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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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Hope S Rugo, MD
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EDITOR

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Breast Cancer Update
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OVERVIEW OF ACTIVITY

Breast cancer continues to be 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 and prognostic tools. In order to offer optimal patient care — including the option of clinical trial participation — the practicing cancer clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME activity is designed to assist medical oncologists, hematologist-oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Develop evidence-based treatment approaches for patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Determine the utility of genomic assays in counseling patients with ductal carcinoma in situ or ER-positive early breast cancer about their risk of recurrence and the potential benefits of radiation therapy or adjuvant chemotherapy, respectively.
- Evaluate the unique mechanisms of action and emerging clinical trial data with novel anti-HER2 agents under investigation in breast cancer.
- Recall emerging data on the role of mTOR inhibition in reversing resistance to endocrine therapy and trastuzumab in metastatic breast cancer, and apply this treatment approach in the research and nonresearch management of appropriate patient cases.
- Formulate individualized, evidence-based approaches to first- and later-line therapy for patients with HER2-negative metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Kimberly L Blackwell, MD

Dr Blackwell is Professor of Medicine and Director of the Breast Cancer Program at the Duke Cancer Institute at Durham, North Carolina.

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Track 1 Lead study author's insight on the initial results from EMILIA, a Phase III study of trastuzumab emtansine (T-DM1) versus capecitabine/lapatinib in HER2-positive locally advanced or metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane

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Track 4 Management of transient thrombocytopenia and transaminitis with monitoring and dose adjustments of T-DM1

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Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the results of the Phase III EMILIA study, which you recently presented in the ASCO 2012 plenary session?

DR BLACKWELL: The EMILIA study evaluated T-DM1 versus lapatinib/capecitabine in 980 patients with HER2-positive locally advanced or metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane. The study had 2 coprimary endpoints — progression-free survival (PFS) determined by an independent review and overall survival (OS).

We paid close attention to median dose intensity — which measures how much drug was successfully administered — on both study arms. The dose intensity for lapatinib on the control arm was 94%. On the T-DM1 arm, it was 100%. So, as much as we have

concerns regarding dose adjustments with lapatinib and capecitabine, we were able to administer the combination to these patients and we still observed a benefit for the T-DM1 arm.

Specifically, the study met its first coprimary endpoint — PFS was improved in absolute terms by 3.2 months in favor of T-DM1 with a hazard ratio of 0.65 and a *p*-value of less than 0.0001, so a 35% proportional improvement in PFS was observed (Verma 2012; [1.1]). The other coprimary endpoint was OS, and at the time the PFS event rate was met, a planned interim survival analysis was prompted.

The median OS at the time of the first analysis was 23.3 months for lapatinib/capecitabine but had not been reached for T-DM1. When you evaluate the hazard ratio for survival, it was 0.621 with a *p*-value of 0.0005. It seems as if that should be statistically significant, but because this was a planned interim analysis the preset efficacy stopping boundary was a *p*-value of 0.0003 (Editor's note: Subsequent to this interview the second interim OS analysis results for EMILIA were published; see figure 1.1).

T-DM1 was well tolerated. Patients on the T-DM1 arm experienced primarily as Grade 3/4 adverse events laboratory abnormalities such as elevations in AST/ALT and transient thrombocytopenia. The latter generally occurs somewhere between days 8 and 10, so if you don't specifically look for it between the 21-day cycles you might not see it. Grade 3/4 thrombocytopenia — platelet counts less than 100,000 and something that historically could put patients at an increased risk for bleeding — was reported in approximately 14% of patients. Patients should be aware of it just as with standard chemotherapy. Increased bleeding or excessive nosebleeds should be checked.

1.1

EMILIA: Results of a Phase III Trial of T-DM1 versus Capecitabine (Cape) with Lapatinib (Lap) for HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated with Trastuzumab and a Taxane

Response	**T-DM1** (n = 495)	**Cape/lap** (n = 496)	Hazard ratio	*p*-value
Median progression-free survival	9.6 mo	6.4 mo	0.65	<0.001
Median overall survival (second interim analysis)*	30.9 mo	25.1 mo	0.68	<0.001
Two-year overall survival	64.7%	51.8%	—	—
Select adverse events (Grade ≥3)	**T-DM1** (n = 490)		**Cape/lap** (n = 488)	
Diarrhea	1.6%		20.7%	
Hand-foot syndrome	0%		16.4%	
Vomiting	0.8%		4.5%	
Nausea	0.8%		2.5%	
Mucosal inflammation	0.2%		2.3%	
Elevated AST	4.3%		0.8%	
Elevated ALT	2.9%		1.4%	
Thrombocytopenia	12.8%		0.2%	

* Conducted on the basis of 331 deaths; met the predefined O'Brien-Fleming stopping boundary (efficacy stopping boundary, $p = 0.0037$ or hazard ratio = 0.73)

Verma S et al. *N Engl J Med* 2012;[Epub ahead of print].

We noted increased liver enzymes on both arms of the study but more frequently on the T-DM1 arm. We've seen elevations in AST and ALT with capecitabine and in ALT with lapatinib. AST/ALT levels must be monitored when patients are receiving both of those agents. The same will apply with T-DM1. Approximately 1 out of 4 patients experienced an increase in AST, but severe increases were observed only in 3% to 4% of patients.

No Grade 3/4 hemorrhage-related deaths occurred on the T-DM1 arm. No difference in the transfusion rate and small differences in anemia rates were observed. No Grade 4 anemia was observed on either arm of the study. We reported considerable diarrhea and hand-foot syndrome with capecitabine/lapatinib — approximately 1 out of 4 women experienced Grade 3/4 diarrhea and about 15% of patients experienced Grade 3/4 hand-foot syndrome.

What is meaningful about these differences in toxicity is that the side effects that we observed in the study on the T-DM1 arm didn't affect patient quality of life. T-DM1 seems to be what we've been searching for, which is cancer treatment without chemotherapy side effects.

DR LOVE: What was your approach to T-DM1 dosing during the trial when patients experienced Grade 3/4 toxicities?

DR BLACKWELL: We followed well-described dose adjustments in this study for T-DM1. The agent is dosed based on milligrams-per-kilogram dosing. On the first dose reduction you decrease from 3.6 mg/kg to 3 mg/kg, and then the second dose adjustment is to 2.4 mg/kg. If you run into any other Grade 3/4 toxicity after those 2 dose reductions, it is recommended that treatment with the drug be stopped. Because of its long half-life, it won't be like dosing weekly chemotherapy. With every 3-week paclitaxel you can dose adjust it and administer it weekly. You can't do that with T-DM1, given its long half-life.

Tracks 5, 7, 11

DR LOVE: An important issue if and when T-DM1 becomes available is how it might fit in the HER2-positive metastatic algorithm, and in this regard can you discuss how you are approaching the use of pertuzumab now in your practice given its recent FDA approval?

DR BLACKWELL: The pertuzumab approval was based on the CLEOPATRA study, which was a first-line trial of docetaxel/trastuzumab with or without pertuzumab for HER2-positive mBC. Results reported earlier this year indicated an improvement in PFS of approximately 6 months with the addition of pertuzumab, and a recent press release after pertuzumab was approved by the FDA reported that an updated survival analysis showed a significant advantage with the addition of pertuzumab to trastuzumab and docetaxel (Baselga 2012; [1.2]).

I believe the standard first-line therapy will be pertuzumab/trastuzumab and docetaxel, considering this survival advantage. What we're all grappling with is, will we be able to use the combination outside of the first-line setting, outside of the actual eligibility criteria for the CLEOPATRA trial, and will it be covered? The other issue is that docetaxel is a particularly difficult regimen for patients with mBC to complete.

1.2

CLEOPATRA: A Phase III Trial of the Addition of Pertuzumab versus Placebo to Docetaxel/Trastuzumab as First-Line Therapy for Patients with HER2-Positive Metastatic Breast Cancer

	Pertuzumab (n = 402)	Placebo (n = 406)	Hazard ratio	*p*-value
Median progression-free survival[1]	18.5 mo	12.4 mo	0.62	<0.001
Interim overall survival analysis (deaths)*[1]	17.2%	23.6%	0.64	0.005

* Not significant because analysis did not meet O'Brien-Fleming stopping boundary; a trend was evident toward overall survival benefit with pertuzumab

Press release (June 22, 2012): Patients with HER2-positive metastatic breast cancer lived significantly longer (overall survival) when treated with the combination of pertuzumab, trastuzumab and docetaxel chemotherapy compared to trastuzumab and docetaxel chemotherapy alone in the Phase III CLEOPATRA study. These data will be submitted for presentation at an upcoming medical meeting.[2]

[1] Baselga J et al. *N Engl J Med* 2012;366(2):109-19.
[2] **www.roche.com/media/media_releases/med-cor-2012-06-22.html**.

When I administer the combination of docetaxel/pertuzumab/trastuzumab, I will almost certainly set a limit to the amount of docetaxel. I'll set an expectation with the patient that if we run into toxicity, we'll dose reduce. I'll likely drop docetaxel soon after the sixth cycle and administer the dual antibody combination and restage after about 9 weeks to ascertain that the chemotherapy backbone wasn't necessary.

DR LOVE: What are your thoughts on substituting either paclitaxel or nanoparticle albumin-bound (*nab*) paclitaxel for docetaxel with pertuzumab and trastuzumab?

DR BLACKWELL: I wouldn't have a problem, if it was covered, administering *nab* paclitaxel or paclitaxel in place of docetaxel. In my practice about once or twice a week we administer an initial dose of docetaxel, and as the first few drops are going in, the patient starts having trouble breathing and then we have to administer corticosteroids. I believe after such experiences we'd consider switching to *nab* paclitaxel or paclitaxel. I believe *nab* paclitaxel has some advantages, including the fact that it doesn't have the allergic reaction rate that we see with paclitaxel. I think the *nab* paclitaxel weekly dosing schedule needs some tweaking. With some better understanding of what the appropriate dosing schedule is, *nab* paclitaxel can be a useful agent.

DR LOVE: And how might T-DM1 fit in?

DR BLACKWELL: My bias will likely be toward using T-DM1 before I use pertuzumab strictly because of the chemotherapy backbone required for pertuzumab. If payers and reimbursement require that pertuzumab be used only in the first chemotherapy-based, HER2-directed combination, then I will probably administer more first-line pertuzumab. If and when T-DM1 is approved, I believe it will be available as first-, second- and third-line therapy because that's how it was evaluated in the EMILIA study. Then the real wild card is getting pertuzumab available to patients beyond the first-line setting. ■

SELECT PUBLICATIONS

Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Verma S et al. **Trastuzumab emtansine for HER2-positive advanced breast cancer.** *N Engl J Med* 2012;[Epub ahead of print].

INTERVIEW

Hope S Rugo, MD

Dr Rugo is Professor of Medicine and Director of Breast Oncology and Clinical Trials Education at the University of California Helen Diller Family Comprehensive Cancer Center in San Francisco, California.

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Track 1 Trial overview, goals and difficulties encountered during the CALGB-40502 study

Track 2 Clinical experience with attenuated dosing and avoidance of steroid premedications with *nab* paclitaxel

Track 3 Perspective on the current utility of the Onco*type* DX® DCIS Score™ in decision-making about radiation therapy

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Track 11 Incorporation of pertuzumab into the treatment algorithm for HER2-positive mBC

Track 12 APHINITY: An ongoing Phase III trial evaluating the addition of pertuzumab to chemotherapy/trastuzumab as adjuvant therapy for HER2-positive early-stage BC

Track 13 Perspective on recent clinical advances associated with hormonal therapy

Track 14 Overview of 5-HT3 antagonists as antiemetics for moderately and highly emetogenic chemotherapy

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the Phase III CALGB-40502 study you presented at ASCO, evaluating 3 microtubule inhibitors as first-line therapy for metastatic breast cancer?

DR RUGO: The goal of the trial was to determine whether *nab* paclitaxel and ixabepilone would be superior to paclitaxel in terms of PFS or equivalent and have less toxicity. For the study, 799 women with chemotherapy-naïve, metastatic, HER2-normal breast cancer were randomly assigned to weekly paclitaxel, *nab* paclitaxel

or ixabepilone (Rugo 2012; [2.1]). Bevacizumab was administered to almost all the patients. After the recommendation that bevacizumab approval for mBC be withdrawn, bevacizumab use was made optional. However, 98% of patients received bevacizumab.

Hematologic toxicity was greater for *nab* paclitaxel compared to paclitaxel. Peripheral and motor neuropathy was higher for both experimental arms. The ixabepilone arm was closed early due to futility. Eventually the entire study was halted for the same reason. The results showed that both the ixabepilone and *nab* paclitaxel arms had a shorter PFS compared to paclitaxel. These newer agents offered the promise of being able to reverse resistance in this patient population, but paclitaxel was as good or better.

DR LOVE: Outside a research setting, do you utilize *nab* paclitaxel and at what dose?

DR RUGO: Yes, definitely. I believe *nab* paclitaxel has an important place in the treatment of advanced breast cancer in patients who cannot tolerate the solvent Cremophor® or steroids. For patients with preexisting peripheral neuropathy, I administer *nab* paclitaxel at a lower dose of 100 mg/m^2 as a measure to avoid the additional toxicity of Cremophor. I have never administered the higher dose of 150 mg/m^2 used in the trial and I would not now.

2.1

CALGB-40502 Study: Weekly Paclitaxel versus *Nab* Paclitaxel or Ixabepilone with or without Bevacizumab for Locally Recurrent or Metastatic Breast Cancer

Efficacy	***Nab* paclitaxel** (n = 271)	**Paclitaxel** (n = 283)	**Ixabepilone** (n = 245)
Median progression-free survival	9.2 mo	10.6 mo	7.6 mo
	Nab paclitaxel vs paclitaxel HR = 1.19, $p = 0.12$ Ixabepilone vs paclitaxel HR = 1.53, $p < 0.0001$		
Select Grade ≥3 adverse events	***Nab* paclitaxel** (n = 258)	**Paclitaxel** (n = 262)	**Ixabepilone** (n = 237)
Hematologic	51%	21%	12%
Nonhematologic	60%	44%	56%
Motor neuropathy	10%	2%	6%
Sensory neuropathy	25%	16%	25%

Rugo HS et al. *Proc ASCO* 2012;**Abstract CRA1002**.

Track 3

DR LOVE: At San Antonio last year for the first time we saw data on an Onco*type* DX assay in DCIS (Solin 2011; [2.2]). What were your thoughts about that?

DR RUGO: The Onco*type* DX Recurrence Score® was the first test that was able to predict who might benefit the most from adjuvant chemotherapy. That is a critical question for patients with ER-positive early-stage breast cancer. Hopefully, over time and with more data, we'll be able to make similar decisions for patients with DCIS.

With the Onco*type* DX DCIS assay, we're not deciding if a patient should receive chemotherapy or not. We're trying to identify patients with low-risk DCIS who can undergo surgery only, without the need for radiation therapy. Slow-growing DCIS could be managed with a fairly conservative approach in elderly patients. The Onco*type*

DX DCIS Score will help us understand who needs less therapy as opposed to us utilizing the same approach for everyone.

2.2

ECOG-E5194 Study: 10-Year Outcome of Ipsilateral Breast Events (IBE) by the Oncotype DX DCIS Score Evaluated by Prespecified Risk Groups

	DCIS Score risk group			
Type of IBE	**Low** (n = 246)	**Intermediate** (n = 45)	**High** (n = 36)	*p*-value*
Any IBE	12.0%	24.5%	27.3%	0.02
Invasive IBE	5.1%	8.9%	19.1%	0.01

* Log-rank *p*-value from a Kaplan-Meier risk curve

"The DCIS Score provides independent information on IBE risk beyond clinical pathologic variables including such important clinical variables as prior tamoxifen use, tumor grade and negative margin width."

Solin LJ et al. San Antonio Breast Cancer Symposium 2011;**Abstract S4-6**.

Tracks 6-7

DR LOVE: Would you discuss the BOLERO-2 trial, which evaluated exemestane and everolimus for patients with ER-positive locally advanced or metastatic breast cancer refractory to nonsteroidal aromatase inhibitors (AIs)?

DR RUGO: The results of BOLERO-2 are exciting because it is the first trial that showed that hormone resistance could be reversed (Baselga 2012; [2.3]). We worked hard to find tissue biomarkers that would determine who might respond to the addition of everolimus to standard hormone therapy. We never found a biomarker, but

2.3

BOLERO-2 Trial: Exemestane and Everolimus in ER/PR-Positive Metastatic Breast Cancer Refractory to Nonsteroidal Aromatase Inhibitors

Efficacy	**Everolimus + exemestane** (n = 485)	**Placebo + exemestane** (n = 239)	HR	*p*-value
Median PFS (by central assessment)	10.6 mo	4.1 mo	0.36	<0.001
ORR (by local assessment)	9.5%	0.4%	—	<0.001
	Everolimus + exemestane (n = 482)		**Placebo + exemestane** (n = 238)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Stomatitis	56%	8%	11%	1%
Fatigue	33%	<4%	26%	1%
Dyspnea	18%	4%	9%	<2%
Anemia	16%	6%	4%	<2%
Hyperglycemia	13%	<5%	2%	<1%
Pneumonitis	12%	3%	0%	0%

HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate

Baselga J et al. *N Engl J Med* 2012;366(6):520-9.

we found that if you administer a steroidal AI such as exemestane to patients who have experienced disease progression on an AI, you have already selected a group of patients in whom this pathway may be activated.

The addition of everolimus to exemestane resulted in a longer PFS. Fewer deaths occurred on that arm, but the OS endpoint has not yet been reached. It is intriguing that everolimus appears to be associated with some bone effects, with preservation of bone density as opposed to the bone loss that we see with AIs.

We would like to prevent relapse and death in patients who have developed resistance rapidly or have up-front resistance to hormone therapy. A trial adding everolimus for patients with higher-risk, ER-positive, early-stage breast cancer is planned. Moving forward it will be critical to find the subgroup of patients who will benefit from everolimus.

Oncologists need to be aware of the toxicity profile of this agent and to dose reduce everolimus and hold the drug when patients develop mouth sores and, rarely, interstitial pneumonitis.

DR LOVE: How significant is the pneumonitis when everolimus is combined with hormonal therapy, and how do you screen patients for it?

DR RUGO: Pneumonitis is not as much of an issue as we feared it might be. It occurs in less than 1% of patients and is usually mild. Patients who develop a cough or interstitial changes on a CT scan and are asymptomatic must be watched carefully. The agent should be held, if necessary, and if the dose is reduced many patients can go back on the drug without a problem.

DR LOVE: What are your thoughts on the BOLERO-1 and BOLERO-3 Phase III studies of everolimus in combination with chemotherapy/trastuzumab in HER2-positive locally advanced or metastatic breast cancer?

DR RUGO: These trials are investigating the addition of everolimus to trastuzumab for first-line and later-line therapy. Data from a Phase II trial reported that the addition of everolimus to trastuzumab for patients with progressive disease on trastuzumab-based therapy resulted in clinical benefit and disease response in a reasonable number of patients (Morrow 2011). So we know that mTOR inhibitors have some ability to counter resistance to trastuzumab in HER2-positive breast cancer. These small molecules also cross the blood-brain barrier and may fill a unique niche for treating metastatic, resistant, HER2-positive breast cancer. ■

SELECT PUBLICATIONS

Baselga J et al. **Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2012;366(6):520-9.

Hurvitz SA et al. **BOLERO-1: A randomized, phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel as first-line therapy in women with HER2-positive (HER2+), locally advanced or metastatic breast cancer (BC).** *Proc ASCO* 2012;**Abstract TPS648**.

Morrow PK et al. **Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy.** *J Clin Oncol* 2011;29(23):3126-32.

Rugo HS et al. **CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC).** *Proc ASCO* 2012;**Abstract CRA1002**.

INTERVIEW

Adam M Brufsky, MD, PhD

Dr Brufsky is Professor of Medicine at the University of Pittsburgh, Associate Director for Clinical Investigation at the University of Pittsburgh Cancer Institute, Co-Director of the Comprehensive Breast Cancer Center and Associate Division Chief in the Department of Medicine's Division of Hematology/Oncology in Pittsburgh, Pennsylvania.

Tracks 1-14

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss what was reported at ASCO on the NSABP-B-38 trial comparing adjuvant TAC to dose-dense AC → P with or without gemcitabine for patients with node-positive breast cancer?

DR BRUFSKY: NSABP-B-38 is an interesting trial. The results were long awaited, but I believe that many of us had already taken sides. The dose-dense aficionados

thought the dose-dense regimen was going to work, the TAC aficionados thought TAC was a superior regimen and other people thought more was better and that adding gemcitabine would be an improvement.

Also interesting is that the trial didn't evaluate what I believe to be a very favorable regimen, at least in terms of tolerability and efficacy, which is AC followed by weekly paclitaxel from the ECOG-E1199 study (Sparano 2008). It is unfortunate that this regimen wasn't one of the arms on the trial.

The bottom line from the study was that, at least statistically, no difference was evident — only a slight trend was detected in favor of dose-dense therapy. Absolutely no benefit was seen with the use of gemcitabine (Swain 2012; [3.1]).

The fact that no benefit was evident with the addition of gemcitabine did not surprise me. If you consider past neoadjuvant studies that have taken similar approaches to adding beyond standard AC → T, you can argue that regardless of the choice of agent not much of a difference is observed.

3.1

NSABP-B-38: Definitive Analysis of an Adjuvant Trial Comparing Dose-Dense (DD) AC → Paclitaxel with Gemcitabine to DD AC → Paclitaxel and to TAC for Patients with Operable, Node-Positive Breast Cancer

Efficacy	DD AC → PG	DD AC → P	TAC
Five-year disease-free survival (n = 1,613; 1,618; 1,610)	80.6%	82.2%	80.1%
Five-year overall survival (n = 1,618; 1,624; 1,617)	90.8%	89.1%	89.6%

AC = doxorubicin/cyclophosphamide; P = paclitaxel; G = gemcitabine; TAC = docetaxel/doxorubicin/cyclophosphamide

Swain SM et al. *Proc ASCO* 2012;**Abstract LBA1000**.

Tracks 10-12

Case discussion

A 38-year-old woman with a 6-cm, ER-positive, PR-negative, HER2-positive infiltrating ductal carcinoma with a 3-cm, biopsy-proven breast cancer metastasis in the liver experiences a near-complete response with docetaxel/carboplatin/trastuzumab (TCH)

DR BRUFSKY: This patient was young and desired aggressive therapy. A number of people may consider administering paclitaxel/trastuzumab but I administered TCH, which is my "go-to regimen." To digress somewhat to the adjuvant treatment of HER2-positive breast cancer, I know there's been a lot of debate about AC followed by docetaxel/trastuzumab versus TCH. I was an involved participant in the adjuvant BCIRG 006 trial that compared these regimens. I used to administer AC followed by docetaxel/trastuzumab somewhat frequently.

In my view the recurrence rate is numerically higher with TCH than with AC followed by docetaxel/trastuzumab, but when you evaluate the overall picture and other potential complications associated with the latter regimen, everything evens out (Slamon 2011; [3.2]). We have to evaluate the big picture, not simply the breast cancer.

This patient actually attained a near-complete response in both the breast and the liver with TCH. This has occurred within the last month, and now we're trying to figure out the best next approach for her. The first question was, "Do we remove the primary breast tumor?" She opted to do so, so we performed a mastectomy. We also discussed options — laparoscopic resection, radiofrequency ablation, cryotherapy, observation, et cetera — for the mass in her liver, and we opted to observe.

The next question was what to do next. The options for a premenopausal patient such as this one would be an LHRH agonist or tamoxifen. I chose tamoxifen and I'm continuing the trastuzumab. But the big issue now is, does she receive pertuzumab? I'd love to be able to administer trastuzumab, pertuzumab and tamoxifen, but we don't have data on this approach. ■

3.2

BCIRG 006: A Phase III Trial Evaluating AC → Docetaxel, AC → Docetaxel/ Trastuzumab and Docetaxel/Carboplatin/Trastuzumab in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer

Outcome	AC → T (n = 1,073)	AC → TH (n = 1,074)	TCH (n = 1,075)
Estimated 5-year disease-free survival	75%	84%	81%
Hazard ratio, *p*-value	—	0.64, <0.001	0.75, 0.04
Estimated 5-year overall survival	87%	92%	91%
Hazard ratio, *p*-value	—	0.63, <0.001	0.77, 0.04
Cardiac-related adverse events	**AC → T**	**AC → TH**	**TCH**
Cardiac-related death	0%	0%	0%
Grade 3 or 4 congestive heart failure	0.7%	2.0%	0.4%
>10% relative reduction in LVEF	11.2%	18.6%	9.4%

AC = doxorubicin/cyclophosphamide; T = docetaxel; H = trastuzumab; TCH = docetaxel/carboplatin/ trastuzumab

Slamon D et al. *N Engl J Med* 2011;365(14):1273–83.

SELECT PUBLICATIONS

Abbott DE et al. **Resection of liver metastases from breast cancer: Estrogen receptor status and response to chemotherapy before metastasectomy define outcome.** *Surgery* 2012;151(5):710–6.

Duan XF et al. **Outcome of patients with liver-only metastases from breast cancer after mastectomy: A retrospective analysis.** *J Cancer Res Clin Oncol* 2011;137(9):1363–70.

Rocque G et al. **Adjuvant therapy for HER2+ breast cancer: Practice, perception, and toxicity.** *Breast Cancer Res Treat* 2012;131(2):713–21.

Ruiterkamp J, Ernst MF. **The role of surgery in metastatic breast cancer.** *Eur J Cancer* 2011;47(Suppl 3):6–22.

Slamon D et al. **Adjuvant trastuzumab in HER2-positive breast cancer.** *N Engl J Med* 2011;365(14):1273–83.

Sparano JA et al. **Weekly paclitaxel in the adjuvant treatment of breast cancer.** *N Engl J Med* 2008;358(16):1663–71.

Swain SM et al. **NSABP B-38: Definitive analysis of a randomized adjuvant trial comparing dose-dense (DD) AC → paclitaxel (P) plus gemcitabine (G) with DD AC → P and with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with operable, node-positive breast cancer.** *Proc ASCO* 2012;**Abstract LBA1000**.

INTERVIEW

Nancy U Lin, MD

Dr Lin is Associate Professor of Medicine at Harvard Medical School and Clinical Director of the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-14

Track 1 LANDSCAPE: Results from a Phase II study of lapatinib and capecitabine in patients with brain metastases from HER2-positive mBC before whole-brain radiation therapy

Track 2 Ongoing clinical trials evaluating novel agents for patients with HER2-positive BC and brain metastasis

Track 3 Management of brain metastasis with stereotactic radiosurgery alone

Track 4 HALT MBC: A Phase III study of HER2 suppression with the addition of lapatinib to trastuzumab in HER2-positive mBC

Track 5 Efficacy results from a Phase II study of the irreversible ErbB family blocker afatinib (BIBW 2992) for patients with HER2-positive mBC progressing after trastuzumab

Track 6 Toxicities associated with the irreversible EGFR/HER2 TKIs afatinib and neratinib for HER2-positive mBC

Track 7 Critical appraisal of anthracycline- and nonanthracycline-containing adjuvant regimens in HER2-positive BC

Track 8 **Case discussion:** A 60-year-old woman with a Grade III, ER/PR-positive, HER2-negative IDC with 5 of 6 residual positive lymph nodes is randomly assigned to adjuvant bevacizumab/metronomic chemotherapy and dietary intervention on the ABCDE trial

Track 9 Efficacy of metronomic chemotherapy in combination with bevacizumab in advanced BC

Track 10 Challenges for inclusion and evaluation of lifestyle interventions in clinical trials

Track 11 Influences of metformin and lifestyle-directed interventions on patient outcomes

Track 12 **Case discussion:** A 45-year-old premenopausal woman with a Grade I, ER/PR-positive, HER2-negative IDC, a negative sentinel lymph node biopsy and an Onco*type* DX assay Recurrence Score of 17

Track 13 Perspective on the utility of the Onco*type* DX assay in node-positive and large node-negative BC

Track 14 RxPONDER: A Phase III trial of adjuvant endocrine therapy with or without chemotherapy for patients with node-positive BC and a Recurrence Score of 25 or lower

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What's new in terms of management of patients with breast cancer and brain metastases?

DR LIN: No systemic agents have been approved for the indication of brain metastasis. However, a number of trials are ongoing in this setting, and some of them are promising. One Phase II trial with multiple study sites across the country is evaluating GRN1005 in both breast cancer and non-small cell lung cancer. This agent was active in a Phase I trial for patients with advanced solid tumors (Kurzrock 2012).

Another study being opened nationally within the Translational Breast Cancer Research Consortium is evaluating the HER2-targeted agent neratinib, which is an oral tyrosine kinase inhibitor (TKI) similar to lapatinib. In a Phase II trial in the non-CNS setting, the response rates were around 25% in patients with trastuzumab-refractory breast cancer.

Some data were also presented recently from the LANDSCAPE trial, which evaluated the combination of lapatinib and capecitabine. In contrast to the way many clinical trials for patients with brain metastases are conducted, the investigators evaluated this combination as initial therapy at the time of brain metastasis presentation. As a result, these patients generally had less heavily pretreated disease than do most patients we tend to enroll on brain metastasis trials.

The authors reported a high response rate in the brain — more than 60% (Bachelot 2011; [4.1]). In terms of safety, they did not observe many patients with symptomatic disease progression while on trial. The patients who did experience disease progression were asymptomatic, and it was only identified at the time of their usual restaging. I'm not sure that I'm ready to administer this regimen in place of the standard, which would be radiation therapy for most patients, but I believe that in some situations it could be useful.

4.1

LANDSCAPE: Results from a Phase II Study of Lapatinib (Lap) and Capecitabine (Cape) for Patients with Brain Metastases from HER2-Positive Breast Cancer Before Whole-Brain Radiation Therapy (WBRT)

Response	Cape + lap
CNS objective response (centrally confirmed, n = 35)*	67.4%
Median time to disease progression (n = 44)	5.5 months
CNS site of first progression (n = 43)	73.4%
Extra-CNS site of first progression (n = 43)	7.0%
Concomitant CNS and extra-CNS sites of first progression (n = 43)	11.6%
Median time to WBRT (n = 43)	7.8 months
Select adverse events (Grade 3 or 4)	**n = 45**
Diarrhea	20.0%
Hand-foot syndrome	20.0%
Fatigue	13.3%
Rash	4.4%
Nausea	2.2%

* ≥50% volumetric reduction of CNS lesions

Bachelot TD et al. *Proc ASCO* 2011;**Abstract 509**.

Tracks 5-6

DR LOVE: Would you talk about the results of your Phase II study of afatinib, an irreversible EGFR TKI we've heard a lot about in lung cancer, for patients with HER2-positive mBC progressing after trastuzumab?

DR LIN: As you know, a number of HER2-targeted TKIs exist, and we recently published results from a Phase II study evaluating afatinib in patients with refractory breast cancer who'd received a median of 3 prior lines of HER2-directed therapy in the metastatic setting. The response rate including stable disease was 46% (Lin 2012; [4.2]). Data have also been reported with neratinib, for which a 25% response rate was observed in a similar patient population.

DR LOVE: What about toxicities with these new TKIs? Lapatinib is a bit of a challenge to start with, and neratinib has a reputation of being difficult to tolerate. What about afatinib?

DR LIN: In the afatinib study we published, the rate of Grade 3 diarrhea was 25%. So these agents do carry toxicities with them, probably related to the EGFR effect. These agents are not associated with alopecia, but the diarrhea, although manageable, is a concerning side effect and is different than we would see with T-DM1 or pertuzumab, for example. Some newer HER2-targeted TKIs that are a little further behind in development target HER2 and not EGFR. It is conceivable that they may be better tolerated, although we don't have the efficacy data yet.

4.2

Phase II Study of Afatinib for Patients with HER2-Positive Metastatic Breast Cancer Progressing After Trastuzumab

Response	All treated patients (n = 41)	Evaluable patients (n = 35)
CR + PR + SD	46%	54%
PR	10%	11%
SD	37%	43%
Progressive disease	39%	46%
Median PFS	15.1 weeks	—
Median overall survival	61.0 weeks	—
Select adverse events (n = 41)	**All grades**	**Grade 3**
Diarrhea	90.2%	24.4%
Rash	65.9%	9.8%

CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival

Lin NU et al. *Breast Cancer Res Treat* 2012;133(3):1057-65.

Tracks 8, 10-11

DR LOVE: I also want to ask you about an issue that doesn't get much exposure in terms of inclusion in clinical research — the role of diet and exercise. The ongoing Phase II ABCDE trial at your institution includes a randomization to these interventions. Would you discuss the status of that trial?

DR LIN: Although it's easy to tell patients to "make sure you're not gaining weight and try to exercise more," it's difficult to make lifestyle changes. If we were able to demonstrate that a particular intervention led to better outcomes, you might imagine that this would then be covered by insurance and that people would have better access to it.

The ABCDE trial includes a 2-by-2 randomization. The first randomization is to a low-dose metronomic cyclophosphamide/methotrexate regimen with bevacizumab

versus no chemotherapy/bevacizumab therapy, and the second randomization is to a series of telephone-based counseling sessions on diet interventions versus the diet intervention counseling in combination with counseling to encourage increased exercise.

DR LOVE: What have you observed with patients who've been randomly assigned to the diet and exercise intervention arm?

DR LIN: The patients who have been assigned to the intensive lifestyle intervention have uniformly felt positive about it. I believe that's because they can immediately see the effect. So regardless of whether lifestyle interventions end up improving disease-free survival, as has been previously reported in other studies (Chlebowski 2006), they have already been shown to yield improvements in endurance and decreases in level of fatigue and in overall weight. These are all factors that people can feel immediately.

Track 14

DR LOVE: Would you provide an update on the TAILORx and RxPONDER trials evaluating Onco*type* DX in patients with node-negative and node-positive disease?

DR LIN: We placed a few patients at our institution on the TAILORx trial. It's interesting because it was predicted that TAILORx would encounter difficulty in accruing patients but in fact this trial has exceeded all expectations.

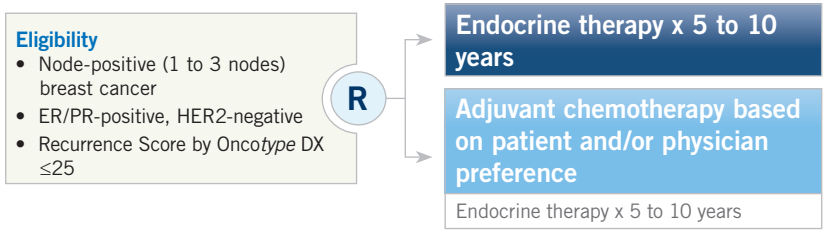
Our institution is also participating in the RxPONDER trial for patients with up to 3 positive nodes (4.3). RxPONDER was designed to anticipate that a number of patients would not accept the randomization, so it was powered to have enough people enter the actual randomization. Some predictions were made of what that rate would be, and so far accrual is going well for the RxPONDER trial. Patients are getting the result and continuing on toward randomization. ■

4.3

Phase III Randomized Clinical Trial of Adjuvant Endocrine Therapy with or without Chemotherapy in Node-Positive Breast Cancer

Protocol IDs: SWOG-S1007; RxPONDER

Target Accrual: 4,000



www.clinicaltrials.gov. Identifier NCT01272037, October 2012.

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study.** *J Natl Cancer Inst* 2006;98(24):1767-76.

Kurzrock R et al. **Safety, pharmacokinetics, and activity of GRN1005, a novel conjugate of angiopep-2, a peptide facilitating brain penetration, and paclitaxel, in patients with advanced solid tumors.** *Mol Cancer Ther* 2012;11(2):308-16.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Primary results from the Phase III EMILIA study evaluating T-DM1 versus capecitabine and lapatinib for patients with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane reported a median PFS of 6.4 months with capecitabine/lapatinib versus 9.6 months with T-DM1.**
   a. True
   b. False

2. **Common side effects of Grade 3 or higher reported for patients receiving T-DM1 on the EMILIA study included which of the following?**
   a. Elevations in ALT, AST
   b. Thrombocytopenia
   c. Anemia
   d. All of the above

3. **The Phase III CLEOPATRA study demonstrated a statistically significant advantage in _____ with the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy for patients with HER2-positive mBC.**
   a. OS
   b. PFS
   c. Both a and b
   d. Neither a nor b

4. **The Phase III CALGB-40502 trial of weekly paclitaxel versus *nab* paclitaxel or ixabepilone with or without bevacizumab for locally recurrent or metastatic breast cancer demonstrated that paclitaxel was inferior to *nab* paclitaxel and ixabepilone.**
   a. True
   b. False

5. **The BOLERO-2 trial of exemestane with or without everolimus for patients with ER-positive locally advanced or metastatic breast cancer refractory to nonsteroidal AIs demonstrated significant improvements in response rate and PFS with the addition of everolimus to exemestane.**
   a. True
   b. False

6. **BOLERO-1 and BOLERO-3 are Phase III studies evaluating _____ in combination with trastuzumab and chemotherapy for women with HER2-positive locally advanced or metastatic breast cancer.**
   a. Temsirolimus
   b. Everolimus
   c. Lapatinib

7. **The 5-year definitive analysis of the Phase III adjuvant NSABP-B-38 trial comparing 3 chemotherapy regimens demonstrated significant improvements in _____ with dose-dense (DD) AC → paclitaxel (P) with gemcitabine compared to DD AC → P.**
   a. Disease-free survival
   b. Overall survival
   c. None of the above

8. **The Phase II LANDSCAPE study evaluating lapatinib and capecitabine for patients with brain metastases from HER2-positive mBC reported a 67% CNS objective response rate in patients receiving this combination _____ whole-brain radiation therapy.**
   a. Prior to
   b. After

9. **A Phase II study of the irreversible ErbB family blocker afatinib reported a 46% overall rate of objective response or stable disease in patients with HER2-positive mBC progressing after trastuzumab.**
   a. True
   b. False

10. **The ongoing Phase II ABCDE trial is evaluating low-dose metronomic cyclophosphamide/methotrexate with _____ versus no therapy with a second randomization to dietary interventions versus dietary and exercise interventions.**
    a. Afatinib
    b. Bevacizumab
    c. Neratinib
    d. Trastuzumab

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 3, 2012

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 1 — 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
EMILIA: Initial efficacy and toxicity data from a Phase III trial of T-DM1 versus capecitabine/lapatinib in HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane	4 3 2 1	4 3 2 1
Use of first-line docetaxel/trastuzumab in combination with pertuzumab for HER2-positive mBC and considerations for taxane substitution with this combination	4 3 2 1	4 3 2 1
Efficacy and toxicity results from a Phase II study of afatinib for patients with HER2-positive mBC progressing after trastuzumab	4 3 2 1	4 3 2 1
BOLERO-2 trial: Exemestane combined with everolimus in ER-positive locally advanced or metastatic breast cancer refractory to nonsteroidal AIs	4 3 2 1	4 3 2 1
Avoidance of steroid premedication with *nab* paclitaxel in patients with 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:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

.....

The content of this activity matched my current (or potential) scope of practice.

☐ 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:

- Develop evidence-based treatment approaches for patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings. ..... 4 3 2 1 N/M N/A
- Determine the utility of genomic assays in counseling patients with ductal carcinoma in situ or ER-positive early breast cancer about their risk of recurrence and the potential benefits of radiation therapy or adjuvant chemotherapy, respectively. ..... 4 3 2 1 N/M N/A
- Evaluate the unique mechanisms of action and emerging clinical trial data with novel anti-HER2 agents under investigation in breast cancer.. ..... 4 3 2 1 N/M N/A
- Recall emerging data on the role of mTOR inhibition in reversing resistance to endocrine therapy and trastuzumab in metastatic breast cancer, and apply this treatment approach in the research and nonresearch management of appropriate patient cases. ..... 4 3 2 1 N/M N/A
- Formulate individualized, evidence-based approaches to first- and later-line therapy for patients with HER2-negative metastatic 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

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

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 2 — 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
Kimberly L Blackwell, MD	4 3 2 1	4 3 2 1
Hope S Rugo, MD	4 3 2 1	4 3 2 1
Adam M Brufsky, MD, PhD	4 3 2 1	4 3 2 1
Nancy U Lin, 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:

.....

.....

.....

REQUEST FOR CREDIT — Please print clearly

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