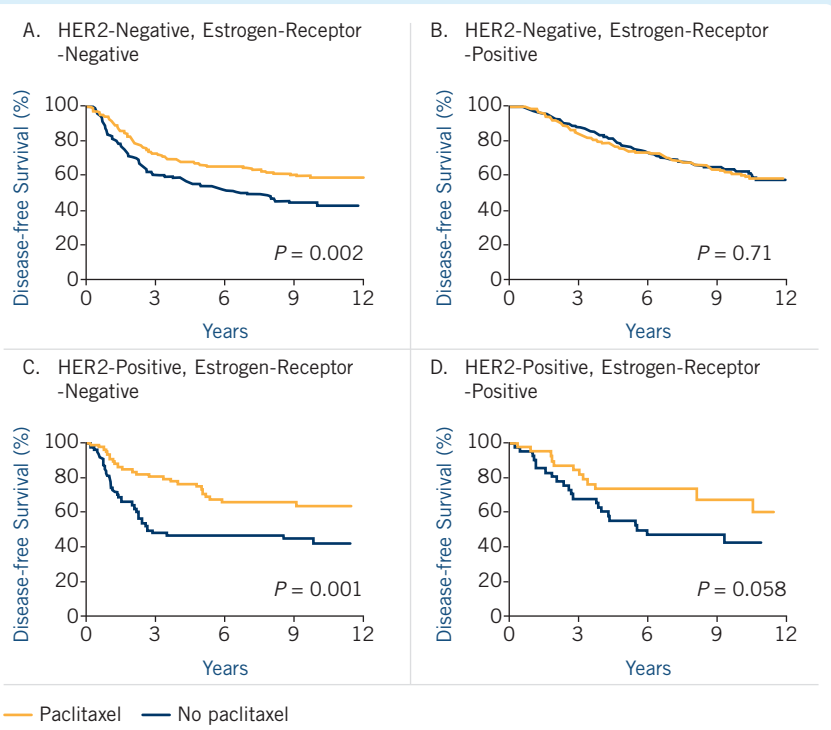
positive disease, ER-negative or ER-positive, they benefited from paclitaxel. Patients with HER2-negative disease benefited less.

We then put the findings together. Statistically it is complicated because now we have a three-way interaction: ER-positive or ER-negative, HER2-positive or HER2-negative and paclitaxel or no paclitaxel. A statistically significant result was recorded for interaction between HER2 and paclitaxel, but we haven't tried to assess the ER-HER2-paclitaxel interaction.

We found that regardless of HER2 status, patients with ER-negative disease benefited from the addition of paclitaxel, and regardless of ER status, patients with HER2-positive disease benefited. But when we evaluated the subgroup with ER-positive and HER2-negative disease — which accounted for 50 percent of the patients in this clinical trial — the curves for paclitaxel versus no paclitaxel overlapped (Hayes 2007; [1.2]). This suggests that we could avoid the extra four cycles of a modestly toxic and expensive drug, even for patients with node-positive disease.

1.2

CALGB-9344: Disease-Free Survival Among Patients with Node-Positive Breast Cancer Who Are Treated with or without Paclitaxel According to ER and HER2 Status



SOURCE: Hayes DF et al. *N Engl J Med* 2007;357(15):1496-506. Copyright © 2007 Massachusetts Medical Society. All rights reserved. **Abstract**

This was, however, a retrospective subset analysis of a single trial. I don't believe that women with ER-positive, HER2-negative, node-positive disease should have paclitaxel withheld at this point.

We have seen a substantial reduction in mortality as a result of chemotherapy in general for patients with node-positive disease during the past 20 years. We need to be sure that these findings are correct before we move forward.

DR LOVE: Do these results reflect the efficacy of paclitaxel specifically, or is this more about chemotherapy in general in this subset of patients?

DR HAYES: You're one step ahead of me. I don't believe this is specific to paclitaxel. This is probably a generic chemotherapy effect.

We hinted around at this idea in the paper, but it was not included in the discussion. It would have been speculation because we didn't have a no-treatment control arm. We did say it was consistent with the effects seen by Don Berry (Berry 2006).

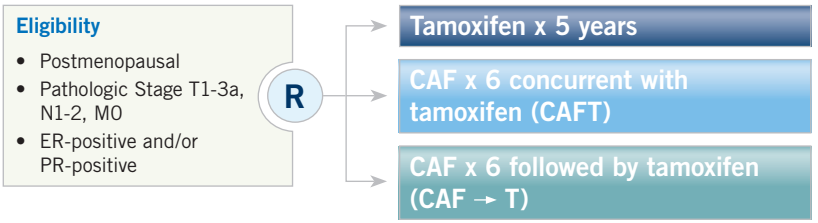
Track 9

DR LOVE: Can you comment on the recent SWOG analysis of the utility of the Onco*type* DX assay for women with node-positive breast cancer?

1.3

SWOG-8814: A Phase III Randomized Trial of Tamoxifen Alone versus Tamoxifen Concurrent or Sequential with CAF for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer

Protocol IDs: SWOG-8814, CAN-NCIC-MA9, CLB-9194, EST-4188, NCCTG-883051, INT-0100, MA9
Accrual: 1,477 (Closed)



Treatment arm	Estimated 10-year disease-free survival
CAF → T	60%
CAFT	53%
Tamoxifen	48%

CAF = oral cyclophosphamide, doxorubicin, 5-FU

SOURCES: Albain K et al. *Breast Cancer Res Treat* 2004;88(Suppl 1);**Abstract 37**; NCI Physician Data Query, April 2008.

DR HAYES: Kathy Albain led a study (SWOG-8814) for postmenopausal patients with node-positive, ER-positive disease who were randomly assigned to tamoxifen alone, tamoxifen concurrent with CAF or CAF followed by tamoxifen. SWOG-8814 demonstrated that chemotherapy concurrent with tamoxifen was not as effective as chemotherapy followed by tamoxifen (Albain 2004; [1.3]).

Tissue blocks were available from approximately 40 percent of those patients. We only compared tamoxifen alone to CAF → tamoxifen. To our pleasure, we saw exactly what we predicted. Among the patients treated with tamoxifen alone, those with low recurrence scores as determined by Onco*type* DX fared better than those with high recurrence scores (Albain 2007; [1.4]).

Nodes are still prognostic here. In fact, as many as 40 percent of patients with node-positive disease and low recurrence scores will still experience a recurrence on tamoxifen alone (Albain 2007; [1.4]).

Among the patients with node-positive disease and high recurrence scores, a statistically significant benefit was seen in disease-free survival with CAF → tamoxifen versus tamoxifen alone. For the patients with low recurrence scores, the curves were overlapping (Albain 2007; [1.5]). Even in node-positive disease, chemotherapy may not be effective for patients with high ER, low HER2 or low Ki-67 — the components of the Onco*type* DX assay.

DR LOVE: In NSABP-B-20, patients with node-negative disease and high recurrence scores demonstrated a relative risk reduction of 75 percent with chemotherapy. What was observed among the patients with node-positive disease?

DR HAYES: It's not that large. I believe all of us felt that the B-20 data were an overestimate. This was a retrospective study with fewer events. I'm not ready to "pull the trigger" on the node-positive situation on this basis. I believe we have two provocative retrospective subset analyses that begin to suggest the same result.

1.4

Prognosis for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer Treated with Tamoxifen Alone According to Onco*type* DX Recurrence Score

	N	10-year DFS[1]	10-year OS[2]
Low-risk recurrence score (<18)	55	60%	77%
Intermediate-risk recurrence score (18-30)	46	49%	68%
High-risk recurrence score (≥31)	47	43%	51%

[1] Stratified log-rank $p = 0.017$ at 10 years; [2] stratified log-rank $p = 0.003$ at 10 years; DFS = disease-free survival; OS = overall survival

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

1.5

Impact of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to Onco*type* DX Recurrence Score

	10-year disease-free survival point estimates (95% CI)	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low recurrence score (<18)	60% (40%, 76%)	64% (50%, 75%)
Intermediate recurrence score (18-30)	49% (32%, 63%)	63% (48%, 74%)
High recurrence score (≥31)	43% (28%, 57%)	55% (40%, 67%)

CI = confidence interval

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

DR LOVE: What do you mean by "pull the trigger"? What if you have a patient who has a node-positive tumor and a low recurrence score? Would it be accurate to say that adjuvant chemotherapy in this situation has an unproven benefit?

DR HAYES: I'd make the opposite argument, which is that for patients with node-positive disease, adjuvant chemotherapy is of proven benefit regardless of biological subsets. Almost every guideline recommends chemotherapy for patients with node-positive disease. The stakes are high in this situation.

I don't believe nodal status indicates whether chemotherapy will work — biology tells you whether chemotherapy will work. I am not sure whether this is the assay we should use to decide whether to withhold adjuvant chemotherapy from patients with node-positive disease.

The question is whether we should run yet another prospective randomized trial. It would be a large trial because it would be an equivalency trial. Patients with low recurrence scores who received adjuvant tamoxifen would be randomly assigned to modern chemotherapy versus none. ■

SELECT PUBLICATIONS

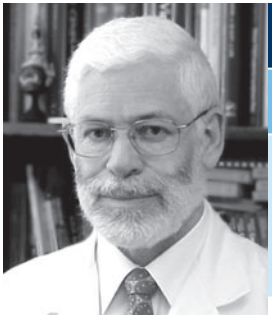
Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

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);**Abstract 37**.

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

Thor AD et al. **erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer.** *J Natl Cancer Inst* 1998;90(18):1346-60. **Abstract**



INTERVIEW

John F Forbes, MD

Prof Forbes is Professor at the University of Newcastle and Director of the Department of Surgical Oncology at Calvary Mater Newcastle Hospital in Newcastle, New South Wales, Australia.

Tracks 1-13

Select Excerpts from the Interview

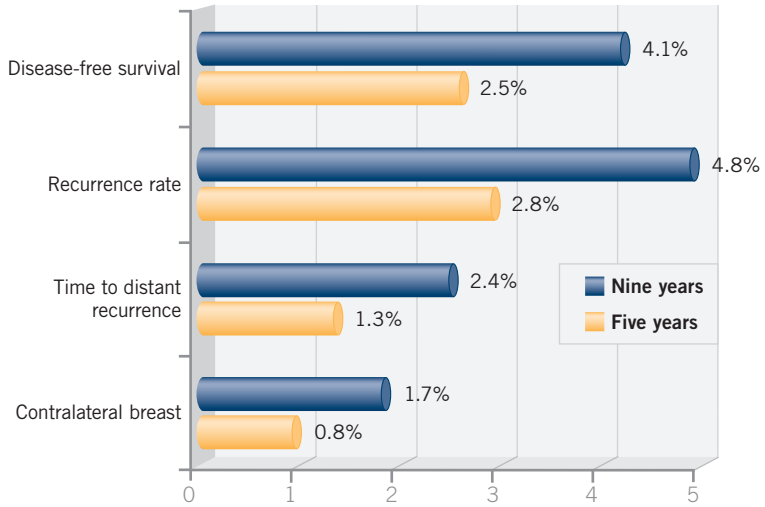
Tracks 4-6

DR LOVE: Can you discuss the 100-month follow-up data from the ATAC trial?

PROF FORBES: With this new data set, we learned some important concepts for practice. First, the advantage of anastrozole over tamoxifen is maintained at least through nine years. It has a carryover effect — the benefit continues after the treatment is stopped. In particular for the post-treatment period from years five to nine, the advantage of anastrozole over tamoxifen remains significant. Furthermore, the absolute difference in the rate of breast cancer relapse increases in magnitude from 2.8 percent at five years to 4.8 percent at nine years (Forbes 2008; [2.1]).

2.1

ATAC Trial 100-Month Update — Carryover Effect: Increased Absolute Difference between Tamoxifen and Anastrozole at Five Years and Nine Years of Follow-Up



"The findings of this report extend the previously reported superior efficacy of anastrozole over tamoxifen at 68 months of follow-up to 100 months. We also show a carryover benefit for recurrence in the hormone-receptor positive population, which is larger than that previously shown for tamoxifen. The difference in recurrence rates has continued to increase, and the smoothed hazard plots show clearly that lower recurrence rates are maintained with anastrozole, even after treatment has been completed."

SOURCE: Forbes JF et al. *Lancet Oncol* 2008;9(1):45-53. **Abstract**

A somewhat unexpected and especially pleasing finding was that upon completion of the treatment, no difference was apparent in the risk of fracture between tamoxifen and anastrozole (2.2). The other surprising finding was the much lower rate of endometrial cancer in women receiving anastrozole compared to those on tamoxifen (Forbes 2008; [2.2]).

This seems to be consistent with a prevention role, and anastrozole may be a future candidate for primary prevention research in endometrial cancer.

When we design these trials, we define the endpoints up front. Overall survival is a safety and efficacy endpoint, which is important but may not tell you a lot about the signal from breast cancer events.

Overall survival becomes diluted by nonbreast cancer mortality. The most indicative endpoint is time to recurrence, which is a measure of breast cancer events — metastatic, local or contralateral.

The ATAC trial produced clear evidence that anastrozole afforded a reduction in total breast cancer events in addition to contralateral breast cancer events. In

2.2

ATAC Trial: Endometrial Cancer and Fracture Episodes On and Off Treatment

	On treatment		Off treatment	
	Anastrozole	Tamoxifen	Anastrozole	Tamoxifen
Women-years of follow-up	12,781	12,331	9,351	9,448
Fracture episodes*	375 (2.93%)	234 (1.90%)	146 (1.56%)	143 (1.51%)
Women with endometrial cancer	4 (0.03%)	12 (0.10%)	1 (0.01%)	12 (0.13%)

* A fracture episode consisted of one or more fractures on the same day based on reports of adverse events and serious adverse events.

SOURCE: Forbes JF et al. *Lancet Oncol* 2008;9(1):45-53. **Abstract**

this trial, we also evaluated time to distant recurrences, which are metastatic events, and they were also significantly reduced.

DR LOVE: What was the magnitude of the reduction in contralateral breast cancer with anastrozole as compared to tamoxifen?

PROF FORBES: The risk was reduced from 1.8 percent to 1.0 percent at five years. The absolute reduction had increased by the nine-year point, the risk being reduced from 4.2 percent to 2.5 percent (Forbes 2008; [2.1]).

If the five-year contralateral breast cancer rate for patients on tamoxifen is 1.8 percent, that's about 0.3 percent a year or about three in a thousand, which is approximately the same risk as that of a 60-year-old woman in the US population developing new breast cancer. That rate is close to halved with anastrozole — it's a 40 percent reduction in relative terms.

DR LOVE: What would you expect you might see for an aromatase inhibitor versus placebo in terms of the reduction in second-primary breast cancer?

PROF FORBES: You can estimate about a 75 percent reduction. It's close to half with tamoxifen and another quarter with anastrozole relative to tamoxifen. If you had a primary prevention trial using anastrozole, you might prevent approximately 75 percent of the hormone-sensitive breast cancer cases, which would be a major impact.

DR LOVE: What about overall survival?

PROF FORBES: Among the patients receiving anastrozole, overall mortality is reduced by three percent, which is not statistically significant. Breast cancer mortality is reduced by 10 percent, and that is not conventionally significant either (Forbes 2008).

The significance, of course, depends on the number of events that are occurring and the magnitude of the difference, and either of these can show up as a particularly small *p*-value.

Conventionally, we regard overall survival as the gold standard of treatment effect, but we treat many chronic illnesses, such as osteoarthritis and rheumatoid arthritis, without taking survival into consideration. We won't say that we will not treat because there is no demonstrated overall survival benefit.

Tracks 11, 13

DR LOVE: Let's talk more about the data on bone fractures that you reported from ATAC.

PROF FORBES: The data on bone fractures from ATAC are informative and pleasantly surprising. For a number of years, we've been aware of the increased risk of fractures associated with the aromatase inhibitors compared to tamoxifen.

What was surprising was that upon completion of the treatment, no difference was detectable in the risk of fractures with anastrozole compared to tamoxifen (Forbes 2008; [2.2]).

It is interesting that no detrimental carryover effect is evident here. Almost as soon as you stop the treatment — within one year — the difference is gone.

I believe we need to be a little cautious about leaping to safety reassurance at this point, however, because the types of fracture risk may vary: Hip fractures may well be different from vertebral fractures.

These are different types of bone, and I believe we need much longer follow-up to be sure that there isn't some unsuspected, longer-term effect on hip fractures.

DR LOVE: Can you talk about the bone substudy from ATAC that had previously been reported (Eastell 2008), and specifically the question of what happens to the women who start out with normal bone density?

PROF FORBES: The bone substudy in ATAC was designed to evaluate the effect of anastrozole on bone density and potential longer-term strategies to correct it. We learned that women who started out with a normal bone density may develop osteopenia but will not develop osteoporosis (Eastell 2008).

Track 9

DR LOVE: Would you discuss the rationale for the LATER trial?

PROF FORBES: The LATER study is a double-blind, randomized trial that compares letrozole to placebo (2.3). It's the only placebo-controlled prevention trial that's being conducted in this context, so it is potentially a paradigm-shifting study.

The trial addresses the issue of the ongoing, long-term risk of relapse for postmenopausal patients who completed primary treatment for an endocrine-

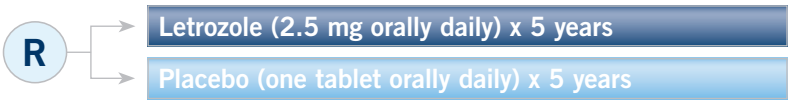
2.3

Later Adjuvant Aromatase Inhibitor Therapy for Postmenopausal Women with Endocrine-Responsive Tumors (LATER)

Protocol IDs: ANZ 0501/LATER, ACTRN12607000137493
Target Accrual: 2,500 (Open)

Eligibility

- Postmenopausal
- Previous completely resected and histologically confirmed hormone-sensitive invasive breast cancer
- Approximately 5 years of adjuvant endocrine therapy (minimum total treatment duration of 4 years) completed at least 12 months previously



Study Contact

Australian New Zealand Breast Cancer Trials Group
Professor John F Forbes
Tel: 61 2 4985 0113

SOURCE: www.anzbctg.org.

sensitive breast tumor, such as five years of adjuvant tamoxifen, at least one year ago.

The ongoing risk of relapse for these women is approximately two percent per year. Interestingly, this group of patients has not received attention as a high-risk population.

By way of comparison, the eligibility criteria for the primary prevention trials required a five-year risk of 1.7 percent. Women in these trials were considered to be at high risk, with a risk of relapse of only 0.3 percent per year. The postmenopausal patients that I'm talking about have a five- to tenfold greater risk than those in the prevention trials.

Another example to consider is the annual risk of breast cancer for women with BRCA mutations. At worst, a 35-year-old woman with this mutation and a 40-year life expectancy has an 80 percent chance of developing breast cancer, which is a risk of two percent per year during 40 years. It's the same risk for the population I'm discussing, women at notably high risk who have been neglected.

Our strategy for managing their risk has been surveillance. We need to approach risk management much more broadly than simply performing a mammogram and noting the family history on a single occasion.

We know tamoxifen prevents contralateral breast cancer and that aromatase inhibitors are approximately twice as good as tamoxifen at preventing these tumors.

It is likely that an aromatase inhibitor some years after diagnosis and completion of treatment would be a positive step. We could probably prevent half the relapses in these women.

I view the LATER study as a primary prevention trial as much as a therapeutic trial because the biology behind these late relapses is unclear. Some of them may be new tumor growth.

Some of them may be dormant tumors that have been there a long time from the time of the original diagnosis, but dormancy is a vague concept. ■

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INTERVIEW

Julie R Gralow, MD

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

Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: What is your usual first-line chemotherapy regimen for a patient with metastatic breast cancer? Do you include bevacizumab?

DR GRALOW: I believe the data with a taxane/bevacizumab regimen are strong. For weekly paclitaxel/bevacizumab, a doubling in progression-free

survival — in absolute terms, adding six months — is clinically meaningful (Miller 2007). So the data support using bevacizumab with weekly paclitaxel.

In the Southwest Oncology Group, we have a lot of experience with the combination of antitubulins and vinca alkaloids — either docetaxel or paclitaxel in combination with vinorelbine.

At ASCO this year, we will be presenting a Phase II study of docetaxel/vinorelbine with trastuzumab for patients with HER2-positive disease.

Docetaxel/vinorelbine is an impressive regimen, whether it's administered in combination with bevacizumab for HER2-negative disease or with trastuzumab for HER2-positive disease. That's my experience.

So I tend to use that as an aggressive regimen up front if I want to obtain a rapid response. We have presented data previously on docetaxel/vinorelbine without bevacizumab for patients with HER2-negative disease (Gralow 2005).

Track 3

DR LOVE: Can you review what we know about *nab* paclitaxel in breast cancer?

DR GRALOW: *Nab* paclitaxel does not require premedications, has a faster infusion time and has the ability to deliver somewhat higher doses of the drug. I believe we are seeing a dose-response effect above what we've traditionally observed with paclitaxel.

Certainly the data with every three-week *nab* paclitaxel versus paclitaxel are in favor of *nab* paclitaxel (Gradishar 2005; [5.3, page 34]). We have randomized Phase II data showing that when administered weekly, *nab* paclitaxel may be as good as, if not better than, docetaxel (Gradishar 2007).

It's a fascinating drug, and I like using it a lot. I like not having to administer steroids and antihistamines and the markedly reduced chance of allergic reactions. I'm excited about trials moving *nab* paclitaxel into the adjuvant setting.

DR LOVE: What about *nab* paclitaxel in combination with bevacizumab?

DR GRALOW: Absolutely. When I can get insurance company approval, I will use that regimen.

DR LOVE: What do we know about that combination at this point?

DR GRALOW: We have no randomized Phase III trial data. However, we do have safety data. I make the leap that it is the same core drug — paclitaxel — at a higher dose.

I don't see the need for a randomized Phase III trial to prove efficacy in that setting when I'm substituting a somewhat higher dose of the core drug, paclitaxel.

Track 6

DR LOVE: What about metastatic disease in the patient with a HER2-positive tumor? How would you approach such a case when the patient has received adjuvant trastuzumab?

DR GRALOW: Fortunately, we now have a second HER2-targeted agent with FDA approval. So for patients who progress on or quickly after stopping adjuvant trastuzumab, I favor using lapatinib, probably in combination with capecitabine (3.1), depending on what other chemotherapy the patient has received. We have some data with lapatinib and paclitaxel, in case I wanted to use that drug.

If the interval between stopping adjuvant trastuzumab and the recurrence was long, then I would seriously consider restarting trastuzumab as my first approach.

I'm interested in trials evaluating whether the two drugs in combination are better than either alone, but that is not something I'd do in a clinical setting right now.

3.1

Phase III Randomized Comparison of Lapatinib with Capecitabine versus Capecitabine Alone in Women with Advanced Breast Cancer that has Progressed on Trastuzumab: Updated Efficacy and Biomarker Analyses

Patients and methods

Eligibility

HER2-positive locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane- and trastuzumab-containing regimens

R

Lapatinib + capecitabine (n = 198)

Lapatinib 1,250 mg qd + **capecitabine** 1,000 mg/m^2 BID days 1-14 q3wk

Capecitabine (n = 201)

1,250 mg/m^2 BID, same schedule

Efficacy results

	Lapatinib + capecitabine	Capecitabine	HR	*p*-value
TTP (median)	6.2 months	4.3 months	0.57	<0.001
Overall survival	15.6 months	15.3 months	0.78	0.177
First progression cases involving CNS	4	13	—	0.045

HR = hazard ratio; TTP = time to progression

Conclusions

The addition of lapatinib to capecitabine provides superior efficacy for women with HER2-positive advanced breast cancer progressing after treatment with anthracycline-, taxane-, and trastuzumab-based therapy.

SOURCE: Cameron D et al. *Breast Cancer Res Treat* 2008;[Epub ahead of print]. **Abstract**

We have a couple of other promising HER2-targeted agents in the pipeline. Pertuzumab is a fascinating drug. I'm most fascinated by T-DM1, which is trastuzumab conjugated to a maytansine derivative.

It delivers chemotherapy directly to the tumor cell. I believe that's smart therapy, with exciting early data (Beeram 2007). Using trastuzumab for drug delivery is a fascinating approach.

Track 7

DR LOVE: Can you describe your experience with lapatinib?

DR GRALOW: I'm using it, and I'm certainly seeing beneficial effects. We're still in the phase of integrating it into practice. Capecitabine/lapatinib can be complicated to administer.

It's a completely oral regimen with many pills. Capecitabine is taken twice a day for only two out of three weeks. Lapatinib is taken once a day. One drug is taken before eating anything, and the other is taken later.

So it's complicated, and we spend a lot of time teaching, reinforcing and making phone calls to make sure patients haven't mixed up the drugs. It has involved a learning curve.

The nurses need to know what must be reinforced, and we need to know how to counsel patients better. We have some great teaching materials now. I've seen efficacy with lapatinib, but also rash and diarrhea. It's a regimen we're still getting comfortable using.

DR LOVE: What have you seen in terms of rash?

DR GRALOW: Facial and truncal rash. My group treats only patients with breast cancer, so we don't have much experience with EGFR-targeted therapy. Many practicing oncologists have already learned how to deal with that, but our group has not had much experience.

We've learned of some topical treatments that we can use. We don't usually use oral antibiotics, but we have done so. We're getting better at managing the rash.

From the patients' standpoint, the rash is visible. They can tolerate it on their chest if they can cover it. When it's on their face, however, they don't like to be labeled or have people ask about it.

Track 8

DR LOVE: Can you talk about brain metastases in patients with HER2-positive breast cancer and where lapatinib might fit in?

DR GRALOW: We're clearly seeing more brain metastases as first or dominant sites of recurrence in patients with HER2-positive disease. Is it related to the

biology of the HER2 tumor cell? My perspective is that we're controlling all the other sites of disease better.

Patients aren't dying as quickly of liver disease, and they're living long enough to manifest the symptoms of their brain metastases, another common site of recurrence.

It's partly biology and partly that we're doing better at controlling the disease in the rest of the body.

Trastuzumab is a large monoclonal antibody that shouldn't be able to cross the intact blood-brain barrier. Some anecdotal case reports, however, indicate that once you have a large metastasis that disrupts the blood-brain barrier, you can obtain tumor shrinkage with trastuzumab.

Lapatinib certainly penetrates the blood-brain barrier, and we have, again, some anecdotal evidence suggesting that we can achieve tumor shrinkage with lapatinib alone. Nancy Lin and the group at Dana Farber have conducted some elegant studies for patients with HER2-positive brain metastases who received radiation therapy and whose disease was progressing. They added lapatinib as a single agent, and then at progression or with no response, they added capecitabine (Lin 2007).

Using conventional measures, lapatinib alone has not produced much of a response. It's making a dent, but it doesn't meet the classic response criteria.

When patients on those studies experienced disease progression or no response on lapatinib, the next step was adding capecitabine, and quite a few responses then met conventional criteria (Lin 2007). Whether it was the combination of capecitabine/lapatinib or capecitabine alone, I'm not sure.

I'm also tantalized by evidence in the Phase III capecitabine/lapatinib versus capecitabine-alone trial, which indicated a numerical trend toward fewer brain metastases with lapatinib (Geyer 2006).

Will that translate in the adjuvant setting to a real difference that can improve survival? I don't know. We will certainly be paying attention to that in the recently opened, international ALTTO trial for patients with HER2-positive disease.

Track 9

DR LOVE: Would you describe the design of the ALTTO trial?

DR GRALOW: ALTTO is a huge, international undertaking between the Breast International Group and the North American Breast Intergroup.

The backbone chemotherapy can vary depending on where you live. In the US, we will predominately use an anthracycline and then weekly paclitaxel, with four different ways of administering the HER2-targeted therapy: trastuzumab alone, lapatinib alone, both agents together or a sequence of the two agents with a washout period (3.2).

3.2

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

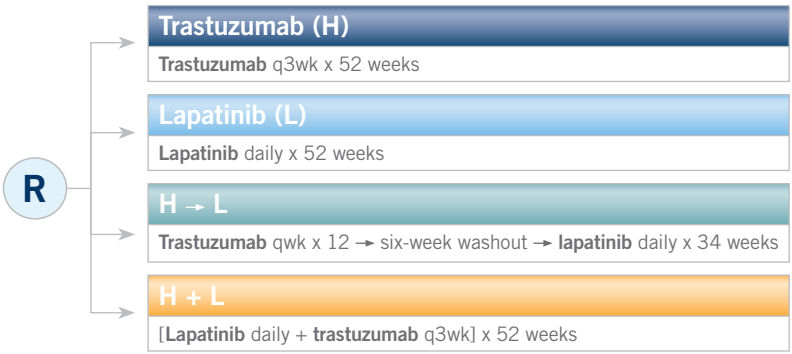
Protocol IDs: BIG 2-06, NCCTG-N063D
Target Accrual: 8,000 (Pending activation)

Eligibility

- HER2-positive breast cancer

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

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



Study Contacts

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

SOURCE: *Breast International Group Newsletter* Spring 2007;9(1).

Everyone receives one year of the HER2-targeted therapy. We will carefully examine the efficacy and toxicity with respect to the heart.

DR LOVE: It is interesting that one of the arms does not include trastuzumab.

DR GRALOW: Much debate goes on about that arm and whether it is ethical. It's standard in this country to use trastuzumab in that setting: Are we omitting an effective therapy in favor of an as-yet unproven therapy? In the metastatic setting, the data with lapatinib are impressive. I've been increasingly reassured that there's activity, especially in combination with paclitaxel, as Angelo Di Leo presented at ASCO 2007 (Di Leo 2007).

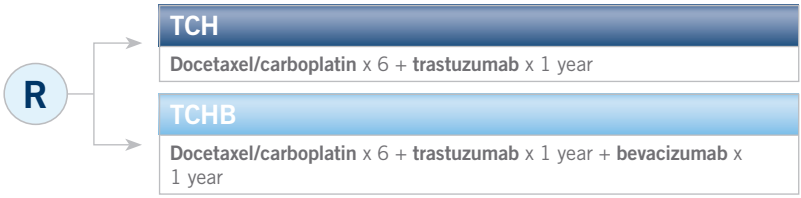
DR LOVE: Can you talk about the BETH trial that the NSABP and CIRG are running?

DR GRALOW: Another important issue is the addition of bevacizumab to chemotherapy and trastuzumab. In the metastatic setting, data for trastuzumab with bevacizumab presented by Mark Pegram and others have shown an impres-

3.3

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

Target Accrual: 3,500



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.

sive response rate for those two agents together (Pegram 2006). Some concern has arisen about cardiac toxicity with trastuzumab and bevacizumab without chemotherapy, and this will be monitored carefully in the BETH trial (3.3). ■

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INTERVIEW

John F R Robertson, MB, ChB, BSc, MD

Prof Robertson is Professor of Surgery and Head of the Academic Division of Breast Surgery at the University of Nottingham and the City Hospital in Nottingham, United Kingdom.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Could you discuss the results from the NEWEST trial that were presented at the 2007 San Antonio Breast Cancer Symposium?

PROF ROBERTSON: This was a neoadjuvant, Phase II, open-label study for postmenopausal women with estrogen-sensitive tumors. Patients were randomly assigned to either standard-dose or high-dose fulvestrant. The patients assigned to the high-dose group received fulvestrant at 500 milligrams per month, with 500 milligrams on day 14 of the first month to reach a plateau more quickly. The standard dose of fulvestrant was 250 milligrams per month (Kuter 2007).

This trial enrolled patients with tumors larger than two centimeters. Ultrasound examinations and tumor biopsies were performed at baseline, week

four and at the time of surgery. In addition to the primary endpoint measurement of Ki-67, other markers of hormone sensitivity, such as ER and PR, were measured. The results indicate that the 500-mg dose caused significantly greater downregulation of the proliferation marker Ki-67 at four weeks than the 250-mg dose (Kuter 2007; [4.1]).

DR LOVE: Can you provide a background of prior related neoadjuvant studies?

PROF ROBERTSON: One was a study published in *Cancer Research* in which we evaluated fulvestrant at 50, 125 and 250 milligrams (Robertson 2001). Results indicated a dose-dependent downregulation of ER, Ki-67 and PR. Data pointed toward antiestrogens being antiproliferative agents, the implication being that increased downregulation of Ki-67 results in increased fulvestrant efficacy.

The second piece of information comes from a Phase III trial in which we evaluated fulvestrant versus anastrozole (Howell 2005). We compared fulvestrant at 250 milligrams and 125 milligrams to anastrozole. People often don't remember that this was initially a three-arm trial. The 125-mg dose was stopped due to lack of disease response. In fact, when we plotted the time to progression, it was significantly shorter than with the 250-mg dose.

Those two pieces of information together implied that this dose-dependent downregulation of ER was clinically important and not just an epiphenomenon. I was also the principal investigator of a study of fulvestrant at 250 milligrams in premenopausal patients, which demonstrated no effect on ER or Ki-67 (Robertson 2007a).

A subsequent study by Mike Dixon demonstrated that in premenopausal women, fulvestrant at 750 milligrams caused a similar downregulation of ER and effect on Ki-67 to what 250 milligrams of fulvestrant did in postmenopausal women (Young 2008). It all began to appear as though the downregulation of ER was important, and that was linked to proliferation.

In the first study evaluating preoperative fulvestrant, a short-acting formulation was administered as a daily subcutaneous injection of either six or 18 milligrams (DeFriend 1994). Results showed greater downregulation of ER

4.1

Effects of High-Dose versus Standard-Dose Fulvestrant on Ki-67 at Four Weeks

Parameter	Fulvestrant HD (n = 109)	Fulvestrant SD (n = 102)	*p*-value
Mean % reduction from baseline	78.8 (95% CI: 70.8 to 84.6)	47.3 (95% CI: 28.5 to 61.2)	<0.0001
Absolute reduction from baseline	-17.5 (95% CI: -15.7 to -18.8)	-10.5 (95% CI: -6.3 to -13.6)	<0.0001

HD = high dose (500 milligrams every month with 500 milligrams on day 14 of first month); SD = standard dose (250 milligrams every month); CI = confidence interval

SOURCE: Kuter I et al. San Antonio Breast Cancer Symposium 2007;**Abstract 23**.

and greater control of Ki-67 compared to long-acting fulvestrant. So the question was, by increasing the dose of fulvestrant beyond 250 milligrams, could we produce this increased downregulation?

Tracks 4-5

DR LOVE: Do you think it's reasonable to consider ovarian suppression in combination with fulvestrant for a premenopausal patient with metastatic breast cancer?

PROF ROBERTSON: Yes, I believe it is. Gunter Steger's work shows response rates in the range that one would expect from an effective endocrine agent (Steger 2005). I believe that if you've used other, perhaps more established, options, such as goserelin and tamoxifen or goserelin and anastrozole, and you're searching for an alternative, then that's reasonable for a hormone-sensitive patient.

DR LOVE: What current clinical trials are evaluating fulvestrant?

PROF ROBERTSON: The FACT study is evaluating the clinical responses to anastrozole monotherapy versus anastrozole/fulvestrant. That will be an important contribution to ascertaining whether we should be combining these drugs.

A second important study is one we are running in the United Kingdom, whereby in a presurgical setting, we're administering fulvestrant at 500 milligrams, fulvestrant at 500 milligrams with an aromatase inhibitor or the aromatase inhibitor alone.

Tracks 6-7

DR LOVE: Can you envision fulvestrant being integrated into the adjuvant setting in any way other than combining it with an aromatase inhibitor?

PROF ROBERTSON: I believe we might want to integrate fulvestrant with certain signal-transduction or growth factor inhibitors. We recently reported that fulvestrant had a 40 percent clinical benefit rate among postmenopausal women with HER2-positive tumors (Robertson 2007b).

These patients were receiving anything from second- to fifth-line therapy. That's good activity for that group of patients with previously treated, HER2-positive disease.

DR LOVE: What about fulvestrant for patients with HER2-positive breast cancer?

PROF ROBERTSON: I believe tamoxifen doesn't work as well in patients with HER2-positive tumors, but it appears as though fulvestrant is effective. In that group of patients, fulvestrant was effective whether or not patients had received or responded to trastuzumab (Robertson 2007b).

I believe that combining fulvestrant with an aromatase inhibitor is not the only alternative. In advanced HER2-positive disease, trastuzumab monotherapy induces only a 30 percent response rate (Vogel 2002). Perhaps the combination of fulvestrant and trastuzumab might increase the response rates.

DR LOVE: What are your thoughts about the TAnDEM trial?

PROF ROBERTSON: The results from the TAnDEM trial demonstrate an increase in response rate and time to progression but no difference in overall survival with the combination of anastrozole and trastuzumab (Mackey 2006; [4.2]). I believe that raises the question as to whether or not sequential therapy is as effective as the combination.

4.2

TAnDEM: A Randomized Trial Comparing Anastrozole with or without Trastuzumab for Patients with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer (N = 208)

Parameter	Anastrozole	Anastrozole + trastuzumab	*p*-value
Median progression-free survival	2.4 months	4.8 months	0.0016
Partial response rate	6.8%	20.3%	0.018
Clinical benefit rate	27.9%	42.7%	0.026
Overall survival	23.9 months	28.5 months	0.325
Overall survival for patients without liver metastasis*	32.1 months	41.9 months	0.0399

* Unplanned subgroup analysis

SOURCE: Mackey JR et al. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

Track 8

DR LOVE: What do you think about the LATER trial evaluating delayed aromatase inhibitor therapy, started one year or more after a patient completes adjuvant endocrine therapy?

PROF ROBERTSON: That trial randomly assigns postmenopausal patients who completed adjuvant endocrine therapy at least one year ago — so they're between six and 20 years from their initial treatment — to letrozole versus placebo. You have a gap between therapies, which makes this an interesting study because essentially it asks, do we need continuous therapy to be able to intervene in breast cancer?

I believe that data from previous trials suggest we don't. When tamoxifen first became adjuvant therapy, a French study evaluated patients more than two years after surgery who'd had 2-cm tumors — a reasonable risk of recurrence. It randomly assigned patients to tamoxifen or placebo and showed a significant

benefit in favor of tamoxifen, so I believe it showed that we can intervene later (Delozier 2000).

The MA17 study also demonstrates this in that patients who were on the placebo control arm were allowed to take letrozole when the study was closed. This wasn't randomized, but those patients also have a reduction in the risk of recurrence compared to those who did not begin letrozole (Robert 2006).

The third, provocative trial that supports this is the HERA trial. Patients were randomly assigned to no trastuzumab versus one or two years of trastuzumab.

Again, after the first analysis, patients who didn't receive trastuzumab were allowed to receive it as delayed therapy. And again, not randomized, this study also reported a lower recurrence rate in the group who received delayed trastuzumab compared to those who did not.

I believe the data from all these trials show that delayed treatment can still reduce a patient's long-term risk of recurrence. ■

SELECT PUBLICATIONS

DeFriend DJ et al. **Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer.** *Cancer Res* 1994;54(2):408-14. **Abstract**

Delozier T et al. **Delayed adjuvant tamoxifen: Ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial).** *Ann Oncol* 2000;11(5):515-9. **Abstract**

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials.** *Cancer* 2005;104(2):236-9. **Abstract**

Kuter I et al. **Fulvestrant 500 mg vs 250 mg: First results from NEWEST, a randomized, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2007;**Abstract 23**.

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Robert NJ et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** *Proc ASCO* 2006;**Abstract 550**.

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Robertson JF et al. **Fulvestrant in the treatment of HER2-positive advanced breast cancer (ABC).** *Proc ASCO* 2007b;**Abstract 1061**.

Robertson JF et al. **Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer.** *Cancer Res* 2001;61(18):6739-46. **Abstract**

Steger G et al. **Fulvestrant (FUL) and goserelin (GOS) in premenopausal women with advanced, hormone-sensitive breast cancer — A pilot study.** *Proc ASCO* 2005;**Abstract 708**.

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

Young OE et al. **Effects of fulvestrant 750mg in premenopausal women with oestrogen-receptor-positive primary breast cancer.** *Eur J Cancer* 2008;44(3):391-9. **Abstract**

ROUNDTABLE DISCUSSION

Management of Metastatic Breast Cancer: Edith A Perez, MD, Nicholas J Robert, MD and Antonio C Wolff, MD

Tracks 1-22

Select Excerpts from the Discussion

Case 1 from the practice of Dr Antonio C Wolff

A woman in her late forties presented with an ER-negative, PR-negative, HER2-negative, T1 tumor and microscopic nodal disease in one sentinel node. She received adjuvant dose-dense AC → paclitaxel and developed peripheral neuropathy that resolved. Six months after finishing her adjuvant therapy, she presented with highly symptomatic metastatic disease in the liver and sternum.

Tracks 3-10

DR LOVE: Edith, this is a challenging situation in which you need to achieve a tumor response because the patient is very ill. How would you be thinking through this case?

DR PEREZ: We're seeing these patients with triple-negative tumors who appear to be faring poorly with standard therapies. The types of agents that have become interesting to consider in this setting are those that target EGFR or HER1.

Several chemotherapy drugs appear to have some interesting response rates in the subset of patients with triple-negative disease, although these are based on fairly small numbers of patients.

In the past, capecitabine would have been the only FDA-approved agent to administer after disease progression on an anthracycline and a taxane. Now we have FDA approval of ixabepilone in combination with capecitabine for situations such as this one (5.1).

If the patient's liver enzymes were not too elevated, ixabepilone/capecitabine would be a consideration. If the liver enzymes were elevated, then she would not be eligible for ixabepilone because that's a contraindication.

Another ongoing study for patients with triple-negative disease involves dasatinib, which is currently used for the treatment of patients with chronic myelogenous leukemia. We are enrolling patients on that study right now.

DR LOVE: Nick, how would you be thinking this through?

DR ROBERT: We are all concerned about this woman having refractory breast cancer. You want to be able to provide something that will control her disease, but you know that whatever you do, it probably will not provide long-term benefit. If this woman had less aggressive disease, less tumor burden, I would have considered single-agent capecitabine.

Edith described a large randomized trial that fits this patient to a tee as someone who's had prior exposure to an anthracycline and a taxane. In that trial, early on, when careful attention was not paid to the liver function tests, they ran into fatal toxicities. It's important that she have adequate liver function to be exposed to ixabepilone and capecitabine.

That combination is superior to capecitabine in terms of response and progression-free survival (PFS). It was not a great difference in PFS, about 1.5 months, but it achieved a significant *p*-value (Thomas 2007; [5.1]).

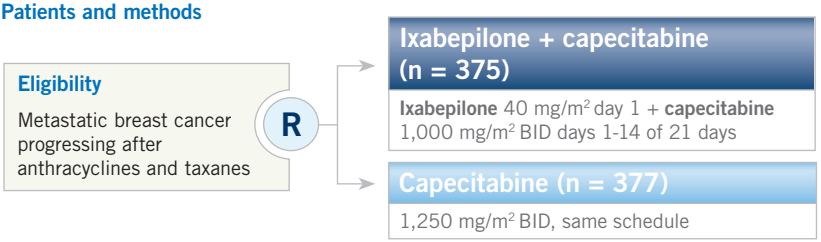
DR LOVE: Antonio, can you follow up on how you treated this patient?

DR WOLFF: This is one example in which I would consider the use of combination therapy, which I normally do not consider for various reasons. I decided to do something for which we did not have data. I thought about bevacizumab.

5.1

Ixabepilone and Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment

Patients and methods



Results

Efficacy	Ixabepilone + capecitabine	Capecitabine	Hazard ratio	*p*-value
Progression-free survival (months)	5.8	4.2	0.75	0.0003
Objective response rate	35%	14%	—	<0.0001

Grade III/IV adverse events	Ixabepilone + capecitabine	Capecitabine
Neuropathy	21%	0%
Fatigue	9%	3%
Neutropenia	68%	11%
Death due to toxicity in patients with liver dysfunction	3%	1%

Conclusions

Ixabepilone with capecitabine demonstrates superior efficacy to capecitabine alone in patients with metastatic breast cancer pretreated with or resistant to anthracyclines and resistant to taxanes.

SOURCE: Thomas ES et al. *J Clin Oncol* 2007;25(33):5210-7. **Abstract**

ECOG-E2100, which treated patients with paclitaxel and bevacizumab or paclitaxel alone, allowed prior exposure to paclitaxel if more than 12 months had elapsed (Miller 2007). So this patient would not have been eligible for that study. In my reimbursement environment, however, I would only have the ability to use bevacizumab as first-line therapy for metastatic disease.

DR LOVE: Edith, in that E2100 trial, patients who had received prior paclitaxel seemed to do at least as well as the other patients.

DR PEREZ: The data were evaluated, and having prior exposure to paclitaxel was not an adverse prognostic factor for progression-free survival benefit from weekly paclitaxel in combination with bevacizumab (Miller 2007; [5.2]).

DR WOLFF: I was out on a limb. This patient had received paclitaxel every two weeks, and then her cancer relapsed within six months.

DR ROBERT: Did you think about using *nab* paclitaxel?

5.2

ECOG-E2100: Progression-Free Survival for Paclitaxel with Bevacizumab versus Paclitaxel Alone as First-Line Therapy for Metastatic Breast Cancer According to Adjuvant Chemotherapy Received

	Paclitaxel + bevacizumab	Paclitaxel alone	Hazard ratio (95% CI)
No adjuvant chemotherapy (n = 237)	13.6 months	6.5 months	0.67 (0.51-0.87)
Adjuvant nontaxane (n = 328)	10.8 months	7.7 months	0.59 (0.47-0.75)
Adjuvant taxane (n = 108)	12.0 months	3.0 months	0.46 (0.30-0.71)

CI = confidence interval

SOURCE: Miller K et al. *N Engl J Med* 2007;357(26):2666-76. **Abstract**

DR WOLFF: I did not consider using *nab* paclitaxel for various reasons. One is that it's not on our formulary.

DR LOVE: Would you be considering it, Nick?

DR ROBERT: Yes, I would.

DR LOVE: US Oncology has done a lot of important work with *nab* paclitaxel. What's your observation in terms of the neuropathy?

DR ROBERT: It occurs and is comparable to the neuropathy associated with paclitaxel. When you stop the drug, it usually disappears or becomes much better.

DR LOVE: When you use bevacizumab, do you combine it with paclitaxel or *nab* paclitaxel?

DR ROBERT: It depends on the situation. If I can use *nab* paclitaxel, I will. I believe it's a better drug.

DR LOVE: Edith, do you believe *nab* paclitaxel is more efficacious than paclitaxel?

DR PEREZ: We have only one randomized trial, comparing *nab* paclitaxel once every three weeks to paclitaxel once every three weeks, and *nab* paclitaxel was better (Gradishar 2005; [5.3]). The challenge is that almost nobody uses paclitaxel once every three weeks. So that comparison is not applicable in today's practice.

We've been interested in weekly *nab* paclitaxel — for example, the work by Joanne Blum evaluating 125 mg/m^2 and 100 mg/m^2 (Blum 2007). At NCCTG, we conducted a Phase II study of weekly *nab* paclitaxel in combination with gemcitabine. We saw good activity, although nothing earthshaking (Roy 2007). We will follow this NCCTG trial with another Phase II trial that will use those two chemotherapy drugs in combination with bevacizumab.

A planned study to be co-led by the CALGB and NCCTG will enroll patients who are eligible to receive first-line chemotherapy for metastatic breast cancer.

5.3

Phase III Randomized Trial Comparing *Nab* Paclitaxel (Every Three Weeks) to Paclitaxel (Every Three Weeks) for Women with Metastatic Breast Cancer

Parameter	*Nab* paclitaxel[1] (n = 229)	Paclitaxel[2] (n = 225)	*p*-value
Complete and partial response			
All patients	33%	19%	0.001
First-line therapy	42%	27%	0.029
Second-line or greater therapy	27%	13%	0.006
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
All patients	65.0 weeks	55.7 weeks	0.374
Second-line or greater therapy	56.4 weeks	46.7 weeks	0.024

[1] *Nab* paclitaxel 260 mg/m^2 every three weeks without premedication
[2] Paclitaxel 175 mg/m^2 every three weeks with premedication

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

5.4

Proposed Randomized Trial of Chemotherapy/Bevacizumab as First-Line Treatment of Metastatic Breast Cancer

SOURCE: Personal communication, Clifford Hudis, MD, December 2007.

Every patient will receive bevacizumab and will then be randomly assigned to weekly paclitaxel, weekly *nab* paclitaxel or weekly ixabepilone (5.4).

DR LOVE: Edith, what ongoing trials will provide useful information on bevacizumab in metastatic disease?

DR PEREZ: RIBBON 2 (5.5) will help us because 650 patients who have recently received chemotherapy will be randomly assigned to chemotherapy or chemotherapy/bevacizumab as second-line therapy.

We have other pending studies of bevacizumab in the first-line setting, which we're eager to learn about when the data are mature. One is the AVADO study, which is evaluating docetaxel versus docetaxel in combination with bevacizumab at two doses.

The RIBBON 1 study is evaluating bevacizumab in combination with a variety of chemotherapy drugs in the first-line setting. This study includes three strata of chemotherapy, which are a taxane, an anthracycline regimen and capecitabine.

DR ROBERT: Interestingly, *nab* paclitaxel is an option in both the RIBBON 1 and RIBBON 2 trials.

DR LOVE: Antonio, what happened with your patient?

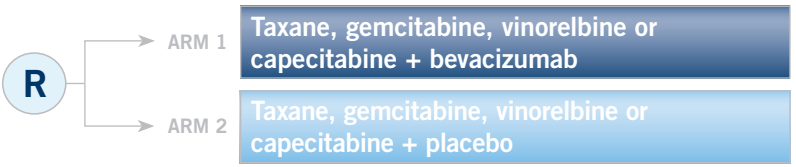
DR WOLFF: I felt that I was conducting a one-patient clinical trial because I had no data to support it, but I wanted to provide her with a chance to receive bevacizumab. She came in and received cycle one of paclitaxel and bevacizumab. She'd had significant ascites, peripheral edema and difficulty walking.

She came back one week later, and she was walking, having previously arrived in a wheelchair. Her peripheral edema had disappeared. Her ascites were almost completely gone, and her liver had shrunk after one dose of paclitaxel and bevacizumab.

I had never seen that kind of response before. One could argue that perhaps weekly paclitaxel would have done it, or one could be excited about the possibility that it was the combination of bevacizumab and paclitaxel.

5.5

RIBBON 2 (AVF3693g): A Phase III, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Patients with Previously Treated Metastatic Breast Cancer



2:1 randomization of Arm 1 to Arm 2

SOURCES: NCI Physician Data Query, March 2008; www.clinicaltrials.gov; Genentech BioOncology, Protocol Schema, March 2008; www.cancer.gov.

Tracks 14-15

Case 2 from the practice of Dr Nicholas J Robert

A woman in her forties was treated with lumpectomy, radiation therapy and five years of adjuvant tamoxifen for a 1.5-cm, Grade II, node-negative, ER-positive, PR-positive, HER2-negative tumor. Seven years later, she developed asymptomatic bone metastases and received several lines of endocrine therapy and then was considered for chemotherapy.

DR LOVE: Antonio, what's your usual approach for a patient who has been treated with a number of endocrine agents and now is no longer responding?

DR WOLFF: This is a situation in which I find capecitabine to be incredibly useful, especially for someone who is asymptomatic. I find it an easy transition, one pill to another pill. So that's usually my approach.

DR PEREZ: I also would consider capecitabine in a situation such as this one. Capecitabine is a well-tolerated drug (5.6). One issue, though, is which dose and schedule to start the patient on. We never use the FDA-approved dose of 2,500 mg/m^2 daily 14 days on and seven days off. We are migrating to 2,000 mg/m^2 daily seven days on and seven days off or a total dose of 2,000 milligrams. The drug is fascinating, but we still don't know how to use it properly.

DR LOVE: Antonio, you are evaluating this in a study.

DR WOLFF: Yes, we started a clinical trial about two and a half years ago. We are using a fixed dose of capecitabine of three grams per day 14 days on, seven days off, regardless of the patient's size (5.7). We're conducting intensive pharmacokinetic and pharmacogenetic studies.

DR LOVE: What do you think about the seven-days-on, seven-days-off schedule suggested by Larry Norton and others?

DR WOLFF: This schedule was proposed shortly after we started our trial, by the folks at Memorial. I don't have personal experience with it at this point, but I expect it's a reasonable approach. We all have patients on chronic capecitabine who ultimately start managing the pills themselves. They figure out exactly how many days they need to take the drug before they have any hand-foot symptoms.

5.6 **Capecitabine as First-Line Therapy for Metastatic Breast Cancer (MBC)**

"Single-agent, first-line capecitabine is a highly effective and well-tolerated option that may be appropriate for several groups of patients, including patients with slowly progressive disease and those who prefer oral treatment, wish to avoid hair loss, are older, or are less fit. In addition, patients with exposure to taxanes in the adjuvant setting may benefit from first-line capecitabine.

Furthermore, capecitabine allows patients to benefit from a long-term treatment that can lead to prolonged survival without the risk for cumulative toxicity. This will be particularly important with the advent of novel targeted agents in long-term treatment, because capecitabine is the only cytotoxic combination partner with no cumulative toxicity.

Capecitabine compares well with the most active agents in breast cancer and should be considered to be an essential component of combination treatment for MBC. It is highly effective in first-line treatment and, when used in combination therapy, has demonstrated overall survival benefits beyond docetaxel alone in two randomized studies. As an oral agent, capecitabine is a flexible combination partner that has a favorable safety profile with minimal myelosuppression and alopecia. Capecitabine allows treatment to be individually tailored to meet each patient's needs with dosing flexibility, which allows better management of side effects. As such, capecitabine can also be an ideal maintenance treatment."

SOURCE: Gelmon K et al. *Oncologist* 2006;11:42-51. **Abstract**

5.7 **Phase II Study of Capecitabine in Patients with Metastatic Breast Cancer**

Protocol IDs: JHOC-J0425, JHOC-SKCCC-J0425, JHOC-IRB-04032502, NCT00274768
Target Accrual: 45 (Open)

Treatment → **Oral capecitabine twice daily on days 1-14**

Courses repeat every 21 days in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients are followed periodically.

Eligibility

- Histologically or cytologically confirmed diagnosis of adenocarcinoma of the breast
- ECOG performance status 0-2
- No previous capecitabine

Study Contact

Antonio Wolff, MD
Principal Investigator
Tel: 410-614-4192

SOURCE: NCI Physician Data Query, April 2008.

DR ROBERT: I agree with Antonio. At the end of the day, everybody has his or her own capecitabine schedule. We're involved in RIBBON 1 and RIBBON 2, and I use capecitabine in those trials. We start off with the original dose and then modify it. Outside a clinical trial, however, I tend to use a flat dose of 3,000 milligrams on days one to 14. ■

SELECT PUBLICATIONS

Blum JL et al. **Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes.** *Clin Breast Cancer* 2007;7(11):850-6. **Abstract**

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

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

Roy V et al. **NCCTG phase II trial N0531 of weekly *nab*-paclitaxel (*nab*-p) in combination with gemcitabine (gem) in patients with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1048**.

Rugo HS et al. **Combination therapy with the novel epothilone B analog, ixabepilone, plus capecitabine has efficacy in ER/PR/HER2-negative breast cancer resistant to anthracyclines and taxanes.** San Antonio Breast Cancer Symposium 2007;**Abstract 6069**.

Thomas ES et al. **Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment.** *J Clin Oncol* 2007;25(33):5210-7. **Abstract**

Vahdat L et al. **Phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer (MBC) previously treated or resistant to an anthracycline and resistant to taxanes.** *Proc ASCO* 2007;**Abstract 1006**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Compared to tamoxifen, the aromatase inhibitors are associated with a(n) _____ incidence of musculoskeletal events.**
   a. Decreased
   b. Equivalent
   c. Increased
2. **In a retrospective subset analysis of CALGB-9344, the addition of paclitaxel to AC as adjuvant therapy improved disease-free survival in all subgroups of patients except those with _____.**
   a. ER-negative disease
   b. HER2-positive disease
   c. ER-positive, HER2-negative disease
3. **The long-term (100-month) follow-up data from the ATAC trial demonstrated a significant difference in the risk of bone fractures after treatment completion for patients treated with tamoxifen versus those treated with anastrozole.**
   a. True
   b. False
4. **In the Phase III randomized trial comparing capecitabine alone to capecitabine with lapatinib for patients with previously treated, HER2-positive metastatic breast cancer, brain metastasis occurred less frequently among the patients treated with _____.**
   a. Capecitabine alone
   b. Capecitabine/lapatinib
   c. None of the above
5. **The ALTTO trial will evaluate adjuvant chemotherapy with which of the following HER2-targeted strategies?**
   a. Trastuzumab alone
   b. Lapatinib alone
   c. Trastuzumab followed by lapatinib
   d. Trastuzumab in combination with lapatinib
   e. All of the above
6. **The primary endpoint in the NEWEST trial was changes in _____.**
   a. PR
   b. Ki-67
   c. ER
   d. None of the above
7. **The Phase II NEWEST trial evaluated which dose(s) of neoadjuvant fulvestrant?**
   a. 750 milligrams
   b. 500 milligrams
   c. 250 milligrams
   d. Both b and c
   e. All of the above
8. **The TAnDEM trial evaluated the impact of adding trastuzumab to _____ for patients with HER2-positive, ER-positive metastatic breast cancer.**
   a. Fulvestrant
   b. Lapatinib
   c. Exemestane
   d. Anastrozole
   e. Letrozole
9. **Ixabepilone in combination with _____ is FDA approved for the treatment of women with anthracycline- and taxane-refractory metastatic breast cancer.**
   a. Bevacizumab
   b. Trastuzumab
   c. Capecitabine
   d. *Nab* paclitaxel
   e. None of the above
10. **In ECOG-E2100, women who were treated with an adjuvant taxane more than 12 months before experiencing a recurrence had an improvement in progression-free survival when bevacizumab was added to paclitaxel.**
    a. True
    b. False
11. **In the only Phase III randomized trial comparing *nab* paclitaxel to paclitaxel, both drugs were administered on which schedule?**
    a. Every three weeks
    b. Every two weeks
    c. Weekly
12. **The RIBBON 2 trial will evaluate bevacizumab in combination with chemotherapy as _____ for patients with metastatic breast cancer.**
    a. First-line therapy
    b. Second-line therapy
    c. Third-line therapy
    d. Any of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 3, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Efficacy of adjuvant paclitaxel according to ER and HER2 status** 4 3 2 1
- **Data on the Onco*type* DX assay** 4 3 2 1
- **Updated ATAC data: 100-month follow-up** 4 3 2 1
- **Emerging data for capecitabine combined with lapatinib or ixabepilone** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Efficacy of adjuvant paclitaxel according to ER and HER2 status** 4 3 2 1
- **Data on the Onco*type* DX assay** 4 3 2 1
- **Updated ATAC data: 100-month follow-up** 4 3 2 1
- **Emerging data for capecitabine combined with lapatinib or ixabepilone** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will:

- 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. ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. ..... 4 3 2 1 N/M N/A
- Select medical and surgical management regimens for early breast cancer based on key clinical and pathological risk factors. ..... 4 3 2 1 N/M N/A
- Assess existing data and emerging research on the optimal duration and sequence of adjuvant endocrine therapy for patients who are postmenopausal with ER-positive breast cancer, and apply this evidence to routine patient care decisions ..... 4 3 2 1 N/M N/A
- Implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for patients with early and advanced HER2-positive breast cancer. ..... 4 3 2 1 N/M N/A
- Evaluate the utility of tissue-based genomic assays for therapeutic decision-making and, when applicable, use these in the selection of individualized treatment regimens for patients with early breast cancer. ..... 4 3 2 1 N/M N/A
- Review the emerging data on various adjuvant chemotherapy approaches, including modified doses and schedules and the use of taxanes, and explain the absolute risks and benefits of these regimens to patients. ..... 4 3 2 1 N/M N/A
- Appraise emerging data on 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, including patients with triple-negative tumors. ..... 4 3 2 1 N/M N/A
- Integrate psychosocial support, optimal patient-physician communication strategies and evidence-based clinical decision-making into a comprehensive approach to patient care. ..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
John F Forbes, MD	4 3 2 1	4 3 2 1
Julie R Gralow, MD	4 3 2 1	4 3 2 1
Daniel F Hayes, MD	4 3 2 1	4 3 2 1
Edith A Perez, MD	4 3 2 1	4 3 2 1
Nicholas J Robert, MD	4 3 2 1	4 3 2 1
John F R Robertson, MB, ChB, BSc, MD	4 3 2 1	4 3 2 1
Antonio C Wolff, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

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BCU308

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