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Breast Cancer® UPDATE

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

EDITOR

Neil Love, MD

INTERVIEWS

Stephen E Jones, MD

Sir Richard Peto, FRS

Kathy S Albain, MD

Joyce O'Shaughnessy, MD

Nancy U Lin, MD

ROUNDTABLE DISCUSSION

Clifford Hudis, MD

Kathy D Miller, MD

SPECIAL EDITION

Best of the San Antonio Breast Cancer Symposium

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from ongoing clinical trials result in 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.
- Consider key clinical and pathologic risk factors when selecting appropriate regimens for the medical and surgical management of early breast cancer.
- Assess existing data and emerging research focusing on the optimal duration and sequence of adjuvant endocrine therapy in the management of the postmenopausal patient with ER-positive breast cancer, and apply this evidence to routine patient care decisions.
- Implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for early and advanced HER2-positive breast cancer.
- Evaluate the practical application of currently available tissue-based genomic assays to assist with therapeutic decision-making in the management of early breast cancer and, when applicable, use these in the selection of individualized treatment regimens.
- Review the emerging data on various adjuvant chemotherapy approaches, including dose-dense or alternative novel scheduling and the contributory roles of taxanes and anthracyclines, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate the emerging data for novel biologic and molecular-targeted therapies with clinical activity in breast cancer, and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- Integrate psychosocial support measures, optimal patient-physician communication strategies and evidence-based clinical decision-making into comprehensive oncology care.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 2 of *Breast Cancer Update* is to support the learning objectives by offering the perspectives of Drs Albain, Hudis, Jones, Lin, Miller, O'Shaughnessy and Peto on the integration of emerging clinical research data into the management of breast cancer.

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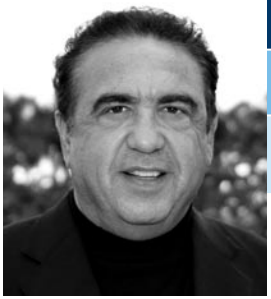


EDITOR'S NOTE

Neil Love, MD

San Antonio adventure, 2007

(Every December brings the annual insanity that is the San Antonio Breast Cancer Symposium, particularly for this intrepid inquisitor who attends far fewer meeting sessions than in the past and instead spends his days and nights with an audio crew asking people about what happened at the conference and what it all means. The result is always a breast cancer research and educational bonanza without parallel. Sitting down at my computer after the first marathon day of the 2007 meeting, I encountered an instant message from a colleague who could not attend but was curious about what happened.)

Thursday, December 13, 2007 @ 11:30 PM

OncMeister: So how was it?

DrNeil: Dude, you have no idea! This morning, I go over to the first oral session and Peto is supposed to give the lead paper. As I walk in, Kent Osborne's semifrantic voice is filling the air, asking, "Does anyone know where Dr Peto is?"

OncMeister: I love it! Peto is like Sting!

DrNeil: Totally! So anyhow, the room is filled with thousands of bright, eager, silent faces, and finally they decide to let the second speaker, Kathy Albain, present.

OncMeister: How was that?

DrNeil: Super-cool. Love RT-PCR. Anyhow, then they say Sir Richard is here and will give his presentation now. So Peto goes up there and says how sorry he is for being late, but he has a bad cold and goes through his talk, stopping like every two minutes for these explosive paroxysms of coughing, looking like he's about to die.

OncMeister: Weren't you supposed to interview him right after the session?

DrNeil: Uh-huh.

OncMeister: Knowing your obsession with germs, I'm sure you were thrilled.

DrNeil: Dude, we ordered like a gallon of Purell® to the interview suite.

OncMeister: Did he show?

DrNeil: Yep…sort of slides in and collapses into his chair. I'm like, "Richard, we don't have to do this," but he's like, "No, I just need a few minutes to catch my breath and get my voice back." Anyhow, after about an hour of him sipping tea, he does his usual amazing interview and announces that tomorrow night, when he presents the initial results of the ATLAS study, there will be about a 15 percent relative reduction in risk of recurrence with 10 versus five years of tamoxifen!

OncMeister: I love it! Remember the 2000 NIH Consensus Conference when he was defiant in continuing the trial, in spite of the NCI alert?

DrNeil: Totally. He's the man.

OncMeister: Who else did you interview?

DrNeil: The venerable cowboy, Steve [Stephen] Jones.

OncMeister: I love him.

DrNeil: Me too. Great voice, super-knowledgeable and he always is nice enough to comment that he enjoys listening to our programs.

OncMeister: Who else?

DrNeil: The aforementioned Kathy Albain, who presented probably the most anticipated paper of the meeting — the Onco*type* node-positive stuff.

OncMeister: What's the bottom line?

DrNeil: Seems like patients with low recurrence scores don't benefit from chemo, but their prognosis without chemo isn't that great either.

OncMeister: Still, why take chemo if it's not going to help?

DrNeil: Totally, but they want more data to be sure.

OncMeister: Always want more data, don't they?

DrNeil: Got to have it! So, later in the afternoon, Kathy Miller and Cliff Hudis drop by for a joint interview to review what happened today.

OncMeister: Interesting duo. Did they behave for a change?

DrNeil: Pretty much, although as we were walking out the door, I heard some pretty choice remarks about the ODAC review of E2100 and bev for breast cancer.

OncMeister: Wish I could have heard that part.

DrNeil: Super-amusing and depressing, simultaneously.

OncMeister: Anybody else?

DrNeil: Nancy Lin.

OncMeister: Brain-met diva!

DrNeil: Totally. Really good stuff on lapat and the brain.

OncMeister: Love TKIs!

DrNeil: Onc-tinib. Our final victim was Joyce O. She just left here in her bright red ensemble.

OncMeister: Encyclopedia of breast cancer.

DrNeil: Totally.

OncMeister: What did she say?

DrNeil: She threw out the interesting concept that if TC is now the new "standard" adjuvant chemo for node-negative and some node-positive patients, and if *nab* is more effective than docetaxel in metastatic disease…

OncMeister: …as per the randomized Phase II by Billy G.

DrNeil: Exactly. So her point is, someday perhaps we will be using *nab*/C rather than TC.

OncMeister: Until something better comes along, G-d willing.

DrNeil: Totally. ■

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
March 13, 2008

SELECT PUBLICATIONS

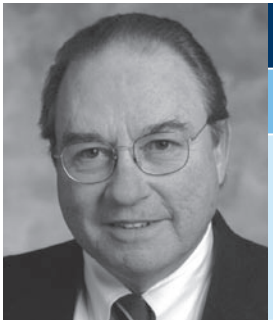
Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814, INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

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

Lin NU et al. **Lapatinib and capecitabine for the treatment of brain metastases in patients with HER2+ breast cancer — An updated analysis from EGF105084.** San Antonio Breast Cancer Symposium 2007;**Abstract 6076**.

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

Peto R, on behalf of the ATLAS Collaboration. **ATLAS (Adjuvant Tamoxifen, Longer Against Shorter): International randomized trial of 10 versus 5 years of adjuvant tamoxifen among 11,500 women: Preliminary results.** San Antonio Breast Cancer Symposium 2007;**Abstract 48**.



INTERVIEW

Stephen E Jones, MD

Dr Jones is Director of Breast Cancer Research at Baylor University Medical Center's Charles A Sammons Cancer Center in Dallas, Texas, Chair of US Oncology Breast Cancer Research and Medical Director of US Oncology Research in Houston, Texas.

Tracks 1-16

Track 1	Critical appraisal of the US Oncology adjuvant trial of docetaxel/cyclophosphamide (TC) versus AC
Track 2	Adjuvant TC versus AC: Efficacy according to HER2 status
Track 3	Adjuvant TC versus AC: Overall survival and long-term toxicities
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Track 5	Adjuvant TC versus AC: Analysis of the elderly population
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Select Excerpts from the Interview

Tracks 1-3

DR LOVE: How have you responded to feedback you have received on the US Oncology adjuvant trial evaluating TC versus AC?

DR JONES: We attempted to address some of the criticisms in our updated San Antonio report of the TC versus AC trial (Jones 2007), although some of the concerns are not "fixable." One criticism was that it's a small trial, which is true in that it involved 1,016 women. Another criticism was the lack of a cardiac monitoring plan, but 10 years ago I don't believe anyone was aware of the cardiotoxicity associated with AC. Likewise, we were not routinely

assessing HER2 status when patients were accrued to the trial. We were able to go back and collect tumor blocks from 170 patients, or 17 percent of the study population, and perform FISH on those tumors.

The final criticism was that no survival difference existed between TC and AC. However, now with a seven-year median follow-up, the absolute survival difference is five percent — 87 versus 82 percent — and the hazard ratio is 0.69, which indicates that the chance of dying with TC is 31 percent less than with AC (Jones 2007; [1.1]).

1.1

US Oncology Adjuvant Trial Comparing Four Cycles of Docetaxel and Cyclophosphamide (TC) to Four Cycles of AC in Women with Node-Negative or Node-Positive Early Breast Cancer: Seven-Year Follow-Up

Endpoint	TC (n = 506)	AC (n = 510)	*p*-value
Disease-free survival	81%	75%	0.033
Overall survival	87%	82%	0.032

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

Track 3

DR LOVE: What about adverse events?

DR JONES: We examined our database for long-term potential toxicities and identified three fatal events: congestive heart failure in a woman younger than age 50, myelodysplastic syndrome and myelofibrosis. Those three patients received AC chemotherapy, and we saw nothing similar in the TC arm.

These are the concerns with anthracyclines. They adversely affect the heart, a fact that has been underappreciated. We are beginning to understand this effect of anthracyclines better, particularly in older patients. Data from MD Anderson and the SEER and Medicare database demonstrate that the occurrence of congestive heart failure may be in excess of 10 or 20 percent among women older than 65 years when treated with anthracyclines (Pinder 2007; [1.2]).

That's scary, and I wonder, did I contribute to this? It would be nice to have a treatment that eliminated doxorubicin, which may be responsible for some of the late congestive heart failures. The anthracyclines also increase nausea and vomiting. In our original report, significantly less Grade III/IV nausea and vomiting was recorded with TC versus AC, and more antiemetics had to be used for those patients with delayed nausea and vomiting (Jones 2005, 2006).

Track 5

DR LOVE: Did you observe any differences in how older patients responded to TC versus AC?

DR JONES: Hy Muss was helpful in the analysis of our data with the elderly. We selected the 16 percent of women who were aged 65 and older when entering the trial. TC was a tolerable treatment in that group. The elderly patients experienced slightly more toxicity, but not much. The older patients treated with TC had better outcomes than those treated with AC (Jones 2007; [1.3]).

1.2

Congestive Heart Failure in Older Women Treated with Adjuvant Anthracycline Chemotherapy for Breast Cancer

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

After 10 years, the increased risk of CHF in anthracycline-treated patients was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when comparing anthracycline-treated patients to the other or no adjuvant chemotherapy groups, respectively.

This effect emerged even though anthracycline treated patients appeared to have been selected for a more favorable cardiac risk profile and were not subjected to more rigorous surveillance for cardiac complications..."

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

1.3

Exploratory Analysis of Disease-Free Survival for Key Subgroups in the US Oncology Adjuvant Clinical Trial of TC versus AC

Subgroup	TC (n)	AC (n)	Hazard ratio (confidence interval)
HER2-negative	55	69	0.56 (0.30-1.05)
HER2-positive	28	18	0.73 (0.32-1.70)
ER- or PR-negative	136	158	0.70 (0.44-1.10)
ER- or PR-positive	368	351	0.79 (0.56-1.13)
Age ≥ 65	78	82	0.70 (0.40-1.24)
Age < 65	428	428	0.76 (0.55-1.04)

Hazard ratio < 1.0 favors TC

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

Tracks 6-7

DR LOVE: What is the rationale for your new US Oncology adjuvant trial for patients with HER2-negative breast cancer (1.4)?

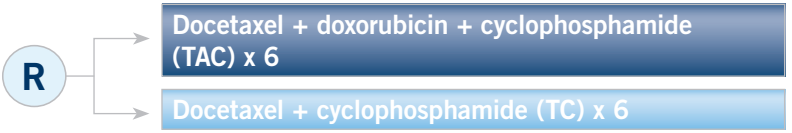
DR JONES: If all the patients who overexpress HER2 are removed from the population, then virtually no patients with TOPO II amplification remain. That is the basis of our current trial, in which we will attempt to prove that adjuvant anthracyclines are unnecessary.

We will be comparing six cycles of TC to six cycles of TAC for patients with HER2-negative early breast cancer. The supposition is that no target for doxorubicin exists in this population. We are collecting tumor blocks and will test them for overexpression of TOPO II and TOPO II protein expression because some controversy remains over the idea that TOPO II protein expression and gene expression are not the same.

1.4

Phase III Trial of Adjuvant TC versus TAC for Patients with HER2-Negative, Early-Stage Breast Cancer

Protocol IDs: NCT00493870, US Oncology 06090, 11271
Target Accrual: 2,000 (Open)
Date Activated: May 2007



Select Eligibility Criteria

- FISH-confirmed HER2-negative breast cancer
- Operable Stage I to IIIC breast cancer
- Meets one of the following criteria: T1-3N1-3M0 if ER-positive or ER-negative; T2-3N0M0 if ER-positive or ER-negative; T1N0M0 if ER-negative and PR-negative
- No prior chemotherapy within the past five years
- Normal cardiac function

Study Contact

Joanne L Blum, MD, Principal Investigator

SOURCES: NCI Physician Data Query, January 2008; **www.clinicaltrials.gov**; Jones SE. *J Clin Oncol* 2007;25(27):4327. **Abstract**

Track 8

DR LOVE: Can you discuss the other US Oncology adjuvant trial that was recently launched for patients with HER2-positive tumors (1.5)?

DR JONES: We are conducting a Phase II pilot study for safety and toxicity. We will try to use data from other trials to obtain a reference point for efficacy, but it's not an efficacy trial.

The regimen being evaluated is docetaxel/cyclophosphamide with trastuzumab. Trastuzumab will be administered for one year — weekly during the four cycles of TC, then every three weeks thereafter.

We haven't encountered any unusual problems with the regimen, and I've spoken to oncologists around the country who are using this treatment off label. They decide a patient with HER2-positive breast cancer needs some, but not too much, chemotherapy, and four cycles of TC combined with trastuzumab seems reasonable.

DR LOVE: Once the safety is established, do you expect physicians will start using the regimen, or would they require a Phase III study comparing it to docetaxel/carboplatin with trastuzumab (TCH), for example?

DR JONES: I believe physicians will recognize that docetaxel/cyclophosphamide/trastuzumab is safe and reasonable and will use it only for selected patients — those with node-negative disease or with one or two positive nodes. If physicians are uncomfortable with this, the other options are six cycles of TCH or eight cycles of AC → TH with its associated cardiotoxicity.

1.5

Phase II Trial of TC (Docetaxel/Cyclophosphamide) with Trastuzumab (H) for HER2-Positive Early Breast Cancer

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

Protocol treatment → **TC x 4 + H qwk x 4 → H q3wk to one year**

Eligibility

- Stage I to IIIA breast cancer
- HER2-positive (immunohistochemistry [IHC] staining of 3+ [uniform, intense membrane staining of >30 percent of invasive tumor cells] or a FISH result of 0.6 HER2 gene copies per nucleus or a FISH ratio [HER2 gene signals to chromosome 17 signals] of >2.2; patients with equivocal FISH ratio results 1.8-2.2 are also eligible if IHC is 3+)
- Adequate tumor specimen available for FISH analysis of TOPO II-A status
- Known ER and PR status

Study Contact

US Oncology
Stephen E Jones, MD, Principal Investigator

SOURCE: www.clinicaltrials.gov

Track 9

DR LOVE: Do you have patients — perhaps older or frail women — for whom you would consider adjuvant trastuzumab without chemotherapy?

DR JONES: That issue does come up, and it makes sense, particularly for a woman with hormone receptor-positive breast cancer with whom you are planning to use an aromatase inhibitor.

Although data from the TAnDEM trial of anastrozole with or without trastuzumab for patients with hormone receptor-positive, HER2-positive metastatic

breast cancer were disappointing (Mackey 2006), they are open to interpretation. Most patients with HER2-positive tumors tend to express ER at lower levels. These are not patients who we expect to respond well to endocrine therapy.

My interpretation is that approximately 20 percent of patients fared well, even at three years, and were still responding to both the aromatase inhibitor and trastuzumab. That subpopulation of patients with relatively indolent, HER2-overexpressing — probably ER-positive *and* PR-positive — breast cancer may fare well. Having said that, some older women coming in will refuse chemotherapy. In those instances you have to consider trastuzumab.

Track 14

DR LOVE: Prior to the results of the E2100 study, many physicians were using capecitabine as first-line therapy. Can you comment on the current use of capecitabine in metastatic disease?

DR JONES: Capecitabine has become a useful drug as physicians have learned how to use it and have found ways to decrease its toxicity by modifying schedules. It is well tolerated and active. Over the years, capecitabine has undergone a major shift in opinion by oncologists. At first we saw a lot of opposition, as it was viewed as being extremely toxic. Now it is thought of as one of the best drugs to use because it is so patient friendly. ■

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.** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

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

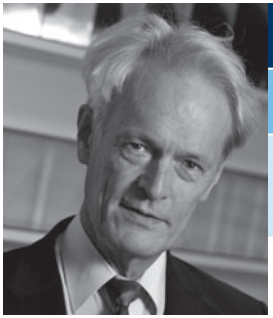
Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 40**.

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

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

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



INTERVIEW

Sir Richard Peto, FRS

Dr Peto is affiliated with the University of Oxford in the United Kingdom.

Tracks 1-10

Select Excerpts from the Interview

Track 3

DR LOVE: Would you talk about the data you presented related to ER and PR status and responsiveness to endocrine therapy?

DR PETO: It's been known for some time that tamoxifen works for ER-positive disease and has little or no effect on ER-negative disease. It had been suggested that tamoxifen might be of some value for patients with ER-poor but PR-positive disease. That turns out not to be true. Tamoxifen is an antiestrogen that doesn't do any good for ER-poor disease (Peto 2007b; [2.1]).

Conversely, it had been suggested that if a patient had ER-positive disease and didn't have a functioning progesterone receptor, you wouldn't gain much from treating with an antiestrogen. That, again, turns out not to be true. In patients with ER-positive and PR-poor disease, tamoxifen has a substantial effect on the long-term risk of recurrence. In fact, it's just as effective as in patients with ER-positive, PR-positive disease (Peto 2007b; [2.1]).

If you want to know whether to use tamoxifen — or, I suspect, any other hormonal treatment — all you need to do is obtain a reliable ER measure-

ment. Measuring PR does not provide any further guidance as to whether to use endocrine treatment.

2.1

EBCTCG: Recurrence After Five Years of Tamoxifen According to Estrogen Receptor and Progesterone Receptor Status

	Recurrence (%)			
	Tamoxifen	Control	10-year benefit	Log rank 2*p*
ER-positive	33.9	47.3	13.4*	<0.00001
ER-positive, PR-positive	25.0	38.4	13.4	<0.00001
ER-positive, PR-poor	29.0	44.6	15.6	<0.00001
ER-poor	31.1	30.9	-0.3	0.92
ER-poor, PR-positive	32.4	33.0	0.6	0.74
ER-poor, PR-poor	29.8	28.2	-1.5	0.66

* Recurrence at 15 years

Receptor-poor is defined as <10 fmol ER or PR per milligram of cytosol protein where quantitative measurements were available, or otherwise accepted as reported.

SOURCES: Peto R et al. San Antonio Breast Cancer Symposium 2007b. No abstract available; Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2005;365:1687–717. **Abstract**

Track 5

DR LOVE: Can you discuss the initial findings from the ATLAS trial?

DR PETO: This study compares 10 years of tamoxifen to five years in terms of the 15-year outcome. It involves a large international group with about 400 centers in 38 countries and is run by Christina Davies. They've randomly assigned 11,500 women who have completed five years of adjuvant tamoxifen. About half of the women had ER-positive disease, and half didn't have their ER status tested, but most of them would have been ER-positive (Peto 2007a).

She followed these patients for an average of four years, so these are preliminary results. But it's clear that further reduction in recurrence is achieved by continuing tamoxifen beyond five years. Continuing tamoxifen beyond five years doesn't increase the recurrence rate of breast cancer. It decreases it further by about 15 percent. This 15 percent decrease is in addition to the decrease from the carryover effect of the first five years. In terms of preventing recurrence, 10 years of adjuvant tamoxifen is better than five years (Peto 2007a).

It's too early to determine how 10 years of tamoxifen will affect breast cancer mortality. Also, longer treatment will increase the incidence of the significant side effect of uterine cancer. There are disadvantages in continuing tamoxifen, but certainly the myth that tamoxifen beyond five years will start stimulating the breast cancer is wrong. This was a mistake that emerged in the mid-90s.

Unfortunately, the NCI decided to issue a Clinical Alert stating that nobody should go beyond five years on tamoxifen. It was an overreaction to a small

preliminary result. The data from the ATLAS trial are about 10 times as extensive as the data on which that NCI Clinical Alert was based (Fisher 2001; NCI 1995). I expect that when the ATLAS data are published, they'll revise that Clinical Alert.

Tracks 7-8

DR LOVE: Would you discuss the data you presented from the EBCTCG Overview on adjuvant chemotherapy?

DR PETO: We don't have trials of taxane-based regimens versus no adjuvant therapy, but we have trials of taxane-based regimens versus anthracycline-based regimens. These regimens will not be so different, but the taxanes are better. Although I must add that a fair number of trials are still not available, and the follow-up isn't long enough. We need the 2010 cycle to include all the taxane trials and data that will be out toward five to 10 years.

From what we have at the moment, taxane-based regimens appear to involve about a 15 percent lower recurrence rate and lower breast cancer mortality rate versus anthracycline-based regimens. With anthracycline-based regimens versus CMF, about a 15 percent lower recurrence rate is evident. I don't mean a 15 percent absolute reduction: These are proportional risk reductions. In the old trials of CMF versus no adjuvant therapy, CMF looked good for young women, but for older women the relative risk reduction was not large (Peto 2007b).

To evaluate chemotherapy, we have to put various trials together. CMF versus nothing — 1970s chemotherapy versus no treatment — provided a moderate gain. Anthracycline-based therapy versus CMF — 1980s chemotherapy versus 1970s chemotherapy — provided another moderate gain. Taxane-based regimens versus anthracycline-based regimens — 1990s chemotherapy versus 1980s chemotherapy — provided yet another moderate gain (Peto 2007b).

If you combine all of these, then you conclude that if we had been comparing taxane-based regimens to no adjuvant therapy, for older women in their fifties and sixties we'd probably be reducing breast cancer mortality by about one third and recurrence rates by about half. For the younger women, the effects are even greater. Taxane-based regimens would be reducing breast cancer mortality by about half and recurrence rates by more than half (Peto 2007b; [2.2]).

A related issue is that when you make this indirect comparison of taxane-based regimens to no chemotherapy separately for ER-poor and ER-positive disease, the proportional risk reduction is the same (Peto 2007b; [2.3]). The idea that ER determines the proportional reduction in risk that chemotherapy can produce is not true. It's widely believed, but the evidence doesn't support it.

If you combine the CMF trials, the anthracycline trials and the taxane trials as I've described and then ask, "What do we see in terms of proportional risk reduction produced by a modern taxane-based regimen?" it's the same for ER-negative and ER-positive disease. There's no difference (Peto 2007b; [2.3]). ■

2.2 EBCTCG: Reduction in Breast Cancer Recurrence and Mortality Associated with Adjuvant Chemotherapy

	RR, recurrence (years 0-4 only)	RR, breast cancer mortality
Age < 50 years		
CMF versus no chemotherapy	0.56	0.68
A versus CMF	0.84	0.81
Taxane versus A	0.84	0.86
Taxane versus no chemotherapy	0.38	0.46
Age 50-69 years		
CMF versus no chemotherapy	0.75	0.91
A versus CMF	0.89	0.90
Taxane versus A	0.82	0.84
Taxane versus no chemotherapy	0.52	0.66

A = anthracycline; RR = rate ratio (also known as odds ratio or risk ratio)

SOURCE: Peto R et al. San Antonio Breast Cancer Symposium 2007b **http://www.sabcs.org/EnduringMaterials/Index.asp#webcast**. No abstract available

2.3 EBCTCG: Impact of Estrogen Receptor Status on Benefit from Adjuvant Taxanes versus No Chemotherapy According to Age

	Recurrence (rate ratio)		Breast cancer mortality (rate ratio)	
	Age < 50 years	Age 50-69 years	Age < 50 years	Age 50-69 years
ER-poor	0.35	0.54	0.41	0.63
ER-positive	0.38	0.52	0.47	0.68

SOURCE: Peto R et al. San Antonio Breast Cancer Symposium 2007b **http://www.sabcs.org/EnduringMaterials/Index.asp#webcast**. No abstract available

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Bryant J et al. **Duration of adjuvant tamoxifen therapy.** *J Natl Cancer Inst Monogr* 2001;(30):56-61. **Abstract**

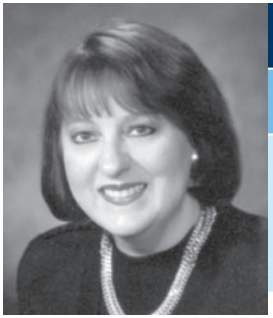
Early Breast Cancer Trialists' Collaborative Group. **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365:1687-717. **Abstract**

Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-90. **Abstract**

National Cancer Institute (NCI). **Clinical alert: Adjuvant therapy of breast cancer — Tamoxifen update.** Available at: **www.nlm.nih.gov/databases/alerts/tamoxifen.html**.

Peto R et al. **ATLAS (Adjuvant Tamoxifen, Longer Against Shorter): International randomized trial of 10 versus 5 years of adjuvant tamoxifen among 11,500 women — Preliminary results.** Presentation. San Antonio Breast Cancer Symposium 2007a;**Abstract 48**.

Peto R et al. **The worldwide overview: Updated (2005-6) meta-analyses of trial results.** San Antonio Breast Cancer Symposium 2007b. No abstract available



INTERVIEW

Kathy S Albain, MD

Dr Albain is Professor of Medicine at Loyola University Stritch School of Medicine and Director of Breast Clinical Research and Thoracic Oncology Programs at Cardinal Bernardin Cancer Center in Maywood, Illinois.

Tracks 1-6

Track 1	SWOG-8814: Tamoxifen versus CAF with concurrent or sequential tamoxifen in node-positive disease	Track 4	Clinical role of Onco*type* DX for patients with hormone receptor-positive, node-positive breast cancer
Track 2	Prognostic value of the Onco*type* DX assay in the tamoxifen-only arm of SWOG-8814	Track 5	Potential for selecting specific chemotherapies based on a patient's risk of recurrence
Track 3	Prognostic value of the Onco*type* DX assay in the chemotherapy-based arms of SWOG-8814	Track 6	Translational research utilizing tissue from prior clinical trials

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you review the background to the data you presented at the 2007 San Antonio Breast Cancer Symposium evaluating the Onco*type* DX assay for postmenopausal women with ER-positive, node-positive early breast cancer?

DR ALBAIN: The Onco*type* DX 21-gene assay has been used with increasing frequency in this country for patients with lymph node-negative breast cancer. We learned that it had prognostic utility for patients with lymph node-negative disease who plan on taking five years of tamoxifen (Paik 2004).

More importantly, it was paradigm shifting in terms of how we thought about the proportional reduction in recurrence achievable by chemotherapy. Instead of a similar degree of benefit across all risk levels, the NSABP reported that the chemotherapy benefit was greatest for patients with a high recurrence score and almost nonexistent for patients with the lowest recurrence scores, with a continuum in between (Paik 2006; [3.1]).

No data for the Onco*type* DX assay existed with a no-chemotherapy control arm in a population of patients with lymph node-positive, ER-positive disease.

3.1 **Impact of Adding Chemotherapy to Tamoxifen According to Oncotype DX Recurrence Score in Women with ER-Positive, Node-Negative Disease**

	10-year distant recurrence-free survival		
Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	*p*-value
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

SWOG-8814 was an ideal study to address the question of prognosis in a tamoxifen-alone arm and, more importantly, the prediction of benefit from chemotherapy, which in this case was an anthracycline-based, second-generation regimen (Albain 2004).

SWOG-8814 included the following treatment arms: tamoxifen alone, CAF concurrent with tamoxifen and CAF followed by tamoxifen. CAF followed by tamoxifen was superior to tamoxifen alone in terms of disease-free and overall survival. The outcome for concurrent CAF and tamoxifen was inferior to CAF followed by tamoxifen (Albain 2004; [3.2]).

Thus, for our analysis at the 2007 San Antonio Breast Cancer Symposium, we did not consider the concurrent arm. In our subset from SWOG-8814, the benefit of chemotherapy followed by tamoxifen versus tamoxifen alone mirrored the benefit in the parent trial, with a statistical significance adjusted for nodes (Albain 2007). We felt confident that this was a representative sample.

In the tamoxifen-alone arm of SWOG-8814, we saw the same strong prognostic utility of the Oncotype DX recurrence score. Approximately 40 percent of the patients had low recurrence scores and about 32 percent had high recurrence scores. The distribution in this population with node-positive disease was different than in the trials with node-negative disease, as you would expect (Albain 2007).

The curves for low, intermediate and high recurrence scores for the patients with node-negative disease indicate that the group with low recurrence scores had excellent outcomes, so you feel confident treating them with standard endocrine therapy (Paik 2004).

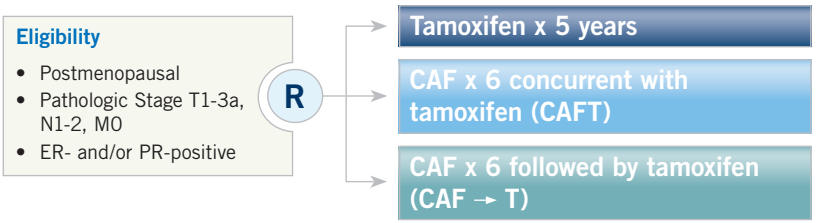
In this trial subset with node-positive disease, our 10-year event rate for the group with low recurrence scores was 40 percent, and that's not a comfortable level (Albain 2007).

- **DR LOVE:** That seems like a high event rate even for node-positive disease.
- **DR ALBAIN:** This was disease-free survival. The Intergroup did not routinely

3.2

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. San Antonio Breast Cancer Symposium 2004;**Abstract 37**; NCI Physician Data Query, January 2008.

3.3

Prognosis for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer Treated with Tamoxifen Alone According to the 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**.

collect data on distant disease or relapse-free intervals, which were collected by the NSABP. So disease-free survival included events due to cancer, new primary cancer and death due to other causes. Disease-free survival was 60 percent at 10 years (Albain 2007; [3.3]). Some of these late events may have been noncompeting causes of death that were included as events.

DR LOVE: What about the patients with high recurrence scores?

DR ALBAIN: At 10 years, disease-free survival was 43 percent. So the event rate was 57 percent. We also considered overall survival, and we saw the same prognostic split. The 10-year overall survival rate for the group with low recurrence scores was 77 percent, whereas for the group with high recurrence scores, it was 51 percent (Albain 2007; [3.3]).

Track 3

DR LOVE: What about the impact of chemotherapy according to the Onco*type* DX recurrence score?

DR ALBAIN: The chemotherapy benefit was strong in the group with high recurrence scores, whereas it was nonexistent in the group with low recurrence scores. If you examine the curves carefully, you notice that in the group with low recurrence scores, the tamoxifen-alone arm tracks above the CAF → tamoxifen arm until the last time point. At 10 years, a 64 percent disease-free survival rate for CAF → tamoxifen versus 60 percent for tamoxifen alone is observed (Albain 2007; [3.4]).

In the group with high recurrence scores, the disease-free survival at 10 years with tamoxifen alone is 43 percent, and it's 55 percent with CAF → tamoxifen, which is a 12 percent absolute difference (Albain 2007; [3.4]).

3.4

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

	10-year disease-free survival estimates	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low recurrence score (<18)	60%	64%
Intermediate recurrence score (18-30)	49%	63%
High recurrence score (≥31)	43%	55%

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

Track 4

DR LOVE: Putting aside reimbursement issues, do you think a role exists for the Onco*type* DX assay among patients with node-positive breast cancer?

DR ALBAIN: Yes, I do. We need to start using it and learn how it's helping. We plan to conduct a prospective trial, but we're 10 to 15 years from an answer. If we can get around issues of reimbursement, which are not insignificant, I want to start using this test in the scenarios in which the standard pathology report leads me to believe patients may have a low recurrence score.

DR LOVE: From the beginning, people were talking about using the Onco*type* DX assay in node-negative disease when the patient or doctor was on the fence about chemotherapy as opposed to a situation in which the patient wanted or didn't want chemotherapy. A similar guideline might relate to patients with node-positive disease.

When you decide, based on the age or the number of nodes, that you will definitely use chemotherapy, perhaps it will not be relevant. Or perhaps the patient's comorbidities are so extensive that there is no way you would even consider it.

DR ALBAIN: Yes, but I'm also going to start ordering it when I think I know the answer. We presented at ASCO 2007 a multicenter study for women with node-negative disease of the impact of the Onco*type* DX assay results on prospective decision-making by doctors and patients.

When you thought you knew what you were doing, you changed your mind in a third of the cases, either to use therapy when you hadn't expected to or vice versa (Lo 2007).

I'm not ready to say it will only be used when the patient and/or doctor are undecided about the use of chemotherapy, but those may be the types of patients with node-positive disease that we should start with.

In other words, that woman with 15 positive nodes is not someone for whom I will order a recurrence score assay right off the bat. ■

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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).** San Antonio Breast Cancer Symposium 2004;**Abstract 37**.

Goldstein LJ et al. **Prognostic utility of 21-gene assay in hormone receptor (HR) positive operable breast cancer and 0-3 positive axillary nodes treated with adjuvant chemohormonal therapy (CHT): An analysis of Intergroup trial E2197.** *Proc ASCO* 2007;**Abstract 526**.

Kamal AH et al. **How well do standard prognostic criteria predict Onco*type* DX (ODX) scores?** *Proc ASCO* 2007;**Abstract 576**.

Lo SS et al. **Prospective multicenter study of the impact of the 21-gene recurrence score (RS) assay on medical oncologist (MO) and patient (pt) adjuvant breast cancer (BC) treatment selection.** *Proc ASCO* 2007;**Abstract 577**.

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

ROUNDTABLE DISCUSSION

Clifford Hudis, MD and Kathy D Miller, MD

Tracks 1-18

Select Excerpts from the Discussion

Track 10

DR LOVE: Kathy, would you comment on the analysis of ECOG-E2100 with regard to VEGF genetic polymorphisms and the effects of bevacizumab?

DR MILLER: We have been struggling with how to identify patients most likely to benefit from bevacizumab — or any other anti-VEGF therapy. We realized that five polymorphisms are in the VEGF ligand, the VEGF-A gene, that somehow decrease VEGF signaling.

Eleven polymorphisms of the VEGF receptor 2 gene are unstudied, but at least one of them, according to computer modeling, affects the ATP binding

domain, so one would expect it to have a significant impact on function.

When tumor blocks collected in the E2100 study were examined, two polymorphisms of the VEGF ligand were identified that seem to clearly influence the risk of toxicity, particularly hypertension (Schneider 2007). Patients who had neither polymorphism and who were homozygous for wild-type VEGF had a low rate of hypertension — in the single digits — whereas patients who were homozygous for one or both of those polymorphisms bore a risk of 40 percent or more.

DR LOVE: Is there a relationship between hypertension and tumor response?

DR MILLER: We haven't found a relationship between hypertension and response. A different VEGF polymorphism in the E2100 data, however, effects or predicts improved overall survival in the bevacizumab-treated group.

It's not purely a prognostic factor — it had no influence on overall survival in the paclitaxel-alone group, but it strongly predicted improved overall survival in the combination-therapy group, with a nice demonstration of a gene-dose effect.

We believe these polymorphisms are important and may help us predict which patients will have better outcomes with bevacizumab, and perhaps other VEGF-targeted therapies, and which patients may bear a greater risk of toxicity. We are still examining more samples and other polymorphisms, but we are sufficiently encouraged to include collecting genomic DNA in the adjuvant trial for this type of analysis.

DR HUDIS: I find these data exciting. Although they don't predict the benefits of bevacizumab, being prepared to manage toxicities with this agent — and maybe even the class of tyrosine kinase inhibitors (TKIs) — will be important.

We have data on 75 patients treated with dose-dense AC followed by *nab* paclitaxel, all combined with bevacizumab in the adjuvant setting. I'm tempted to apply this analysis to that data set.

DR LOVE: What have you seen so far in this adjuvant trial?

DR HUDIS: It's a safety study, and the data are still maturing because some patients are still completing the year of bevacizumab. At this point, we have seen reasonable tolerance of this regimen, with a modest incidence of hypertension and proteinuria (McArthur 2007; [4.1]).

The detailed cardiac safety analysis is forthcoming. At this moment, it appears to be no more toxic than one would expect of an anthracycline-based regimen.

Tracks 12-13

DR LOVE: Cliff, in your experience using paclitaxel and *nab* paclitaxel, how much difference does it make to patients not to receive premedication with steroids?

4.1

Safety of Adjuvant Bevacizumab with Dose-Dense AC Followed by *Nab* Paclitaxel (N = 80)

Protocol ID: MSKCC-06019
Accrual: 80

Protocol treatment

AC + bevacizumab (B) → *nab* paclitaxel (P) + B → B

(**AC** + **bevacizumab** 10 mg/kg) q2wk x 4 → (***nab* paclitaxel** 260 mg/m^2 + **bevacizumab** 10 mg/kg) q2wk x 4 → **bevacizumab** 15 mg/kg q3wk x 12

Pegfilgrastim was administered on day 2 after chemotherapy. Radiation and endocrine therapy were administered according to standard practice.

Incidence of Grade III/IV toxicities

Toxicity	Grade III	Grade IV
Fatigue	8.6%	0
Nausea	1.2%	0
Sensory neuropathy	9.9%	0
Oral mucositis	2.5%	0
Headache	4.9%	0
Dyspnea	1.2%	0
Hypertension	8.6%	1.2%
Wound-healing complications	1.2%	0

"At the time of this analysis, no symptomatic LV dysfunction has been observed with B + ddAC-*nab*-P. Accrual to this trial is complete, but follow-up is ongoing. Correlative studies, including analysis of troponin, renin, and circulating endothelial and tumor cells, are underway."

SOURCE: McArthur HL et al. Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3065**.

DR HUDIS: Patients like not receiving the steroids. They sleep better and experience less aggravation. However, I don't believe *nab* paclitaxel is globally less toxic than conventional paclitaxel.

DR LOVE: How does the efficacy of *nab* paclitaxel compare to docetaxel or paclitaxel?

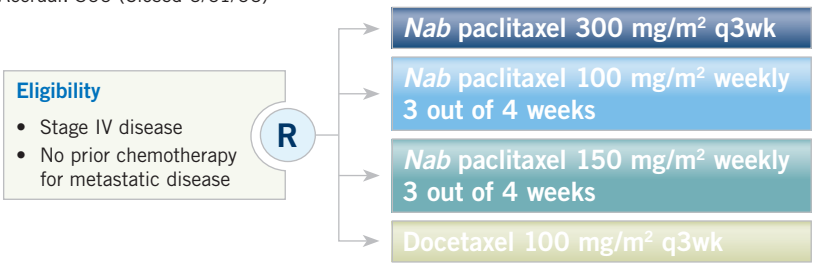
DR HUDIS: Bill Gradishar reported on a randomized Phase II trial comparing three different schedules of *nab* paclitaxel to docetaxel (Gradishar 2006; [4.2]). This was a regimen-finding study, and it's my understanding that they will pick the winner to compare to docetaxel in a Phase III study.

Andrew Seidman is conducting a randomized Phase II trial with three different regimens of *nab* paclitaxel — the standard regimen administered every three weeks versus a dose-dense, full dose administered every two weeks versus a weekly schedule. Those data are forthcoming and may be reported at ASCO in 2008.

4.2

Randomized Phase II Study of Weekly or Every Three-Week *Nab* Paclitaxel versus Every Three-Week Docetaxel as First-Line Therapy for Patients with Metastatic Breast Cancer

Accrual: 300 (Closed 6/01/06)



	Nab paclitaxel 300 mg/m² q3wk	*Nab* paclitaxel 100 mg/m² weekly 3 out of 4 weeks	*Nab* paclitaxel 150 mg/m² weekly 3 out of 4 weeks	Docetaxel 100 mg/m² q3wk
Objective response rate	33%	58%*	62%†	36%
Grade III/IV neutropenia	37%	19%	35%	95%
Grade III/IV peripheral neuropathy	14%	7%	12%	5%
Grade III/IV fatigue	4%	0%	3%	15%

* *p*-value = 0.004 versus docetaxel arm; † *p*-value = 0.016 versus docetaxel arm

SOURCE: Gradishar W et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 46**.

I don't expect a different formulation of a taxane will represent a dramatic change in outcomes for patients with breast cancer. We spent many years comparing docetaxel and paclitaxel, but the randomized clinical trials in the adjuvant setting, for example, don't show much difference. I imagine the *nab* paclitaxel story will play out similarly.

Track 14

DR LOVE: Kathy, would you discuss the ECOG-E2104 study of bevacizumab in the adjuvant setting?

DR MILLER: This trial was designed to ensure that no prohibitive toxicity was associated with adding bevacizumab to an anthracycline- and taxane-based adjuvant regimen. We were particularly interested in cardiotoxicity. Although few data exist on the concurrent use of bevacizumab and anthracyclines, the data that are available raise the question of whether such use might increase the risk of cardiomyopathy and congestive heart failure.

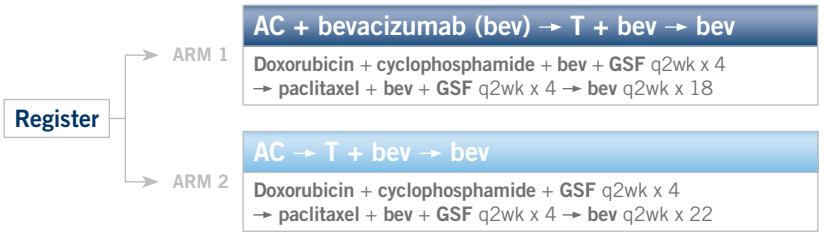
The E2104 trial compares our preferred option of administering the bevacizumab concurrently with all of the chemotherapy to the sequential option, in

4.3

Phase II Feasibility Trial Incorporating Bevacizumab with Dose-Dense AC Followed by Paclitaxel for Patients with Lymph Node-Positive Breast Cancer

Protocol ID: ECOG-E2104
Accrual: 226

Schema*



* Patients were sequentially assigned to Arm 1 or Arm 2

Changes in LVEF	Arm 1	Arm 2
Median follow-up (months)	14.6	10.8
Median pretreatment LVEF	65%	64%
Median postcycle 4 LVEF	63%	61%
Median postcycle 8 LVEF	62%	62%

LVEF = left ventricular ejection fraction

"Preliminary data suggests incorporation of bevacizumab into anthracycline-containing adjuvant therapy is feasible. Ongoing cardiac monitoring is required to define the true impact of bevacizumab on cardiac function."

SOURCE: Miller KD et al. Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3063**.

which patients receive AC followed by bevacizumab with paclitaxel. Patients are enrolled sequentially — not randomly assigned — so we can't directly compare the two arms.

However, if you examine the points in time for which we have relatively similar amounts of follow-up and data, the results appear similar between these two groups, and we have seen no prohibitive toxicities (Miller 2007; [4.3]).

Track 15

DR LOVE: Can you discuss the design of ECOG-E5103?

DR MILLER: Although this trial appears complicated, the simple version is AC followed by weekly paclitaxel versus that same chemotherapy with bevacizumab versus the same chemotherapy with bevacizumab followed by an additional six months of bevacizumab as maintenance (4.4).

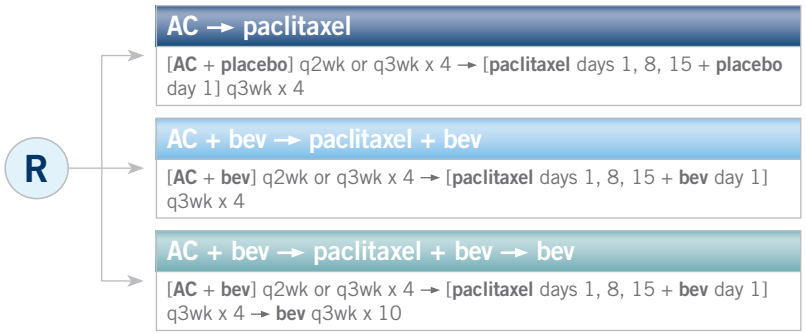
The trial allows the patient and her physician to choose whether to receive AC in a dose-dense or an every three-week fashion. Also, a placebo was mandated, so patients who are not receiving bevacizumab will receive a placebo during the chemotherapy in a double-blinded fashion. When patients complete chemotherapy, they'll all be unblinded and either be finished with treatment or, if they are in the third arm, they'll be asked to continue the bevacizumab for another six months.

I'm excited about this study. To make it more palatable to patients and their physicians, it's a one-to-two-to-two randomization. Thus, patients have a four-out-of-five likelihood of receiving bevacizumab for at least some duration. ■

4.4

Phase III Randomized Study of Adjuvant AC → Paclitaxel with or without Bevacizumab (Bev)

Protocol IDs: ECOG-E5103, NCT00433511
Accrual: 4,950 (Open)



Eligibility

- Pre- or postmenopausal
- ER and PR status known, HER2-negative

SOURCE: NCI Physician Data Query, January 2008.

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Gradishar W et al. **A randomized phase 2 trial of qw or q3w ABI-007 (ABX) vs q3W solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC).** Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 46**.

McArthur HL et al. **Cardiac safety of adjuvant bevacizumab plus dose-dense doxorubicin/cyclophosphamide followed by nanoparticle albumin-bound paclitaxel in patients with early stage breast cancer.** Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3065**.

Miller KD et al. **Phase II feasibility trial incorporating bevacizumab into dose dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with lymph node positive breast cancer: A trial of the Eastern Cooperative Oncology Group (E2104).** Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3063**.

Schneider B et al. **Association of genetic polymorphisms of VEGF and VEGFR-2 with outcome in E2100.** Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 1107**.

INTERVIEW

Joyce O'Shaughnessy, MD

Dr O'Shaughnessy is Co-Director of the Breast Cancer Research Program at Baylor-Charles A Sammons Cancer Center in Dallas, Texas and is affiliated with Texas Oncology, PA and US Oncology.

Tracks 1-14

Select Excerpts from the Interview

Track 3

DR LOVE: In the last year in our Patterns of Care surveys, we've seen more use of TC (docetaxel/cyclophosphamide) both by investigators and oncologists in practice. What are your thoughts about this regimen (Jones 2007)?

DR O'SHAUGHNESSY: Interestingly, TC versus AC shows about the same improvement in outcome that TAC versus FAC shows. With TAC versus FAC, the hazard ratio is 0.72 (Martin 2003). In Steve Jones's trial of TC or AC, it is 0.67 (Jones 2006).

People aren't wrong to use TC for higher-risk, node-positive disease, but the question of duration remains for patients with higher nodal burden and

presumably higher micrometastatic burden. The question is whether four cycles are enough, so most of us will err on the side of six or eight. I use TC all the time in cases for which I used to use AC, which were the patients at lower risk, such as those with ER-positive, node-negative disease or the patients with tiny, triple-negative disease, who will gain that one to four percent absolute benefit from chemotherapy.

Track 4

DR LOVE: Where do you see things headed with *nab* paclitaxel?

DR O'SHAUGHNESSY: Bill Gradishar's randomized Phase II trial, with weekly *nab* paclitaxel appearing considerably better than the docetaxel at 100 mg/m^2 (Gradishar 2007; [4.2]), makes me wonder whether the opportunity exists to substitute *nab* paclitaxel for docetaxel in the TC regimen.

The nadir with cyclophosphamide occurs around day seven, which is early, so the feasibility must be evaluated. Considering it is not myelosuppressive, *nab* paclitaxel should be tolerated when administered on day eight and day 15. Evaluating weekly *nab* paclitaxel/cyclophosphamide versus TC would be a reasonable follow-up to Bill Gradishar's trial.

Track 6

DR LOVE: What are your thoughts on quality of life with *nab* paclitaxel versus paclitaxel versus docetaxel?

DR O'SHAUGHNESSY: I believe weekly *nab* paclitaxel is less neurotoxic than weekly paclitaxel. *Nab* paclitaxel is virtually nonmyelosuppressive, whereas docetaxel is myelosuppressive even if you administer a moderate dose of 75 or 85 mg/m^2 in the metastatic setting. With docetaxel, eventually you are limited by fluid retention. *Nab* paclitaxel unquestionably offers the advantage in the palliative setting for minimizing side effects. I can't recall a single patient who has experienced that lingering, painful neuropathy with *nab* paclitaxel that I'm used to seeing with paclitaxel.

Track 7

DR LOVE: We've seen now in two consecutive Patterns of Care surveys that in breast cancer, although investigators simply do not use steroids with *nab* paclitaxel, one quarter to one third of practicing oncologists are using corticosteroids with *nab* paclitaxel (5.1).

DR O'SHAUGHNESSY: Wow! One of the main advantages of the drug is that you don't need steroids. Steroids weren't used in the *nab* paclitaxel trials, and an increasing body of anecdotal evidence suggests that patients who suffer reactions with paclitaxel or docetaxel can receive *nab* paclitaxel without having anaphylactoid problems. I don't know of any reason to administer steroids to them.

5.1

A 53-Year-Old Woman with Metastatic Breast Cancer, Bone-Only Metastases and Minimal Symptoms Will Receive One of the Following Taxanes. Which Premedications Would You Use?

	Antihistamines		Dexamethasone		Other*		None	
	CI	PO	CI	PO	CI	PO	CI	PO
Paclitaxel	93%	91%	98%	94%	31%	30%	1%	4%
Docetaxel	34%	53%	94%	93%	10%	18%	6%	6%
Nab paclitaxel	2%	22%	1%	30%	6%	17%	93%	52%

* Primarily antiemetics

CI = clinical investigators; PO = practicing oncologists

SOURCE: Love N et al. *Patterns of Care in Medical Oncology* 2007;4(1):39. Available at: www.PatternsOfCare.com

Track 8

DR LOVE: What are some of the current clinical trials evaluating *nab* paclitaxel?

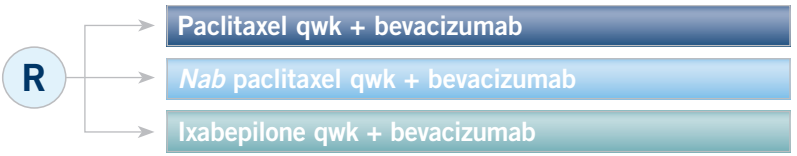
DR O'SHAUGHNESSY: In the metastatic setting, we have the three-arm, front-line randomized trial that Hope Rugo is heading (5.2). The worldwide ABIDE trial is a direct comparison to confirm that *nab* paclitaxel is superior to docetaxel at 100 mg/m^2 because so many people worldwide still like docetaxel. That is an important trial. Data will be presented at ASCO with *nab* paclitaxel at 130 mg/m^2 three weeks on, one week off, with bevacizumab at 10 mg/kg every two weeks. That's a Phase II, front-line, multicenter trial.

DR LOVE: We see some people using *nab* paclitaxel and bevacizumab together. Do you use that combination?

DR O'SHAUGHNESSY: I do. We have Kathy Miller's Phase III data with bevacizumab and regular paclitaxel (Miller 2007). The Phase II experience with *nab* paclitaxel appears to be reasonable so far.

5.2

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



SOURCES: *Personal Communication,* Clifford Hudis, MD, 2007; Interview. O'Shaughnessy J. December 2007.

DR LOVE: What about *nab* paclitaxel and trastuzumab?

DR O'SHAUGHNESSY: Memorial Sloan-Kettering is evaluating *nab* paclitaxel/carboplatin and trastuzumab in a Phase II study. Smaller Phase II studies have been conducted of *nab* paclitaxel and trastuzumab (Bernstein 2006). No issues have emerged with it at all, so I believe that's also reasonable.

Track 9

DR LOVE: What is your approach to metastatic visceral disease in the first-line setting for the patient who previously received an anthracycline and a taxane?

DR O'SHAUGHNESSY: When somebody needs a response on the first line, I turn to a bevacizumab regimen. I want to use it up front, when the safety is the best, and I want to obtain that prolonged progression-free survival. My choices are paclitaxel or *nab* paclitaxel. I don't have a strong preference between the two. All things being equal, I'd probably use *nab* paclitaxel, with the idea of trying to provide a longer run on the taxane before getting into toxicity. I would do that if the patient were chemotherapy naïve, if she'd recently received or if she never received an anthracycline in the adjuvant setting or if she'd received TC in the adjuvant setting.

DR LOVE: I guess this is based on indirect comparison. We do not know what the antitumor efficacy of an anthracycline with a taxane would be versus a taxane with bevacizumab in a patient who is chemotherapy naïve. Yet I hear from investigators exactly what you said — that they would prefer a taxane and bevacizumab, for example, to an anthracycline and a taxane. Is that correct?

DR O'SHAUGHNESSY: Yes. Almost every time two doublets are compared, they appear to be similar. To me, it's comparable to either paclitaxel or *nab* paclitaxel with bevacizumab versus a well-tolerated, effective doublet like gemcitabine/paclitaxel (Albain 2004) or capecitabine/docetaxel (O'Shaughnessy 2002). I've been happy with those regimens over the years, but these days I want to use the bevacizumab up front.

Track 14

DR LOVE: Can you provide an update on the adjuvant trial of AC followed by docetaxel with or without capecitabine in node-positive or higher-risk node-negative breast cancer (5.3)?

DR O'SHAUGHNESSY: That trial compared AC followed by docetaxel to AC followed by docetaxel with capecitabine at a total daily dose of 1,650 mg/m^2. It closed to accrual a couple years ago with 2,610 patients enrolled, and we are coming up on a median follow-up of nearly three years. The interim analysis is event driven, not time driven. These patients are faring better. We've seen fewer events than anticipated, so we are waiting. ■

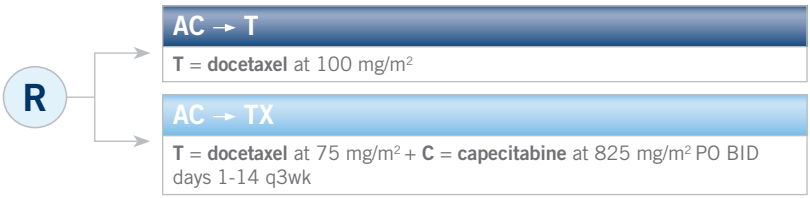
5.3

A Randomized, Open-Label, Multicenter Phase III Trial of Adjuvant Chemotherapy with or without Capecitabine

Protocol ID: US Oncology 01-062
Accrual: 2,600 (Closed)

Eligibility

- Node-positive or high-risk node-negative early breast cancer



SOURCES: US Oncology Protocol 01-062, June 14, 2002; O'Shaughnessy J. *Eur J Cancer* 2007;Suppl 5(1):3-10. **Abstract**

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**.

Bernstein JA et al. **Weekly carboplatin and *nab*-paclitaxel plus trastuzumab, or plus or minus bevacizumab: Clinical response in patients with breast cancer.** *Proc ASCO* 2006;**Abstract 10699**.

Gradishar W et al. **Randomized comparison of weekly or every-3-week (q3w) *nab*-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1032**.

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

Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** San Antonio Breast Cancer Symposium 2003. No abstract available

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

Roché H et al. **Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 trial.** *J Clin Oncol* 2006;24(36):5664-71. **Abstract**

Sartor CI et al. **Effect of addition of adjuvant paclitaxel on radiotherapy delivery and locoregional control of node-positive breast cancer: Cancer and Leukemia Group B 9344.** *J Clin Oncol* 2005;23(1):30-40. **Abstract**

INTERVIEW

Nancy U Lin, MD

Dr Lin is Instructor in Medicine at Harvard Medical School and Medical Oncologist at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-21

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: What is known from the adjuvant trastuzumab trials about brain metastases and patterns of relapse?

DR LIN: The HERA trial and the joint analysis of NCCTG-N9831 and NSABP-B-31 have reported the incidence of CNS recurrences separately from

other distant first-site recurrences. No decrease in the risk of CNS relapse is apparent with the use of adjuvant trastuzumab (Romond 2005; Piccart-Gebhart 2005; [6.1]). If anything, there was a trend toward an increased number of CNS relapses as first event. In comparison, when *any* first distant recurrences are considered, those are clearly reduced with trastuzumab.

DR LOVE: What proportion of patients relapsed with brain-only metastasis?

DR LIN: The range across those three studies is one to two percent at the most. If you evaluate subsequent sites of relapse, in fact, you do not find any apparent trend toward an increase in CNS relapse. I believe those two pieces of data together point to the CNS as a sanctuary site.

DR LOVE: Is that because of the blood-brain barrier, or maybe I should say the blood-tumor barrier?

DR LIN: Yes, and I believe trastuzumab is a particularly large molecule and probably doesn't penetrate well. Dr Burstein evaluated CNS relapse and CNS progression versus non-CNS progression among patients receiving first-line trastuzumab-containing chemotherapy. This analysis revealed that approximately 10 percent of patients in the first-line setting experienced isolated CNS progression at a time when their non-CNS disease was completely quiescent (Burstein 2005; [6.2]).

DR LOVE: Were the numbers similar for patients treated with trastuzumab versus those not receiving trastuzumab?

DR LIN: Separation occurred only among the patients who received trastuzumab. If you evaluate time to CNS progression versus time to non-CNS progression, you see a big separation in the curves. The patients who relapsed in the CNS experienced the recurrence much later and with control of their systemic disease, and that effect was recorded among the patients who received trastuzumab.

DR LOVE: Again suggesting a sanctuary phenomenon?

DR LIN: Yes. The data on trastuzumab levels in the cerebrospinal fluid (CSF) are limited, and it does not seem to penetrate the CSF well. A recent paper

6.1

Incidence of Brain/CNS as First Distant Recurrence in the NCCTG-N9831, NSABP-B-31 and HERA Adjuvant Trastuzumab Trials

	NCCTG-N9831*		NSABP-B-31*		HERA†	
Recurrence site	T (n = 808)	C (n = 807)	T (n = 864)	C (n = 872)	T (n = 1,694)	Observation (n = 1,693)
Brain/CNS metastases (n, %)	12 (1.5)	4 (0.5)	21 (2.4)	11 (1.3)	21 (1.2)	15 (0.9)

T = trastuzumab; C = control

SOURCES: * Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**; † Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353(16):1659-72. **Abstract**

6.2

First-Line Treatment of HER2-Overexpressing Advanced Breast Cancer with Trastuzumab: Prevalence and Time to Initial Isolated CNS Progression Compared to Initial Progression to Other Tumor Sites

	Initial tumor progression (%)			Median time to progression (months)	
Study treatment	Isolated CNS	Other sites	No PD	Isolated CNS	Other sites
Trastuzumab + chemotherapy*	9.8	58.5	31.6	NR	7.8†
Chemotherapy alone*	7.0	83.4	9.6	NR	4.9†

CNS = central nervous system; PD = progressive disease; NR = not reached

* Phase III study with chemotherapy of doxorubicin/cyclophosphamide or paclitaxel q3wk with prior anthracycline.

† Log rank $p = 0.0001$ for isolated CNS sites versus other sites

SOURCE: Burstein HJ et al. *Ann Oncol* 2005;16(11):1772-7. **Abstract**

reported testing CSF soon after patients received cranial radiation therapy to ascertain whether radiation therapy makes the blood-brain barrier more leaky (Stemmler 2007). Trastuzumab penetration was improved, but only slightly.

DR LOVE: What were the clinical research implications of these data sets?

DR LIN: We know that about a third of women with HER2-positive disease ultimately develop clinically evident, symptomatic CNS metastases. If you evaluate the prognosis of patients with CNS metastases in the pretrastuzumab era versus the post-trastuzumab era, you observe a clear difference.

The MD Anderson investigators conducted a retrospective series in which they evaluated survival time from CNS diagnosis for patients with either HER2-positive or HER2-negative disease (Pinder 2007). All the patients fared poorly, but the patients with HER2-positive disease fared particularly poorly.

MD Anderson presented an analysis of a cohort of patients from the post-trastuzumab era, in which patients with HER2-positive disease fared better. The median survival after CNS diagnosis was approximately two years, which is extraordinary for this population (Dawood 2007; [6.3]). I believe we can attribute that to the fact that people are no longer dying from liver metastases.

Track 8

DR LOVE: What do we know about lapatinib and the brain?

DR LIN: Initial studies evaluated structurally related compounds, such as gefitinib or erlotinib, in patients with non-small cell lung cancer and CNS disease, and a series of case reports led to our pilot Phase II study evaluating the role of lapatinib for women with brain metastases from HER2-positive breast cancer (Lin 2006, 2007).

6.3

Prognosis for Women with Breast Cancer and CNS Metastases by HER2 Status and Treatment with Trastuzumab (H): Retrospective Analysis of 598 Patients Treated between 1994 and 2006

Endpoint	HER2-positive, H treatment	HER2-positive, no H treatment	HER2-negative
Time to CNS metastasis (median)	13.1 months	2.1 months (HR 2.13, 95% CI: 1.51-3.00, $p < 0.0001$)	8.9 months (HR 1.50, 95% CI: 1.15-1.95, $p = 0.003$)
Survival after CNS metastasis (median)	11.6 months	6.1 months (HR 1.34, 95% CI: 0.78-2.30, $p = 0.28$)	6.3 months (HR 1.66, 95% CI: 1.31-2.12, $p < 0.0001$)

HR = hazard ratio; CI = confidence interval

"In a cohort of pts with breast cancer and CNS mets, pts with HER2+ve disease treated with trastuzumab had longer times to development of and better survival from CNS mets compared to patients with HER2+ve disease who never received trastuzumab and pts with HER2-ve disease."

SOURCE: Dawood SS et al. ASCO Breast Cancer Symposium 2007;**Abstract 104**.

Objective RECIST response rates were modest. Some patients experienced volumetric reductions in their CNS tumor burden, and in fact, the one responder according to RECIST was able to remain on the study for over 11 months and showed a dramatic response.

Tracks 13, 15

DR LOVE: Where do you see lapatinib fitting into disease management right now in the clinical setting?

DR LIN: Approval for lapatinib came out of the study by Dr Geyer evaluating capecitabine with or without lapatinib. The addition of lapatinib improved time to progression and response rates for patients with HER2-positive breast cancer after treatment with trastuzumab (Cameron 2008; [6.4]). For patients whose disease progresses after trastuzumab, switching to lapatinib and capecitabine is a reasonable option to consider.

DR LOVE: What have you seen in terms of side effects and toxicity with lapatinib or lapatinib/capecitabine?

DR LIN: I believe that the most relevant toxicity is diarrhea. We learned early on that it is important to gain control of the diarrhea. Patients — often because we are treating them after progression on trastuzumab — tend to continue receiving the capecitabine/lapatinib even when they are experiencing diarrhea because they are afraid of missing a dose: What I would call "overadherence." Now we are extremely proactive about educating patients from the beginning to call us if they have more than two loose bowel movements a day.

6.4

Lapatinib and Capecitabine for HER2-Positive Advanced Breast Cancer: Efficacy Endpoints in the Intention-to-Treat Population

Endpoint	Lapatinib and capecitabine (n = 198)	Capecitabine alone (n = 201)	Hazard ratio (95% CI)	*p*-value
Median TTP	6.2 months	4.3 months	0.57 (0.43-0.77)	<0.001
Median OS	15.6 months	15.3 months	0.78 (0.55-1.12)	0.177
Response rate CR PR	23.7% <1% 23%	13.9% 0% 14%	1.9 (1.1-3.4)	0.017
Clinical benefit	29.3%	17.4%	2.0 (1.2-3.3)	0.008

TTP = time to progression; OS = overall survival; CR = complete response; PR = partial response

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

DR LOVE: Do you see any other side effects or toxicity from that regimen (6.5)?

DR LIN: Some people report fatigue or mild nausea, and there is the acneiform rash that is typical of any of the EGFR inhibitors. Typically it appears over the lower part of the face and the upper chest.

Whether it's responding to treatment or going away on its own is hard to say, but we've used topical antibiotics with good results. You definitely see hand-foot syndrome with capecitabine, and this study suggests it may be worse with the addition of lapatinib.

6.5

Lapatinib and Capecitabine for HER2-Positive Advanced Breast Cancer: Most Frequent Adverse Events

Adverse event	Lapatinib and capecitabine (n = 198)		Capecitabine alone (n = 191)	
	Grades I/II	Grades III/IV	Grades I/II	Grades III/IV
Diarrhea	51%	14%	30%	10%
PPE	42%	12%	37%	14%
Nausea	42%	2%	42%	2%
Vomiting	24%	2%	20%	2%
Fatigue	21%	3%	21%	4%
Rash	27%	2%	13%	1%

PPE = palmar plantar erythrodysesthesia

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

Track 16

DR LOVE: How have the ECOG data with paclitaxel/bevacizumab affected the treatment of HER2-negative metastatic disease — either in the ER-negative setting or for patients who are no longer responding to hormonal therapy?

DR LIN: Before the E2100 data were presented (Miller 2007), we used a lot of first-line capecitabine, as most patients received an anthracycline and a taxane in the adjuvant setting.

The data indicate that the order in which one administers cytotoxic chemotherapy will probably not effect survival, but when E2100 came we moved toward using a lot of first-line paclitaxel/bevacizumab.

I believe that we were compelled by the significant prolongation of time to progression that was seen in E2100. That benefit was not evident in every patient.

So in the patients who have hormonally sensitive, relatively indolent disease that has progressed through hormonal therapy, I am still comfortable administering first-line capecitabine. I will treat most patients with triple-negative breast cancer and multiple liver metastases with paclitaxel/bevacizumab. ■

SELECT PUBLICATIONS

Burstein HJ et al. **Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy.** *Ann Oncol* 2005;16(11):1772-7. **Abstract**

Cameron D et al. **A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: Updated efficacy and biomarker analyses.** *Breast Cancer Res Treat* 2008;[Epub ahead of print]. **Abstract**

Dawood SS et al. **Prognosis of women with breast cancer and CNS metastases by HER2 status.** ASCO Breast Cancer Symposium 2007;**Abstract 104**.

Lin NU et al. **EGF105084, a phase II study of lapatinib for brain metastases in patients (pts) with HER2+ breast cancer following trastuzumab (H) based systemic therapy and cranial radiotherapy (RT).** *Proc ASCO* 2007;**Abstract 1012**.

Lin NU et al. **Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer.** *Proc ASCO* 2006;**Abstract 503**.

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Pinder MC et al. **Trastuzumab treatment and the risk of central nervous system (CNS) metastases.** *Proc ASCO* 2007;**Abstract 1018**.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Stemmler HJ et al. **Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier.** *Anticancer Drugs* 2007;18(1):23-8. **Abstract**

Storniolo AM et al. **Cardiac safety in patients (pts) with metastatic breast cancer (MBC) treated with lapatinib (L) and trastuzumab (TRA).** *Proc ASCO* 2007;**Abstract 514**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The seven-year follow-up of the US Oncology adjuvant trial demonstrated a statistically significant improvement in _____ with docetaxel/cyclophosphamide (TC) compared to AC chemotherapy.**
   a. Disease-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above

2. **In a randomized Phase II trial of weekly or every three-week *nab* paclitaxel versus every three-week docetaxel, the *nab* paclitaxel schedule with the greatest antitumor activity appears to be _____.**
   a. 300 mg/m^2 every three weeks
   b. 100 mg/m^2 weekly three out of four weeks
   c. 150 mg/m^2 weekly three out of four weeks

3. **The US Oncology Phase III TC-TAC trial will evaluate adjuvant TC versus docetaxel/doxorubicin/cyclophosphamide (TAC) for patients who have undergone surgical resection for early-stage, HER2-negative breast cancer.**
   a. True
   b. False

4. **Compared to the standard formulation of paclitaxel, *nab* paclitaxel requires _____.**
   a. No premedication with steroids
   b. Premedication with steroids for antiemetic purposes
   c. Premedication with steroids to prevent hypersensitivity reactions
   d. Either b or c

5. **The Phase III ABIDE registration trial will compare weekly *nab* paclitaxel at 100 mg/m^2 with no standard premedication to _____ in first-line treatment of 1,000 patients with metastatic breast cancer.**
   a. Weekly docetaxel at 100 mg/m^2 with premedication
   b. Every three-week docetaxel at 100 mg/m^2 with premedication
   c. Every three-week docetaxel at 100 mg/m^2 with no standard premedication

6. **Preliminary results from the ATLAS trial, comparing five to 10 years of adjuvant tamoxifen, demonstrated that 10 years of therapy improved the _____.**
   a. Breast cancer recurrence rate
   b. Breast cancer mortality rate
   c. Both a and b
   d. None of the above

7. **In SWOG-8814, the 10-year disease-free survival rate for postmenopausal patients with ER-positive, node-positive breast cancer treated with tamoxifen alone was _____ if they had low recurrence scores with the Onco*type* DX assay.**
   a. Six percent
   b. 16 percent
   c. 43 percent
   d. 60 percent

8. **In SWOG-8814, the 10-year disease-free survival rate for postmenopausal patients with ER-positive, node-positive breast cancer treated with tamoxifen alone was _____ if they had high recurrence scores with the Onco*type* DX assay.**
   a. Six percent
   b. 16 percent
   c. 43 percent
   d. 60 percent

9. **In the US Oncology adjuvant trial, patients receiving TC experienced significantly more nausea and vomiting than those who were treated with AC chemotherapy.**
   a. True
   b. False

10. **ECOG trial E5103 is evaluating bevacizumab in combination with _____ in the adjuvant setting.**
    a. AC alone
    b. AC → paclitaxel
    c. AC → docetaxel
    d. TCH

11. **In a Phase II study, the combination of lapatinib/capecitabine improved time to progression and response rates in comparison to capecitabine treatment alone for patients with HER2-positive breast cancer.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 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

- **Nonanthracycline-containing adjuvant chemotherapy** 4 3 2 1
- **Onco*type* DX assay in node-negative and node-positive early breast cancer** 4 3 2 1
- **Updated EBCTCG Overview results** 4 3 2 1
- **Major ongoing adjuvant trials in HER2-negative and HER2-positive breast cancer** . . 4 3 2 1
- **Novel therapeutic options in the metastatic setting** 4 3 2 1
- **CNS recurrence after trastuzumab** 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

- **Nonanthracycline-containing adjuvant chemotherapy** 4 3 2 1
- **Onco*type* DX assay in node-negative and node-positive early breast cancer** 4 3 2 1
- **Updated EBCTCG Overview results** 4 3 2 1
- **Major ongoing adjuvant trials in HER2-negative and HER2-positive breast cancer** . . 4 3 2 1
- **Novel therapeutic options in the metastatic setting** 4 3 2 1
- **CNS recurrence after trastuzumab** 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
- Consider key clinical and pathologic risk factors when selecting appropriate regimens for the medical and surgical management of early breast cancer. . . . . 4 3 2 1 N/M N/A
- Assess existing data and emerging research focusing on the optimal duration and sequence of adjuvant endocrine therapy in the management of the postmenopausal patient with ER-positive breast cancer, and apply this evidence to routine patient care decisions. . . . . 4 3 2 1 N/M N/A
- Implement an algorithm for HER2 testing and selection of evidence-based treatment strategies for early and advanced HER2-positive breast cancer. . . . . 4 3 2 1 N/M N/A
- Evaluate the practical application of currently available tissue-based genomic assays to assist with therapeutic decision-making in the management of early breast cancer and, when applicable, use these in the selection of individualized treatment regimens. . . . . 4 3 2 1 N/M N/A
- Review the emerging data on various adjuvant chemotherapy approaches, including dose-dense or alternative novel scheduling and the contributory roles of taxanes and anthracyclines, and explain the absolute risks and benefits of these regimens to patients. . . . 4 3 2 1 N/M N/A
- Evaluate the emerging data for novel biologic and molecular-targeted therapies with clinical activity in breast cancer, and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . . . . 4 3 2 1 N/M N/A
- Integrate psychosocial support measures, optimal patient-physician communication strategies and evidence-based clinical decision-making into comprehensive oncology 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			
Kathy S Albain, MD	4	3	2	1	4	3	2	1
Clifford Hudis, MD	4	3	2	1	4	3	2	1
Stephen E Jones, MD	4	3	2	1	4	3	2	1
Nancy U Lin, MD	4	3	2	1	4	3	2	1
Kathy D Miller, MD	4	3	2	1	4	3	2	1
Joyce O'Shaughnessy, MD	4	3	2	1	4	3	2	1
Sir Richard Peto, FRS	4	3	2	1	4	3	2	1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Degree:

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

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

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Research To Practice designates this educational activity for a maximum of 4 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

BCU208

Breast Cancer® UPDATE

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