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Breast Cancer® UPDATE

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

FACULTY 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 clinical 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

- Appraise the potential utility of genomic assays to aid in the quantification of risk and the selection of individualized treatment for patients with node-negative or node-positive breast cancer.
- Communicate the efficacy and safety of various chemotherapy regimens in combination with bevacizumab to patients with HER2-negative metastatic breast cancer who may be eligible for anti-angiogenic treatment.
- Recount the role of poly(ADP-ribose) polymerase (PARP) in the DNA repair pathway, and review the efficacy and safety of the PARP inhibitors for women with triple-negative breast cancer.
- Consider the efficacy and tolerability of novel agents for the later-line treatment of metastatic breast cancer.
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based chemotherapy regimens.
- Define the role of sentinel lymph node resection versus conventional axillary lymph node dissection in early breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Charles E Geyer Jr, MD

Dr Geyer is Director of Medical Affairs for the National Surgical Adjuvant Breast and Bowel Project and Vice-Chair of the Department of Human Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania.

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you describe the NSABP study investigating PARP inhibition in the neoadjuvant setting for triple-negative breast cancer (TNBC)?

DR GEYER: NSABP-B-48 will be a randomized Phase III trial evaluating the addition of iniparib (BSI-201) to neoadjuvant chemotherapy in palpable and operable TNBC, and the primary endpoint will be pathologic complete response (pCR). The regimens being evaluated include the standard control regimen of weekly paclitaxel x 12 followed by AC for four cycles compared to TC x 4 followed by carboplatin/gemcitabine. Both chemotherapy options are with or without the PARP inhibitor iniparib. The total sample size will be 540 patients, and if the effect with iniparib is large — with a hazard ratio of 0.65 or lower — then longer-term endpoints could also be affected.

DR LOVE: Where are we in terms of the clinical development of iniparib or PARP inhibitors in general?

DR GEYER: Among the clinical studies, the Phase II study with iniparib has shown the most striking results (O'Shaughnessy 2010; [1.1]).

One of the issues that has slowed down the development of other PARP inhibitors is synergistic toxicity with chemotherapy (Dent 2010; Isakoff 2010), which, for some reason, is not present with iniparib (O'Shaughnessy 2009b; [1.2]). Our perspective has been that the Phase II trial results with iniparib, though not definitive, are strong enough to conduct Phase III trials and also to move the agent into the neoadjuvant setting, in which efficacy could be quickly determined based on pCR. We believe that concurrent chemotherapy/iniparib is so well tolerated that it makes sense to evaluate it quickly in the neoadjuvant setting rather than wait for the recurrence events, which could take years, in the adjuvant setting.

1.1

Final Efficacy Results of a Randomized Phase II Study of Iniparib in Combination with Carboplatin/Gemcitabine (C/G) in Metastatic Triple-Negative Breast Cancer

	C/G (n = 62)	C/G + iniparib (n = 61)	Hazard ratio	*p*-value
Overall response rate (ORR)	32.3%	52.5%	—	0.023
Clinical benefit rate (CBR)*	33.9%	55.7%	—	0.015
Median progression-free survival	3.6 months	5.9 months	0.59	0.012
Median overall survival	7.7 months	12.3 months	0.57	0.014

* CBR = ORR + stable disease ≥ 6 months

O'Shaughnessy J et al. *Proc ESMO* 2010;**Abstract LBA11**.

1.2

Frequently Observed Grade III/IV Adverse Events in a Randomized Phase II Study of Iniparib in Combination with Carboplatin/ Gemcitabine (C/G) in Metastatic Triple-Negative Breast Cancer

	C/G (n = 59)		C/G + iniparib (n = 57)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	14%	2%	21%	0%
Thrombocytopenia	17%	10%	14%	16%
Neutropenia	32%	24%	37%	21%
Febrile neutropenia	5%	2%	0%	0%
Fatigue	22%	2%	7%	0%

O'Shaughnessy J et al. Poster. San Antonio Breast Cancer Symposium 2009b;**Abstract 3122**.

Tracks 4-5

DR LOVE: What are your thoughts on the combination of anti-HER2 agents in the metastatic setting?

DR GEYER: A study recently reported on women who had disease refractory to trastuzumab who were randomly assigned to full-dose lapatinib versus an attenuated dose of lapatinib with continued trastuzumab (Blackwell 2009; [1.3]). When you examine the design of that study, it appears as if the deck is stacked in favor of lapatinib.

What's remarkable, however, is that in this population with heavily pretreated advanced breast cancer, the combination resulted in an improvement in progression-free survival and a strong trend toward a survival advantage with the combination. This has greatly affected how I practice. I find myself using trastuzumab/ lapatinib to give patients some time off chemotherapy.

DR LOVE: What about capecitabine/trastuzumab in the metastatic setting?

DR GEYER: I believe it's a reasonable combination. With the multitude of available treatment options, it is increasingly difficult to describe how I treat advanced HER2-positive breast cancer. Capecitabine combinations have an advantage in offering activity against central nervous system disease, which is a problem for women with metastatic HER2-positive breast cancer.

Track 11

DR LOVE: Where are we with the TAILORx study and other studies incorporating the Onco*type* DX Recurrence Score in clinical decision-making?

DR GEYER: The TAILORx trial will be completing its accrual within a few months. The interest in the trial has been tremendous, and ECOG has done a great job in leading the trial. I know that SWOG has wanted to follow up

on the SWOG-8814 data to conduct a prospective TAILORx-like trial for women with node-positive, ER-positive breast cancer.

Some of the surgeons on our breast committee are interested in developing a trial using the Onco*type* DX Recurrence Score in the decision-making process in the neoadjuvant setting. We are in the early stages of the design and are considering how that trial might be conducted. One would broadly expect that pCR rates would be highest in the patient group for whom the benefits from chemotherapy were the largest in the adjuvant setting — that is, the high/intermediate Recurrence Score group. For me, neoadjuvant endocrine therapy is interesting if I can figure out a way to use it confidently and forego chemotherapy.

1.3

EGF104900: A Randomized Phase III Study of Lapatinib versus Lapatinib/Trastuzumab in Patients with HER2-Positive Trastuzumab-Refractory Metastatic Breast Cancer (mBC)

	Lapatinib (n = 145)	Lapatinib + trastuzumab (n = 146)	Hazard ratio	*p*-value
Median progression-free survival	8.1 wk	12.0 wk	0.73	0.008
Median overall survival	38.0 wk	56.0 wk	0.74	0.026

Median number of prior trastuzumab regimens for mBC: 3

"This study demonstrated that lapatinib in combination with trastuzumab offers a chemotherapy-free option that has an acceptable tolerability profile and, versus lapatinib alone, reduced the risk of disease progression by 26% ($P = 0.026$). The efficacy benefits arose in a treatment setting that lacked many of the well-known chemotherapy-related toxicities."

Blackwell KL et al. San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Tracks 14-15

DR LOVE: What is your opinion regarding the use of *nab* paclitaxel versus standard-formulation paclitaxel in metastatic breast cancer?

DR GEYER: I like to use *nab* paclitaxel because I am convinced that it offers advantages in terms of neuropathy. I believe neuropathy develops later with *nab* paclitaxel, and it is always an issue when I have to stop the standard paclitaxel formulation earlier because of neuropathy. In such situations, the patient is not receiving as much drug as I would like and the persisting neuropathy can make the administration of subsequent therapies more problematic. So I consistently use *nab* paclitaxel, whenever possible, for metastatic breast cancer. Since I have been using it, my patients have had less trouble and my clinical experience has been consistent with the research data.

I also believe *nab* paclitaxel may be more efficacious than standard-formulation taxanes. We conducted a Phase II neoadjuvant study using weekly *nab*

paclitaxel followed by AC, and what stood out was the remarkable lack of toxicity with 12 weekly doses of *nab* paclitaxel. We did not have many treatment delays, and little neuropathy was observed. The pCR rate was 29 percent in that study, and *nab* paclitaxel seemed to be as active as paclitaxel with better tolerability than weekly paclitaxel (Robidoux 2010).

Track 16

DR LOVE: What is your take on the role of bevacizumab for patients with metastatic TNBC?

DR GEYER: I definitely believe that bevacizumab is an attractive option for metastatic TNBC because these patients have fewer treatment options and often we see nice responses to bevacizumab-containing regimens. Bevacizumab has consistently improved response rates and time to disease progression. In view of this, when I am treating metastatic TNBC I routinely administer bevacizumab because it is particularly important to optimize the chemotherapy and I see bevacizumab as a way of optimizing chemotherapy. ■

SELECT PUBLICATIONS

Baselga J et al. **First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER 2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Blackwell KL et al. **Updated survival analysis of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy.** San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Dent RA et al. **Safety and efficacy of the oral PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the first- or second-line treatment of patients with metastatic triple-negative breast cancer: Results from the safety cohort of a phase I/II multicenter trial.** *Proc ASCO* 2010;**Abstract 1018**.

Isakoff SJ et al. **A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer.** *Proc ASCO* 2010;**Abstract 1019**.

O'Shaughnessy J et al. **Final efficacy and safety results of a randomized phase II study of the PARP inhibitor iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ESMO* 2010;**Abstract LBA11.**

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* 2009a;**Abstract 3**.

O'Shaughnessy J et al. **Updated results of a randomized phase II study demonstrating efficacy and safety of BSI-201, a PARP inhibitor, in combination with gemcitabine/carboplatin in metastatic triple-negative breast cancer.** Poster. San Antonio Breast Cancer Symposium 2009b;**Abstract 3122**.

Robidoux A et al. **A phase II neoadjuvant trial of sequential nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in locally advanced breast cancer.** *Clin Breast Cancer* 2010;10(1):81-6.

Tutt A et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial.** *Lancet* 2010;376(9737):235-44.

INTERVIEW

Kathy D Miller, MD

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

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-5

DR LOVE: Would you discuss some of the newer anti-HER2 agents under investigation in breast cancer and their mechanisms of action?

DR MILLER: Pertuzumab and T-DM1 are two of the novel anti-HER2 agents. Pertuzumab is a monoclonal antibody, like trastuzumab, but it differs from trastuzumab in binding to a different epitope on the extracellular portion of the HER2 receptor. This is considered important because it blocks both homo- and heterodimerization of the HER2 receptor.

Trastuzumab can inhibit signaling, but it doesn't block dimerization. So signaling could still occur through HER3 with trastuzumab on board. Though HER3 does not have an active kinase, it has the most docking sites for the PI3 kinase, and with HER2-HER3 dimerization, activation of the PI3 kinase bound to HER3 may still occur. Because pertuzumab blocks the binding of HER2 and HER3, signaling through HER3 is also expected to be affected.

Pertuzumab was initially studied as monotherapy (Cortes 2009) and then in combination with trastuzumab (Cortes 2010). In both of these studies, enrolled patients had HER2-positive disease that had progressed during trastuzumab-based therapy. The response rates with pertuzumab monotherapy ranged from 10 to 20 percent, with an additional 10 to 15 percent of patients having stable disease. I believe pertuzumab monotherapy in trastuzumab-resistant disease is quite encouraging. The large Phase III CLEOPATRA trial is now evaluating the addition of pertuzumab to docetaxel/trastuzumab in the up-front setting.

DR LOVE: What do we know about T-DM1?

DR MILLER: T-DM1 is another novel anti-HER2 agent that takes a different tactic. It focuses on using the unique expression of the HER2 receptor on breast cancer cells as a way to deliver chemotherapy to the cancer cells. The T-DM1 molecule contains chemotherapy derivatives chemically bound to trastuzumab. The idea is that as the trastuzumab portion of T-DM1 binds to the HER2 receptor, the entire complex will then be internalized and chemotherapy will be released directly into the tumor cell. In theory, that should deliver a much higher concentration of chemotherapy to the tumor cell, which might increase activity. In addition, the side effects should also dramatically decrease because the circulating levels of the chemotherapy should be lower.

Data from Phase II trials in patients with trastuzumab-refractory disease have reported response rates of approximately 30 percent and progression-free survival of six months (Vogel 2009; [2.1]; LoRusso 2010). The toxicity profile is favorable, and thus overall it is encouraging and may challenge the current paradigm of trastuzumab/chemotherapy for patients with HER2-positive breast cancer.

2.1 **Phase II Trial of T-DM1 for Patients with HER2-Positive Metastatic Breast Cancer Who Experienced Disease Progression on Prior HER2-Directed Therapy**

	Investigator		Independent review	
	All (N = 112)	HER2 centrally confirmed (N = 75)	All (N = 112)	HER2 centrally confirmed (N = 75)
Overall response rate	38.4%	48.0%	25.0%	32.0%
Clinical benefit rate (CBR)*	44.6%	54.7%	34.8%	44.0%

* CBR = complete response + partial response + stable disease ≥ 6 months

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

DR LOVE: Would you discuss your study evaluating the combination of T-DM1 with pertuzumab that was presented at ASCO?

DR MILLER: We presented data for the first 28 patients out of the 44 in the refractory cohort. The toxicity appeared to be similar to T-DM1 alone. Minor systemic issues arose, such as fatigue and thrombocytopenia not associated with bleeding, and no obvious cardiotoxicity was evident. Response rates were between 25 and 30 percent in this refractory population, and we are certainly encouraged by these results and by the lack of an apparent increase in toxicity (Miller 2010; [2.2]).

DR LOVE: What do we know about T-DM1-related thrombocytopenia?

DR MILLER: Thrombocytopenia occurs quite early, often within a couple of days of infusion, and for most patients it is fairly moderate, though some patients might experience significant thrombocytopenia. However, it resolves quickly, within three to four days. I believe thrombocytopenia will garner a lot of attention in the early clinical trials, but as the agent moves into practice and people become accustomed to it, this will not be nearly such a big issue.

2.2

Efficacy Data from a Phase Ib/II Trial of Pertuzumab (P) and T-DM1 for Patients with Previously Treated HER2-Positive Breast Cancer (N = 28)

Partial response	Stable disease	Progressive disease	Missing
35.7%	46.4%	14.3%	3.6%

"Safety, tolerability, and preliminary efficacy of full dose T-DM1 + P are encouraging, with no substantial increase in toxicity over single agent T-DM1, and no new safety signals. Hepatic and Grade 4 thrombocytopenia events were infrequent. T-DM1 dosing was established at 3.6 mg/kg."

Miller K et al. *Proc ASCO* 2010;**Abstract 1012**.

Track 6

DR LOVE: Would you comment on the meta-analysis of studies of bevacizumab-containing first-line therapy in metastatic breast cancer?

DR MILLER: In the individual trials, bevacizumab had no effect on survival, though none of the trials were powered to show a survival advantage. The meta-analysis presented at ASCO revealed no overall survival advantage with bevacizumab (O'Shaughnessy 2010; [2.3]).

Overall survival is an important endpoint, and we obviously want our patients to live longer. However, overall survival is a composite that is driven by the patient's age and comorbidities, the inherent biology of the disease and the efficacy and toxicity of the therapies we administer in multiple lines. So in my view, to a small extent, overall survival might be altered by initial first-line therapy. For an initial therapy to affect overall survival, the effect on other efficacy endpoints must be much greater to see an overall survival difference.

In contrast, progression-free survival is more directly tied to the effect of the therapy being studied. Progression-free survival is also influenced by the inherent biology of the disease, the efficacy and toxicity of the therapy and the ability to deliver the therapy. However, other confounding factors, such as effects from subsequent therapies, can affect overall survival but do not affect progression-free survival. ■

2.3

Meta-Analysis of Three Phase III Studies of Bevacizumab (BV)-Containing First-Line Therapy in HER2-Negative Metastatic Breast Cancer: ECOG-E2100, AVADO and RIBBON-1

	Chemo only (N = 1,008)	Chemo/BV (N = 1,439)	Hazard ratio	*p*-value
Progression-free survival (PFS)	6.7 mo	9.2 mo	0.64	<0.0001
Overall survival (OS)	26.4 mo	26.7 mo	0.97	0.560
One-year survival	77%	82%	—	0.003

"Results from the exploratory analysis of the pooled PFS data show that BV, when combined with first-line chemotherapy (taxane-, anthracycline-, or capecitabine-based regimens), results in clinically meaningful and statistically significant improvements in PFS. Though no statistically significant difference in median OS was seen, the pooled OS data from these trials suggest an early benefit at 1 year."

O'Shaughnessy J et al. *Proc ASCO* 2010;**Abstract 1005**.

SELECT PUBLICATIONS

Baselga J et al. **Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy.** *J Clin Oncol* 2010;28(7):1138-44.

Cortes J et al. **Pertuzumab and trastuzumab: Exploratory biomarker correlations with clinical benefit in patients with metastatic HER2-positive breast cancer.** *Proc ASCO* 2010;**Abstract 1066**.

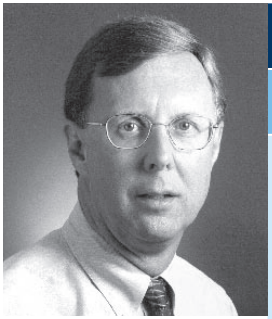
Cortes J et al. **Pertuzumab monotherapy following trastuzumab-based treatment: Activity and tolerability in patients with advanced HER2-positive breast cancer.** *Proc ASCO* 2009;**Abstract 1022**.

LoRusso P et al. **Quantitative assessment of diagnostic markers and correlations with efficacy in two phase II studies of trastuzumab-DM1 (T-DM1) for patients (pts) with metastatic breast cancer (MBC) who had progressed on prior HER2-directed therapy.** *Proc ASCO* 2010;**Abstract 1016**.

Miller K et al. **A phase Ib/II trial of trastuzumab-DM1 (T-DM1) with pertuzumab (P) for women with HER2-positive, locally advanced or metastatic breast cancer (BC) who were previously treated with trastuzumab (T).** *Proc ASCO* 2010;**Abstract 1012**.

O'Shaughnessy J et al. **A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC).** *Proc ASCO* 2010;**Abstract 1005**.

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

C Kent Osborne, MD

Dr Osborne is Dudley and Tiny Sharp Chair in Cancer Research, Director of the Dan L Duncan Cancer Center, Director of the Lester and Sue Smith Breast Center and Professor of Medicine and Molecular and Cellular Biology at Baylor College of Medicine in Houston, Texas.

Tracks 1-12

Track 1 Emerging role of PARP inhibitors in the treatment of BC and other solid tumors

Track 2 Association between DNA repair signature and response to anthracyclines in TNBC

Track 3 Objectives of the ASCO/College of American Pathologists guidelines for ER testing with immunohisto-chemistry (IHC)

Track 4 Discordance in measurement of ER between primary BC and metastatic disease after hormonal therapy

Track 5 Analysis of the BIG 1-98 trial: Up-front letrozole versus switching from tamoxifen to letrozole or vice versa

Track 6 Potential mechanisms of tumor resistance to endocrine therapy

Track 7 Differing mechanisms of acquired resistance to trastuzumab and lapatinib in HER2-positive BC

Track 8 Potential explanation for the apparent benefit of adjuvant trastuzumab for patients with HER2-normal BC

Track 9 EMBRACE trial: Improved survival with eribulin mesylate (E7389) compared to physician's choice of treatment for patients with previously treated locally recurrent BC or mBC

Track 10 Prognostic and predictive value of the Onco*type* DX assay for postmenopausal women with ER-positive, node-positive BC who are receiving chemotherapy

Track 11 Defining the role of sentinel lymph node resection compared to conventional axillary lymph node dissection in BC

Track 12 Value of IHC in the evaluation of lymph nodes of patients with lobular BC

Select Excerpts from the Interview

Track 9

DR LOVE: What are your thoughts on the study presented at ASCO this year on the novel agent eribulin mesylate (3.1)?

DR OSBORNE: Eribulin mesylate is a new chemotherapeutic agent that is derived from a marine sponge and works as a microtubule inhibitor. We participated in the trial, and the data appear promising (Twelves 2010; [3.2]). A survival advantage was evident among patients with advanced breast cancer who had previously received a median of four regimens. Typically our

standard chemotherapy drugs do not show a survival advantage in this setting, so that was interesting. In view of this, I would be interested in seeing its activity in earlier lines of therapy compared to other standard agents.

3.1

EMBRACE: An Open-Label, Global Phase III Study Comparing Eribulin Mesylate to Treatment of Physician's Choice (TPC) in Locally Recurrent or Metastatic Breast Cancer

Accrual: 762

Eligibility

Locally recurrent or metastatic breast cancer

- Two to five prior chemotherapies
- Received two or more chemotherapy regimens for advanced disease

Prior anthracyclines and taxanes

R

2:1

Eribulin mesylate 1.4 mg/m²; 2-5 min IV days 1, 8 q21d

TPC*

* Any monotherapy (chemotherapy, hormonal, biologic) or supportive care

Twelves C et al. *Proc ASCO* 2010;**Abstract CRA1004**.

3.2

EMBRACE Phase III Study: Efficacy Data of Eribulin versus Treatment of Physician's Choice (TPC) in Locally Recurrent or Metastatic Breast Cancer

	Eribulin (n = 508)	TPC[1] (n = 254)	Hazard ratio	*p*-value
Median overall survival	13.1 months	10.7 months	0.81	0.041
One-year survival	53.9%	43.7%	—	—
Median PFS (independent review)	3.7 months	2.2 months	0.87	0.14
Median PFS (investigator review)	3.6 months	2.2 months	0.76	0.002
Overall response	12.2%	4.7%	—	0.0002

[1] No patients on the TPC arm received biologic therapy alone or supportive care.
PFS = progression-free survival

Twelves C et al. *Proc ASCO* 2010;**Abstract CRA1004**.

Track 10

DR LOVE: As a coauthor of the paper published in *Lancet Oncology* that evaluated the Onco*type* DX assay in patients with node-positive breast cancer, would you comment on the clinical implications of this study?

DR OSBORNE: The growing body of data indicating that certain patients with node-positive disease fare well with hormonal therapy alone led us to

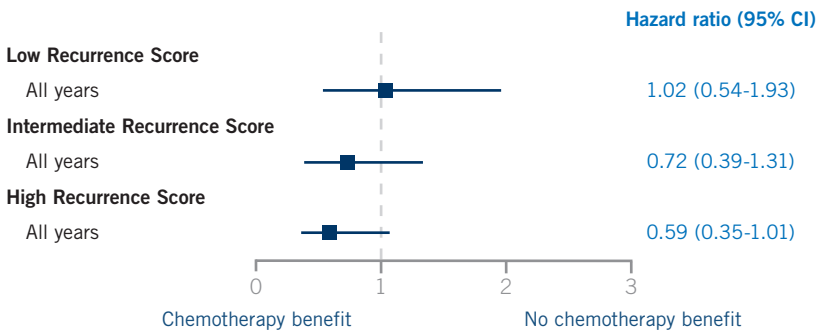
retrospectively evaluate the 21-gene Onco*type* DX assay for approximately 40 percent of the patients who participated in the SWOG-8814 trial.

Our analysis of the Onco*type* DX assay in patients with node-positive breast cancer demonstrated that a much larger proportion of patients who might not receive additional benefit with adjuvant chemotherapy could be identified by the Recurrence Score than by ER and HER2 scores alone (Albain 2010; [3.3]). Patients with low Recurrence Scores don't benefit from chemotherapy, but patients with high Recurrence Scores clearly obtain a substantial benefit (Albain 2009).

It is interesting to note that a strong trend for benefit from adjuvant chemotherapy was evident in patients with intermediate Recurrence Scores, which is different than what was seen in an analysis of patients with node-negative breast cancer (Paik 2004). I must caution that this was a retrospective analysis of a fraction of the larger clinical trial. Therefore, these findings are not definitive, but they are similar to observations that patients with endocrine-responsive tumors don't benefit from chemotherapy. I have changed my practice, and I infrequently use adjuvant chemotherapy for patients with strongly ER-positive, PR-positive, HER2-negative tumors with a low Ki-67 or low Recurrence Scores, even if the nodes are positive. ■

3.3

Disease-Free Survival Hazard Ratios for Tamoxifen Alone versus CAF-T According to Recurrence Risk Group



Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

SELECT PUBLICATIONS

Albain KS et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial.** *Lancet Oncol* 2010;11(1):55-65.

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

Twelves C et al. **A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane.** *Proc ASCO* 2010;**Abstract CRA1004**.

INTERVIEW

Matthew J Ellis, MB, BChir, PhD

Dr Ellis is Professor of Medicine, Head of the Section of Medical Oncology and Director of the Breast Cancer Program at the Washington University School of Medicine in St Louis, Missouri.

Tracks 1-15

Select Excerpts from the Interview

Tracks 8-9

DR LOVE: Would you summarize the key current data sets with fulvestrant in advanced breast cancer and where we are moving with this drug?

DR ELLIS: The so-called "FIRST" trial compared fulvestrant 500 mg to anastrozole as first-line treatment for advanced breast cancer (Robertson

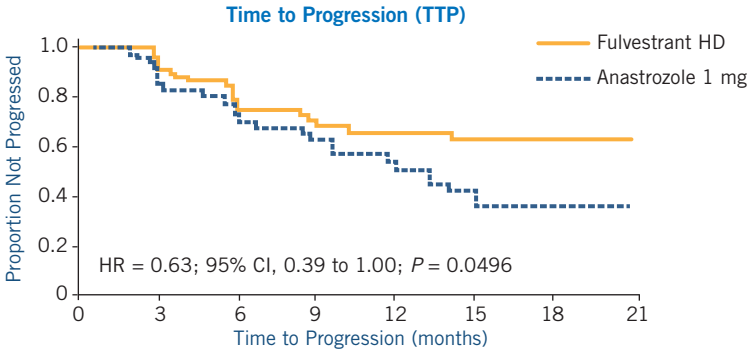
2009; [4.1]). Another study evaluated two doses of fulvestrant in the second-line setting. Evidence from the dose response curve indicated that increasing from 250 mg to 500 mg appeared to be of clinical benefit (di Leo 2010; [4.2]). So both of those trials suggest that the higher dose is more active. Moving forward I believe fulvestrant will be a good partner for combination therapy. I believe we'll be administering more high-dose fulvestrant and evaluating fulvestrant in combination with a variety of signal transduction inhibitors, including the PI3 kinase.

DR LOVE: How do you currently approach fulvestrant dosing in your practice outside of a protocol setting?

DR ELLIS: I'm not convinced the loading dose makes any difference because the curves don't break in favor of the higher dose until two or three months. I administer 500 mg on day one, 500 mg on day 29 and don't bring the patient back in for that extra dose at 14 days. Patients seem to tolerate this approach well.

4.1

FIRST Study: Fulvestrant 500 mg versus Anastrozole for ER-Positive Advanced Breast Cancer



Primary endpoint	Fulvestrant HD (n = 102)	Anastrozole 1 mg (n = 103)	*p*-value
Clinical benefit rate (CBR)*	72.5%	67.0%	0.386

* CBR = complete response + partial response + stable disease ≥ 24 weeks

"The high CBRs for fulvestrant HD and anastrozole of 72.5% and 67.0%, respectively, confirm the high clinical efficacy of both agents. Furthermore, results from the analysis of the primary end point (CBR) indicated that fulvestrant HD was at least as effective as anastrozole. The secondary end points further confirmed the activity of fulvestrant HD in this setting, most notably median TTP, which 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. This is the first clinical trial to compare fulvestrant with anastrozole in first-line advanced breast cancer and to show that another endocrine agent may be more effective than a third-generation AI in this setting."

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

4.2

CONFIRM: A Phase III Trial of Fulvestrant 250 mg versus Fulvestrant 500 mg in ER-Positive Advanced Breast Cancer

	Fulvestrant 500 mg (n = 362)	Fulvestrant 250 mg (n = 374)	Hazard ratio	*p*-value
Median progression-free survival	6.5 months	5.5 months	0.80	0.006
Clinical benefit rate*	45.6%	39.6%	—	—

* Clinical benefit rate = complete response + partial response + stable disease ≥ 24 weeks

Di Leo A et al. *J Clin Oncol* 2010;28(30):4594-600.

Track 11

DR LOVE: What are your thoughts on the overall survival data meta-analysis of bevacizumab and first-line chemotherapy presented at ASCO 2010, and what's the bottom line in terms of how you put together the effect of this agent and its clinical utility?

DR ELLIS: We've discovered that bevacizumab doesn't have single-agent activity in breast cancer and is an obligatory chemotherapy partner. We need more research on bevacizumab to understand the correct population in which to use it. I believe, based on the data, that for patients who need a rapid response — such as those who have visceral crisis, lung and liver disease with increasing LFTs or shortness of breath — a bevacizumab-based regimen seems to yield a benefit faster.

This might be the patient population we should focus on to ascertain if a survival benefit exists with bevacizumab, as all the trials performed in Europe and the United States included a number of patients with more indolent disease for whom death from breast cancer was not a near-term likelihood. Thus survival was difficult to show. ■

SELECT PUBLICATIONS

Di Leo A et al. **Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** *J Clin Oncol* 2010;28(30):4594-600.

O'Shaughnessy J et al. **A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC).** *Proc ASCO* 2010;**Abstract 1005**.

Robertson JFR et al. **A comparison of fulvestrant 500 mg with anastrozole as first-line treatment for advanced breast cancer: Follow-up analysis from the 'FIRST' study.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-3**.

Robertson JF 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 addition of iniparib to carboplatin/gemcitabine in patients with triple-negative metastatic breast cancer resulted in significant improvements in _____.**
   a. Overall response rate
   b. Clinical benefit rate
   c. Progression-free survival
   d. Overall survival
   e. All of the above

2. **Which of the following arms has shown improved clinical benefit in the randomized Phase III EGF104900 study among patients with trastuzumab-resistant breast cancer?**
   a. Lapatinib alone
   b. Lapatinib/trastuzumab

3. **Patients with ER-positive, node-negative or node-positive breast cancer are eligible for the ongoing TAILORx trial.**
   a. True
   b. False

4. **What was the pCR rate with neoadjuvant *nab* paclitaxel in the Phase II study reported by Robidoux and colleagues?**
   a. 10 percent
   b. 29 percent
   c. 51 percent

5. **The Phase III CLEOPATRA study is evaluating the addition of _____ to first-line docetaxel/trastuzumab for patients with HER2-positive metastatic breast cancer.**
   a. T-DM1
   b. Lapatinib
   c. Pertuzumab

6. **What is the mechanism of action of eribulin?**
   a. Microtubule inhibition
   b. Anti-VEGF
   c. HER2 inhibition
   d. Pyrimidine analog

7. **The international Phase III EMBRACE trial evaluated eribulin versus _____ for patients with locally recurrent or metastatic breast cancer who received a median of four prior treatment regimens.**
   a. Capecitabine
   b. Paclitaxel
   c. Treatment of physician's choice

8. **In the EMBRACE trial, eribulin resulted in a statistically significant improvement in overall survival compared to the control arm.**
   a. True
   b. False

9. **The FIRST study demonstrated an improvement in the overall response rate with fulvestrant administered at a dose of _____ in patients with advanced ER-positive breast cancer.**
   a. 500 mg
   b. 250 mg
   c. 750 mg

10. **The CONFIRM trial, which evaluated the 250-mg versus the 500-mg dose of fulvestrant for postmenopausal women with advanced breast cancer, demonstrated a statistically significant difference in time to disease progression favoring the high-dose strategy.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 4, 2010

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
Role of the Onco*type* DX Recurrence Score in clinical decision-making	4 3 2 1	4 3 2 1
NSABP-B-48: A proposed Phase III neoadjuvant trial of TC → carboplatin/gemcitabine or paclitaxel → AC with or without the PARP1 inhibitor iniparib for TNBC	4 3 2 1	4 3 2 1
Novel mechanisms of action of the nontaxane microtubule inhibitor eribulin mesylate in metastatic breast cancer	4 3 2 1	4 3 2 1
Tolerability of *nab* paclitaxel compared to standard-formulation taxanes in metastatic breast cancer	4 3 2 1	4 3 2 1
Emerging data with the estrogen receptor downregulator fulvestrant alone and in combination with anastrozole for ER-positive metastatic breast cancer	4 3 2 1	4 3 2 1
Novel anti-HER2 investigational agents: T-DM1 and pertuzumab	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 (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:

- Appraise the potential utility of genomic assays to aid in the quantification of risk and the selection of individualized treatment for patients with node-negative or node-positive breast cancer. . . . . 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 who may be eligible for anti-angiogenic treatment. . . . . 4 3 2 1 N/M N/A
- Recount the role of poly(ADP-ribose) polymerase (PARP) in the DNA repair pathway, and review the efficacy and safety of the PARP inhibitors for women with triple-negative breast cancer. . . . . 4 3 2 1 N/M N/A
- Consider the efficacy and tolerability of novel agents for the later-line treatment of metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based chemotherapy regimens . . . . . 4 3 2 1 N/M N/A
- Define the role of sentinel lymph node resection versus conventional axillary lymph node dissection in early 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

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
Charles E Geyer Jr, MD	4 3 2 1	4 3 2 1
Kathy D Miller, MD	4 3 2 1	4 3 2 1
C Kent Osborne, MD	4 3 2 1	4 3 2 1
Matthew J Ellis, MB, BChir, 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:

.....

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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).

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UPDATE

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