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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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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 with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Counsel patients about the impact of menopausal hormone replacement therapy (HRT) on breast cancer incidence and risk.
- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care.
- Apply the results of recent clinical trials when recommending aromatase inhibitors and/or tamoxifen as primary therapy for postmenopausal women with ER-positive early breast cancer.
- Review the long-term risk of recurrence for patients with ER-positive early breast cancer, and consider on- and off-protocol extended adjuvant endocrine therapy for appropriately selected patients.
- Develop an approach to monitor and facilitate patient adherence to orally administered antineoplastic therapies.
- Formulate an evidence-based algorithm for the identification and treatment of localized or metastatic HER2-positive breast cancer.
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens.
- Recount the role of VEGF in breast cancer pathogenesis, and discern how genotypic variation may affect the efficacy and toxicity of targeted anti-angiogenic therapy.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Hyman B Muss, MD

Dr Muss is Professor of Medicine at the University of Vermont and Vermont Cancer Center Hematology Oncology Unit in Burlington, Vermont.

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Select Excerpts from the Interview

Case 1

A 59-year-old woman was treated nine years ago with AC → paclitaxel/trastuzumab on CALGB-49909 for a 2.7-cm, ER-positive, PR-positive, HER2-positive, poorly differentiated infiltrating ductal carcinoma and one out of 14 positive nodes. After 11 weeks of therapy, she developed trastuzumab-related congestive heart failure (CHF).

Tracks 2, 4-6

DR LOVE: What happened when this patient developed CHF?

DR MUSS: She presented to the emergency room with shortness of breath in essentially pulmonary edema. They treated her with furosemide, and she fared well. I subsequently sent her to a cardiologist. She was prescribed an ACE inhibitor and a beta-blocker and slowly recovered. The last time we evaluated her, which was nine years after receiving trastuzumab, she was fine. It took one to two years for her ejection fraction to normalize, and it remains normal today.

DR LOVE: What was your approach to this patient's endocrine therapy?

DR MUSS: She received approximately two and a half years of tamoxifen and was switched to an aromatase inhibitor for another five years after the IES data were reported. So she was eligible for the CAN-NCIC-MA17R replacement trial — the follow-up to the trial for patients on five years of adjuvant tamoxifen who were randomly assigned to five years of letrozole or placebo. In this initial part of the trial, extended treatment with letrozole led to a substantial improvement in relapse-free survival. For patients with node-positive disease, letrozole was also significantly better in terms of overall survival (Goss 2005).

Among patients with ER-positive disease, most relapses occur after five years, which is a concept that's slowly filtering through the advocacy community. Many oncologists still feel that a major milestone is reached at five years, when in truth the risk period extends 10 to 20 years or perhaps the patient's entire life. After eight years of adjuvant endocrine therapy, this patient didn't want to enroll on MA17R, but we kept her on exemestane.

DR LOVE: If this patient presented today with one positive node, which anti-HER2 regimen would you recommend?

DR MUSS: I'd probably use the same one again. I have used docetaxel/carboplatin/trastuzumab (TCH) for some patients. We have excellent data for TCH, but I realize they haven't been published or formally peer reviewed (Slamon 2006). I am still a little reticent in abandoning anthracyclines altogether, but I am using more TCH, especially for older patients or those with any type of comorbidity, such as hypertension.

Track 7

DR LOVE: Can you comment on the results of the NSABP-B-30 trial presented by Sandy Swain at the 2008 San Antonio Breast Cancer Symposium?

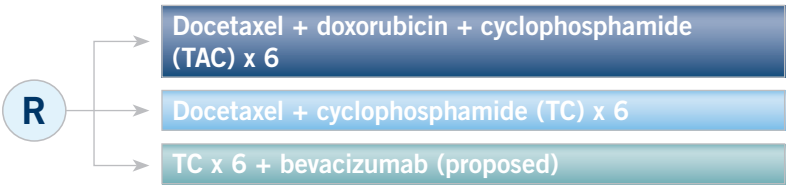
DR MUSS: NSABP-B-30 compared four cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) to four cycles of AC followed by four cycles of docetaxel versus four cycles of doxorubicin/docetaxel. Investigators found that

AC → docetaxel was the superior regimen. In that trial, the results could have been related to the duration of therapy because they compared eight cycles of chemotherapy to four cycles of chemotherapy (Swain 2008). So perhaps four cycles are not enough. Physicians frequently ask me about using six cycles of docetaxel/cyclophosphamide (TC). To answer this question, I believe we need to wait for the TIC-TAC trial, which is evaluating six cycles of TC versus six cycles of TAC. The trial designers are working on developing the study into "TIC-TAC-TOE," with a third arm of TC/bevacizumab (1.1).

1.1

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

Protocol IDs: NCT00493870, US Oncology 06090, 11271
Target Accrual: 3,900



Select Eligibility Criteria

- FISH-confirmed HER2-negative breast cancer
- Normal cardiac function
- T1-3N1-3M0; T2-3N0M0; T1N0M0 if ER-negative and PR-negative

SOURCES: NCI Physician Data Query, May 2009; **www.clinicaltrials.gov**; Jones SE. *J Clin Oncol* 2007;25(27):4327; Wolmark N. Personal communication. NSABP Group Meeting, June 2008.

Case 2

A 69-year-old woman presented with bone metastases, back pain and an elevated CA27.29 level 20 years after resection of a right breast cancer. At the time of her initial diagnosis, she did not receive adjuvant therapy, and no pathologic information from her original disease is available.

The metastatic disease was empirically treated with tamoxifen, which improved her bone pain and tumor markers for three years. Subsequently, when her liver became palpable and liver function tests were elevated, she was switched to letrozole with zoledronic acid and treated for two years before disease progression occurred and a decision was made to initiate chemotherapy.

Tracks 12-14

DR LOVE: Which chemotherapy did you consider for this patient?

DR MUSS: This patient is a little uncomfortable and wary of treatment. Otherwise, I would have considered using paclitaxel/bevacizumab at that point. For a patient like this with a palpable liver and multiple metastases, the progression-free survival is about one year with paclitaxel/bevacizumab (Miller 2007; [1.2]). With capecitabine, the progression-free survival is about six months.

We discussed the options and elected to use capecitabine. Because this patient was fearful of chemotherapy, I started with a low dose. I utilized the Memorial Sloan-Kettering schedule of one week on and one week off (Traina 2008).

She had a miraculous response. Her CA27.29 level and her liver size decreased. She has been receiving capecitabine for two years, but I believe her disease is now progressing. I'm not aware of any extensive data with paclitaxel/bevacizumab as second-line therapy, but I would be tempted to try it for a patient like this. ■

1.2

ECOG-E2100: A Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy for Patients with Locally Recurrent or Metastatic Breast Cancer

Efficacy data (N = 673)	Paclitaxel + bevacizumab	Paclitaxel alone	Hazard ratio	*p*-value
Objective response rate				
All patients	36.9%	21.2%	NR	<0.001
Patients with measurable disease at baseline	49.2%	25.2%	NR	<0.001
Median progression-free survival	11.8 months	5.9 months	0.60	<0.001
Median overall survival	26.7 months	25.2 months	0.88	0.16

NR = not reported

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

SELECT PUBLICATIONS

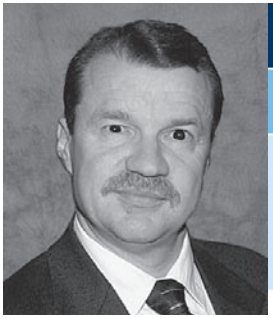
Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71.

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

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

Swain SM et al. **NSABP B-30: Definitive analysis of patient outcome from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 75**.

Traina TA et al. **Phase I study of a novel capecitabine schedule based on the Norton-Simon mathematical model in patients with metastatic breast cancer.** *J Clin Oncol* 2008;26(11):1797-802.



INTERVIEW

Michael F Press, MD, PhD

Dr Press is Harold E Lee Chair in Cancer Research, Director of the Women's Cancer Program and Professor in the Department of Pathology at the USC/Norris Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-12

Select Excerpts from the Interview

Track 2

DR LOVE: You participated in the joint ASCO/American College of Pathologists (CAP) panel that recommended guidelines for HER2 testing in breast cancer (Wolff 2007). Would you outline some of the key recommendations from that panel and discuss your recent publication in the *Journal of Clinical Oncology* regarding points of dissension with some of the guideline conclusions (Sauter 2009)?

DR PRESS: The panel recommended the use of either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) to determine HER2 status. IHC 2+ results should be reflexively sent for FISH testing. IHC 0/1+ results are considered negative and IHC 3+ are considered HER2-positive, assuming the laboratory shows 95% concordance with another validated test for positive and negative assay values.

Between two and as many as eight percent of patients with IHC 0 results for HER2 have amplification by FISH. We would recommend FISH testing for that IHC 0 group (Sauter 2009; [2.1]), and we would make the same argument for the IHC 1+ group because the rate of FISH amplification in that group is even higher.

I would use the reverse argument for the IHC 3+ group. Our CIRG laboratory screen for entry to one of the adjuvant clinical trials found that only 78 percent of cases called 3+ by IHC were FISH amplified. Wide variability can occur depending on how the IHC samples are processed.

Even if a laboratory had demonstrated 95 percent concordance for IHC 3+ results, one out of 20 women would be falsely labeled as having HER2-positive disease and would receive trastuzumab or lapatinib when they probably should not because they have little expectation of responding to these agents. Therefore, we would recommend FISH testing for the IHC 3+ group also (Sauter 2009; [2.1]).

2.1

HER2 Status by FISH as the Primary Testing Modality for Clinical Decision-Making

"[HER2] protein is not consistently analyzed in formalin-fixed tissues as a result of variability in fixation methods and times and the impact of fixation on HER-2 protein antigenicity. Conversely, gene amplification and FISH are significantly less dependent on tissue fixation methods, making this assay more reproducible between central and peripheral laboratories than IHC.

Moreover, review of the existing data demonstrate that FISH is more strongly correlated with responsiveness to either trastuzumab or lapatinib treatment...we suggest FISH as the primary HER-2 testing modality for women with breast cancer who are candidates for HER-2-targeted therapies."

SOURCE: Sauter G et al. *J Clin Oncol* 2009;27(8):1323-33.

Track 8

DR LOVE: What are your thoughts on the data presented at San Antonio recently evaluating lapatinib in combination with letrozole for patients with ER-positive, HER2-positive metastatic breast cancer?

DR PRESS: These results suggest cross talk between the growth factor and steroid receptor pathways so that when HER2 is activated through amplifi-

cation and overexpression, it activates the estrogen receptor pathway, either directly or indirectly. The data suggest that the best therapy for those patients would be to receive a therapeutic agent that interacts with and interferes with both the HER2 pathway and the estrogen receptor pathway (Johnston 2008; [2.2]). ■

2.2

EGF30008: Efficacy of Lapatinib/Letrozole versus Letrozole Alone as First-Line Therapy for Postmenopausal Women with ER-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. San Antonio Breast Cancer Symposium 2008;**Abstract 46**.

SELECT PUBLICATIONS

Carlson RW et al. **HER2 testing in breast cancer: NCCN Task Force report and recommendations.** *J Natl Compr Canc Netw* 2006;4(Suppl 3):1-22.

Di Leo A et al. **Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer.** *J Clin Oncol* 2008;26(34):5544-52.

Emlet DR et al. **Response to trastuzumab, erlotinib, and bevacizumab, alone and in combination, is correlated with the level of human epidermal growth factor receptor-2 expression in human breast cancer cell lines.** *Mol Cancer Ther* 2007;6(10):2664-74.

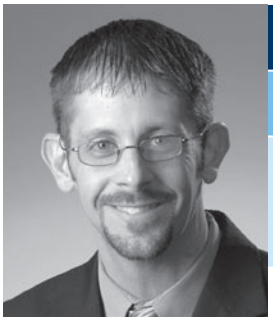
Gomez HL et al. **Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer.** *J Clin Oncol* 2008;26(18):2999-3005.

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.** San Antonio Breast Cancer Symposium 2008;**Abstract 46**.

Sauter G et al. **Guidelines for human epidermal growth factor receptor 2 testing: Biologic and methodologic considerations.** *J Clin Oncol* 2009;27(8):1323-33.

Wen XF et al. **HER2 signaling modulates the equilibrium between pro- and antiangiogenic factors via distinct pathways: Implications for HER2-targeted antibody therapy.** *Oncogene* 2006;25(52):6986-96.

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.** *J Clin Oncol* 2007;25(1):118-45.



INTERVIEW

Bryan P Schneider, MD

Dr Schneider is Assistant Professor in the Department of Medicine at the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: Would you review your group's analysis of ECOG-E2100, which compared paclitaxel/bevacizumab to paclitaxel alone as first-line therapy for metastatic breast cancer?

DR SCHNEIDER: We evaluated the association between VEGF genotype and the efficacy and toxicity of bevacizumab. With regard to efficacy, two VEGF polymorphisms predicted a highly significant prolongation in median overall survival. In fact, one of these polymorphisms suggested almost a two-year incremental benefit in overall survival compared to the other genotypes for patients who received bevacizumab (Schneider 2008; [3.1]).

3.1

ECOG-E2100: Relationship between VEGF Genotype and Overall Survival in Patients with Metastatic Breast Cancer Receiving Paclitaxel/Bevacizumab

VEGF genotype	Median overall survival
VEGF-2578 AA	37.0 months
VEGF-2578 CA	24.4 months
VEGF-2578 CC	22.2 months
VEGF-1154 AA	46.5 months
VEGF-1154 GA	29.8 months
VEGF-1154 GG	22.3 months

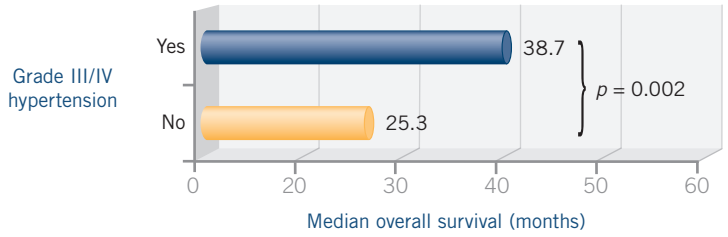
SOURCE: Schneider BP et al; ECOG 2100. *J Clin Oncol* 2008;26(28):4672-8.

Importantly, the same VEGF-genotype differences in the control arm yielded no differences in outcome, suggesting that these polymorphisms aren't prognostic markers but are rather predictive markers for bevacizumab (Schneider 2008). We also evaluated whether these patients developed hypertension. Two separate VEGF polymorphisms predicted significant protection against Grade III/IV hypertension. One had a zero percent incidence of Grade III/IV hypertension, and the other had about an eight percent incidence. This was in contradistinction to an approximately 20 percent incidence for the other genotypes (Schneider 2008).

Interestingly, those patients who had VEGF polymorphisms associated with a good outcome did not appear to be protected from hypertension. Based on that finding, we went back to ECOG-E2100 and analyzed for a correlation between high blood pressure and outcome. We found that those patients with Grade III/IV hypertension had a significant prolongation in overall survival (Schneider 2008; [3.2]).

3.2

ECOG-E2100: Relationship between Hypertension and Overall Survival in Patients with Metastatic Breast Cancer Receiving Paclitaxel/Bevacizumab



SOURCE: Schneider BP et al; ECOG 2100. *J Clin Oncol* 2008;26(28):4672-8.

Case 1

A 44-year-old premenopausal woman was treated three years ago with four cycles of adjuvant AC followed by radiation therapy and tamoxifen for a 2.6-cm, ER-positive, HER2-negative, node-negative breast tumor. She experienced chemotherapy-induced amenorrhea, and she was subsequently treated with an aromatase inhibitor for locally recurrent disease and asymptomatic pulmonary nodules. After about one month, she experienced rapid disease progression with two highly vascular and protruding nodules on her breast and extensive lymphadenopathy.

Track 10

DR LOVE: What were your thoughts about treating this patient at that point?

DR SCHNEIDER: Fortunately, she had not received a taxane. Therefore, this became a "no-brainer," and we started her on weekly paclitaxel with bevacizumab according to the schedule in ECOG-E2100 (Miller 2007; [1.2, page 6]).

I saw her again roughly four weeks later. Though I did not intend to restage her disease at that point, I wanted to make sure that she was tolerating the treatment well and that the disease wasn't continuing to progress. The bulky lymphadenopathy had completely resolved. Her breast still had a firm, palpable area under the skin, but the two large vascular nodules had almost completely normalized. She has now received three cycles of therapy, and she's experiencing minimal neuropathies in her fingertips and toes. Her performance status is excellent. After two cycles, some interval decrease was evident in her lung disease. So we're going to continue.

I'll watch her neuropathies carefully. At some point, if those continue to become worse, I will probably stop paclitaxel and continue bevacizumab. She has not developed much hypertension, and we've not had to introduce antihypertensive medication.

This case is anecdotal, but the vascularity of her lesions suggested that she would benefit from anti-angiogenic therapy. However, tumors that grow this quickly often will respond to standard cytotoxic agents, and she had never received a taxane previously. It would have been reasonable to consider a single-agent taxane.

Case 2

A 59-year-old violinist had a lumpectomy for a 2.7-cm, Grade II, ER-positive, HER2-negative invasive ductal carcinoma. A 0.3-mm focus of disease in one lymph node was found on sentinel lymph node biopsy. She refused complete axillary dissection because of a fear of lymphedema. She was also reluctant to receive adjuvant chemotherapy because of potential neuropathy.

Track 12

DR LOVE: Did you discuss with this patient recent data evaluating the Onco*type* DX assay for patients with node-positive disease?

DR SCHNEIDER: Yes, I informed her that SWOG-8814 demonstrated that patients with node-positive disease and low Onco*type* DX Recurrence Scores don't derive much benefit from adjuvant chemotherapy (Albain 2007) but that a subgroup of patients with ER-positive disease derives benefit from the addition of chemotherapy. We discussed Onco*type* DX and I convinced her that if she was in the high-risk category, we would pursue a nontaxane-based chemotherapy regimen. She had an intermediate-risk Recurrence Score, and she elected to receive only radiation therapy and hormonal therapy.

Case 3

A 41-year-old premenopausal woman had a lumpectomy for a 0.7-cm, Grade III, ER-negative, HER2-positive, node-negative infiltrating ductal carcinoma.

Tracks 13-14

DR LOVE: Did you recommend adjuvant chemotherapy with trastuzumab for this patient?

DR SCHNEIDER: I did, and we had a long discussion, during which I acknowledged that we don't know the risk of relapse for this group of women with subcentimeter HER2-positive tumors. She would not have been eligible for any of the reported large adjuvant trastuzumab trials, making this a tough discussion. When you're considering trastuzumab for a young, healthy patient, the risk of heart damage exists. I opted not to include an anthracycline because then we would be pushing the risk of cardiac toxicity in a patient who may be facing minimal benefit. She enrolled in Dana-Farber's multicenter trial and is receiving 12 weeks of weekly paclitaxel with trastuzumab. ■

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**.

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.** San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

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

Schneider BP et al; ECOG 2100. **Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100.** *J Clin Oncol* 2008;26(28):4672-8.

INTERVIEW

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is Professor of Medicine at the David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.

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Track 3 Results of the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial for postmenopausal patients with ER-positive BC

Track 4 Perspective on the ATAC retrospective analysis of treatment-emergent endocrine symptoms and risk of BC recurrence

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Track 8 Increased risk of BC recurrence in patients treated with tibolone for climacteric symptoms

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4 Clinical use of adjuvant bisphosphonates as anticancer therapy

5 Time from promising clinical trial results to availability of treatment in clinical practice

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What's the bottom line on the BIG 1-98 data presented at the San Antonio Breast Cancer Symposium in 2008, evaluating letrozole versus tamoxifen for five years, versus two switching strategies?

DR CHLEBOWSKI: I think the most important finding was a trend toward improvement in overall survival favoring letrozole for five years versus tamoxifen, with a hazard ratio of 0.87 and a *p*-value of 0.08 in the intent-to-treat analysis (Mouridsen 2008; [4.1]).

DR LOVE: What about the switch at two to three years from tamoxifen to letrozole or from letrozole to tamoxifen?

DR CHLEBOWSKI: It was a little surprising that both the switching approaches were compared to five years of up-front letrozole (Mouridsen 2008; [4.2]).

A couple of issues are emerging. First, it's apparently difficult to keep patients on tamoxifen for five years, even in a clinical trial setting. Second, one of the conclusions at the presentation was the suggestion that, based on the data showing not much difference, it is reasonable to consider a switch to tamoxifen after two to three years of an AI.

I believe that's premature because the switching data were from a median follow-up of 71 months. My threshold for stopping an aromatase inhibitor to switch to tamoxifen would be higher because we don't know what happens in that five- to 10-year period.

Until these data were presented at San Antonio, we had no reason to switch to tamoxifen. Some may consider that now, but I don't believe a strong rationale exists to consider it. If a patient develops limiting arthralgias, then it might be a reasonable approach.

4.1

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

	Events			
	Letrozole (n = 2,463)	Tamoxifen (n = 2,459)	Hazard ratio* (95% CI)	*p*-value
Disease-free survival				
ITT population	509	565	0.88 (0.78-0.99)	0.03
Censored			0.84 (0.74-0.95)	
Overall survival				
ITT population	303	343	0.87 (0.75-1.02)	0.08
Censored			0.81 (0.69-0.94)	
Time to distance recurrence				
ITT population	257	298	0.85 (0.72-1.00)	0.05
Censored			0.81 (0.68-0.96)	

* Hazard ratio < 1.0 favors letrozole

"With this long term follow-up, adverse events for Let and Tam are consistent with the known safety profile of both agents. A protocol-specified update of the previously-reported comparison of Let x 5 vs Tam x 5 (ie, the monotherapy arms, including patients in both the 2-arm and 4-arm options; N = 4,922) suggests improved survival for patients treated with Let (HR = 0.87, 95% CI = 0.75-1.02, $p = 0.08$, 76 months median follow-up)."

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

4.2

BIG 1-98: Letrozole Monotherapy or in Sequence with Tamoxifen as Adjuvant Therapy for Postmenopausal Women with ER-Positive Early Breast Cancer

	Letrozole monotherapy* (n = 1,546)	Letrozole → tamoxifen† (n = 1,540)	Tamoxifen → letrozole† (n = 1,548)
Five-year disease-free survival	87.9%	87.6%	86.2%
Hazard ratio (99% CI) Sequence versus letrozole	—	0.96 (0.76-1.21)	1.05 (0.84-1.32)

* Median follow-up: 76 months; † Median follow-up: 71 months; CI = confidence interval

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

Tracks 4-5

DR LOVE: What are your thoughts about the ATAC analysis that Jack Cuzick published in *Lancet Oncology* (Cuzick 2008), demonstrating a correlation between treatment-emergent endocrine symptoms and outcome?

DR CHLEBOWSKI: I found those data very interesting. The development of arthralgias or hot flashes seems to me to be a downstream signal about how the host interacts with the agent. If patients have hot flashes and arthralgias, that suggests something about the interaction that might be more important than insight gained from biopsying the tumor.

Does it mean that greater suppression of estradiol levels leads to the hot flashes, or might the significant factor be the way your body responds to the estradiol? It is fair to say that the drug is working better. You could say to patients, "You're fortunate because you have arthralgias and hot flashes," as we do with the rash in lung cancer with EGFR TKIs.

Track 12

DR LOVE: Can you comment on the study of high-dose fulvestrant versus anastrozole for postmenopausal patients with ER-positive mBC that was presented at San Antonio (Ellis 2008; [4.3])?

DR CHLEBOWSKI: That's an "up-and-comer." Matt Ellis presented the results of the FIRST trial, a Phase II randomized study for approximately 200 patients with previously untreated mBC, who were randomly assigned to anastrozole versus high-dose fulvestrant — 500 milligrams on days one, 14 and 28 and 500 milligrams every 28 days thereafter. Compared to the regular dosing, this was three times as much fulvestrant in the first 28 days. The time to disease progression was 12 months with anastrozole, which is to be expected in this setting, but it was not yet reached at 21 months with fulvestrant. Interestingly,

no difference was apparent in the side effects between patients treated with anastrozole and those receiving high-dose fulvestrant.

The greater than 21-month time to disease progression with high-dose fulvestrant is a substantial benefit to patients who will be receiving the same therapy for two years after being diagnosed and beginning treatment for metastatic breast cancer. ■

4.3

FIRST: A Phase II Randomized Study of High-Dose (HD) Fulvestrant* versus Anastrozole for Postmenopausal Patients with Previously Untreated ER-Positive Metastatic Breast Cancer

Efficacy	HD fulvestrant (n = 102)	Anastrozole (n = 103)
Overall response rate (ORR)	31.4%	32.1%
Stable disease (SD) ≥ 24 weeks	41.2%	35.0%
Clinical benefit (ORR + SD)	72.5%	67.0%
Time to progression	Not reached	12.5 months
	HR = 0.63, $p < 0.05$	
Duration of response	Not reached	14.2 months

* HD fulvestrant = 500 mg days 1, 14 and 28 and 500 mg every 28 days thereafter

The incidence of injection-site pain with fulvestrant HD (5.9%) was similar to that previously seen with fulvestrant AD (4.6%), despite patients receiving twice as many injections per month on the HD regimen.

The ongoing Phase III CONFIRM (COmparisoN of Fulvestrant In Recurrent or Metastatic breast cancer) trial, which compares high-dose to standard-dose fulvestrant, will provide further clarification of the role of fulvestrant HD in the treatment of advanced breast cancer.

SOURCE: Ellis MJ et al. San Antonio Breast Cancer Symposium 2008;**Abstract 6126**.

SELECT PUBLICATIONS

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.

Ellis MJ et al. **A comparison of high-dose (HD, 500 mg) fulvestrant vs anastrozole (1 mg) as first-line treatments for advanced breast cancer: Results from FIRST.** San Antonio Breast Cancer Symposium 2008;**Abstract 6126**.

Koeberle D, Thuerlimann B. **Letrozole as upfront endocrine therapy for postmenopausal women with hormone-sensitive breast cancer: BIG 1-98.** *Breast Cancer Res Treat* 2007;105 (Suppl 1):55-66.

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.** San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

Robertson JF. **Fulvestrant (Faslodex) — How to make a good drug better.** *Oncologist* 2007;12(7):774-84.

Wardley AM. **Understanding the BIG results: Insights from the BIG 1-98 trial analyses.** *Adv Ther* 2008;25(12):1257-75.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **CAN-NCIC-MA17R randomly assigns women who have already received adjuvant endocrine therapy, including an aromatase inhibitor, to another five years of an aromatase inhibitor or to placebo.**
   a. True
   b. False

2. **In NSABP-B-30, which of the following adjuvant chemotherapy regimens was found to be superior in terms of disease-free survival?**
   a. TAC x 4
   b. AC x 4 → docetaxel x 4
   c. TC x 4
   d. TCH x 4
   e. None of the above

3. **In ECOG-E2100, the median progression-free survival associated with paclitaxel/bevacizumab as first-line therapy for metastatic breast cancer was approximately _____.**
   a. Three months
   b. Six months
   c. 12 months
   d. None of the above

4. **In a randomized trial, the combination of lapatinib/letrozole resulted in nearly a doubling of the overall response rate and nearly a tripling of progression-free survival compared to letrozole alone as first-line therapy for patients with ER-positive, HER2-positive metastatic breast cancer.**
   a. True
   b. False

5. **The BETH trial will evaluate adjuvant chemotherapy/trastuzumab with or without _____ for patients with HER2-positive breast cancer.**
   a. Lapatinib
   b. Bevacizumab
   c. T-DM1
   d. Pertuzumab

6. **In an analysis of ECOG-E2100, certain VEGF genotypes predicted for _____ among patients receiving paclitaxel/bevacizumab as first-line therapy for metastatic breast cancer.**
   a. A prolongation in median overall survival
   b. The development of Grade III/IV hypertension
   c. Both a and b
   d. None of the above

7. **In an analysis of ECOG-E2100, patients treated with paclitaxel/bevacizumab who developed Grade III/IV hypertension had a _____ median overall survival compared to those who did not develop Grade III/IV hypertension.**
   a. Longer
   b. Shorter
   c. Comparable

8. **In the BIG 1-98 study, a trend was observed for improvement in overall survival for patients with ER-positive breast cancer treated with up-front adjuvant letrozole compared to tamoxifen.**
   a. True
   b. False

9. **In the FIRST trial, what was the time to disease progression for patients with ER-positive advanced breast cancer treated with first-line anastrozole versus high-dose fulvestrant at 21 months?**
   a. 8.2 months versus 12.5 months
   b. 13.3 months versus 12.5 months
   c. 12.5 months versus not yet reached

10. **US Oncology and the NSABP will collaborate in an adjuvant trial to evaluate docetaxel/cyclophosphamide (TC) versus _____.**
    a. Dose-dense AC followed by paclitaxel
    b. TAC
    c. TC and bevacizumab
    d. Both a and b
    e. Both b and c

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 3, 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

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
BIG 1-98: Adjuvant letrozole, tamoxifen or the sequence	4 3 2 1	4 3 2 1
Selection and reliability of HER2 testing	4 3 2 1	4 3 2 1
A novel schedule of capecitabine for metastatic BC (mBC)	4 3 2 1	4 3 2 1
Association of VEGF genotype and hypertension with outcome with bevacizumab in ECOG-E2100	4 3 2 1	4 3 2 1
Letrozole with or without lapatinib for postmenopausal patients with ER-positive, HER2-positive mBC	4 3 2 1	4 3 2 1
FIRST: High-dose fulvestrant versus anastrozole as first-line therapy for mBC	4 3 2 1	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 learning objectives (LO) by circling the appropriate selection:

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

As a result of this activity, I will be able to:

- Counsel patients about the impact of menopausal hormone replacement therapy (HRT) on breast cancer incidence and risk. . . . . 4 3 2 1 N/M N/A
- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care. . . . . 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 ER-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Review the long-term risk of recurrence for patients with ER-positive early breast cancer, and consider on- and off-protocol extended adjuvant endocrine therapy for appropriately selected patients. . . . . 4 3 2 1 N/M N/A
- Develop an approach to monitor and facilitate patient adherence to orally administered antineoplastic therapies. . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based algorithm for the identification and treatment of localized or metastatic 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
- Recount the role of VEGF in breast cancer pathogenesis, and discern how genotypic variation may affect the efficacy and toxicity of targeted anti-angiogenic therapy. . . . . 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

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 faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Hyman B Muss, MD	4 3 2 1	4 3 2 1
Michael F Press, MD, PhD	4 3 2 1	4 3 2 1
Bryan P Schneider, MD	4 3 2 1	4 3 2 1
Rowan T Chlebowski, MD, PhD	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 faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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

Signature: ..... Date: .....

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BCU309

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Breast Cancer® UPDATE

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