

# Breast Cancer<sup>®</sup>

U P D A T E

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

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**INTERVIEWS**

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**SPECIAL FEATURE**

*Three Perspectives on US  
Cooperative Group Research*

Norman Wolmark, MD  
Joyce O'Shaughnessy, MD  
Eric P Winer, MD

**CME**  
Certified



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# Breast Cancer Update

## A Continuing Medical Education Audio Series

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### OVERVIEW OF ACTIVITY

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. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

### LEARNING OBJECTIVES

- Integrate validated tissue biomarkers and genomic assays into the clinical management of node-negative and node-positive early breast cancer.
- Develop an evidence-based adjuvant treatment algorithm for patients with localized breast cancer, addressing the individualized selection of chemotherapy and the optimal schedule and duration of endocrine therapy.
- Compare and contrast the efficacy, safety and current clinical utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens.
- Discuss the adjunctive role of oral and intravenous bisphosphonates in the management of ER-positive and/or PR-positive early breast cancer, and identify patients who may benefit from this course of therapy.
- Explain the benefits and risks of HER2-directed therapy for patients with early and advanced breast cancer, and discuss how combination treatment regimens may overcome the development of resistant disease.
- Demonstrate knowledge of the evidence-based use of bevacizumab in the first-line treatment of metastatic breast cancer, and recognize the rationale for its ongoing investigation in the adjuvant setting.
- Appraise the value of the neoadjuvant platform, precise patient selection and translational research in the successful development of novel breast cancer therapeutics.
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation.

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## INTERVIEW

### Nancy E Davidson, MD

Dr Davidson is Breast Cancer Research Professor of Oncology and Director of the Breast Cancer Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

#### Tracks 1-12

- |                |   |                 |   |
|----------------|---|-----------------|---|
| <b>Track 1</b> | ABCSG-12: Adjuvant ovarian suppression and tamoxifen or anastrozole, with or without zoledronic acid, in premenopausal women with ER/PR-positive breast cancer (BC) | <b>Track 6</b>  | Clinical trials of the HDAC inhibitor vorinostat                            |
| <b>Track 2</b> | SOFT and TEXT: Ovarian suppression combined with endocrine therapy for premenopausal patients with ER/PR-positive BC  | <b>Track 7</b>  | Long-term therapeutic strategies for ER/PR-positive BC                      |
| <b>Track 3</b> | ABCSG-12: Cancer recurrence and zoledronic acid   | <b>Track 8</b>  | ATLAS and aTTom trials of adjuvant tamoxifen beyond five years              |
| <b>Track 4</b> | Ongoing clinical trials of adjuvant bisphosphonates   | <b>Track 9</b>  | Adjuvant endocrine therapy for women with chemotherapy-induced amenorrhea   |
| <b>Track 5</b> | Prospective study of adjuvant anastrozole and gene promoter methylation in the contralateral breast of women at high risk   | <b>Track 10</b> | Pathophysiology of aromatase inhibitor-associated arthralgias               |
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|                |   | <b>Track 12</b> | Anti-EGFR tyrosine kinase inhibitors (TKIs) combined with endocrine therapy |

## Select Excerpts from the Interview

### Track 1

► **DR LOVE:** What is your take on the ABCSG-12 data presented at the ASCO plenary session?

► **DR DAVIDSON:** This exciting Austrian trial addressed two questions about premenopausal patients with estrogen receptor (ER)-positive early breast cancer (Gnant 2008). First, it evaluated endocrine therapy, randomly assigning patients receiving an LHRH agonist to either tamoxifen or anastrozole, and no significant efficacy advantage was evident for either arm.

These data tell me that the international trials SOFT and TEXT are absolutely vital to determine optimal endocrine therapy (1.1) for these women. Many people expected that the aromatase inhibitor combination would be superior, and I hope they will now step back and realize that this question is still unanswered.

Another interesting point regarding these data is that the vast majority of patients in the study had not received chemotherapy. Nonetheless, the outcome for these women was extremely good — approximately six percent experienced recurrence in the first five years.

This should reassure us that young women don't always need chemotherapy. We should be guided much more by the biology of the tumor and less by our bias that perhaps youth means the patient needs to receive chemotherapy.

**1.1 Trials of Adjuvant Endocrine Therapy with Ovarian Suppression**

Study	N	Eligibility	Randomization
ABCSG-12*	1,803 (Closed)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	T x 3y T + Z x 3y A + Z x 3y A x 3y
IBCSG-24-02 (SOFT)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	T x 5y OFS + T x 5y OFS + E x 5y
IBCSG-25-02 (TEXT)	2,639 (Closed)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + T x 5y Triptorelin ± chemotherapy + E x 5y

\* All patients receive goserelin prior to randomization

T = tamoxifen; Z = zoledronic acid; A = anastrozole; OFS = ovarian function suppression with triptorelin, surgical oophorectomy or ovarian irradiation; E = exemestane

SOURCES: [www.ibcsg.org](http://www.ibcsg.org); NCI Physician Data Query, August 2008.

 **Tracks 3-4**

▶ **DR LOVE:** What are your thoughts about the second randomization in ABCSG-12 to zoledronic acid (ZDA) versus no bisphosphonate therapy in these premenopausal patients, demonstrating about 35 percent fewer events in patients receiving ZDA?

▶ **DR DAVIDSON:** That randomization was based on data from previous clodronate trials that suggested a bisphosphonate might have antineoplastic effects in addition to bone-preserving effects. That would certainly be desirable when treating young women with endocrine therapy.

The data presented at ASCO indeed demonstrated that the patients who received zoledronic acid had longer disease-free survival. They experienced fewer recurrences, and not only bone recurrences as one might have predicted, but fewer recurrences at other sites also (4.2, page 24).

▶ **DR LOVE:** As a result of this study, will you be recommending adjuvant bisphosphonates for this subset of patients in your clinical practice?

▶ **DR DAVIDSON:** I was affected by Martine Piccart-Gebhart's discussion of this

abstract (1.2). She decided that before she would embrace routine adjuvant bisphosphonate therapy in her practice, she would wait to see the outcome of other large randomized bisphosphonate trials that are coming to an end.

She had a slide illustrating that several of these studies are in progress, incorporating thousands of women, and she suggested that if we're lucky, data might be released from the first of these later this year (1.3).

I took her counsel. ABCSG-12 is a relatively small trial, and of the three randomized clodronate trials that have been conducted, although two appeared positive, the third was negative. At least for the moment, I am not using zoledronic acid routinely for premenopausal women, but I am waiting for the data from the ongoing trials.

**1.2**

**Dr Piccart-Gebhart's ASCO Discussion on the Clinical Implications of the ABCSG-12 Data on Zoledronic Acid**

"Before recommending the wide use of zoledronic acid in routine clinical care, I am convinced that we have to wait for the results of at least one of these other important first-generation adjuvant bisphosphonate trials and, in particular, for the interim results of the BIG 1-04 AZURE trial, which are expected in the summer, with 472 disease-free survival events. This is an even larger trial than ABCSG-12, which uses a more intensive schedule of zoledronic acid and targets a higher-risk population that includes women receiving adjuvant chemotherapy, which is certainly more in line with clinical practice, at least in the United States.

So in conclusion, ABCSG-12, I think, is not yet a practice-changing trial but is an important trial, announcing a paradigm shift targeting both seed and soil. And it is certainly a trial opening a plethora of new strategies likely to further improve outcomes for women with early breast cancer."

SOURCE: Piccart-Gebhart M. Plenary session, ASCO 2008.

**1.3**

**Phase III Trials of Adjuvant Bisphosphonate Therapy**

Study	N	Stage	Bisphosphonate arms	Status
SWOG-S0307	4,500	I-III	Zoledronate x 3y Clodronate x 3y Ibandronate x 3y	Open
GAIN	3,000	II	Ibandronate x 2y Observation	Open
NATAN	543	II/III	Zoledronate x 5y Observation	Open
BIG 1-04 (AZURE)	3,349	II/III	Zoledronate x 5y Observation	Closed
NSABP-B-34	3,323	I/II	Clodronate x 3y Placebo	Closed

SOURCES: Gnant M. Discussant. *Proc ASCO* 2008; [Abstract LBA4](#); NCI Physician Data Query, August 2008.

## Track 5

▶ **DR LOVE:** Can you discuss the rationale for the prospective study at Johns Hopkins examining adjuvant anastrozole and gene promoter methylation in the contralateral breast of women at high risk for breast cancer (Prowell 2008)?

▶ **DR DAVIDSON:** My colleague Vered Stearns has been enthusiastic about the idea of using the contralateral breast as a short-term model system to evaluate chemoprevention.

She is also interested in examining molecular markers of response, both in the tumor and in the patient. The questions addressed in this study were whether that could be a useful way to monitor response to aromatase inhibitors and whether these might be useful in the prevention setting.

The study consists of postmenopausal women who were about to receive adjuvant anastrozole and were asked to do so in the context of a trial that allowed us to collect a lot of data. Patients were required to undergo a biopsy of the contralateral breast before they were exposed to the aromatase inhibitor and again after six months of exposure.

The first report consisted of 25 women, and we examined the status of approximately a dozen genes that are frequently methylated in breast cancer. We found that methylation of one or more of these genes was observed in more than 80 percent of these women who were at high risk of breast cancer in the contralateral breast. In approximately half of them, we observed a decrease in the quantitative methylation index after six months of anastrozole therapy.

## Tracks 7-9

▶ **DR LOVE:** You have been very involved in clinical trials, such as MA17, trying to determine the optimal duration of adjuvant endocrine therapy. What is your current approach to this decision outside a trial setting?

▶ **DR DAVIDSON:** Increasingly, I am a believer in long-term strategies for hormone-responsive breast cancer. Many of us were struck more than a decade ago by the ECOG study published by Saphner, Tormey and Gray that examined the natural history of ER-positive versus ER-negative breast cancer and suggested a difference (Saphner 1996; [1.4]). We appreciate that difference more now, and we have more options, such as aromatase inhibitors, for addressing this issue.

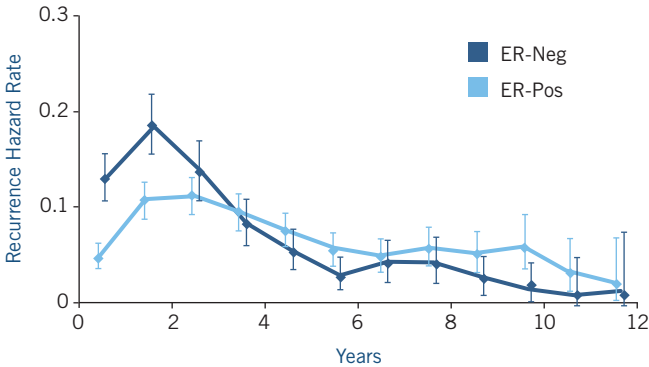
However, I'm not sure how long "long-term" is, and I wish we had a better way to stratify a patient's risk. When a patient who had a node-negative, 1-cm, ER-positive breast tumor comes to the end of five years of tamoxifen or five years of an aromatase inhibitor, I wonder whether she needed all that therapy and whether some of them need more (1.5).



The question of how long to administer these therapies is a huge issue, and it's difficult to address in trials because these studies require such long follow-up (1.5). I am hoping that some of the biomarker research will help us hone that down over time.

#### 1.4

### Annual Hazard Rates of Recurrence for Breast Cancer by ER Status



SOURCE: Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. [Abstract](#)

#### 1.5

### Late Risk of Relapse and Mortality Among Postmenopausal Women with Estrogen-Responsive Early Breast Cancer After Five Years of Tamoxifen

"An individualized estimate of the risk of relapse and death after 5 years of tamoxifen could improve decisions regarding extended hormonal therapy.

The British Columbia Breast Cancer Outcomes database was used to identify women aged 45 years or older at the time of diagnosis with early-stage (I-IIIa) breast cancer who received tamoxifen and were disease free 5 years after diagnosis.

Ten-year breast cancer event rates and mortality were calculated as well as annualized hazard rates of recurrence. A total of 1,086 women were identified with a median age of 64 years and follow-up of 10.5 years....

Annual breast cancer risk between years 6 and 10 was, respectively, 2.2%, 3.5% and 7.6% for N0, N1 and N2 disease and 2.6% and 4.5% for T1 and T2 breast cancer."

SOURCE: Kennecke HF et al. *Ann Oncol* 2007;18(1):45-51. [Abstract](#)

► **DR LOVE:** Let's get more specific. How would you approach a premenopausal patient who has positive nodes, has received five years of tamoxifen and is tolerating it well?

► **DR DAVIDSON:** I discuss the information that exists and present three strategies. One is continuing tamoxifen, year to year, and I tell the patient that although I'm certain it contributes to toxicity, I'm not quite sure what it

contributes in terms of benefit. A second option is to quit therapy altogether, and the third is to transition to an aromatase inhibitor with an LHRH agonist. I've had patients select each of these options. Most commonly they stop therapy because they feel they are done and ready to move on. Rarely, the patients elect to cross over to the hormonal blockade. The few patients who do opt to continue tamoxifen are often women who perceive themselves to be at high risk.

► **DR LOVE:** When you see a premenopausal patient who experienced chemotherapy-induced amenorrhea and has recently completed five years of tamoxifen, do you use an aromatase inhibitor?

► **DR DAVIDSON:** I believe all of us were captivated by Ian Smith's paper examining these patients who then received an aromatase inhibitor (Smith 2006). In some cases they retained or regained ovarian function, and one even became pregnant. In each case, we think carefully about whether we believe the benefit outweighs the risk.

In my practice, I discuss with the patient whether she wants to consider extended endocrine therapy. If she does, then I stop the tamoxifen for a few months to see how she feels off therapy, establish a new baseline and watch to see whether her ovarian function kicks in, either clinically or by laboratory parameters. If the patient then begins an aromatase inhibitor, I watch her carefully. I've been following these patients clinically, although I've considered monitoring laboratory studies too. The key there, of course, is to have access to a lab that can perform high-sensitivity estrogen assays.

## Track 10

► **DR LOVE:** What's your take on the pathophysiology of arthralgias secondary to aromatase inhibitors?

► **DR DAVIDSON:** At Hopkins we are involved in a randomized clinical trial to study the pharmacogenomics of exemestane and letrozole in women with early-stage, hormone receptor-positive breast cancer. Lynn Henry published a paper examining the first 100 patients in the trial, and a large proportion saw a rheumatologist because they crossed a predefined symptomatology threshold (Henry 2008; [1.6]).

The findings are all over the map, and no single explanation for these symptoms is clear to me. What to do about them is also complicated, and one purpose of our study is to determine whether it is possible to predict which aromatase inhibitor a patient will tolerate better or perhaps to identify patients who are more prone to these musculoskeletal symptoms.

I believe these symptoms were underreported in the large, randomized aromatase inhibitor trials. Now that we have more experience and are paying attention to this side effect, we are recognizing that the problem is critical to address because compliance is important with these drugs, and if women aren't feeling well, they may not be as compliant. ■

## Prospective Characterization of Musculoskeletal Symptoms in Women Receiving Adjuvant Aromatase Inhibitors

“Women with early stage hormone receptor-positive breast cancer were recruited into a multicenter randomized clinical trial to study the pharmacogenomics of two AIs, exemestane, and letrozole.

Forty-four of 97 eligible patients (45.4%) met criteria for rheumatologic referral...No baseline characteristics were significantly associated with referral. Median time to onset of symptoms was 1.6 months (range 0.4-10 months).

Clinical and laboratory evaluation of patients evaluated by rheumatology suggested that the majority developed either non-inflammatory musculoskeletal symptoms or inflammation localized to tenosynovial structures. Thirteen patients discontinued AI therapy because of musculoskeletal toxicity after a median 6.1 months (range 2.2-13 months).

Musculoskeletal side effects were common in AI-treated patients, resulting in therapy discontinuation in more than 10% of patients. There are no identifiable pre-therapy indicators of risk, and the etiology remains elusive.”

SOURCE: Henry NL et al. *Breast Cancer Res Treat* 2008;111(2):365-72. [Abstract](#)

### SELECT PUBLICATIONS

Arnedos M, Smith I. **Progression of endocrine therapies for breast cancer: Where are we headed?** *Expert Rev Anticancer Ther* 2007;7(11):1651-64. [Abstract](#)

Gnant M et al. **Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12.** *Proc ASCO* 2008;[Abstract LBA4](#).

Henry NL et al. **Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors.** *Breast Cancer Res Treat* 2008;111(2):365-72. [Abstract](#)

Kennecke HF et al. **Late risk of relapse and mortality among postmenopausal women with estrogen responsive early breast cancer after 5 years of tamoxifen.** *Ann Oncol* 2007;18(1):45-51. [Abstract](#)

Parton M, Smith IE. **Controversies in the management of patients with breast cancer: Adjuvant endocrine therapy in premenopausal women.** *J Clin Oncol* 2008;26(5):745-52. No abstract available

Prowell TM et al. **A prospective study of adjuvant anastrozole and gene promoter methylation in the contralateral breast of high-risk women.** *Proc ASCO* 2008;[Abstract 1514](#).

Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. [Abstract](#)

Smith IE, Arnedos M. **The evolution of adjuvant endocrine therapy: Developments since St Gallen 2005.** *Breast* 2007;16(Suppl 2):54-9. [Abstract](#)

Smith IE et al. **Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: Caution and suggested guidelines.** *J Clin Oncol* 2006;24(16):2444-7. [Abstract](#)



## INTERVIEW

### Professor John Crown, MD

Prof Crown is Consultant Medical Oncologist at St Vincent's University Hospital and Thomas Baldwin Chair in Cancer Research at Dublin City University in Dublin, Ireland.

#### Tracks 1-17

- Track 1** tAnGo: A Phase III trial of adjuvant EC → paclitaxel with or without gemcitabine
- Track 2** Use of adjuvant docetaxel/cyclophosphamide (TC) for patients with HER2-negative BC
- Track 3** Weighing the risks and benefits of adjuvant anthracyclines
- Track 4** Clinical trials of adjuvant docetaxel/cyclophosphamide with bevacizumab for patients with HER2-negative BC
- Track 5** Use of adjuvant docetaxel/carboplatin/trastuzumab (TCH) for patients with HER2-positive BC
- Track 6** Adjuvant chemotherapy/trastuzumab for small (<1-cm), node-negative, HER2-positive tumors
- Track 7** Trastuzumab/chemotherapy regimens and risk of cardiotoxicity
- Track 8** Dual action of lapatinib, targeting HER2 and EGF receptors
- Track 9** Management of lapatinib-induced toxicities
- Track 10** Clinical trials evaluating lapatinib-based combination therapies
- Track 11** ALTO and BETH: Clinical trials of adjuvant anti-HER2 therapy
- Track 12** Rationale for the TCH-based regimen in the BETH trial
- Track 13** AVADO results: First-line docetaxel with or without bevacizumab for locally recurrent or metastatic breast cancer (mBC)
- Track 14** BEATRICE: Adjuvant chemotherapy with or without bevacizumab for triple-negative BC
- Track 15** Importance of patient selection in the development of molecularly targeted therapies
- Track 16** Perspective on ABCSG-12
- Track 17** Clinical impact of the zoledronic acid data from ABCSG-12

#### Select Excerpts from the Interview

##### Tracks 2, 4

► **DR LOVE:** What's your view on the role of anthracyclines in the adjuvant setting?

► **PROF CROWN:** We know that topoisomerase II (TOPO II) is one of the principal targets for the anthracyclines. Dr Slamon's data from BCIRG 005 strongly suggest that HER2-negative tumors are invariably TOPO II-negative (Slamon 2007). In addition, the recent meta-analysis from Gennari strongly suggests that the benefit — a fairly weak benefit — we have observed in

the past from anthracycline-containing versus nonanthracycline-containing regimens in the adjuvant setting may be confined to the HER2-positive population (Gennari 2008). Based on the combined data, we would hypothesize further that it is confined to the TOPO II-positive subset.

► **DR LOVE:** In terms of nonanthracycline options, what’s your take on the US Oncology data on TC (docetaxel/cyclophosphamide)?

► **PROF CROWN:** The TC regimen is receiving a good deal of attention, and the TC versus AC trial was an excellent study (Jones 2006; [2.1]). In my practice, I use the TC regimen frequently and have largely moved to a nonanthracycline regimen as my standard for these patients with HER2-negative tumors.

My decision was based on a number of factors, including the repeated observation that for patients with HER2-negative disease, it’s difficult to know exactly how much benefit they are receiving. In addition, the toxicity associated with anthracyclines may be worse than we thought, including an alarming report detailing as much as a one percent incidence of leukemia and myelodysplastic syndrome among patients treated with aggressive anthracycline regimens. In the Irish Clinical Oncology Research Group, we have launched a new generation of studies for our patients with HER2-negative early breast cancer. Soon we will be enrolling patients on a large-scale adjuvant pilot trial of TC with bevacizumab, and I know others are piloting similar regimens.

► **DR LOVE:** My understanding is that the NSABP and US Oncology are expanding the TC-TAC trial comparing TC to TAC to a larger study with a third arm also evaluating TC/bevacizumab.

► **PROF CROWN:** I’d be supportive of that trial. I’m eager to know the answers to both the anthracycline-versus-no-anthracycline and the bevacizumab questions.

► **DR LOVE:** In terms of the HER2-positive population, based on the BCIRG 006 data, the TCH regimen appears to have similar efficacy to anthracycline-based therapy and less cardiotoxicity (2.2). What do you think of those data, and how are you treating your patients?

► **PROF CROWN:** I chaired that study with Dr Slamon, so I may not be the most unbiased observer, but I have stopped administering regimens containing both trastuzumab and an anthracycline. I routinely administer TCH as my adjuvant regimen for HER2-positive disease.

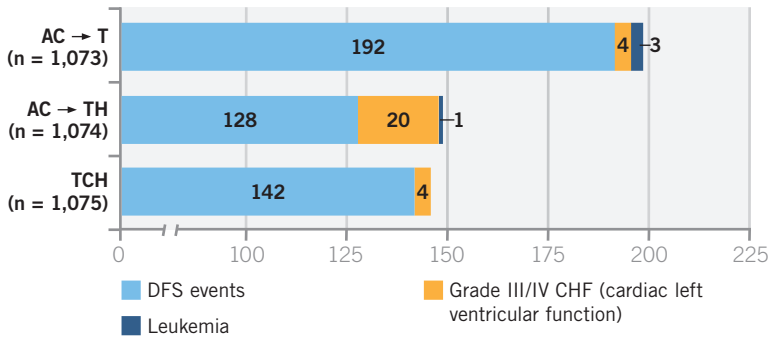
**2.1**

**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.**

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



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

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006; [Abstract 52](#).

### Track 8

▶ **DR LOVE:** The ALTTO adjuvant trial (2.3) is evaluating lapatinib and the combination of lapatinib and trastuzumab. What do we know about the mechanism of action of lapatinib and the effect of combining it with trastuzumab?

▶ **PROF CROWN:** Lapatinib is a fascinating agent, and what interests me most is the possibility that combined lapatinib and trastuzumab therapy may produce superior results compared to either molecularly targeted agent alone. Several lab groups have shown an additive value or even a synergy between these two agents in HER2-positive cell lines. In addition, a trial presented at ASCO 2008 by Dr O’Shaughnessy suggested that this may be applicable in the clinic, which is good news for those interested in adjuvant trials combining these agents (Scaltriti 2008; [2.4]).

At this point, lapatinib offers heavily treated patients who experience disease progression despite trastuzumab another treatment with the prospect of further meaningful benefit, which is always worthwhile in the palliative setting. However, my hope is that in combining it with trastuzumab, we will see even better results.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTO) trial is being inaugurated, and we hope a broader portfolio of studies evaluating the combination will become available.

► **DR LOVE:** What do we know about lapatinib in HER2-negative disease?

### 2.3 Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTO) Trial

Protocol ID: BIG 2-06; Target Accrual: 8,000

#### Eligibility

- HER2-positive breast cancer

**In Design 1, patients will complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy.**

**In Design 2, patients will receive weekly paclitaxel concurrently for 12 weeks with targeted therapy after any anthracycline-based (neo)adjuvant chemotherapy.**



SOURCES: [www.breastinternationalgroup.org](http://www.breastinternationalgroup.org); [www.altotrials.com](http://www.altotrials.com).

### 2.4 Effect of Lapatinib on Accumulation of Inactive HER2 at the Cell Membrane and on Antibody-Dependent Cellular Cytotoxicity (ADCC) Mediated by Trastuzumab: A Novel Mechanism for the Enhanced Effects of Combined Anti-HER2 Therapy

“In vitro and clinical studies have shown that lapatinib enhances the effects of the monoclonal antibody trastuzumab suggesting partially non-overlapping mechanisms of action. In order to dissect the differential mechanisms of these agents, we have studied the effects of lapatinib and trastuzumab on receptor expression and signaling and have explored a new potential mechanism underlying the profound antitumor activity of the combination....

Lapatinib results in a marked accumulation of inactive HER2 receptors at the cell surface both in vitro and in vivo. This increase in receptor number at the cell surface enhances ADCC by trastuzumab. We propose that this is a novel mechanism that may be clinically relevant and exploitable in the therapy of patients with HER2+ tumors.”

SOURCE: Scaltriti M et al. *Proc ASCO* 2008; **Abstract 3594**.

- ▶ **PROF CROWN:** The benefit of lapatinib appears to be confined to HER2-positive breast cancer. If activity occurs in HER2-negative disease, it is minimal. This may seem surprising as four or five years ago lapatinib was being initiated into trials because of its dual action on EGFR and HER2. Although an interplay may occur between these two receptors that accounts for some of lapatinib's activity, using it to target HER2-negative tumors by virtue of a targeting effect on EGFR does not appear to be a productive strategy at the moment.
- ▶ **DR LOVE:** In HER2-positive cancer, what do we know about the contribution, if any, of the anti-EGFR effect of lapatinib?
- ▶ **PROF CROWN:** Lapatinib works in a fundamentally different way than trastuzumab. It works on the intracellular side, and a number of different downstream regulators of HER2 may be differentially affected by lapatinib as opposed to trastuzumab.

## Track 9

▶ **DR LOVE:** You recently published a paper on the important issue of lapatinib-induced diarrhea (Crown 2008). What side effects do you generally see with this agent?

▶ **PROF CROWN:** In general, lapatinib is a well-tolerated drug. A mild level of skin rash can occur, and a little diarrhea is relatively common (2.5). Severe diarrhea is not common, and when it does occur, it must be managed aggressively. The combination of capecitabine and lapatinib can cause diarrhea, but in the absence of a diarrhea-inducing chemotherapy agent, diarrhea is less of a problem.

In my jurisdiction in Ireland, lapatinib use is confined to a specific indication, which is coadministration with capecitabine to patients with HER2-positive metastatic breast cancer whose disease has progressed after anthracyclines, taxanes and trastuzumab. These patients have been heavily pretreated and have particularly bad cancer, so they need to be treated carefully.

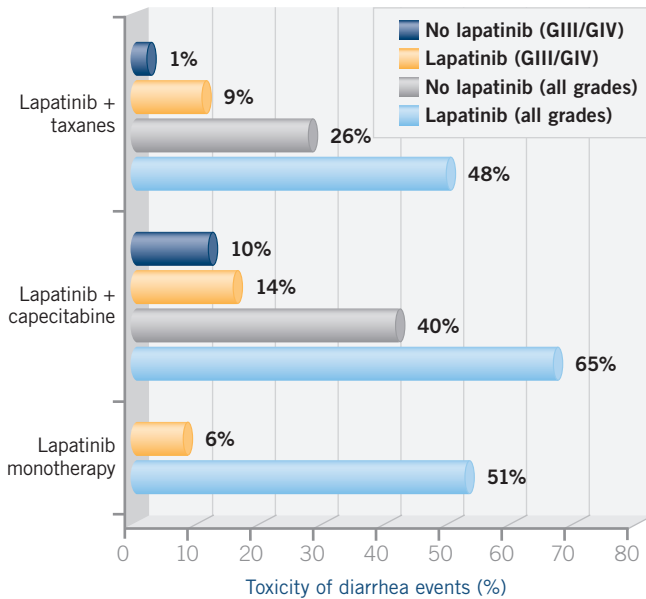
Patients need to be attuned to the possibility of side effects, and I warn them about diarrhea. If they experience severe diarrhea, we advise them to stop taking the tablets and call us. Depending on where they are in their capecitabine cycle, we make recommendations on dose reduction, generally of the capecitabine, and we administer antidiarrhea therapy as needed.

▶ **DR LOVE:** How do you manage the rash?

▶ **PROF CROWN:** As with any EGFR rash, we generally stop the treatment for a few days to let it settle down. For many patients it's simply a matter of reinstating the drug at a lower dose, although some need specific interventions such as antibiotics. ■



## Pooled Analysis of Diarrhea Events in Patients with Cancer Treated with Lapatinib



SOURCE: Crown JP et al. *Breast Cancer Res Treat* 2008;[Epub ahead of print]. [Abstract](#)

### SELECT PUBLICATIONS

Crown JP et al. **Pooled analysis of diarrhea events in patients with cancer treated with lapatinib.** *Breast Cancer Res Treat* 2008;[Epub ahead of print]. [Abstract](#)

Gennari A et al. **HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: A pooled analysis of randomized trials.** *J Natl Cancer Inst* 2008;100(1):14-20. [Abstract](#)

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](#)

Scaltriti M et al. **Effect of lapatinib on accumulation of inactive HER2 at the cell membrane and on antibody-dependent cellular cytotoxicity (ADCC) mediated by trastuzumab: A novel mechanism for the enhanced effects of combined anti-HER2 therapy.** *Proc ASCO* 2008;[Abstract 3594](#).

Slamon DJ et al. **Role of anthracycline-based therapy in the adjuvant treatment of breast cancer: Efficacy analyses determined by molecular subtypes of the disease.** San Antonio Breast Cancer Symposium 2007;[Abstract 13](#).

Slamon D et al. **BCIRG 006: 2<sup>nd</sup> interim analysis phase III randomized trial comparing 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

### Kathy D Miller, MD

Dr Miller is Sheila D Ward Scholar of Medicine and Associate Professor of Medicine at Indiana University Simon Cancer Center in Indianapolis, Indiana.

### Tracks 1-11

- |                |  |                 |   |
|----------------|--|-----------------|---|
| <b>Track 1</b> | Bevacizumab-related toxicities and its incorporation into adjuvant clinical trials | <b>Track 6</b>  | Accrual to E5103  |
| <b>Track 2</b> | ECOG-E5103: AC → weekly paclitaxel with or without bevacizumab in early BC         | <b>Track 7</b>  | Need for continued evaluation of the role for adjuvant anthracyclines                             |
| <b>Track 3</b> | Potential effects of bevacizumab in the adjuvant setting                           | <b>Track 8</b>  | BETH trial: Adjuvant chemotherapy and trastuzumab with or without bevacizumab in HER2-positive BC |
| <b>Track 4</b> | US Oncology TC-TAC-TC/bevacizumab adjuvant trial in HER2-negative early BC         | <b>Track 9</b>  | Research on trastuzumab/bevacizumab for patients with mBC   |
| <b>Track 5</b> | AVADO: Docetaxel with or without bevacizumab for locally recurrent or mBC          | <b>Track 10</b> | Novel anti-HER2 therapeutics in BC: pertuzumab, T-DM1   |
|                |  | <b>Track 11</b> | Clinical trial results with EGFR TKIs and hormonal therapy in mBC                                 |

## Select Excerpts from the Interview

### Track 1

► **DR LOVE:** In your ECOG-E5103 trial, what were the safety issues relative to evaluating bevacizumab in the adjuvant setting?

► **DR MILLER:** When designing trials in the adjuvant setting, we had to consider whether unique safety concerns existed for bevacizumab. Even in the adjuvant trials for patients at the highest risk, more than half of the patients in the control groups fare well, and many do so with no systemic therapy. So toxicities that might be rare and of no concern in the metastatic setting are a bigger concern in the adjuvant setting.

We believed that most of the bevacizumab toxicities were not likely to be major issues. Arterial thrombotic events are rare in the metastatic population: We expect them to be even more rare in the healthier, younger adjuvant population. The venous thromboembolic events are also likely to be uncommon and certainly not prohibitive. Proteinuria is a fairly rare toxicity to be of any clinical importance, and it improves with time off therapy.

With bevacizumab in the adjuvant setting, I am most concerned about hyper-

tension, but that is a long-term concern that may not become apparent for 10, 15 or 30 years. We were concerned about cardiac toxicity. At the time we first started considering adjuvant therapy, reports existed of patients treated collectively in three separate trials in different settings with different anthracycline regimens, but they all raised the question of either clinical congestive heart failure or asymptomatic decreases in ejection fraction to levels that are of concern (lower than 40 percent).

With such small numbers, the confidence intervals were wide, and clinical event reports of congestive heart failure ranged from zero to 27 percent of patients (Swain 2003). That’s a big difference. If the incidence were zero, you would move forward with an adjuvant trial with little monitoring. If it were 27 percent, you would not move forward.

We designed a pilot trial (3.1) to make sure that the rates of clinically apparent congestive heart failure were not prohibitive. We agreed in advance that a clinical rate of 10 percent or more would be prohibitive. For the average patient, it would be unlikely that the benefits of therapy, if they existed, would outweigh that potential risk, and so we should examine other strategies.

**3.1 Toxicity Results from E2104 Phase II Feasibility Trial Incorporating Bevacizumab (B) into Dose-Dense (dd) Doxorubicin (A) and Cyclophosphamide (C) → Paclitaxel (T) in Patients with Lymph Node-Positive Breast Cancer**

	Arm A ddBAC → BT → B (N = 103)	Arm B ddAC → BT → B (N = 120)
<b>Cardiac toxicity</b>		
Clinical CHF (symptomatic decline in LVEF to <40%)	2%	1%
Asymptomatic decline in LVEF to <40%	3%	0%
<b>Select Grade III/IV noncardiac toxicity</b>		
Febrile neutropenia	4%	3%
Hypertension	14%	8%
Thrombosis/embolism	2%	2%
Hemorrhage	1%	0%
CNS ischemia	1%	0%

SOURCE: Miller KD et al. ASCO 2008; [Abstract 520](#).

 **Track 2**

▶ **DR LOVE:** What is the design of the ECOG-E5103 trial?

▶ **DR MILLER:** ECOG-E5103 is a large adjuvant study that encompasses several features (3.2). It has a practical element in that we allow patients and their

physicians to select administration of AC every two weeks or every three weeks. We'll stratify for that choice, so it won't affect our results. This design builds on the improvements we've made in adjuvant therapy. The backbone of the chemotherapy is four cycles of AC followed by weekly paclitaxel. That's building on ECOG-E1199 (Sparano 2005), the adjuvant trastuzumab studies and the E2100 trial in the metastatic setting (Miller 2007).

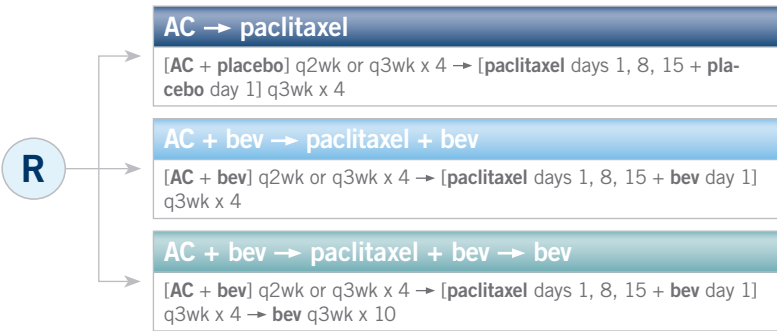
It also incorporates preclinical data on the potential synergy between lower-dose but more continuous taxane exposure and bevacizumab. In laboratory studies, at doses much lower than the doses that are required to have any direct cytotoxic effect on the tumor cells, the taxanes have a separate effect on endothelial cells (Ng 2004). To obtain that effect, however, you need prolonged exposure. With weekly schedules, we have a lower dose but more continuous exposure to the drug.

The entry criteria are different from what has been seen: We allow patients with node-negative disease but who are at high risk. We consider anyone with ER-negative disease and a tumor larger than one centimeter to be at

3.2

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

Protocol IDs: ECOG-E5103, NCT00433511; Accrual: 4,950



**Eligibility**

- Pre- or postmenopausal
- ER and PR status known, HER2-negative
- Node-positive or high-risk, node-negative
- Patients enrolled on ECOG-PACCT-1 (TAILORx)

**Study Contacts**

*Eastern Cooperative Oncology Group*  
 Kathy D Miller, MD, Protocol Chair  
 Tel: 888-600-4822

Ramona Swaby, MD, Protocol Co-Chair  
 Tel: 888-369-2427

*North Central Cancer Treatment Group*  
 Donald Northfelt, MD, Protocol Chair  
 Tel: 507-538-7623

*Cancer and Leukemia Group B*  
 Chau Dang, MD, Protocol Co-Chair  
 Tel: 800-525-2225

SOURCE: NCI Physician Data Query, September 2008.

increased risk. Patients with ER-positive, node-negative disease are considered at high risk only if the tumors are larger than five centimeters or if they are between one and five centimeters and the *Oncotype DX*<sup>®</sup> Recurrence Score<sup>®</sup> is not low. We chose the *Oncotype DX* cutoff as 11 to match TAILORx. If a patient on TAILORx has a high- or intermediate-risk score and is assigned to chemotherapy, she's welcome to participate in E5103 as a way to receive chemotherapy.

### Track 3

▶ **DR LOVE:** Based on your perspective on the mechanism of action of bevacizumab, are you expecting it to be active in the adjuvant setting?

▶ **DR MILLER:** I believe that bevacizumab will be effective, but hypotheses with evidence exist on both sides of the question. Angiogenesis may be regarded as one of the earliest events that a tumor cell must accomplish. We see evidence of angiogenesis even in DCIS, in which the tumors are not yet invasive. It is an early phenomenon, which suggests that adjuvant therapy might be effective. Studies examining the expression of pro-angiogenic factors in atypical (but not yet malignant) lesions, DCIS and invasive disease show that more angiogenic factors are expressed as the tumors become older. These observations suggest that agents like bevacizumab might be more effective earlier in the course of the disease, which would bring you into the adjuvant setting.

I also have questions about the duration of therapy. We administer bevacizumab for two durations in E5103: approximately six months and approximately one year. Perhaps that's not long enough. Perhaps you need chronic therapy, not to eliminate microscopic disease but rather to keep it from growing. If we remove that foot from the brake, we may prolong time to progression but perhaps not prevent recurrence or change overall survival.

### Track 5

▶ **DR LOVE:** Would you describe what was found in the AVADO trial?

▶ **DR MILLER:** AVADO was the European equivalent of my E2100 trial with an important addition. AVADO had three arms: docetaxel alone at the European-favored 100-mg/m<sup>2</sup> dose with placebo, docetaxel and bevacizumab at 7.5 milligrams per kilogram every three weeks (half the dose we typically use in breast cancer studies) or docetaxel and bevacizumab at 15 milligrams per kilogram.

It wasn't designed to compare the two bevacizumab arms but to effect two pairwise comparisons: low-dose bevacizumab versus placebo and high-dose bevacizumab versus placebo. We saw statistically significant improvements in response rates and progression-free survival with bevacizumab, but in absolute terms it was disappointing (Miles 2008). In the control group, progression-free survival was eight months. It increased to 8.7 months for patients in the low-dose bevacizumab group and to 8.8 months in the high-dose group (Miles 2008; [3.3]).

It's clear that the curves separate early and remain separate throughout most of the follow-up period. This is a real difference and a bigger difference than the roughly one-month medians might suggest. But 8.8 months is still not 11.8 months. With the high dose and the intermittent schedule, we wouldn't predict that the docetaxel regimen would take advantage of the potential anti-angiogenic activity of the taxanes.

I'm even more interested in the future results of the RIBBON 1 trial, which questions the assumption that you can add bevacizumab to any chemotherapy and obtain the same results. Particular drugs and schedules may be much more synergistic and offer a greater benefit for the combination than what you would obtain with others. ■

**3.3**

**AVADO Trial: Progression-Free Survival (PFS) with Docetaxel with or without Two Doses of Bevacizumab (Bev)**

	<b>Docetaxel + placebo (n = 241)</b>	<b>Docetaxel + bev 7.5 mg/kg (n = 248)</b>	<b>Docetaxel + bev 15 mg/kg (n = 247)</b>
Median PFS	8.0 months	8.7 months	8.8 months
HR (95% CI) vs placebo	—	0.79 (0.63-0.98)	0.72 (0.57-0.90)
p-value	—	0.0318	p = 0.0099

SOURCE: Miles D et al. *Proc ASCO* 2008; [Abstract LBA1011](#).

**SELECT PUBLICATIONS**

Homsí J, Daud AI. **Spectrum of activity and mechanism of action of VEGF/PDGF inhibitors.** *Cancer Control* 2007;14(3):285-94. [Abstract](#)

Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008; [Abstract LBA1011](#).

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).** *ASCO* 2008; [Abstract 520](#).

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

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Roodhart JM et al. **The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway.** *Curr Clin Pharmacol* 2008;3(2):132-43. [Abstract](#)

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** San Antonio Breast Cancer Symposium 2005; [Abstract 48](#).

Swain SM et al. **Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials.** *Cancer* 2003;97(11):2869-79. [Abstract](#)



## INTERVIEW

### Peter M Ravdin, MD, PhD

Dr Ravdin is Research Professor of Biostatistics at The University of Texas MD Anderson Cancer Center in Houston, Texas.

#### Tracks 1-11

- |                |  |                 |  |
|----------------|--|-----------------|--|
| <b>Track 1</b> | Implications of recent increased incidence of BC due to earlier detection  | <b>Track 6</b>  | ASCO Tumor Marker Committee and NCCN recommendations for use of <i>Oncotype</i> DX |
| <b>Track 2</b> | Use of paraffin-embedded tissue with the <i>Oncotype</i> DX® assay versus frozen tissue with the MammaPrint® assay         | <b>Track 7</b>  | Risk predictors for BC based on biological subtypes                                |
| <b>Track 3</b> | MINDACT: Comparison of MammaPrint to Adjuvant! in selecting patients with node-negative BC for adjuvant chemotherapy       | <b>Track 8</b>  | Quantitative assessment of ER and HER2 with the <i>Oncotype</i> DX assay           |
| <b>Track 4</b> | Use of standard pathology criteria in combination with the <i>Oncotype</i> DX assay in clinical decision-making            | <b>Track 9</b>  | Viewpoint on the ABCSG-12 zoledronic acid data                                     |
| <b>Track 5</b> | Utility of <i>Oncotype</i> DX in predicting benefit from chemotherapy for patients with node-negative and node-positive BC | <b>Track 10</b> | Translation of treatment benefits from the metastatic to the adjuvant setting      |
|                |  | <b>Track 11</b> | Incorporation of adjuvant therapy with trastuzumab into Adjuvant! Online           |

## Select Excerpts from the Interview

### Tracks 2-3, 5

► **DR LOVE:** Would you discuss the similarities and differences between the *Oncotype* DX and MammaPrint assays?

► **DR RAVDIN:** Each of these two tests provides a molecular profile based on RNA. In theory, they're similar. In practice, however, they're quite different.

The *Oncotype* DX assay, also called the 21-gene assay, analyzes fragments of mRNA in archived tissue. The assay is performed on paraffin-embedded, fixed tumor tissue. This attribute opens up rapid development of the assay because most of the large cooperative groups have been collecting block materials for more than a decade, back into the 1980s. So this test has an enormous advantage in terms of development.

We also have the 70-gene test, or MammaPrint assay, which is dependent on intact mRNA. Because the large clinical trials haven't historically banked intact tissue, MammaPrint requires samples to be frozen or specially preserved in alcohol. This assay is dependent on institutional series, in which the therapy has not been standardized as it has been in cooperative group trials.

► **DR LOVE:** Do data exist with MammaPrint predicting benefit from chemotherapy as with *Oncotype DX*?

► **DR RAVDIN:** No. The problem is the lack of a good comparison group. The MammaPrint assay requires fresh tissue, and all of the data are focused on prognosis.

That's the genesis of the prospective MINDACT trial, in which patients are being randomly assigned to receive chemotherapy or not (Cardoso 2008). Those patients are undergoing MammaPrint profiles, and the study results should tell us what we already know for the *Oncotype DX* test.

Two studies have already reported results on *Oncotype DX*. NSABP-B-20 randomly assigned patients with node-negative disease to tamoxifen or tamoxifen with CMF — also, some patients received MF in that trial (Paik 2006).

Late last year, *Oncotype* results were reported for SWOG-8814, which randomly assigned postmenopausal patients with ER-positive, node-positive disease to tamoxifen alone or tamoxifen with CAF (Albain 2007; [4.1]).

► **DR LOVE:** In Albain's study with *Oncotype DX*, the baseline risk of recurrence for patients with node-positive disease — even those in the low Recurrence Score group — was substantial. However, patients with a low Recurrence Score did not appear to benefit from chemotherapy (Albain 2007; [4.1]).

► **DR RAVDIN:** With classic pathology we have not been able to predict benefit from chemotherapy, whereas the genetic profiles across studies consistently show that the patients with low-risk genetic profiles do not benefit from chemotherapy (Paik 2006; Albain 2007). In trials that have reported clear benefit from chemotherapy in one or more arms, the benefit has been for patients with high *Oncotype DX* Recurrence Scores. I believe the jury is still

4.1

**Impact of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to the *Oncotype 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](#).



out regarding the patients with intermediate *Oncotype* DX Recurrence Scores. As a clinician, if you're evaluating a patient for whom you're undecided about treating on the basis of prognosis and you note that she has a low *Oncotype* DX Recurrence Score, then an additional piece of information that may strongly sway you is the fact that substantial clinical evidence from these two studies, performed in somewhat different populations with different chemotherapeutic regimens, indicates that those patients don't benefit from either CMF or CAF (Paik 2006; Albain 2007). This doesn't cover the entire spectrum of questions that might be asked, but it's a consistent story that those patients don't benefit from chemotherapy.

## Track 8

▶ **DR LOVE:** Where do you think we are headed in terms of the measurement of ER and HER2? Is RT-PCR the future?

▶ **DR RAVDIN:** I believe so. It's useful because we've had numerous indications that ER level does help predict response to tamoxifen, and I've seen suggestions that it may eventually refine prediction of responsiveness to chemotherapy also.

▶ **DR LOVE:** Can you envision a situation in which the quantitative ER assessment might drive decisions in metastatic disease?

▶ **DR RAVDIN:** Yes, I believe that it would be useful in the treatment of metastatic disease. So often in a clinical situation, you don't want to waste weeks waiting for hormonal therapy to work unless you are confident that the patient will respond.

## Track 9

▶ **DR LOVE:** What is your take on the plenary presentation of ABCSG-12 at ASCO 2008 by Mike Gnant (Gnant 2008) reporting a 35 percent reduction in relapse rate in women who received adjuvant zoledronic acid?

▶ **DR RAVDIN:** It was a spectacular effect. In addition, we've seen hints of it in other trials. In this case, however, they administered a strong IV bisphosphonate every six months. This is another trastuzumab in that it is similar to the magnitude of benefit seen with adjuvant trastuzumab.

However, it's different from the trastuzumab story in that we don't have three trials reported at the same meeting. I hope these data are corroborated because a 35 percent reduction in relapse rate from a drug whose major side effect is that you don't become osteopenic would be wonderful.

▶ **DR LOVE:** It was interesting that the rates of contralateral disease, local recurrence and distant metastasis — even nonbone metastasis — were lower among patients receiving zoledronic acid (4.2).

▶ **DR RAVDIN:** That is enormously important, suggesting an effect on visceral

disease also, which was surprising. It may be broader than simply a local bone effect. We will have more information about this soon. The NSABP-B-34 study evaluating adjuvant clodronate with or without chemotherapy and/or hormonal therapy is closed and will probably report soon.

► **DR LOVE:** In terms of clinical decision-making today, assuming reimbursement is not an issue, is this reasonable to recommend to patients as an option, or should we wait?

► **DR RAVDIN:** If a patient is receiving an aromatase inhibitor and you're already unsure whether or not you should treat, I believe that this story becomes compelling and that those patients should be treated with a bisphosphonate. Perhaps before, if a patient had mild osteopenia, we would simply observe, and if it worsened, we would begin bisphosphonate treatment. These results argue that you should probably start treating those patients earlier. The study was performed with premenopausal patients, but I believe that the argument that they're essentially postmenopausal after the ovarian suppression is convincing. ■

4.2

**ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Prolongs Disease-Free Survival (DFS) in Premenopausal Patients with ER-Positive Early Breast Cancer**

	First DFS event per patient, n	
	ZDA (n = 899)	No ZDA (n = 904)
Locoregional recurrence	10	20
Distant recurrence	29	41
Contralateral breast cancer	6	16
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS, versus no ZDA = 0.643 (0.48-0.91),  $p = 0.011$

SOURCE: Gnant M et al. *Proc ASCO* 2008; [Abstract LBA4](#).

**SELECT PUBLICATIONS**

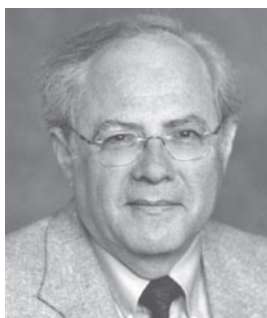
Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007; [Abstract 10](#).

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## Three Perspectives on US Cooperative Group Research



### INTERVIEW

#### Norman Wolmark, MD

Dr Wolmark is Chairman of the National Surgical Adjuvant Breast and Bowel Project, Chairman of the Department of Human Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania and Professor of Human Oncology at Drexel University College of Medicine in Philadelphia, Pennsylvania.

### Tracks 1-6

**Track 1** BETH trial: Adjuvant chemotherapy/trastuzumab with or without bevacizumab in HER2-positive BC

**Track 2** Role of adjuvant anthracycline-based therapy in BC

**Track 3** NSABP/US Oncology partnership in the adjuvant TC-TAC-TC/bevacizumab study

**Track 4** Does adjuvant trastuzumab provide benefit to patients with “HER2-low” BC?

**Track 5** Perspective on the ALTTO trial evaluating adjuvant trastuzumab with lapatinib

**Track 6** NSABP-B-45: Sunitinib for residual BC after neoadjuvant chemotherapy

## Select Excerpts from the Interview

### Track 1

▶ **DR LOVE:** Would you discuss the new adjuvant trial being conducted by the NSABP and CIRG evaluating trastuzumab with or without bevacizumab?

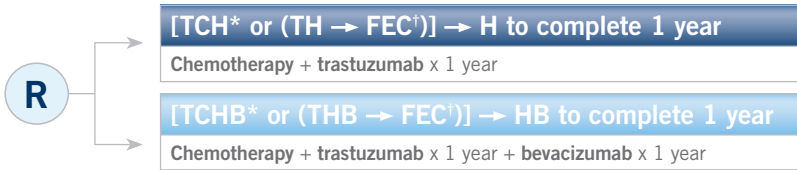
▶ **DR WOLMARK:** The BETH study opened recently (5.1). I believe we need to know what the addition of bevacizumab to trastuzumab will yield in the adjuvant setting, based on some interesting preclinical work and early clinical findings (Pegram 2006).

▶ **DR LOVE:** What are the cardiac issues with this combination? Is the main cardiovascular issue with bevacizumab hypertension?

▶ **DR WOLMARK:** Both agents are concerns. The NSABP and the CIRG are offering TCH as the template. We made the decision not to use an anthracycline template to test the combination of trastuzumab and bevacizumab, with one of the rationales being the potential toxicity of using both agents on an anthracycline template. However, some participating physicians, particularly those in Europe, will administer an anthracycline template along with bevacizumab.

## BETH: NSABP/CIRG Trial of Chemotherapy and Trastuzumab with or without Bevacizumab in Patients with HER2-Positive Early Breast Cancer

Protocol IDs: NSABP-B-44-I, CIRG (TRIO) 011, BETH, NCT00625898  
Target Accrual: 3,500



### Eligibility

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

### Stratification

- Nodal status
- Hormone receptor status

T = docetaxel; C = carboplatin; H = trastuzumab; F = 5-FU; E = epirubicin;  
C<sup>†</sup> = cyclophosphamide; B = bevacizumab

\* Chemotherapy used by NSABP/CIRG investigators (Cohort 1)

<sup>†</sup> Chemotherapy used by independent investigators (Cohort 2)

SOURCE: NCI Physician Data Query, September 2008.

zumab and trastuzumab, so I believe we will receive an answer rapidly as to whether that regimen is tolerable.

## 🎧 Track 2

▶ **DR LOVE:** What's your take on the controversy about the use of adjuvant anthracyclines in HER2-negative disease?

▶ **DR WOLMARK:** I have some deep-seated thoughts on this issue. I believe that the retreat from and abandonment of anthracyclines is proceeding with vigor and with some degree of mysticism. However, we don't have the definitive data to abandon anthracyclines.

## 🎧 Track 3

▶ **DR LOVE:** Would you discuss the new collaboration between the NSABP and US Oncology on the TC-TAC-TC/bevacizumab study?

▶ **DR WOLMARK:** Sarah Cannon and US Oncology are evaluating six cycles of TAC versus six cycles of TC, but will that be a definitive trial? The target sample size is 2,000 patients, and the study has 80 percent power to detect a 3.4 percent absolute difference in disease-free survival in favor of the anthracycline. What if the difference is only three percent and the *p*-value is 0.08? What conclusions will we derive?

So the NSABP, along with Steve Jones and US Oncology, would like to fold that trial into the “TIC-TAC-TOE” trial, or the 3T trial, in which we’re comparing TAC to TC to TC/bevacizumab in 3,900 patients (5.3).

We hope the last arm will determine whether bevacizumab on a nonanthracycline template can add benefit, and it will increase the sample size for the pairwise comparison of TAC to TC to approximately 3,600, which would provide more power to determine the value of an anthracycline or the lack thereof in a HER2-negative cohort.

 **Track 4**

► **DR LOVE:** Can you discuss the letter to the editor in *The New England Journal of Medicine* about the effects of adjuvant trastuzumab in “HER2-low” tumors that Soon Paik and you published recently?

► **DR WOLMARK:** This work by Soon has far-reaching ramifications that I believe challenge some of the concepts that many people thought were inviolate. In evaluating the 500 or so patients in NSABP-B-31, who on review were not IHC3+ and were not FISH-positive using the standard criteria (5.2), the forest plots indicate little difference in benefit of trastuzumab between those who were HER2-low and those who were HER2-positive.

Dr Paik exhaustively analyzed this using a number of methodologies — with expression and with mRNA-based assays. Consistently, those individuals with HER2-low disease on IHC or FISH had HER2-low disease in terms of expression also. He went so far as to evaluate genes that were adjacent to HER2, and if the HER2 level was low, the levels of adjacent genes were also low. We’re confident that this is not a misinterpretation of morphology, IHC or FISH analysis — this is real (5.4).

We submitted to CTEP a concept, which has been accepted pending requirements, for addressing the trastuzumab question in this HER2-low subset — IHC1+, IHC2+ and FISH-negative — which accounts for 40 percent of patients and is not a trivial number.

**5.2 HER2 Status and the Efficacy of Adjuvant Trastuzumab in NSABP-B-31**

Endpoint	ACT	ACTH	Relative risk (95% CI)	p-value	p-value for the interaction
	Number of events/ total number of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37-0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14-0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43-0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01-0.64)	0.017	

SOURCE: Paik S et al. *N Engl J Med* 2008;358(13):1409-11. No abstract available

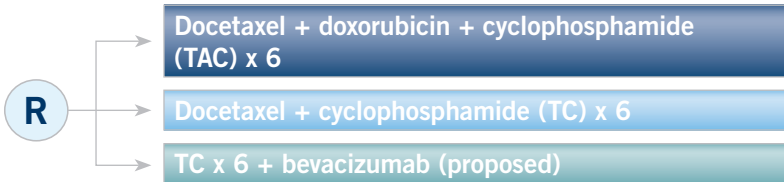
We submitted the concept of a trial looking at TC (docetaxel/cyclophosphamide) versus TC/trastuzumab for patients with HER2-low, high-risk, node-negative and node-positive breast cancer.

CTEP first required a blinded round-robin review of the slides, IHC and FISH, by three objective pathologists. If their findings are in concordance with the NSABP pathology findings, then this trial will move forward.

### 5.3

#### NSABP-Proposed Amendment to US Oncology 06090: A Phase III Trial of Adjuvant TC versus TAC versus TC/Bevacizumab in Patients with HER2-Negative, Early-Stage Breast Cancer

Protocol IDs: NCT00493870, US Oncology 06090, 11271  
Target Accrual: 3,900  
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, September 2008; [www.clinicaltrials.gov](http://www.clinicaltrials.gov); Jones SE. *J Clin Oncol* 2007;25(27):4327. **Abstract**; Wolmark N. Personal communication. NSABP Group Meeting, June 2008.

### Track 6

► **DR LOVE:** Another study I want to ask you about is the new NSABP-B-45 study, evaluating patients with residual tumor after neoadjuvant anthracycline/taxane therapy.

► **DR WOLMARK:** This trial will evaluate patients considered to be at high risk based on the observation that they did not achieve a pathologic complete response, either in the primary breast or in the axillary nodes, after preoperative therapy.

Patients will be randomly assigned to one year of sunitinib or to placebo (5.5). This is an exciting setting in which to determine the value of a biologic agent for this patient population. Currently we do not have an algorithm to predict patient benefit in this particular subset, so robust tissue collection will be a prerequisite as we evaluate possible predictive markers for likelihood of patient benefit from sunitinib therapy. ■

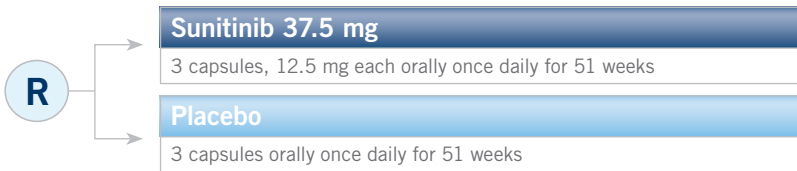
"The mRNA data provide strong evidence that the central HER2-negative tumors in the B-31 trial are indeed HER2-negative. Independent validation of the central FISH testing and immunohistochemical findings from the B-31 trial is being initiated. Assuming that the validation studies are confirmatory, our findings suggest that the benefit of adjuvant trastuzumab may not be limited to patients with HER2 amplification. Since our findings are based on an exploratory analysis, they should not alter current criteria used for selecting patients for adjuvant trastuzumab. Validation of the findings from central testing would justify a phase 3 trial of adjuvant trastuzumab in women with breast cancers that do not meet established criteria for therapy."

SOURCE: Paik S et al. *N Engl J Med* 2008;358(13):1409-11. No abstract available

### Phase III Clinical Trial Comparing Adjuvant Sunitinib to Placebo in Women with Residual Invasive Breast Cancer After Neoadjuvant Chemotherapy\*

Protocol ID: NSABP-B-45

Target Accrual: 2,000 (Pending activation)



#### Eligibility

- Residual invasive disease of breast or axillary nodes
- Patients who had clinical Stage II, IIIA or IIIB, HER2-negative, invasive carcinoma prior to neoadjuvant therapy

\* Minimum of four cycles of neoadjuvant therapy that included at least two of the following: an anthracycline, a taxane, cyclophosphamide

SOURCE: [www.nsabp.pitt.edu](http://www.nsabp.pitt.edu).

## SELECT PUBLICATIONS

Gennari A et al. **Epirubicin plus low-dose trastuzumab in HER2 positive metastatic breast cancer.** *Breast Cancer Res Treat* 2008;[Epub ahead of print]. [Abstract](#)

Gown AM. **Current issues in ER and HER2 testing by IHC in breast cancer.** *Mod Pathol* 2008;21(Suppl 2):8-15. [Abstract](#)

Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11. No abstract available

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

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *Arch Pathol Lab Med* 2007;131(1):18. [Abstract](#)



## 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

- |                |  |                 |   |
|----------------|--|-----------------|---|
| <b>Track 1</b> | A “Manhattan Project” for understanding the molecular circuitry of cancer                            | <b>Track 8</b>  | Clinical use of chemotherapy with lapatinib/trastuzumab in HER2-positive mBC  |
| <b>Track 2</b> | US Oncology TC-TAC-TC/bevacizumab adjuvant trial   | <b>Track 9</b>  | Rationale for combining bevacizumab with a nonanthracycline-containing regimen (TC) in the US Oncology adjuvant trial |
| <b>Track 3</b> | US Oncology neoadjuvant studies evaluating the impact of anti-HER2 therapy on stem cells             | <b>Track 10</b> | Use of anthracycline-containing adjuvant regimens in node-positive or high-risk, node-negative BC                     |
| <b>Track 4</b> | Dose reductions and patient education in managing side effects of paclitaxel/lapatinib               | <b>Track 11</b> | Selection of patients for treatment with adjuvant TC chemotherapy   |
| <b>Track 5</b> | Lapatinib with or without trastuzumab in heavily pretreated mBC progressing on trastuzumab           | <b>Track 12</b> | Applicability of the <i>Oncotype</i> DX assay for treatment decision-making in node-positive BC                       |
| <b>Track 6</b> | Capecitabine/lapatinib in the treatment of brain metastases from HER2-positive BC                    | <b>Track 13</b> | Quantitative assessment of ER and PR with the <i>Oncotype</i> DX assay  |
| <b>Track 7</b> | Dramatic reduction of liver metastases in a heavily pretreated woman receiving lapatinib/trastuzumab | <b>Track 14</b> | Clinical management of bevacizumab- and trastuzumab-associated hypertension in the adjuvant setting                   |

## Select Excerpts from the Interview

### Track 5

► **DR LOVE:** Would you discuss the trial you presented at ASCO, combining trastuzumab and lapatinib in patients with HER2-positive metastatic disease?

► **DR O'SHAUGHNESSY:** This study consisted of patients who were heavily pretreated for metastatic disease. Prior treatments included an average of three trastuzumab-based regimens and a median of four to five chemotherapy regimens. Twenty-five percent of the patients had received 10 or more treatments. In addition, patients were required to have already experienced disease progression through an anthracycline and a taxane and at least one trastu-



zumab-based regimen, and they must have been experiencing progression on trastuzumab at study entry.

Approximately 300 patients were randomly assigned to lapatinib alone at 1,500 milligrams daily, or a lower dose at 1,000 milligrams daily, with weekly trastuzumab. The primary endpoint was progression-free survival, and the median increased from eight weeks with monotherapy to 12 weeks with the combination (O’Shaughnessy 2008; [6.1]). That was statistically significant, with a hazard ratio of 0.75.

An increase of four weeks may not seem that impressive, but the proportion of patients who were progression free at six months — which I believe is more important clinically — doubled, from 13 percent with lapatinib to 28 percent with lapatinib/trastuzumab. In addition, the survival data were almost significant once adjusted for performance status and extent of disease.

Continuing the trastuzumab and adding lapatinib was better for patients, and it was well tolerated. One implication is that lapatinib and trastuzumab appears to be a reasonable option for patients with metastatic disease indolent enough to take a chemotherapy holiday.

The other implication is that this double blockade of the HER2 pathway — blocking from the outside with trastuzumab and the inside with lapatinib — seems worthy of pursuit in additional clinical trials, such as the ALTO adjuvant trial and other front-line and preoperative trials that are underway.

**6.1**

**Phase III Study of Lapatinib with or without Trastuzumab for Heavily Pretreated Patients with HER2-Positive Metastatic Disease Progressing on Trastuzumab**

Efficacy parameter	Lapatinib alone	Lapatinib + trastuzumab	Odds ratio	p-value
Response rate <sup>1</sup>	6.9%	10.3%	1.5	0.46
Clinical benefit ratio <sup>2</sup>	12.4%	24.7%	2.2	0.01
<b>Hazard ratio</b>				
Progression-free survival <sup>3</sup>	8.1 weeks	12.0 weeks	0.73	0.008
Overall survival	39 weeks	51.6 weeks	0.75	0.106
Adjusted overall survival <sup>3</sup>	NR	NR	0.71	0.0596

<sup>1</sup> Confirmed complete response (CR) + partial response (PR)

<sup>2</sup> CR + PR + stable disease ≥ 6 months

<sup>3</sup> Adjusted for extent of disease and performance status (significant baseline covariates)

SOURCE: O’Shaughnessy J et al. *Proc ASCO* 2008; [Abstract 1015](#).

 **Track 6**

▶ **DR LOVE:** What do you think of the combination of lapatinib and capecitabine?

► **DR O'SHAUGHNESSY:** This is an important combination, particularly for patients who have or are at high risk for developing brain metastases. At ASCO 2008, Boccardo reported an 18 percent objective response rate among patients who had definitive progressing brain metastases at the time of study entry (Boccardo 2008; [6.2]). These data corroborated Lin and Winer's experience presented at the San Antonio Breast Cancer Symposium in 2007 (Lin 2007). The responses are impressive. Brain metastases are a scourge, and we have so little to offer these patients other than radiation therapy. Thus I am "bullish" on the capecitabine/lapatinib regimen as our most promising strategy to help these patients, and I like to use it earlier in the metastatic setting.

► **DR LOVE:** What is your first-line regimen for patients with HER2-positive metastatic disease?

► **DR O'SHAUGHNESSY:** For patients who received adjuvant trastuzumab and experienced at least a one-year disease-free interval since stopping the therapy, I start with vinorelbine/trastuzumab. I like this combination for its efficacy and quality of life. I then use capecitabine/lapatinib as my next line of therapy. If a patient experiences toxicity with the lapatinib/capecitabine regimen, I can easily imagine using lapatinib/trastuzumab based on the data I presented at ASCO with this combination in heavily pretreated patients (O'Shaughnessy 2008).

► **DR LOVE:** Have you seen responses to the lapatinib/capecitabine regimen in patients with brain metastases?

► **DR O'SHAUGHNESSY:** I have seen minor responses, but even more impressive, I've seen prolonged stable disease. For example, I have patients who have undergone whole-brain radiation therapy and resection and then received this combination when they returned with progressive disease. In these patients, I have seen prolonged disease control — for more than a year and for some patients even pushing two years.

6.2

**Efficacy of Lapatinib and Capecitabine in Patients with Brain Metastases from HER2-Positive Breast Cancer (N = 138)**

**Summary of unconfirmed CNS response**

Complete response (CR)	2%
Partial response (PR)	16%
Objective response rate (CR + PR)	18%
Stable disease	47%
Progressive disease	14%
Unknown	21%

SOURCE: Boccardo F et al. *Proc ASCO* 2008;[Abstract 1094](#).

 **Tracks 9-11**

► **DR LOVE:** What was the rationale for combining bevacizumab with the nonanthracycline regimen TC in the adjuvant setting on the US Oncology/NSABP "TIC-TAC-TOE" trial (5.3, page 28)?

► **DR O'SHAUGHNESSY:** The hypothesis is that a HER2-negative population exists that does not need anthracyclines. Many groups are interested in that hypothesis, including US Oncology, Sarah Cannon, TORI and the NSABP. If indeed that is the case, then we want to see what bevacizumab contributes to a nonanthracycline regimen. This is similar to the BETH trial approach examining TCH and bevacizumab.

I want to add a cautionary note that I don't believe we are ready to drop anthracyclines without a prospective trial. We have decades of efficacy data with anthracyclines, so although I love the TC regimen, for patients with node-positive disease I believe that one of the proven three- or four-drug regimens — TAC, dose-dense AC/paclitaxel or FEC followed by docetaxel — is still the standard.

► **DR LOVE:** What about patients with node-negative disease in the adjuvant setting?

► **DR O'SHAUGHNESSY:** At ASCO 2008, Miguel Martin presented the five-year efficacy analysis of the GEICAM 9805 trial, which showed that adjuvant TAC was associated with a significant improvement in disease-free survival compared to FAC in patients with high-risk, node-negative breast cancer (Martin 2008).

I believe that we should treat patients with node-negative disease who will benefit from chemotherapy, such as those with ER-negative disease or highly proliferative ER-positive disease, with effective chemotherapy. At MD Anderson, all patients who receive adjuvant chemotherapy receive 12 doses of weekly paclitaxel followed by four cycles of FAC.

I believe that patients who we feel will benefit significantly from chemotherapy should receive an anthracycline-based regimen such as TAC or dose-dense chemotherapy or the MD Anderson regimen. Also, these patients at high risk are eligible for our TC versus TAC trial.

However, for patients who have more indolent disease, I believe a role exists for the four cycles of TC in patients whose benefit from chemotherapy may be small — somewhere between zero and three percent.

## Track 13

► **DR LOVE:** *Oncotype DX* is now reporting quantitative ER and PR in addition to a Recurrence Score. Do you see that being helpful in practice?

► **DR O'SHAUGHNESSY:** Yes, it is helpful because with the RT-PCR mRNA methodology, you have approximately a 200-fold or higher dynamic range of ER and PR. The way we currently test ER, for example, results cluster at zero or maybe 10 to 30 percent, with a few at 50 and some at 90 or 100 percent, and the PR antibody is unreliable.

► **DR LOVE:** How does this quantitative information help you clinically?

► **DR O'SHAUGHNESSY:** The quantitative data provide more information on

the extent to which women will benefit from endocrine therapy. At the San Antonio Breast Cancer Symposium in 2006, data were presented on quantitative ER and PR from the NSABP-B-14 trial, comparing tamoxifen to placebo, and they categorized it by tertiles (Baehner 2006). They definitively demonstrated that the degree to which a patient will benefit from tamoxifen is dependent on the ER tertile — the stronger the ER, the greater the benefit.

It is interesting that ER was not prognostic and, inversely, PR was prognostic but not predictive of benefit (6.3). ■

**6.3**

**Quantitative Levels of ER and PR from RT-PCR Analysis in the Prognosis and Prediction of Tamoxifen Benefit for Patients with ER-Positive Breast Cancer Treated with Tamoxifen or Placebo in NSABP-B-14**

Quantitative tertile levels by RT-PCR	Distant recurrence-free interval	
	Placebo (prognosis indicator)	Tamoxifen benefit (predictive indicator)
<b>ER-positive</b>		
High	Similar across all tertiles	Large
Medium		Large
Low		Little
<b>PR-positive</b>		
High	High	Similar across all tertiles
Medium	Medium	
Low	Low	

“The level of expression of ER is primarily predictive of tamoxifen benefit and is not significantly associated with prognosis in untreated patients. In contrast, quantitative PR by RT-PCR is primarily prognostic and is not predictive of tamoxifen benefit. Quantitative expression in individual patients suggests that ER and PR have very different roles in the biology of ER+ breast cancer.”

SOURCE: Baehner FL et al. San Antonio Breast Cancer Symposium 2006; [Abstract 45](#).

**SELECT PUBLICATIONS**

Baehner FL et al. **Quantitative RT-PCR analysis of ER and PR by Oncotype DX™ indicates distinct and different associations with prognosis and prediction of tamoxifen benefit.** San Antonio Breast Cancer Symposium 2006; [Abstract 45](#).

Boccardo F et al. **Evaluation of lapatinib (Lap) plus capecitabine (Cap) in patients with brain metastases (BM) from HER2+ breast cancer (BC) enrolled in the Lapatinib Expanded Access Program (LEAP) and French Authorisation Temporaire d’Utilisation (ATU).** *Proc ASCO* 2008; [Abstract 1094](#).

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

Martin M et al. **Multicenter, randomized phase III study of adjuvant chemotherapy for high-risk, node-negative breast cancer comparing TAC with FAC: 5-year efficacy analysis of the GEICAM 9805 trial.** *Proc ASCO* 2008; [Abstract 542](#).

O’Shaughnessy J et al. **A randomized study of lapatinib in combination with trastuzumab versus lapatinib monotherapy in heavily pretreated HER2+ metastatic breast cancer patients progressing on trastuzumab therapy.** *Proc ASCO* 2008; [Abstract 1015](#).



## INTERVIEW

### Eric P Winer, MD

Dr Winer is Thompson Investigator in Breast Cancer Research, Director of the Breast Oncology Center at the Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

#### Tracks 1-4

**Track 1** Evaluating biological subtypes in BC clinical trials

**Track 2** Anticipated translation of clinical trials targeting biologic subtypes into reductions in breast cancer mortality

**Track 3** Controversy regarding the benefit of adjuvant trastuzumab in patients with “HER2-low” BC

**Track 4** Proposal for an adjuvant clinical trial to evaluate “HER2-low” BC

## Select Excerpts from the Interview

### Tracks 1-2

▶ **DR LOVE:** What’s your take on tissue biomarkers and the design of new clinical trials?

▶ **DR WINER:** HER2-positive disease is clearly separate from everything else at this point, and I believe that’s truer in 2008 than it was in 2004 or 2002. With the recognition from the large randomized trials that trastuzumab works in the adjuvant setting (Joensuu 2006; Romond 2005; Slamon 2006; Smith 2007) and with the development of post-trastuzumab therapies like lapatinib (Di Leo 2007; Geyer 2006; O’Shaughnessy 2008), I believe that in both the adjuvant setting and the metastatic setting we will have HER2-positive trials and HER2-negative trials. With the exception of some Phase I trials or perhaps some limited other examples, we will not see a great deal of mixing.

I believe that classifying breast cancer into clinically relevant subtypes will allow us, and has already allowed us, to design trials that will lead to far more tangible benefits than in the past. We’ve recently begun to see the results of that with trials of trastuzumab in the adjuvant setting. Now it must be taken several steps further.

We need more work conducted for patients with triple-negative disease. At the moment we have chemotherapy and the added benefits of bevacizumab in the metastatic setting but not much else. I believe that for patients with ER-positive, HER2-negative disease, the key is identifying who will benefit from

chemotherapy and who will not. We also need to figure out how to better utilize hormonal therapy.

We have good clues, and they relate largely to the duration of therapy and potentially selecting the right drug for the right patient rather than believing the same approach will work for everyone.

► **DR LOVE:** Do you think that type of research strategy will result in a significant reduction in breast cancer mortality in the next 10 or 15 years?

► **DR WINER:** I believe adjuvant HER2-directed therapy will ultimately result in close to a 50 percent reduction in the deaths from HER2-positive breast cancer among women who present with early-stage breast cancer.

At the moment, the treatment for those patients is trastuzumab, but we may evolve beyond that. I'm phrasing it that way deliberately because a fair number of women with HER2-positive breast cancer, unfortunately, still present with advanced disease.

In another seven or eight years, I believe we will have almost all, if not all, the tools we need to eliminate death from HER2-positive breast cancer.

## Tracks 3-4

► **DR LOVE:** Do you have any predictions about how the “HER2-low” issue will play out in terms of benefit from adjuvant trastuzumab?

► **DR WINER:** What troubles all of us about Soon Paik's data (Paik 2007, 2008; [5.2]) is that everything we know in the metastatic setting indicates that patients with disease not classified as HER2-positive by our current standards — FISH-positive or IHC 3+ — do not benefit from trastuzumab (7.1).

Maybe trastuzumab is working in a different way in the adjuvant setting, but that seems to be a stretch. I'm open to the possibilities, but I need a lot more data before concluding that trastuzumab or other HER2-directed therapy has a role for patients whose tumors we believe are HER2-negative.

I believe that the next step should be a study of patients whose tumors are considered HER2-intermediate — defined as 1.8 to 2.2 by FISH. I'd also consider IHC 2+ without anything else, for that matter. No one knows what to do with those patients. We should enroll them in a study and answer the question.

► **DR LOVE:** What about IHC 1+?

► **DR WINER:** Patients in the NSABP-B-31 trial all had HER2 that was defined as positive somewhere. It would seem easier to justify the low risk and the added burden associated with trastuzumab for those patients with IHC 2+ readings. Considering the benefits that have been reported with trastuzumab, including the benefits in this small subset, it wouldn't require a huge trial to find out. ■

## Absence of Benefit from Trastuzumab in Tumors Lacking HER2 Overexpression or Gene Amplification in CALGB-9840

Our study showed no benefit for the addition of trastuzumab in patients whose tumors lacked HER-2 overexpression or gene amplification. Although this result was expected, we know of no other prospective demonstration of this observation. Further, this observation addresses the concern that substantial numbers of patients with HER-2-dependent breast cancers might have been mislabeled as “negative” for this receptor. In our study, HER-2 assessment was performed locally. Patients with either IHC 3 or IHC 2 and FISH-amplified tumors were considered HER-2 positive and assigned to trastuzumab; all others were considered HER-2 normal and randomly assigned to trastuzumab versus no trastuzumab. Our findings provide a counterbalance to the recently reported results from National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-31 suggesting an apparent benefit for adjuvant trastuzumab in patients whose tumors tested negative at a central laboratory by both immunohistochemistry and FISH.

SOURCE: Seidman A et al. *J Clin Oncol* 2008;26(10):1642-9. [Abstract](#)

### SELECT PUBLICATIONS

Di Leo A et al. **Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A phase III randomized, double-blind study of 580 patients.** *Proc ASCO* 2007; [Abstract 1011](#).

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43. [Abstract](#)

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

O'Shaughnessy J et al. **A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy.** *Proc ASCO* 2008; [Abstract 1015](#).

Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11. No abstract available

Paik S et al. **Benefit from adjuvant trastuzumab may not be confined to patients with IHC 3+ and/or FISH-positive tumors: Central testing results from NSABP B-31.** *Proc ASCO* 2007; [Abstract 511](#).

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

Seidman A et al. **Randomized Phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: Final results of Cancer and Leukemia Group B Protocol 9840.** *J Clin Oncol* 2008;26(10):1642-9. [Abstract](#)

Slamon D et al. **BCIRG 006: 2<sup>nd</sup> 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](#).

Smith I et al. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. [Abstract](#)

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. In the ABCSG-12 trial, evaluating endocrine therapy for premenopausal women with ER-positive breast cancer, the vast majority of the patients received (neo)adjuvant chemotherapy.
  - a. True
  - b. False
2. In ECOG-E5103, evaluating AC and paclitaxel with or without bevacizumab, the taxane is administered \_\_\_\_\_.
  - a. Weekly
  - b. Every two weeks
  - c. Every three weeks
3. In the AVADO trial, the addition of bevacizumab to docetaxel as first-line therapy for women with metastatic breast cancer resulted in significant improvements in which endpoint?
  - a. Overall survival
  - b. Progression-free survival
  - c. Both a and b
  - d. None of the above
4. Which genomic assay requires fresh tumor specimens?
  - a. Oncotype DX 21-gene assay
  - b. MammaPrint 70-gene assay
  - c. Both a and b
  - d. Neither a nor b
5. The CIRG/NSABP BETH trial will evaluate the combination of chemotherapy/trastuzumab with \_\_\_\_\_ for women with HER2-positive, early breast cancer.
  - a. Lapatinib
  - b. Bevacizumab
  - c. Erlotinib
  - d. None of the above
6. The joint NSABP/US Oncology adjuvant “TIC-TAC-TOE” study will evaluate TC versus TAC versus TC with \_\_\_\_\_ in patients with HER2-negative early breast cancer.
  - a. Bevacizumab
  - b. Erlotinib
  - c. Trastuzumab
  - d. None of the above
7. In ABCSG-12, premenopausal patients with ER-positive, PR-positive breast cancer treated with adjuvant zoledronic acid experienced \_\_\_\_\_ compared to those who did not receive zoledronic acid.
  - a. A reduction in contralateral breast cancer
  - b. A reduction in locoregional recurrence
  - c. A reduction in distant metastases, including extraskeletal metastases
  - d. All of the above
8. The Phase III NSABP-B-45 placebo-controlled trial will evaluate \_\_\_\_\_ in women with residual invasive breast cancer after neoadjuvant chemotherapy.
  - a. Erlotinib
  - b. Lapatinib
  - c. Sunitinib
  - d. Bevacizumab
9. In a randomized clinical trial, heavily pretreated patients with HER2-positive metastatic breast cancer whose disease progressed on trastuzumab and who were treated with lapatinib/trastuzumab experienced significant improvements in \_\_\_\_\_ compared to those treated with lapatinib alone.
  - a. Tumor response
  - b. Progression-free survival
  - c. Overall survival
  - d. Both a and b
  - e. a, b and c
10. Analysis of data from NSABP-B-31 by Paik and colleagues indicates that women treated with adjuvant trastuzumab have reductions in the risk of disease progression and death, regardless of HER2 status.
  - a. True
  - b. False



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 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Ongoing and proposed adjuvant trials evaluating bevacizumab in HER2-negative and HER2-positive early breast cancer.....4 3 2 1
- Clinical implications of the ABCSG-12 zoledronic acid data.....4 3 2 1
- Current viewpoints on the controversial role of adjuvant anthracyclines.....4 3 2 1
- Safety and efficacy for lapatinib with trastuzumab or chemotherapy in HER2-positive metastatic breast cancer.....4 3 2 1
- Comparison of the Oncotype DX and MammaPrint assays.....4 3 2 1

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Ongoing and proposed adjuvant trials evaluating bevacizumab in HER2-negative and HER2-positive early breast cancer.....4 3 2 1
- Clinical implications of the ABCSG-12 zoledronic acid data.....4 3 2 1
- Current viewpoints on the controversial role of adjuvant anthracyclines.....4 3 2 1
- Safety and efficacy for lapatinib with trastuzumab or chemotherapy in HER2-positive metastatic breast cancer.....4 3 2 1
- Comparison of the Oncotype DX and MammaPrint assays.....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 be able to:**

- Integrate validated tissue biomarkers and genomic assays into the clinical management of node-negative and node-positive early breast cancer. ....4 3 2 1 N/M N/A
- Develop an evidence-based adjuvant treatment algorithm for patients with localized breast cancer, addressing the individualized selection of chemotherapy and the optimal schedule and duration of endocrine therapy.....4 3 2 1 N/M N/A
- Compare and contrast the efficacy, safety and current clinical utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens. ....4 3 2 1 N/M N/A
- Discuss the adjunctive role of oral and intravenous bisphosphonates in the management of ER-positive and/or PR-positive early breast cancer, and identify patients who may benefit from this course of therapy. ....4 3 2 1 N/M N/A
- Explain the benefits and risks of HER2-directed therapy for patients with early and advanced breast cancer, and discuss how combination treatment regimens may overcome the development of resistant disease.....4 3 2 1 N/M N/A
- Demonstrate knowledge of the evidence-based use of bevacizumab in the first-line treatment of metastatic breast cancer, and recognize the rationale for its ongoing investigation in the adjuvant setting.....4 3 2 1 N/M N/A
- Appraise the value of the neoadjuvant platform, precise patient selection and translational research in the successful development of novel breast cancer therapeutics.....4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation.....4 3 2 1 N/M N/A

**EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)**

**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:**

.....

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

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

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

4 = Very good    3 = Above average    2 = Adequate    1 = Suboptimal

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Professor John Crown, MD	4	3	2	1	4	3	2	1
Kathy D Miller, MD	4	3	2	1	4	3	2	1
Peter M Ravdin, MD, PhD	4	3	2	1	4	3	2	1
Norman Wolmark, MD	4	3	2	1	4	3	2	1
Joyce O'Shaughnessy, MD	4	3	2	1	4	3	2	1
Eric P Winer, MD	4	3	2	1	4	3	2	1
Editor	Knowledge of subject matter				Effectiveness as an educator			
Neil Love, MD	4	3	2	1	4	3	2	1

**Please recommend additional faculty for future activities:**

.....

**Other comments about the editor and faculty for this activity:**

.....

**REQUEST FOR CREDIT — Please print clearly**

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