

Breast Cancer[®]

U P D A T E

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

EDITOR

Neil Love, MD

INTERVIEWS

Dennis J Slamon, MD, PhD

Clifford Hudis, MD

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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

- Recall the prevalence of vitamin D deficiency among patients with breast cancer, and consider its effect on the risk of disease recurrence.
- Recognize the effects of advanced age, poor performance status and obesity on the benefits and risks of adjuvant chemotherapy for breast cancer.
- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care.
- Develop an approach to monitor and facilitate patient adherence to orally administered antineoplastic therapies.
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens.
- Communicate the efficacy and safety of various chemotherapy regimens in combination with bevacizumab to patients with HER2-negative metastatic breast cancer that may be eligible for anti-angiogenic treatment.
- Use actual body weight in place of ideal body weight to establish appropriate adjuvant treatment doses for patients who are obese.
- Delineate novel classes of molecular-targeted agents currently under investigation for the treatment of breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEWS

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INTERVIEW

Dennis J Slamon, MD, PhD

Dr Slamon is Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical/Translational Research at the David Geffen School of Medicine at UCLA's Jonsson Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-16

- Track 1** BETH and ALTO second-generation adjuvant clinical trials in HER2-positive early breast cancer (BC)
- Track 2** US Oncology-NSABP TC-TAC-TC/bevacizumab adjuvant trial in HER2-negative, node-positive or high-risk node-negative early BC
- Track 3** VEGF upregulation in HER2-positive BC
- Track 4** Combined blockade of the HER2 pathway with trastuzumab/lapatinib
- Track 5** Trastuzumab-DM1 (T-DM1), a first-in-class HER2 antibody-drug conjugate
- Track 6** ALTO: Adjuvant lapatinib or trastuzumab alone, in sequence or in combination for HER2-positive early BC
- Track 7** Long-term follow-up of a patient with HER2-positive early BC treated with adjuvant TCH in 2002
- Track 8** **Case discussion:** A 57-year-old woman with a 2.1-cm, Grade III, node-negative, ER-poor, PR-negative, HER2-positive, TOPO II-normal infiltrating ductal carcinoma (IDC) who was scheduled to receive AC → TH on BCIRG 006
- Track 9** Anthracycline-associated cardiotoxicity
- Track 10** TEACH: Adjuvant lapatinib versus placebo for patients with HER2-positive BC who completed (neo)adjuvant chemotherapy
- Track 11** Timing of recurrence in HER2-positive BC
- Track 12** Role of anthracyclines in the treatment of HER2-positive early BC
- Track 13** Incidence of HER2-positive metastatic BC (mBC) in the era of trastuzumab
- Track 14** **Case discussion:** A 61-year-old woman with a high-grade, ER-positive, HER2-negative IDC with lymphovascular invasion who experienced a pathologic complete response with neoadjuvant docetaxel/cyclophosphamide (TC)
- Track 15** **Case discussion:** A 52-year-old perimenopausal woman with a 1.3-cm, high-grade, ER-positive, HER2-positive ductal carcinoma in situ (DCIS) and a 3-mm focus of IDC with negative nodes
- Track 16** Implications of the rapid identification of novel pathways in cancer

Select Excerpts from the Interview

Tracks 1, 3

▶ **DR LOVE:** Would you review the second-generation adjuvant clinical trials for patients with HER2-positive breast cancer?

► **DR SLAMON:** The current major trials enrolling in the adjuvant setting are the ALTTO trial and the BETH trial (1.1). ALTTO is evaluating combined blockade of the HER2 receptor with two different molecules — trastuzumab and lapatinib. One targets the extracellular domain, and the other targets the kinase domain.

Preliminary Phase II data appear promising, and this definitive trial will provide further data. Although it won't be reported for another couple of years, it's close to its enrollment goal.

BETH is evaluating the blockade of both the HER2 and the VEGF pathways by combining trastuzumab and bevacizumab. BETH is approximately one third of the way accrued, so we're a couple of years from obtaining results from this trial also.

Initial data from the 50-patient Phase II trial evaluating this combination have been reported (Pegram 2006), and the trial is now complete, and we will present the updated data at San Antonio this year. The efficacy data are similar to what we reported originally, and a cardiac signal is present in patients who received prior anthracycline therapy, which is why BETH is built primarily on a nonanthracycline arm. The trial is also evaluating an anthracycline-containing arm in Europe.

1.1 Ongoing Adjuvant Phase III Trials for Patients with HER2-Positive Early Breast Cancer

Protocol	No. of patients	Eligibility	Randomization arms
ALTTO	8,000	→ HER2+ → At least 4 cycles of (neo)adjuvant chemotherapy prior to surgery ALTTO Design 1: Will be randomized to treatment arm with no concurrent taxane ALTTO Design 2: Will be randomized to treatment arm with concurrent taxane (12 weeks)	→ H q3wk x 52 wk → L daily x 52 wk → H qwk x 12 → 6-wk washout → L daily x 34 wk → [L daily + H q3wk] x 52 wk
BETH	3,500	→ HER2+ central FISH → Node+ or high-risk node-negative	→ TCH* or (TH → FEC [†]) → H to complete 1 y → TCHB* or (THB → FEC [†]) → HB to complete 1 y

H = trastuzumab; L = lapatinib; T = docetaxel; C = carboplatin; F = 5-FU; E = epirubicin; C[†] = cyclophosphamide; B = bevacizumab

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

† Chemotherapy used by independent investigators (Cohort 2)

SOURCES: NCI Physician Data Query, September 2009; www.breastinternationalgroup.org; www.alttotrials.com.

▶ **DR LOVE:** What was the rationale for evaluating an anti-VEGF therapy in combination with trastuzumab for patients with HER2-positive breast cancer?

▶ **DR SLAMON:** The whole concept behind BETH came from the laboratory observation that when HER2 is introduced into cells that don't normally have HER2 and the gene changes are evaluated, one of the factors that increases dramatically and consistently across multiple cell lines is the level of VEGF.

For the practicing clinician the question was, does this happen in vivo? Analysis of patients with HER2-normal tumors versus those with HER2-positive disease revealed that the number of patients expressing high levels of VEGF was disproportionately greater in the HER2-positive tumors.

Those findings led to preclinical studies of combined HER2 and VEGF blockade, which were exciting and better than either single agent alone (Pegram 2006). Those data were positive with only the two biologic agents, and as a result the BETH trial was launched.

 **Track 5**

▶ **DR LOVE:** What do we know about T-DM1, and where do you see it heading in terms of integration into the treatment algorithm?

▶ **DR SLAMON:** T-DM1 is an exciting agent because it combines the anti-HER2 effect of trastuzumab with the added benefit of delivering the cytotoxic agent maytansine directly to the HER2-positive tumor cells.

In Phase I and Phase II studies for women with metastatic disease who experienced progression on trastuzumab, the response rates with T-DM1 are extremely promising, exceeding 20 to 25 percent (Vogel 2009; [1.2]). The safety profile is favorable with only transient thrombocytopenia, minimal asthenia and fatigue.

1.2 Clinical Activity of Trastuzumab-DM1 (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer Previously Treated with Trastuzumab (N = 75*)

Assessment	Independent review	Investigator assessment
Overall response rate (CR + PR)	32.0%	48.0%
Clinical benefit rate (CR + PR + stable disease ≥ 6 months)	44.0%	54.7%

CR = complete response; PR = partial response

* Seventy-five of the 112 patients who either received one or more doses of T-DM1 and had one or more postbaseline tumor assessments or died on therapy

SOURCE: Vogel CL et al. *Proc ASCO* 2009; **Abstract 1017.**

Tracks 8-9

Case discussion

A 57-year-old woman with a 2.1-cm, Grade III, node-negative, ER/PR-negative, HER2-positive, TOPO II-normal infiltrating ductal carcinoma (IDC) who was randomly assigned to receive AC → TH on BCIRG 006

► **DR SLAMON:** This patient was scheduled to receive four cycles of AC followed by four cycles of TH but was found to be among the five percent of patients who, during the run-in phase with the anthracycline, experienced a significant enough decrease in left ventricular ejection fraction (LVEF) that she was unable to receive targeted trastuzumab therapy.

Her LVEF declined to 46 percent and was 44 percent when rechecked two weeks later, so it wasn't a random low value, although she was not experiencing any cardiac symptoms. The upshot is that this patient was unable to receive trastuzumab and didn't receive any incremental benefit from the anthracycline because she did not have TOPO II amplification. She went off study and received docetaxel/cyclophosphamide (TC).

Track 14

Case discussion

A 61-year-old woman with a high-grade, ER-positive, HER2-negative IDC with lymphovascular invasion who experienced a pathologic complete response with neoadjuvant docetaxel/cyclophosphamide (TC)

► **DR SLAMON:** This patient received two additional cycles of TC postoperatively for a total of six cycles. She's fared well after completing radiation therapy and was started on an aromatase inhibitor because she had weakly ER-positive disease. Since her last visit, she remained with no symptoms and has no evidence of disease recurrence.

► **DR LOVE:** What went into your decision to administer TC?

► **DR SLAMON:** We routinely use TC. I don't know anyone who's using an anthracycline-based regimen for patients with HER2-negative disease. This patient had HER2-negative disease, and no incremental benefit exists in the literature based on more than 10,000 patients with HER2-negative disease comparing an anthracycline to a nonanthracycline regimen (EBCTCG 2005), even if you use FEC at 120 mg/m².

When Steve Jones's data evaluating four cycles of TC versus four cycles of AC reported a disease-free survival advantage with TC in comparison to AC, we adopted TC usage. Ultimately, a statistically significant survival advantage was also reported, so I am comfortable that TC is an effective regimen (Jones

2009; [1.3]). Patients are agreeable to it because their adjuvant therapy is finished much sooner than sequential regimens of anthracyclines/taxanes, and it seems to be tolerable in terms of the safety profile.

1.3

US Oncology 9735: An 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)	Hazard ratio (95% CI)	p-value
Disease-free survival (DFS)	81%	75%	0.74 (0.56-0.98)	0.033
Overall survival (OS)	87%	82%	0.69 (0.50-0.97)	0.032

“With longer follow-up, four cycles of TC was superior to standard AC (DFS and OS) and was a tolerable regimen in both older and younger patients...”

SOURCE: Jones S et al. *J Clin Oncol* 2009;27(8):1177-83.

 **Track 15**

Case discussion

A 52-year-old perimenopausal woman with a 1.3-cm, high-grade, ER-positive, HER2-positive ductal carcinoma in situ (DCIS) and a 3-mm focus of IDC with negative nodes

► **DR SLAMON:** The question with this case was, do you administer chemotherapy and trastuzumab to a patient who has node-negative disease and a small amount of invasive disease, or could you treat with surgery, postoperative radiation therapy and hormonal therapy? If a patient has invasive disease and HER2 positivity, then that should be considered high-risk disease.

The wiring of the tumor dictates the biologic behavior, rather than how many nodes you count or what you measure with a ruler. So this patient received trastuzumab-based chemotherapy on the TCH regimen for six cycles. ■

SELECT PUBLICATIONS

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365(9472):1687-717.

Jones S et al. **Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology research trial 9735.** *J Clin Oncol* 2009;27(8):1177-83.

Pegram M et al. **Phase II combined biological therapy targeting the HER2 proto-oncogene 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.**

Vogel CL et al. **A phase II study of trastuzumab-DM1 (T-DM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): Final results.** *Proc ASCO* 2009; **Abstract 1017.**



INTERVIEW

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Cancer Medicine Service Solid Tumor Division of the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-17

- Track 1** Perspective on CALGB-49907: Adjuvant capecitabine versus AC or CMF for elderly patients with early BC
- Track 2** A physician's viewpoint on patient adherence to oral therapy
- Track 3** Randomized, Phase II study of nanoparticle albumin-bound (*nab*) paclitaxel in three dosing schedules with bevacizumab as first-line therapy for HER2-negative mBC
- Track 4** CALGB-40502: Bevacizumab and weekly paclitaxel, *nab* paclitaxel or ixabepilone as first-line therapy for locally recurrent or metastatic BC
- Track 5** Role of bone scintigraphy in evaluating patients for suspected mBC in the era of integrated PET/CT
- Track 6** Rationale for a novel seven days on, seven days off schedule of capecitabine
- Track 7** Evaluation of Src inhibitors for triple-negative mBC
- Track 8** Phase II feasibility study of bicalutamide for the treatment of androgen receptor-positive, ER-negative, PR-negative mBC
- Track 9** CALGB-40503: A Phase III trial of endocrine therapy with bevacizumab for ER-positive mBC
- Track 10** CALGB-40302: Fulvestrant with or without lapatinib for postmenopausal patients with ER-positive, HER2-positive mBC
- Track 11** Treatment approach for ER-positive, HER2-positive mBC
- Track 12** CALGB portfolio of neoadjuvant chemobiologic studies in BC
- Track 13** Rationale for combining trastuzumab with lapatinib for HER2-positive BC
- Track 14** Potential role of PARP inhibitors in the treatment of BC and other solid tumor types
- Track 15** Current challenges in clinical trial development
- Track 16** Clinical implications of RIBBON 1: Chemotherapy with or without bevacizumab as first-line therapy for HER2-negative, locally recurrent or metastatic BC
- Track 17** Perspective on the NSABP-C-08 study of adjuvant FOLFOX with or without bevacizumab for Stage II/III colon cancer

Select Excerpts from the Interview

Tracks 3-4

▶ **DR LOVE:** Would you discuss the trial from your group evaluating various dosing schedules of *nab* paclitaxel with bevacizumab for metastatic breast cancer (Conlin 2009)?

► **DR HUDIS:** This randomized Phase II study was meant to provide us with insight as to which iteration of *nab* paclitaxel we should take forward in the metastatic setting and to help us with the design of adjuvant trials. It compared the standard dose of 260 mg/m² every three weeks to the same dose administered every two weeks, a dose-dense variation, and to half of that dose, 130 mg/m², administered weekly. All of the patients received concurrent bevacizumab.

The data showed that the dose-dense schedule was feasible. The patients received four cycles without too much trouble, which is what you would typically plan in the adjuvant setting, and that was consistent with the experience in the pilot studies. However, beyond four cycles the patients began experiencing trouble with toxicities, so the dose-dense arm was dropped. The data from the remaining two arms suggest that the weekly dose of 130 mg/m² may be the better way to go (2.1).

An Intergroup study (CALGB-40502) is now evaluating bevacizumab combined with *nab* paclitaxel, paclitaxel or ixabepilone — each administered on a weekly schedule — as first-line therapy for locally recurrent or metastatic breast cancer. The target accrual is 900 patients, and enrollment has been brisk. This study is asking a pragmatic question about how these newer formulations — *nab* paclitaxel and the newer antimicrotubule agent ixabepilone — compare to weekly paclitaxel, both with bevacizumab.

2.1

Randomized Phase II Trial of Nanoparticle Albumin-Bound Paclitaxel (*nab* p) with Bevacizumab as First-Line Therapy for Metastatic Breast Cancer

	<i>nab</i> p 260 mg/m ² q3wk (n = 73)	<i>nab</i> p 130 mg/m ² qw (n = 78)	p-value
Overall response rate	44%	46%	0.575
Median time to progression*	7.7 mo	9.0 mo	Not reported

* Data were immature, with only 50 percent of patients having experienced disease progression. All analyses were performed on the treated population.

SOURCE: Conlin AK et al. *Proc ASCO* 2009; **Abstract 1006**.

 **Track 6**

► **DR LOVE:** Would you comment on the schedule and dose of capecitabine you have been using at Memorial?

► **DR HUDIS:** Tiffany Traina has conducted four clinical trials exploring a seven-days-on, seven-days-off schedule of capecitabine at a fixed dose, which we believe will provide maximal cytotoxic impact without the toxicity of the 14-days-on, seven-days-off schedule. We routinely utilize the seven-days-on, seven-days-off schedule for capecitabine, and we are close to launching a

Phase III international trial comparing that to the 14-days-on, seven-days-off schedule.

Track 14

► **DR LOVE:** Would you comment on data from the Phase II trial of olaparib, a PARP inhibitor, for patients with BRCA-deficient advanced breast cancer that was recently reported at ASCO (Tutt 2009)?

► **DR HUDIS:** The simple observation that an oral, relatively nontoxic single agent can yield response rates similar to what we see with chemotherapy is remarkable (2.2). What’s disappointing is that the cohort of patients who will benefit from such a therapy is not large. The trial focused on patients with BRCA-deficient tumors or patients with overwhelming family histories.

The positive data that Joyce O’Shaughnessy presented on the PARP1 inhibitor BSI-201 combined with carboplatin and gemcitabine for patients with triple-negative metastatic breast cancer raise the possibility that either all PARP inhibitors aren’t the same or that the PARP inhibitors have activity that can be exploited beyond BRCA mutation carriers (O’Shaughnessy 2009).

To be clear, the argument is that a specific DNA defect can be introduced as a consequence of the chemotherapy drugs and that you can amplify that effect through inhibition of one of the repair pathways — that is, PARP. If that’s true, it would be good news because it would suggest, for example, that we might have a drug that’s useful for any number of epithelial solid tumors.

That should be explored, and we would also need correlative studies to address whether all triple-negative breast cancer or only a subtype has this BRCA-like quality of having defective BRCA proteins. A phase III study will rapidly accrue and provide us with an answer (NCT00938652).

2.2

Phase II Trial of the PARP Inhibitor Olaparib for BRCA1/BRCA2 Carriers with Refractory, Advanced Breast Cancer

Intent-to-treat cohort

	Olaparib 400 mg BID (n = 27)	Olaparib 100 mg BID (n = 27)
Overall response rate	41%	22%
Complete response rate	4%	0%
Partial response rate	37%	22%

“Olaparib at 400 mg bd [BID] is well tolerated and highly active in advanced chemotherapy-refractory BRCA-deficient breast cancer. Toxicity in BRCA1/BRCA2 carriers was similar to that reported previously in non-carriers. This first study with olaparib in BRCA-deficient breast cancers provides positive proof of concept for high activity and tolerability of a genetically defined targeted therapy.”

SOURCE: Tutt A et al. *Proc ASCO* 2009; **Abstract CRA501.**

Track 16

► **DR LOVE:** Would you comment on the results of the RIBBON 1 trial presented at ASCO?

► **DR HUDIS:** In this study, patients received a taxane or an anthracycline-based regimen or capecitabine in combination with bevacizumab (Robert 2009; [2.3]). The groups were not officially divided into subsets, but the point estimates for benefit are consistent across the three options. The data shoot down the belief that bevacizumab activity is chemotherapy specific. They directly counter the suggestion that capecitabine is an inferior partner with bevacizumab, which some people believed based on the randomized Phase III trial evaluating capecitabine with or without bevacizumab in the salvage setting (Miller 2005). ■

2.3

RIBBON 1: A Phase III Randomized Trial of Chemotherapy with Bevacizumab (BEV) or Placebo (PL) as First-Line Therapy for HER2-Negative, Locally Recurrent or Metastatic Breast Cancer

	Capecitabine		Taxane/anthracycline	
	BEV (n = 409)	PL (n = 206)	BEV (n = 415)	PL (n = 207)
Median progression-free survival	8.6 mo	5.7 mo	9.2 mo	8.0 mo
Hazard ratio (<i>p</i> -value)	0.69 (<i>p</i> = 0.0002)		0.64 (<i>p</i> < 0.0001)	
Median overall survival	29.0 mo	21.2 mo	25.2 mo	23.8 mo
Hazard ratio (<i>p</i> -value)	0.85 (<i>p</i> = 0.27)		1.03 (<i>p</i> = 0.83)	
Objective response rate*	35.4%	23.6%	51.3%	37.9%
<i>p</i> -value	0.0097		0.0054	

* Includes only patients with measurable disease at baseline

SOURCE: Robert NJ et al. *Proc ASCO* 2009; **Abstract 1005**.

SELECT PUBLICATIONS

Conlin AK et al. **Randomized phase II trial of nanoparticle albumin-bound paclitaxel in three dosing schedules with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer (MBC).** *Proc ASCO* 2009; **Abstract 1006**.

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O'Shaughnessy J et al. **Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial.** *Proc ASCO* 2009; **Abstract 3**.

Robert NJ et al. **RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC).** *Proc ASCO* 2009; **Abstract 1005**.

Tutt A et al. **Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer.** *Proc ASCO* 2009; **Abstract CRA501**.



INTERVIEW

Jennifer J Griggs, MD, MPH

Dr Griggs is Associate Professor in the Department of Internal Medicine's Hematology/Oncology Division at the University of Michigan in Ann Arbor, Michigan.

Tracks 1-12

- Track 1** Undertreatment for patients who are obese and are receiving chemotherapy for early BC
- Track 2** **Case discussion:** A 74-year-old woman with a history of deep vein thrombosis and well-controlled hypertension who was diagnosed with a 4.5-cm, Grade III, weakly ER-positive, PR-negative, HER2-negative IDC with eight positive nodes
- Track 3** Relationship among patient adherence, treatment-related endocrine symptoms and clinical benefit from aromatase inhibitor (AI) therapy
- Track 4** Adjuvant chemotherapy for patients older than age 70
- Track 5** Prevalence of vitamin D deficiency in patients with cancer and the general population
- Track 6** Vitamin D deficiency and risk of breast cancer recurrence
- Track 7** BIG 1-98: Switching to adjuvant tamoxifen for patients intolerant to AI therapy
- Track 8** Potential relationship between obesity and the development of cancer
- Track 9** Counseling patients about maintaining a healthy weight
- Track 10** Obesity and response to cancer treatment
- Track 11** Breast cancer survivorship program at the University of Rochester
- Track 12** Rates of patient nonadherence and nonpersistence with adjuvant oral hormonal therapy

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Would you discuss the paper you published on undertreatment of patients who are obese and are receiving chemotherapy for early breast cancer?

► **DR GRIGGS:** It has long been a conscious practice to systematically reduce chemotherapy doses for patients who are obese. It's something we've been taught to do. Until about 25 years ago, clinical trials required that doses be capped at a certain body surface area for patients who are obese. Because this practice was standard in clinical trials, it made sense for physicians to dose reduce off trial.

The study we published in the *Archives of Internal Medicine* evaluated approximately 10,000 patients who received AC chemotherapy. We reported that 37 percent of patients with severe obesity had their doses reduced by more than 10 percent, so only 63 percent of patients with severe obesity received full doses.

Patients with severe obesity, including those who received full doses of AC, were less likely to be hospitalized with febrile neutropenia, the most common short-term toxicity associated with chemotherapy (Griggs 2005). The odds ratio was 0.6, so it's possible that even administering full doses to patients with severe obesity results in slightly underdosing.

Track 3

▶ **DR LOVE:** What are your thoughts on Jack Cuzick's retrospective analysis of the ATAC trial published in *Lancet Oncology* suggesting that patients with more vasomotor symptoms and arthralgias from either tamoxifen or an aromatase inhibitor experienced fewer cancer recurrences (Cuzick 2008; [3.1])?

▶ **DR GRIGGS:** The data bring a couple of questions to mind: Are patients who experience more symptoms also more adherent to their medicines and thus experience lower levels of estradiol? Do interindividual differences in how people metabolize the drugs exist and create differences in the benefit they receive in terms of suppression of estrogen production?

▶ **DR LOVE:** Would you say to a patient who is experiencing these symptoms, "This might be a sign that the drug is working better," or is it too experimental to mention that to a patient?

3.1

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.

► **DR GRIGGS:** We use various approaches to help people tolerate their medicines. Patients do say, “At least I know the treatment is working.” However, if a patient weren’t experiencing any symptoms, I believe it would be premature to say that that person is not benefiting from the drug. We have to be careful not to simplify the story between symptoms and treatment benefit.

Track 12

► **DR LOVE:** What are your thoughts on the issue of adherence to oral adjuvant endocrine therapy?

► **DR GRIGGS:** We know that up to 40 percent of patients are no longer adhering to the adjuvant endocrine therapy at five years, and several factors are associated with nonpersistence. Those include not understanding why they’re taking the medicine, lack of informational support and — interestingly enough — feeling as if they made the decision, not the doctor.

Katherine Kahn reported that patients who believed that they made the decision to initiate therapy, without much investigator support, were less likely to continue taking the medicine (Kahn 2007). Patients need to know that their doctors believe that receiving this therapy is important. I believe that at the end of multimodality therapy we frequently forget to emphasize the value of continuing adjuvant endocrine therapy.

Obviously, side effects are an important predictor of early treatment discontinuation, and doctors are not good at assessing side effects. Patients don’t like complaining to us. We often forget to ask, “How are you tolerating the treatment? What can I do to support you to complete the full course of therapy?” ■

SELECT PUBLICATIONS

Chlebowski R et al. **Clinical perspectives on the utility of aromatase inhibitors for the adjuvant treatment of breast cancer.** *Breast* 2009;18(Suppl 2):1-11.

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.

Griggs JJ et al. **Undertreatment of obese women receiving breast cancer chemotherapy.** *Arch Intern Med* 2005;165(11):1267-73.

Kahn KL et al. **Patient centered experiences in breast cancer: Predicting long-term adherence to tamoxifen use.** *Med Care* 2007;45(5):431-9.

Partridge AH et al. **Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer.** *J Clin Oncol* 2008;26(4):556-62.

Ruddy KJ, Partridge AH. **Adherence with adjuvant hormonal therapy for breast cancer.** *Ann Oncol* 2009;20(3):401-2.

Sestak I et al; ATAC Trialists’ Group. **Risk factors for joint symptoms in patients enrolled in the ATAC trial: A retrospective, exploratory analysis.** *Lancet Oncol* 2008;9(9):866-72.

Ziller V et al. **Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer.** *Ann Oncol* 2009;20(3):431-6.



INTERVIEW

William J Gradishar, MD

Dr Gradishar is Director of Breast Medical Oncology and Professor of Medicine at Northwestern University's Robert H Lurie Comprehensive Cancer Center and Feinberg School of Medicine in Chicago, Illinois.

Tracks 1-14

- Track 1** Feasibility of high-dose fulvestrant for postmenopausal patients with ER-positive mBC
- Track 2** Combining targeted agents with endocrine therapy to overcome acquired resistance
- Track 3** CYP2D6 polymorphisms and tamoxifen
- Track 4** AIs with anti-HER2 therapy for patients with ER-positive, HER2-positive mBC
- Track 5** Adjuvant bisphosphonate therapy
- Track 6** Phase II study results of weekly or three-weekly *nab* paclitaxel compared to three-weekly docetaxel as first-line therapy for mBC
- Track 7** Evaluation of SPARC as a predictor of response to *nab* paclitaxel
- Track 8** Treatment approach for small, node-negative early BC
- Track 9** Inclusion of genomic breast cancer assays in current clinical practice guidelines
- Track 10** Perspective on the RIBBON 1 study of first-line chemotherapy with or without bevacizumab in HER2-negative, locally recurrent or metastatic BC
- Track 11** Ongoing and recently reported trials of chemotherapy/sorafenib in mBC
- Track 12** Use of the *Oncotype DX*® assay in clinical practice
- Track 13** Clinical dilemmas secondary to the routine use of PET-CT imaging in BC
- Track 14** Ongoing study of IGFR therapy with or without endocrine therapy for ER-positive mBC

Select Excerpts from the Interview

Track 1

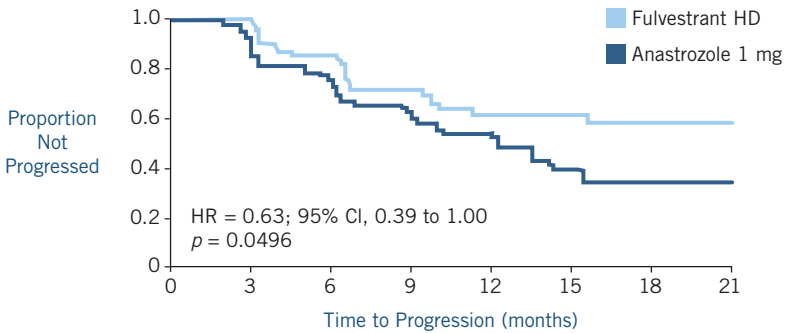
► **DR LOVE:** Would you comment on the recent reports of high-dose fulvestrant for postmenopausal patients with advanced ER-positive breast cancer?

► **DR GRADISHAR:** The development plan for fulvestrant focused primarily on a monthly administration of 250 milligrams, but pharmacokinetic data suggested a steady state could be reached more quickly with a loading dose, which has also been supported by the EFECT study (Chia 2008). More recently, data from the FIRST study suggested that a greater response rate may be achieved by administering fulvestrant at a 500-mg monthly dose (Robertson 2009; [4.1]).

There is interest in using a higher dose or different schedules of fulvestrant, and I believe that we can incrementally improve outcome, but I don't believe we will change the landscape of endocrine therapy by dialing up the dose.

4.1

FIRST: First-Line High-Dose Fulvestrant versus Anastrozole for Postmenopausal Patients with ER-Positive Advanced Breast Cancer



“[Time to progression (TTP)] was estimated to be 60% longer in patients treated with fulvestrant HD compared with TTP for those treated with anastrozole, a statistically significant difference. DoR and DoCB data also favored fulvestrant HD.”

DoR = duration of response; DoCB = duration of clinical benefit

SOURCE: With permission from Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-5.

Track 4

▶ **DR LOVE:** What's your perspective on the studies combining aromatase inhibitors (AIs) with anti-HER2 agents for patients with ER-positive, HER2-positive metastatic breast cancer?

▶ **DR GRADISHAR:** The data evaluating the combination of AIs with anti-HER2 agents from the TAnDEM study (Mackey 2006) and from the EGF30008 trial (Johnston 2008) are concordant.

Patients with ER-positive, HER2-positive tumors have tended to fare poorly on AI therapy alone. Both of these trials showed progression-free survival periods of several months with AI therapy alone, but the outcomes were incrementally improved when the anti-HER2 agent was added (4.2). You are obtaining an effect by leveraging two different pathways.

Track 12

▶ **DR LOVE:** What are some of the current clinical scenarios in breast cancer that you find to be the most challenging?

► **DR GRADISHAR:** My colleagues and I share the same dilemma: How to manage small tumors. Our prior framework of thinking that small, node-negative tumors were essentially free of a risk of recurrence is being rethought. Now the whole arena has changed.

Not only do we consider ordering an *Oncotype DX* assay for subcentimeter tumors, but we also consider chemotherapy. We're telling patients with small ER-positive, HER2-positive tumors that they will receive everything that we have available. We are essentially sending the message, which I believe is probably true, that biology drives the outcome.

► **DR LOVE:** How have you incorporated *Oncotype DX* into your practice?

► **DR GRADISHAR:** For patients with ER-positive, node-negative breast cancer we have increased our usage of *Oncotype DX*, particularly for patients with tumors that are between one and three centimeters. We have also begun using it for patients with smaller tumors and those with microscopically positive nodes. ■

4.2

Combined AI and HER2-Targeted Treatments for Postmenopausal Patients with HER2-Positive, ER-Positive Metastatic Breast Cancer

	TAnDEM			EGF30008		
	Anastrozole + trastuzumab	Anastrozole	p-value	Letrozole + lapatinib	Letrozole	p-value
Median PFS	4.8 mo	2.4 mo	0.0016	8.2 mo	3.0 mo	0.019
Median OS	28.5 mo	23.9 mo	0.325	33.3 mo	32.3 mo	0.113
CBR	42.7%	27.9%	0.026	48%	29%	0.003

PFS = progression-free survival; OS = overall survival; CBR = objective response + stable disease

SOURCES: Johnston S et al. San Antonio Breast Cancer Symposium 2008; **Abstract 46**; Mackey JR et al. San Antonio Breast Cancer Symposium 2006; **Abstract 3**.

SELECT PUBLICATIONS

Chia S et al. **Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT.** *J Clin Oncol* 2008;26(10):1664-70.

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**.

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

Robertson JFR et al. **Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study.** *J Clin Oncol* 2009;27(27):4530-5.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The BETH trial is evaluating adjuvant chemotherapy/trastuzumab with or without _____ for patients with HER2-positive breast cancer.
 - a. Lapatinib
 - b. Bevacizumab
 - c. T-DM1
 - d. Pertuzumab
2. In the international Phase III ALTTO trial for patients with HER2-positive early breast cancer, which treatment arm receives a six-week treatment break?
 - a. Trastuzumab
 - b. Lapatinib
 - c. Trastuzumab followed by lapatinib
 - d. Trastuzumab with concurrent lapatinib
3. T-DM1 is a novel agent that combines a maytansine derivative with _____.
 - a. Docetaxel
 - b. Trastuzumab
 - c. Bevacizumab
 - d. None of the above
4. A Phase II trial of the PARP inhibitor olaparib demonstrated that the agent was well tolerated and highly active in patients with advanced _____ breast cancer.
 - a. Triple-negative
 - b. BRCA-deficient
 - c. None of the above
5. In the RIBBON 1 trial, the addition of bevacizumab to capecitabine improved median progression-free survival by approximately three months for patients with previously untreated metastatic breast cancer.
 - a. True
 - b. False
6. In the randomized Phase II trial evaluating various doses and schedules of *nab* paclitaxel combined with bevacizumab as first-line therapy for metastatic breast cancer, which regimen appeared to have the most favorable therapeutic index?
 - a. *Nab* paclitaxel 260 mg/m² every three weeks
 - b. *Nab* paclitaxel 130 mg/m² weekly
7. Only _____ of patients with severe obesity received full doses in the retrospective analysis reported by Griggs and colleagues.
 - a. 37 percent
 - b. 63 percent
8. 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
9. The FIRST study demonstrated that an improved response to fulvestrant in patients with advanced breast cancer could be obtained by administering the drug at a higher, _____ dose.
 - a. 500-mg
 - b. 250-mg
 - c. 750-mg
10. The TAnDEM study and the EGF30008 trial demonstrated increased progression-free survival for patients with metastatic breast cancer that was treated with _____ and anti-HER2 targeted agents.
 - a. Docetaxel
 - b. Tyrosine kinase inhibitors
 - c. Aromatase inhibitors

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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
Ongoing second-generation adjuvant clinical trials — BETH and ALTTO — for patients with HER2-positive early breast cancer	4 3 2 1	4 3 2 1
Ongoing and reported clinical trials of <i>nab</i> paclitaxel with or without bevacizumab	4 3 2 1	4 3 2 1
Rationale for a novel capecitabine seven-days-on, seven-days-off dosing schedule	4 3 2 1	4 3 2 1
RIBBON 1 clinical trial results: Chemotherapy with or without bevacizumab as first-line therapy for HER2-negative metastatic breast cancer	4 3 2 1	4 3 2 1
Prevalence of vitamin D deficiency and its relationship to risk of breast cancer recurrence	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

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Did the activity meet your educational needs and expectations?

Yes No

If no, please explain:

Please respond to the following learning objectives (LOs) 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:

- Recall the prevalence of vitamin D deficiency among patients with breast cancer, and consider its effect on the risk of disease recurrence 4 3 2 1 N/M N/A
- Recognize the effects of advanced age, poor performance status and obesity on the benefits and risks of adjuvant chemotherapy for breast cancer. 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
- Develop an approach to monitor and facilitate patient adherence to orally administered antineoplastic therapies 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
- Communicate the efficacy and safety of various chemotherapy regimens in combination with bevacizumab to patients with HER2-negative metastatic breast cancer that may be eligible for anti-angiogenic treatment 4 3 2 1 N/M N/A
- Use actual body weight in place of ideal body weight to establish appropriate adjuvant treatment doses for patients who are obese. 4 3 2 1 N/M N/A
- Delineate novel classes of molecular-targeted agents currently under investigation for the treatment of breast cancer. 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:

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- 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	
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Clifford Hudis, MD	4	3	2	1	4 3 2 1
Jennifer J Griggs, MD, MPH	4	3	2	1	4 3 2 1
William J Gradishar, 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 faculty and editor for this activity:

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