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Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

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Jack Cuzick, PhD

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CME Certified

Breast Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Results from numerous ongoing trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic/prognostic tools. 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 genomic assays into the clinical management of hormone receptor (HR)-positive, node-negative or node-positive early breast cancer.
- Apply the results of recent clinical trials when recommending aromatase inhibitors and/or tamoxifen as primary therapy for postmenopausal women with HR-positive early breast cancer.
- Formulate an evidence-based algorithm for the treatment of localized or metastatic, HER2-positive breast cancer.
- Demonstrate knowledge of ongoing investigational approaches to the management of triple-negative or HER2-positive breast cancer.
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens.
- Consider the unique benefits and risks associated with novel epothilones and taxanes when selecting and sequencing chemotherapeutic regimens.
- Recall emerging clinical trial results with bevacizumab for metastatic breast cancer, and assess their application to current patient care.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Harold J Burstein, MD, PhD

Dr Burstein is Assistant Professor of Medicine at the Harvard Medical School Breast Oncology Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the TransATAC analysis data presented at the 2008 San Antonio Breast Cancer Symposium (1.1)?

DR BURSTEIN: The ATAC investigators in collaboration with Genomic Health analyzed data from a subset of approximately 1,200 patients who received endocrine therapy only. This was not a randomly selected subset of patients. However, it was a large, representative subset from the ATAC study. They reported that the trends, in terms of using the Onco*type* DX Recurrence Score® to predict the likelihood of distant metastatic disease through nine years of follow-up, were similar with tamoxifen and anastrozole (Dowsett 2008).

That is to say, you can utilize the Onco*type* DX assay to determine the risk estimates for patients being treated with aromatase inhibitors and for patients being treated with tamoxifen.

DR LOVE: What about the issue of quantitative assessment of ER and HER2, which is being reported in the Onco*type* DX assay?

DR BURSTEIN: Quantitative HER2 testing has not yet yielded subsets of patients who should or should not receive HER2-directed therapy. For ER testing, we have known for 40 years that more ER in a tumor translates into increased sensitivity to endocrine therapy.

In Giuseppe Viale's papers from the BIG 1-98 study, patients whose tumors were strongly ER-positive fared well with either tamoxifen or letrozole (Viale 2007), whereas those who had tumors with lower levels of ER and/or high Ki-67 did not fare quite as well (Viale 2008). Similarly, patients with ER-positive, HER2-positive disease demonstrated poorer outcomes, but patients treated with letrozole fared better than those treated with tamoxifen (Rasmussen 2008). So these are important biomarkers and the Onco*type* DX is built around all of them, which is an appealing aspect of this assay since it resonates with all of this other biomarker literature. ■

1.1

TransATAC: Proportion of Patients Treated with Anastrozole or Tamoxifen Who Are Free of Distant Recurrence at Nine Years by Onco*type* DX Recurrence Score Group: Analysis of Nodal Status

	Low	Int.	High	High vs low	Int. vs low
Node-negative (n = 513, 229, 130)	96%	88%	75%	HR* = 5.2	HR* = 2.5
Node-positive (n = 160, 94, 52)	83%	72%	51%	HR* = 2.7	HR* = 1.8

* HR = hazard ratio for RS group, adjusted for tumor size, grade, age and treatment

SOURCE: Dowsett M et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

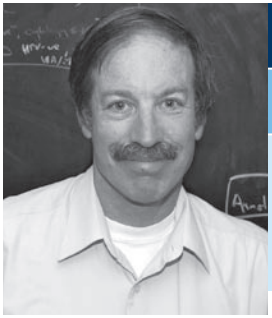
SELECT PUBLICATIONS

Dowsett M et al. **Risk of distant recurrence using Onco*type* DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: A TransATAC study.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

Rasmussen BB et al. **Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: Supplementary results from the BIG 1-98 randomised trial.** *Lancet Oncol* 2008;9(1):23-8. **Abstract**

Viale G et al. **Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: Results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole.** *J Clin Oncol* 2008;26(34):5569-75. **Abstract**

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



INTERVIEW

Jack Cuzick, PhD

Prof Cuzick is John Snow Professor of Epidemiology at Wolfson Institute of Preventive Medicine's Cancer Research UK Centre for Epidemiology, Mathematics and Statistics in London, United Kingdom.

Tracks 1-9

Track 1 Meta-analyses of randomized trials of monotherapy and switching strategies with adjuvant aromatase inhibitors versus tamoxifen

Track 2 BIG 1-98: Letrozole versus tamoxifen as adjuvant endocrine therapy for postmenopausal women with ER/PR-positive BC

Track 3 BIG 1-98: Analysis of sequencing letrozole and tamoxifen

Track 4 Risk of recurrence after five years of adjuvant endocrine therapy

Track 5 Potential relationship between treatment-emergent endocrine symptoms and antitumor effects of hormonal agents

Track 6 TEAM: Tamoxifen Exemestane Adjuvant Multinational trial for postmenopausal women with ER/PR-positive early BC

Track 7 Clinical implications of the association between treatment-related symptoms and impact of endocrine therapy

Track 8 Use of Onco*type* DX in assessing risk of distant recurrence for postmenopausal patients with BC treated with anastrozole or tamoxifen

Track 9 Role of Onco*type* DX in treatment decision-making

Select Excerpts from the Interview

Track 1

DR LOVE: Would you review the AI meta-analyses presented by Jim Ingle at the 2008 San Antonio Breast Cancer Symposium?

PROF CUZICK: We evaluated two separate cohorts: patients receiving adjuvant treatment with an up-front aromatase inhibitor versus tamoxifen and patients receiving a switching strategy of tamoxifen for approximately two years followed by a further three years of tamoxifen or an aromatase inhibitor (Ingle 2008).

We found no surprises. Up-front therapy with an aromatase inhibitor versus tamoxifen reduced the rate of relapse by approximately 23 percent. However, no difference in breast cancer survival was apparent in the up-front therapy trials (Ingle 2008; [2.1]). The challenge was that the switching trials could

not be directly compared to the up-front trials because they included different patient populations. The results of the switching studies were generally similar to those of the up-front studies in terms of recurrence. However, the switching studies have also shown a reduction in overall mortality (Ingle 2008; [2.2]).

2.1

Meta-Analysis: Adjuvant Trials of Up-Front Aromatase Inhibitors (AIs) versus Tamoxifen for Postmenopausal Women with ER-Positive Breast Cancer

Eight-year outcomes

	AI (n = 4,954)	Tamoxifen (n = 4,902)	*p*-value
Recurrence	15.3%	19.2%*	<0.00001
Breast cancer mortality	10.0%	10.5%	0.1
Death without recurrence	9.1%	8.8%	0.9
Any death	17.8%	18.0%	0.3

* 23 percent proportional reduction

SOURCE: Ingle JN et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

2.2

Meta-Analysis: Adjuvant Trials of Tamoxifen for Two to Three Years Followed by an Aromatase Inhibitor (AI) versus Continued Tamoxifen for Postmenopausal Women with ER-Positive Breast Cancer

Six-year outcomes

	Tamoxifen → AI (n = 4,508)	Tamoxifen (n = 4,507)	*p*-value
Recurrence	12.6%	16.1%*	<0.00001
Breast cancer mortality	6.3%	8.0%	0.02
Death without recurrence	5.0%	5.7%	0.08
Any death	10.8%	13.0%	0.004

* 29 percent proportional reduction

SOURCE: Ingle JN et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

Tracks 2-3

DR LOVE: Would you discuss the updated results of the BIG 1-98 study presented at the SABCS meeting?

PROF CUZICK: The update comparing up-front letrozole to tamoxifen was difficult to interpret because, in response to early results from ATAC and other trials, the patients on the tamoxifen arm were unblinded and one fourth of patients chose to switch to letrozole (Mouridsen 2008).

The conventional analysis for all patients as randomly assigned (intent to treat) showed a nonsignificant trend toward better overall survival with up-front letrozole. The alternate analysis, which censored patients when they crossed over from tamoxifen to letrozole, showed a significant effect of letrozole on overall survival (Mouridsen 2008; [2.3]).

DR LOVE: What were the results from the sequencing aspect of BIG 1-98?

PROF CUZICK: The trial enrolled approximately 1,500 patients per arm (Mouridsen 2008). The differences between the sequential and up-front use of an aromatase inhibitor are smaller than the differences between letrozole and tamoxifen. So we need trials that are bigger than any of the individual trials, and BIG 1-98 was smaller. It was clear that no differences would be evident.

2.3

BIG 1-98: Letrozole versus Tamoxifen as Adjuvant Monotherapy for Postmenopausal Women with Receptor-Positive Breast Cancer

76-month median follow-up

	Hazard ratio (95% CI)	Intent to treat *p*-value
Disease-free survival		
Intent to treat	0.88 (0.78-0.99)	0.03
Censored*	0.84 (0.74-0.95)	
Overall survival		
Intent to treat	0.87 (0.75-1.02)	0.08
Censored*	0.81 (0.69-0.94)	
Time to distant recurrence		
Intent to treat	0.85 (0.72-1.00)	0.05
Censored*	0.81 (0.68-0.96)	

Hazard ratio < 1 favors letrozole over tamoxifen; CI = confidence interval; * 25 percent of patients who were randomly assigned to tamoxifen and crossed over to letrozole were censored at crossover.

SOURCE: Mouridsen HT et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

Tracks 5, 7

DR LOVE: Would you discuss the paper you recently published in *The Lancet Oncology* evaluating endocrine therapy?

PROF CUZICK: We evaluated patients who reported endocrine symptoms — such as hot flashes, night sweats or arthralgias — during the first follow-up visit at three months in the ATAC trial.

Although more arthralgias were reported in the anastrozole arm and more hot flashes were reported in the tamoxifen arm, the overall numbers of patients reporting symptoms were about the same. Approximately 50 percent of the women in each arm had something to report at three months (Cuzick 2008).

Then we evaluated recurrences subsequent to that visit. The striking observation was that in both treatment arms, patients with symptoms fared substantially better than patients without symptoms. The size of the effect was larger than the difference between tamoxifen and anastrozole (Cuzick 2008; [2.4]).

The first value of these results is that they will encourage women who have mild to moderate symptoms to recognize that this is an indicator that the drug is doing what it's meant to do. So we hope it will encourage compliance, which is a crucial issue in the use of these drugs. ■

2.4

ATAC Trial: Annual Breast Cancer Recurrence Rate According to Endocrine Symptoms Reported at Three-Month Follow-Up

	Anastrozole (n = 1,967)	Tamoxifen (n = 1,997)	Overall (n = 3,964)	Hazard ratio* (95% CI)	*p*-value
Vasomotor symptoms	1.7%	2.4%	2.1%	0.84 (0.71-1.00)	0.04
Joint symptoms	1.6%	1.9%	1.7%	0.60 (0.5-0.72)	<0.0001
Neither side effect	2.8%	3.5%	3.2%	1.0†	—

* Hazard ratios adjusted for age, body mass index, previous use of hormone replacement therapy, nodal status, tumor grade and tumor size; † reference group; CI = confidence interval

"The appearance of new vasomotor symptoms or joint symptoms within the first 3 months of treatment is a useful biomarker, suggesting a greater response to endocrine treatment compared with women without these symptoms. Awareness of the relation between early treatment-emergent symptoms and beneficial response to therapy might be useful when reassuring patients who present with them, and might help to improve long-term treatment adherence when symptoms cannot be alleviated effectively."

SOURCE: Cuzick J et al. *Lancet Oncol* 2008;9(12):1143-8. **Abstract**

SELECT PUBLICATIONS

Coleman E et al. **Aromatase inhibitor-induced arthralgia: Clinical experience and treatment recommendations.** *Cancer Treat Rev* 2008;34(3):275-82. **Abstract**

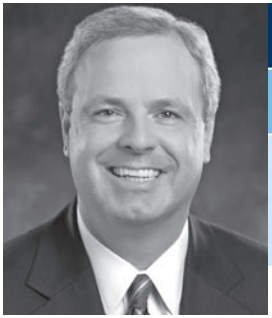
Crew KD et al. **Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer.** *J Clin Oncol* 2007;25(25):3877-83. **Abstract**

Cuzick J et al. **Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: A retrospective analysis of the ATAC trial.** *Lancet Oncol* 2008;9(12):1143-8. **Abstract**

Ingle JN et al. **Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

Morales L et al. **Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome.** *J Clin Oncol* 2008;26(19):3147-52. **Abstract**

Mouridsen HT et al. **BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 13**.



INTERVIEW

Howard A Burris III, MD

Dr Burris is Chief Medical Officer and Director of Drug Development at Sarah Cannon Research Institute in Nashville, Tennessee.

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Track 1 Efficacy and side effects of the HER2 antibody-cytotoxic drug conjugate T-DM1

Track 2 Case discussion: A patient with trastuzumab-refractory, HER2-positive mBC who experienced a durable, near-complete remission with T-DM1

Track 3 Rationale for continuation of biologic therapies upon metastatic disease progression

Track 4 Forecast role of T-DM1 in the clinical algorithm for HER2-positive mBC

Track 5 Pertuzumab: A first-in-class HER dimerization inhibitor

Track 6 Tolerability and side effects of orally administered TKIs

Track 7 Pilot study of adjuvant AC → paclitaxel/sorafenib in patients with high-risk BC

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Track 9 Lack of cardiac toxicity associated with adding bevacizumab to three docetaxel-based adjuvant regimens: TCH, AC → docetaxel and TAC

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Track 14 Pathologic CR rate and SPARC tumor correlatives from a Phase II neoadjuvant trial of gemcitabine, epirubicin and nanoparticle albumin-bound (*nab*) paclitaxel

Track 15 Lack of steroid premedication and hypersensitivity reactions with *nab* paclitaxel

Track 16 Mechanism of action of the epothilone analog ixabepilone

Track 17 Rationale for TITAN: A Phase III trial of adjuvant AC followed by ixabepilone versus paclitaxel for triple-negative BC

Track 18 Potential role for bevacizumab in the treatment of triple-negative BC

Track 19 Capecitabine with or without ixabepilone in triple-negative BC: Pooled analysis of two Phase III trials

Track 20 Paclitaxel/bevacizumab as first-line therapy for patients with mBC

Select Excerpts from the Interview

Tracks 1, 4

DR LOVE: You are coauthor of a study presented at San Antonio on trastuzumab-DM1 (T-DM1). Can you comment?

DR BURRIS: I was a skeptic about the idea that a cytotoxic agent could be linked to an antibody, retained with the antibody and then delivered to the cancer cells. We have tried this a few times through the years without success. In T-DM1 the cytotoxic agent is mertansine. Maytansine was the parent compound, and this is a derivative. We knew that the maytansine compounds were extremely active but too toxic. With T-DM1, we did not see pancytopenia, hair loss or other classic toxicities associated with maytansine. However, we did observe transient changes in platelet counts, which were probably an immunologic effect.

In the Phase II trial, the median time on prior trastuzumab was approximately 76 weeks, and the response rates to T-DM1 were 30 to 40 percent among patients with previously treated, HER2-positive metastatic disease (Vukelja 2008).

DR LOVE: Where do you see T-DM1 heading?

DR BURRIS: T-DM1 is moving forward, and I believe that in a year it will be utilized as second-line therapy. The data from this study are so promising that a randomized trial (NCT00679341) has recently been initiated comparing T-DM1 to trastuzumab/docetaxel as first-line therapy for HER2-positive metastatic disease.

Track 9

DR LOVE: Would you discuss your group's study headed by Denise Yardley evaluating the addition of bevacizumab to three different docetaxel-containing adjuvant regimens?

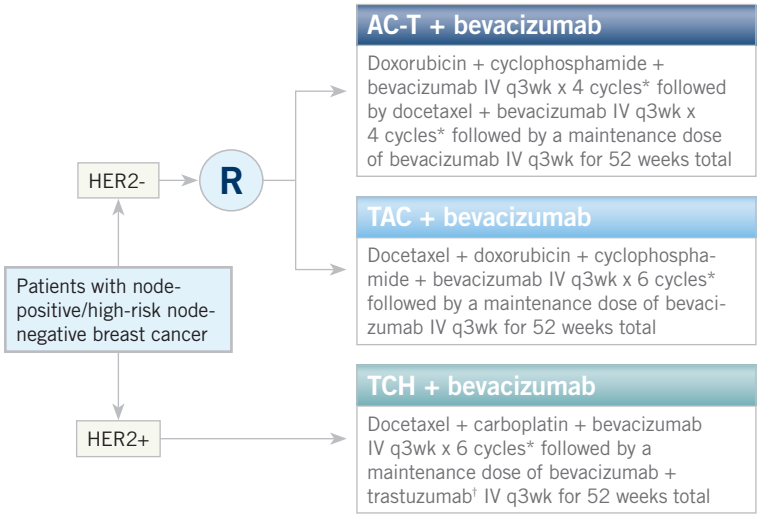
DR BURRIS: The idea was to take the docetaxel-containing regimens that were becoming standards — such as TCH (docetaxel/carboplatin/trastuzumab) — and add the VEGF inhibitor bevacizumab. The goal of our trial was to provide safety data for the BETH study and other trials.

We presented preliminary results at ASCO 2008 (Hart 2008), and the report at San Antonio was a follow-up confirmation. We treated 75 patients with bevacizumab in combination with the following regimens: TCH, AC → docetaxel or TAC (docetaxel/doxorubicin/cyclophosphamide; Yardley 2008a; [3.1]). With TCH and bevacizumab, the main concern was cardiac toxicity. We didn't have any problems — only two of 75 patients showed declines in their ejection fractions (Yardley 2008a).

As we proceed into adjuvant trials with bevacizumab, the results improve with regard to cardiac toxicity because nurses and doctors are becoming internists and are treating hypertension. We no longer have hypertension problems with bevacizumab because we administer ACE inhibitors and diuretics earlier.

3.1

Phase II Randomized Trial of Adjuvant Bevacizumab with Three Docetaxel-Containing Regimens



* Each cycle included mandated prophylactic granulocyte or myeloid colony-stimulating factors (pegfilgrastim, filgrastim or sargramostim) beginning at least 24 hours after chemotherapy.
† A trastuzumab loading dose of 8 mg/kg was administered IV on day 2 of cycle 1 only.

SOURCE: Yardley DA et al. Poster. San Antonio Breast Cancer Symposium 2008a; **Abstract 4107**.

Tracks 14-15

DR LOVE: Would you discuss your neoadjuvant study presented at the 2008 SABCS meeting?

DR BURRIS: The neoadjuvant trial involved an aggressive regimen of gemcitabine in combination with epirubicin and nanoparticle albumin-bound (*nab*) paclitaxel administered as a dose-dense, every other-week approach.

Our pathologic complete response (CR) rate in the breast and lymph nodes was 18 percent. These were patients with initially unresectable or difficult to resect tumors (Yardley 2008b). This was an interesting result. We used pegfilgrastim support, and the toxicity was manageable. We also evaluated the patients' SPARC status, and a trend toward a higher pathologic CR rate was recorded among the patients with SPARC-positive disease (Yardley 2008b).

DR LOVE: What benefits do you believe *nab* paclitaxel provides?

DR BURRIS: Not having to use steroids is attractive, particularly for patients with diabetes or other preexisting conditions. The second benefit is being able to administer the drug without fear of a hypersensitivity reaction. They're uncommon, but in a busy clinic such as ours, we see one every few weeks.

DR LOVE: What about the potential for increased efficacy?

DR BURRIS: In the trial comparing it to paclitaxel in metastatic disease, the response rate and time to progression were better (Gradishar 2005). In Bill Gradishar's follow-up randomized Phase II study, weekly *nab* paclitaxel appears to carry a preferential advantage compared to docetaxel (Gradishar 2007; [3.2]). ■

3.2

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

	Nab paclitaxel 300 mg/m² q3wk (n = 76)	*Nab* paclitaxel 100 mg/m² weekly 3 out of 4 weeks (n = 76)	*Nab* paclitaxel 150 mg/m² weekly 3 out of 4 weeks (n = 74)	Docetaxel 100 mg/m² q3wk (n = 74)
Objective response rate by investigator assessment	43%	62%*	70%†	38%
Grade III/IV neutropenia	44%	25%	43%	94%
Grade III/IV peripheral neuropathy	17%	9%	16%	11%
Grade III/IV fatigue	4%	0%	3%	19%

* *p*-value = 0.002 versus docetaxel arm; † *p*-value = 0.003 versus docetaxel arm

SOURCE: Gradishar W et al. *Proc ASCO* 2007;**Abstract 1032**.

SELECT PUBLICATIONS

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

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

Hart LL et al. **A multicenter study of 3 docetaxel regimens with bevacizumab as adjuvant therapy for breast cancer (BC): Preliminary results.** *Proc ASCO* 2008;**Abstract 575**.

Vukelja S et al. **A phase II study of trastuzumab-DM1, a first-in-class HER2 antibody-drug conjugate, in patients with HER2+ metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 33**.

Yardley DA et al. **Preliminary safety results: Addition of bevacizumab to 3 docetaxel regimens as adjuvant therapy for early stage breast cancer.** Poster. San Antonio Breast Cancer Symposium 2008a;**Abstract 4107**.

Yardley DA et al. **Preliminary progression free survival and SPARC tumor correlatives from a phase II neoadjuvant trial of gemcitabine, epirubicin, and *nab* paclitaxel.** Poster. San Antonio Breast Cancer Symposium 2008b;**Abstract 5116**.

INTERVIEW

Mark D Pegram, MD

Dr Pegram is Director for the Translational Research Program at the UM Sylvester Comprehensive Cancer Center's Braman Family Breast Cancer Research Institute in Miami, Florida.

Tracks 1-15

Track 1	Letrozole with or without lapatinib as first-line therapy for postmenopausal women with ER/PR-positive mBC
Track 2	TAnDEM (trastuzumab/anastrozole) and EGF30008 (lapatinib/letrozole) trial results for postmenopausal patients with ER/PR-positive, HER2-positive mBC
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Track 6	Combined anti-HER2 therapy and trastuzumab/lapatinib with or without chemotherapy
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Track 15	FinXX trial results with adjuvant capecitabine/docetaxel → CEF for high-risk early BC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the Phase III randomized trial of lapatinib in combination with letrozole as first-line therapy for postmenopausal women with ER/PR-positive metastatic breast cancer?

DR PEGRAM: The trial was conducted in a patient population not selected for HER2 status, but it was statistically powered to evaluate the subset with

HER2-positive disease as the primary endpoint. In fact, the statistical plan called for the analysis of that subset first, and only if that reached statistical significance would they analyze the intent-to-treat population, which included all the patients with HER2-negative disease (Johnston 2008).

The result was a statistically significant increase in progression-free survival and response rate with lapatinib/letrozole compared to letrozole alone among patients with ER/PR-positive, HER2-positive disease. The overall survival data are immature, with an interesting trend that did not reach statistical significance — a longer data-capture period is required (Johnston 2008; [4.1]).

As the results were positive for patients with HER2-positive disease, they studied the entire cohort of 1,286 subjects, most of whom had ER/PR-positive, HER2-negative disease. In the group with HER2-negative disease, no efficacy signal was noted (Johnston 2008; [4.2]).

Another interesting twist in the statistical plan stipulated evaluating those patients who experienced disease progression within six months of discontinuing adjuvant tamoxifen. In that portion, which by protocol definition was an endocrine-resistant subpopulation of the patients with HER2-negative disease, a statistically nonsignificant increase in progression-free survival was observed with lapatinib/letrozole (Johnston 2008; [4.2]).

This raises the possibility that something of note might be occurring in endocrine-resistant, HER2-negative disease, which would require confirmation in prospective randomized trials. It's not practice changing in this population at this point. But the primary endpoint of the study in HER2-positive disease might be practice changing. It offers an appealing, perhaps therapeutic, option for patients with ER-positive, HER2-positive metastatic disease. Now you can consider targeting HER2 and ER with an oral-only regimen.

4.1

EGF30008: Efficacy of Lapatinib/Letrozole versus Letrozole Alone as First-Line Therapy for Postmenopausal Women with ER/PR-Positive, HER2-Positive Metastatic Breast Cancer

	Lapatinib + letrozole (n = 111)	Letrozole (n = 108)	Hazard/odds ratio (95% CI)	*p*-value
Overall response rate	28%	15%	0.40 (0.20-0.90)	0.021
Clinical benefit rate	48%	29%	0.40 (0.20-0.80)	0.003
Median progression-free survival	8.2 months	3.0 months	0.71 (0.53-0.96)	0.019
Median overall survival	33.3 months	32.3 months	0.74 (0.50-1.10)	0.113

CI = confidence interval

SOURCE: Johnston S et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 46**.

4.2

EGF30008: Efficacy of Lapatinib/Letrozole versus Letrozole Alone as First-Line Therapy for Postmenopausal Women with ER/PR-Positive, HER2-Negative Metastatic Breast Cancer

	Lapatinib + letrozole	Letrozole	Hazard ratio (95% CI)	*p*-value
Median progression-free survival (n = 478, 474)	13.7 months	13.4 months	0.90 (0.77-1.05)	0.188
<6 months since discontinuing adjuvant tamoxifen	8.3 months	3.1 months	0.78 (0.57-1.07)	0.117
≥6 months since discontinuing adjuvant tamoxifen	14.7 months	15.0 months	0.94 (0.79-1.13)	0.522

CI = confidence interval

SOURCE: Johnston S et al. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 46**.

Track 3

DR LOVE: So at this point, how do you think through treatment for a patient with ER-positive, HER2-positive metastatic disease who has not received prior anti-HER2 therapy?

DR PEGRAM: Disease that is naïve to HER2-targeted agents responds well to either trastuzumab or lapatinib. You can present the pros and cons of each to the patients and allow them to participate in the decision. It depends on IV access, cardiac history and so on. Either agent is acceptable.

Another option, based on data presented by Joyce O'Shaughnessy at ASCO 2008, is the combination of lapatinib and trastuzumab (O'Shaughnessy 2008).

I was a coauthor of the recent Phase I trial of that regimen, and we recorded some remarkable anecdotal activity (Storniolo 2008). Joyce O'Shaughnessy's randomized trial clearly shows that the combination is efficacious (O'Shaughnessy 2008).

DR LOVE: What about the use of endocrine therapy alone and postponing the use of anti-HER2 agents as first-line therapy for metastatic disease?

DR PEGRAM: The results in a population with HER2-positive disease are disappointing, but a few percent will achieve long periods of progression-free survival with endocrine manipulation alone.

It's certainly on the table for discussion with patients, and many view it as a viable option. You must follow those patients closely, however, because their disease-progression rates can be extreme in the case of HER2-positive disease.

Track 5

DR LOVE: What were your thoughts on the German trial presented at ASCO 2008 by von Minckwitz?

DR PEGRAM: Whether any benefit exists in the continuation of trastuzumab after the first disease progression has long been debated. The cooperative groups in the United States had attempted to conduct a randomized trial twice in the past.

They failed because of lack of accrual because the bias in the United States was to keep using trastuzumab for patients with HER2-positive disease through multiple lines of disease progression. As a consequence of that bias, it was difficult to convince referring doctors, investigators and patients to randomize to a nontrastuzumab-containing arm.

In Europe this was less problematic, and they accomplished the study, which von Minckwitz reported. Sure enough, continuation of trastuzumab with capecitabine was statistically superior compared to capecitabine and discontinuation of trastuzumab in terms of time to disease progression in the salvage second-line setting (Von Minckwitz 2008; [4.3]). This trial supports the overarching concept of prolonged HER2 perturbation in metastatic disease.

4.3

Phase III Study of Capecitabine (X) versus Capecitabine/Trastuzumab (XH) for Patients with HER2-Positive Metastatic Breast Cancer Progressing During Trastuzumab Therapy

Endpoint	X (n = 78)	XH (n = 78)	*p*-value
Time to progression	5.6mo	8.2mo	0.03
Overall survival	20.4mo	25.5mo	Nonsignificant trend
Response rate	27%	48%	0.01
Clinical benefit rate	54.0%	75.3%	0.007

SOURCE: Von Minckwitz G et al. *Proc ASCO* 2008;**Abstract 1025**.

Tracks 14-15

DR LOVE: What are your thoughts on the Finnish study (Joensuu 2008) that was presented at San Antonio, which is similar to the major, unreported adjuvant clinical trial Joyce O'Shaughnessy and US Oncology are conducting that compares AC → docetaxel to AC → docetaxel/capecitabine?

DR PEGRAM: The Finnish trial was interesting and had a similar basis to Joyce's study, specifically the concept of upregulating thymidine phosphorylase, which is the final step in conversion of the capecitabine prodrug analog in its various metabolites into 5-fluoropyrimidine, intratumorally. Docetaxel can upregulate thymidine phosphorylase, and that was the rationale for combining capecitabine with docetaxel.

The FinXX trial randomly assigned approximately 1,500 patients with early-stage breast cancer to an interesting standard arm: Docetaxel at 80 mg/m^2 for three cycles followed by CEF versus docetaxel at 60 mg/m^2 with capecitabine at 900 mg/m^2 BID followed by CE with capecitabine at 900 mg/m^2 (CEX).

They demonstrated a statistically significant improvement in distant disease-free survival in favor of the capecitabine arm, with a hazard ratio of 0.64 (Joensuu 2008; [4.4]). It's an intriguing observation and supports the concept of integrating capecitabine into the adjuvant setting. On the other hand, the control arm is not one that we use, so I'm uncertain how to incorporate this information into my clinical practice. If another randomized Phase III trial, such as the US Oncology study, showed similar efficacy, then it would probably move capecitabine into the limelight.

DR LOVE: When I spoke to Joyce, we were questioning whether this could become another "TC" regimen with capecitabine/docetaxel as opposed to cyclophosphamide/docetaxel.

DR PEGRAM: Or DCF, with docetaxel, cyclophosphamide and a fluoropyrimidine, which is similar to the regimen used in gastric cancer or head and neck cancer. ■

4.4

FinXX: Efficacy of Adjuvant Docetaxel/Capecitabine (TX) → CEX versus T-CEF in Patients with High-Risk Early Breast Cancer

	T → CEF (n = 745)	TX → CEX (n = 751)	HR	*p*-value
Recurrence-free survival	88.9%	92.5%	0.66	0.020
Distant disease-free survival	89.2%	93.0%	0.64	0.014
Overall survival	94.9%	95.6%	0.66	0.089

SOURCE: Joensuu H et al. San Antonio Breast Cancer Symposium 2008;**Abstract 82**.

SELECT PUBLICATIONS

Joensuu H et al. **Significant improvement in recurrence-free survival (RFS) when capecitabine (X) is integrated into docetaxel (T) 5-FU + epirubicin + cyclophosphamide (CEF) adjuvant therapy for high-risk early breast cancer (BC): Interim analysis of the FinXX-trial.** San Antonio Breast Cancer Symposium 2008;**Abstract 82**.

Johnston S et al. **Lapatinib combined with letrozole vs letrozole alone for front line postmenopausal hormone receptor positive (HR+) metastatic breast cancer (MBC): First results from the EGF30008 trial.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 46**.

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**.

Storniolo AM et al. **Phase I dose escalation and pharmacokinetic study of lapatinib in combination with trastuzumab in patients with advanced ErbB2-positive breast cancer.** *J Clin Oncol* 2008;26(20):3317-23. **Abstract**

Von Minckwitz G et al. **Capecitabine vs capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05).** *Proc ASCO* 2008;**Abstract 1025**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Results of the TransATAC analysis on using the Onco*type* DX Recurrence Score to predict the likelihood of distant metastatic disease through nine years of follow-up were similar for tamoxifen and anastrozole.**
   a. True
   b. False
2. **In the meta-analyses of the trials evaluating the role of adjuvant aromatase inhibitors, aromatase inhibitors in both up-front and switching strategies significantly reduced the risk of relapse.**
   a. True
   b. False
3. **In BIG 1-98, which of the following treatment strategies had the highest five-year breast cancer recurrence rate?**
   a. Letrozole alone
   b. Letrozole followed by tamoxifen
   c. Tamoxifen followed by letrozole
4. **In an analysis of endocrine symptoms reported at the first follow-up visit in the ATAC trial, women who experienced _____ had a lower breast cancer recurrence rate.**
   a. Vasomotor symptoms
   b. Joint symptoms
   c. Vaginal symptoms
   d. Both a and b
   e. All of the above
5. **T-DM1 is a novel agent that combines a maytansine derivative with _____.**
   a. Docetaxel
   b. Trastuzumab
   c. Bevacizumab
   d. None of the above
6. **Patients with HER2-positive metastatic disease previously treated with HER2-directed therapies had a response rate of approximately _____ percent with T-DM1.**
   a. Five
   b. 10
   c. 30
   d. 60
7. **Which of the following is a potential advantage with *nab* paclitaxel?**
   a. Lack of steroid premedication
   b. No hypersensitivity reactions
   c. Both a and b
   d. None of the above
8. **In a Phase III randomized trial for women with hormone receptor-positive metastatic breast cancer, the combination of lapatinib/letrozole demonstrated a statistically significant increase in progression-free survival compared to letrozole alone for those with _____ disease.**
   a. HER2-positive
   b. HER2-negative
   c. Both a and b
   d. None of the above
9. **In a Phase III randomized trial for women with HER2-positive metastatic breast cancer that progressed during treatment with trastuzumab, capecitabine/trastuzumab demonstrated a statistically significant increase in time to disease progression compared to capecitabine alone.**
   a. True
   b. False
10. **In the FinXX trial, patients with high-risk early breast cancer who received TX → CEX had statistically significant improvements in _____ compared to those treated with T → CEF.**
    a. Recurrence-free survival
    b. Distant disease-free survival
    c. Overall survival
    d. Both a and b
    e. a, b and c

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 2009

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 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- **TransATAC: Prediction of distant recurrence with Onco*type* DX for postmenopausal patients with node-negative/node-positive, ER/PR-positive early breast cancer (BC)** 4 3 2 1
- **Meta-analysis of up-front aromatase inhibitors versus tamoxifen and tamoxifen → aromatase inhibitors versus tamoxifen for postmenopausal patients with ER/PR-positive early BC** 4 3 2 1
- **BIG 1-98: Updated analysis of letrozole versus tamoxifen and sequencing strategies** 4 3 2 1
- **Efficacy and side effects of trastuzumab-DM1 in patients with metastatic BC (mBC) previously treated with HER2-directed therapy** 4 3 2 1
- **Phase III trial results of lapatinib/letrozole as first-line therapy for postmenopausal patients with ER/PR-positive mBC** 4 3 2 1
- **Capecitabine/trastuzumab versus capecitabine alone for patients with HER2-positive mBC progressing during trastuzumab therapy** 4 3 2 1

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- **TransATAC: Prediction of distant recurrence with Onco*type* DX for postmenopausal patients with node-negative/node-positive, ER/PR-positive early breast cancer (BC)** 4 3 2 1
- **Meta-analysis of up-front aromatase inhibitors versus tamoxifen and tamoxifen → aromatase inhibitors versus tamoxifen for postmenopausal patients with ER/PR-positive early BC** 4 3 2 1
- **BIG 1-98: Updated analysis of letrozole versus tamoxifen and sequencing strategies** 4 3 2 1
- **Efficacy and side effects of trastuzumab-DM1 in patients with metastatic BC (mBC) previously treated with HER2-directed therapy** 4 3 2 1
- **Phase III trial results of lapatinib/letrozole as first-line therapy for postmenopausal patients with ER/PR-positive mBC** 4 3 2 1
- **Capecitabine/trastuzumab versus capecitabine alone for patients with HER2-positive mBC progressing during trastuzumab therapy** 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 genomic assays into the clinical management of hormone receptor (HR)-positive, node-negative or node-positive early breast cancer . . . . . 4 3 2 1 N/M N/A
- Apply the results of recent clinical trials when recommending aromatase inhibitors and/or tamoxifen as primary therapy for postmenopausal women with HR-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based algorithm for the treatment of localized or metastatic, HER2-positive breast cancer. . . . . 4 3 2 1 N/M N/A
- Demonstrate knowledge of ongoing investigational approaches to the management of triple-negative or HER2-positive breast cancer. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens. . . . . 4 3 2 1 N/M N/A
- Consider the unique benefits and risks associated with novel epothilones and taxanes when selecting and sequencing chemotherapeutic regimens. . . . . 4 3 2 1 N/M N/A
- Recall emerging clinical trial results with bevacizumab for metastatic breast cancer, and assess their application to current patient care. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials. . . . . 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 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Harold J Burstein, MD, PhD	4 3 2 1	4 3 2 1
Jack Cuzick, PhD	4 3 2 1	4 3 2 1
Howard A Burris III, MD	4 3 2 1	4 3 2 1
Mark D Pegram, 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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