BCU | 2011 VOL 10 | ISSUE 2

Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Clifford Hudis, MD
Harold J Burstein, MD, PhD
Adam M Brufsky, MD, PhD
Melody A Cobleigh, MD

EDITOR

Neil Love, MD

CME Certified

Subscribe to Podcasts or download MP3s of this program at ResearchToPractice.com/BCU211

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 and 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/oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Determine the utility of genomic assays in counseling patients with ER-positive early breast cancer about their risk of recurrence and the potential benefits of adjuvant chemotherapy.
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic role of bisphosphonates and other bone-targeted agents in disease management.
- 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.
- Evaluate the unique mechanisms of action and the emerging clinical data with novel anti-HER2 agents under investigation in breast cancer.
- Consider the efficacy and tolerability of novel agents for the later-line treatment of metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph, complete the Post-test with a score of 70 percent or better and fill out the Educational Assessment and Credit Form located in the back of this monograph or on our website at **ResearchToPractice.com/BCU211/CME**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/BCU211** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in **blue, bold text**.

This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Eisai Inc, Genentech BioOncology, Genomic Health Inc and Sanofi.

Last review date: August 2011; Release date: August 2011; Expiration date: August 2012

TABLE OF CONTENTS

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — **Dr Burstein** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Hudis** — Paid Research: Merck and Company Inc, Onyx Pharmaceuticals Inc. **Dr Brufsky** — Consulting Agreements: Genentech BioOncology, Novartis Pharmaceuticals Corporation; Speakers Bureau: Novartis Pharmaceuticals Corporation, Sanofi. **Dr Cobleigh** — Advisory Committee: Eisai Inc, Genentech BioOncology, Genomic Health Inc; Paid Research: Genentech BioOncology.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Allos Therapeutics, Amgen Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

INTERVIEW

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the data analysis of the BIG 1-98 and ATAC trials presented at SABCS 2010 in relation to CYP2D6 genotyping and clinical outcome in postmenopausal women with early breast cancer?

DR HUDIS: This has been an area of controversy because we have conflicting evidence on the use of CYP2D6 testing to assist with making treatment decisions. The hypothesis that CYP2D6 genotype could predict response to

tamoxifen was sound, but some past studies were positive and others were negative, which left clinicians scratching their heads.

The bottom line is that CYP2D6 status did not allow clinicians to predict with any accuracy which patients did or did not benefit from tamoxifen (Leyland-Jones 2010; Rae 2010). The data sets presented at San Antonio were clean and well-studied, prospectively followed patient populations. This is likely the highest level of evidence we're ever going to acquire, and this is almost a unique resource at this point. I believe this story is over.

Track 8

DR LOVE: Would you discuss the Neo-ALTTO study, evaluating multiple anti-HER2 strategies in the neoadjuvant setting?

DR HUDIS: The Neo-ALTTO study demonstrated that response rates were similar between paclitaxel/lapatinib and paclitaxel/trastuzumab and that the combination of three drugs — trastuzumab/paclitaxel/lapatinib — was associated with the best response (Baselga 2010; [1.1]). The three-drug combination appeared better than paclitaxel/trastuzumab, a factor that suggests the three-drug arm of the ongoing ALTTO trial will be the winner.

Because previous studies of the two anti-HER2 drugs showed activity in patients with heavily pretreated disease that progressed multiple times, in most cases during treatment with trastuzumab, the Neo-ALTTO strategy may be a viable one to increase response in the early-stage setting. However, based on the results of this study, when using a two-drug strategy we have no reason to substitute paclitaxel/lapatinib for paclitaxel/trastuzumab.

One might speculate that the former regimen has less cardiac toxicity, but more gastrointestinal and skin toxicity occurs and nothing indicates that the lapatinib combination is more active.

1.1 **Pathologic Complete Response (pCR) Rates in the Neo-ALTTO Phase III Neoadjuvant Trial of Lapatinib (L), Trastuzumab (T) and the Combination with Paclitaxel (P) in HER2-Positive Primary Breast Cancer**

Response	P + L (n = 154)	P + T (n = 149)	P + L + T (n = 152)
pCR[1]	24.7%	29.5%	51.3%
	p-value: 0.34 (L vs T); 0.0001 (L + T vs T)		
	P + L (n = 150)	P + T (n = 145)	P + L + T (n = 145)
Total pCR[2]	20.0%	27.6%	46.9%
	p-value: 0.13 (L vs T); 0.001 (L + T vs T)		

[1] No invasive cancer in the breast; [2] No invasive cancer in the breast and lymph nodes (excludes 15 patients with nonevaluable nodal status)

Baselga J et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Track 10

DR LOVE: Can you discuss the results of a second anti-HER2 study, NEOSPHERE, reported at San Antonio?

DR HUDIS: The four arms of the NEOSPHERE trial included neoadjuvant treatment with (1) trastuzumab and docetaxel, (2) pertuzumab and docetaxel, (3) trastuzumab, pertuzumab and docetaxel or (4) an interesting combination of trastuzumab and pertuzumab alone (Gianni 2010; [1.2]).

The results of the NEOSPHERE trial echoed those of the Neo-ALTTO study. The three-drug combination — both antibodies in combination with docetaxel — was associated with the highest in-breast response rate. This result was most clearly observed in the population with ER-negative disease, in which the pathologic complete response (pCR) rate was 63.2 percent. The pCR rate in the patients with ER-positive disease was 26 percent.

Omitting the chemotherapy clearly yielded inferior results. The pCR rate was only six percent for the patients with ER-positive disease who received the two antibodies, and the in-breast response rate for antibody treatment alone was 16.8 percent. The trastuzumab/docetaxel and the pertuzumab/docetaxel arms had respectable response activity but were inferior to the three-drug combination.

1.2

NEOSPHERE Study: Pathologic Complete Response (pCR) in the Breast and Lymph Node Status of Patients Receiving Neoadjuvant Trastuzumab and/or Pertuzumab

	TH (n = 107)	THP* (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node-negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node-positive at surgery	7.5%	6.5%	5.6%	6.3%

T = docetaxel; H = trastuzumab; P = pertuzumab

* *p*-value was significant for THP versus all other arms for each outcome shown

Gianni L et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Track 13

DR LOVE: Let's talk about new agents in breast cancer. What are your thoughts on the most recently approved treatment, eribulin?

DR HUDIS: Eribulin — a synthetic analog of a compound derived from the sea sponge — is a novel antitubulin agent that is interesting in terms of drug

development. Its approval was based on a clinical trial that randomly assigned patients to salvage treatment with eribulin or investigator's treatment of choice — gemcitabine, capecitabine, vinorelbine, weekly paclitaxel, anthracyclines, hormone therapy or best supportive care. Despite lumping together all those salvage therapies as a comparator, an overall survival advantage was reported in the patients randomly assigned to eribulin (Cortes 2011; [1.3]).

I believe this finding is profound because it indicates that the treatment choices we make, even in the salvage setting, can make a difference. All of our current salvage therapy approaches may be inferior to eribulin.

This trial shows that we should not be dismissive or cavalier in the salvage treatment setting. I believe eribulin deserves a fairly steady place in our treatment algorithm at this point because we don't have many treatments that have been shown to improve survival. ■

1.3

EMBRACE Trial: Eribulin versus Treatment of Physician's Choice (TPC) for Patients with Previously Treated Locally Recurrent or Metastatic Breast Cancer

Endpoint (ITT population)	Eribulin	TPC	Hazard ratio	*p*-value
Median OS (n = 508, 254)	13.1 mo	10.6 mo	0.81	0.041
Median PFS* (n = 508, 254)	3.7 mo	2.2 mo	0.87	0.14
ORR* (CR + PR) (n = 468, 214)	12%	5%	—	0.002
CBR* (CR + PR + SD) (n = 468, 214)	23%	17%	—	—

* Independent review

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; CBR = clinical benefit rate; SD = stable disease ≥6 months

Cortes J et al. *Lancet* 2011;377(9769):914-23.

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 HER2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Cortes J et al. **Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study.** *Lancet* 2011;377(9769):914-23.

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized Phase II study ('NeoSphere').** San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Leyland-Jones B et al. **Outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG 1-98 trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-8**.

Rae JM et al. **Lack of correlation between gene variants in tamoxifen metabolizing enzymes with primary endpoints in the ATAC trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-7**.

INTERVIEW

Harold J Burstein, MD, PhD

Dr Burstein is Associate Professor of Medicine at Harvard Medical School and a breast cancer specialist at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-21

Track 1 **Case discussion:** A woman in her midforties develops bone and liver metastases three years after receiving dose-dense AC → paclitaxel for node-positive, triple-negative BC (TNBC)

Track 2 Activity of platinum agents in TNBC

Track 3 Use of chemotherapy/bevacizumab in metastatic TNBC (mTNBC)

Track 4 Second- and later-line treatment of mTNBC

Track 5 Mechanism of action of antitubulins

Track 6 Bevacizumab-associated nasal side effects

Track 7 Carboplatin/gemcitabine and iniparib in mTNBC

Track 8 Survival as an endpoint of clinical trials of first-line therapy for mBC

Track 9 Perspective on the EMBRACE study results with eribulin in patients with heavily pretreated mBC

Track 10 **Case discussion:** A 71-year-old woman presents with an ER-positive, HER2-positive, node-positive locally advanced BC and concomitant pulmonary metastases

Track 11 Orally administered pan-HER TKI neratinib under investigation in HER2-positive mBC

Track 12 Dual TKIs — lapatinib, neratinib and afatinib — under investigation for HER2-positive BC

Track 13 Endocrine therapy in combination with trastuzumab in ER-positive, HER2-positive mBC

Track 14 Activity of neoadjuvant pertuzumab/trastuzumab in the NEOSPHERE trial

Track 15 Trastuzumab/lapatinib in HER2-positive mBC

Track 16 T-DM1: Direct delivery of maytansinoid to cancer cells abrogates chemotherapy-related toxicity

Track 17 Chronic anti-HER2 therapy for patients with HER2-positive mBC

Track 18 **Case discussion:** A 57-year-old woman with a 1.6-cm, moderately differentiated, ER-positive, HER2-negative, node-negative BC with an Onco*type* DX® Recurrence Score® of 17

Track 19 Development of an Onco*type* DX prostate cancer (PC) test to be used in conjunction with Gleason Score and other PC clinical parameters

Track 20 Use of the Onco*type* DX assay in patients with node-positive BC

Track 21 Investigation of genomic assays in the neoadjuvant setting

Select Excerpts from the Interview

Tracks 3, 6

DR LOVE: The use of chemotherapy and bevacizumab is a bit murky for metastatic breast cancer in light of the current FDA and ODAC stance. What is your current nonprotocol approach to using bevacizumab?

DR BURSTEIN: I still use paclitaxel and bevacizumab in the metastatic setting, based on the strength of the ECOG-E2100 data (Miller 2007). I was not convinced by the AVADO, RIBBON 1 or RIBBON 2 trial data that adding bevacizumab materially improves outcomes in terms of time to disease progression, response or symptom control with other agents (Brufsky 2009; Miles 2010; Robert 2011). I believe, assuming the ECOG-E2100 data remain robust, a substantial difference still exists compared to the other chemotherapies.

However, bevacizumab is not without its side effects, including headaches, high blood pressure and nasal congestion — we typically see postnasal drip, chronic sinus congestion, semipurulent discharge and blood-tinged nasal secretions. I don't have a precise definition and I can't say that the incidence is well described in the literature, but in my experience it's prevalent.

For refractory triple-negative tumors I am inclined to offer bevacizumab because of the sense that chemotherapy alone isn't enough. Triple-negative tumors have a faster rate of progression, so the shift in progression-free survival is narrower in absolute terms.

Track 7

DR LOVE: Would you discuss the updated data with iniparib in TNBC?

DR BURSTEIN: PARP enzymes are involved in DNA repair, and iniparib was initially developed for TNBC because triple-negative tumors have so-called "BRCAness," which is to say they are particularly genetically unstable.

The original presentation at ASCO 2009 reported an improvement in response rate, time to disease progression and overall survival with iniparib and gemcitabine/carboplatin (O'Shaughnessy 2011a). In the Phase III study, eligibility was similar — metastatic TNBC, with many cases being refractory to treatment — and the randomization was also gemcitabine/carboplatin with or without iniparib. However, the results of the study did not meet the coprimary endpoints of improvement in overall survival and progression-free survival (O'Shaughnessy 2011b; [2.1]).

Track 12

DR LOVE: What are your thoughts on some of the new agents being investigated for HER2-positive breast cancer?

2.1

Phase III Trial of Gemcitabine/Carboplatin (GC) with or without Iniparib (I) for Metastatic Triple-Negative Breast Cancer

	GC (n = 258)	GCI (n = 261)	Hazard ratio (95% CI)	*p*-value
Intent-to-treat (ITT) population				
Median OS	11.1 mo	11.8 mo	0.88	0.284
Median PFS	4.1 mo	5.1 mo	0.79	0.027
Exploratory analysis: Second-/third-line ITT population				
	GC (n = 109)	GCI (n = 113)	Hazard ratio (95% CI)	*p*-value
Median OS	91 mo	108 mo	0.65	0.012
Median PFS	29 mo	43 mo	0.67	0.011

OS = overall survival; PFS = progression-free survival

O'Shaughnessy J et al. *Proc ASCO* 2011b;**Abstract 1007**.

DR BURSTEIN: It's a great time for new agent development in HER2-positive breast cancer because once you know a target, it's easy to go after it. We have trastuzumab, which is the antibody that targets HER2, and we have next-generation antibody products. Pertuzumab targets both HER2 and HER3, and T-DM1, a conjugated trastuzumab molecule, targets HER2. Lapatinib is a dual kinase inhibitor of EGFR and HER2. Neratinib and afatinib are competing in the sense that they are also dual kinase inhibitors that are orally available and may have a similar niche in treating patients who have failed prior anti-HER2 therapy (2.2).

2.2

Ongoing Trials of Anti-HER2 Therapy for Patients with HER2-Positive Metastatic Breast Cancer Previously Treated with Trastuzumab

Trial identifier	Phase	N	Treatment arms
NCT01125566	III	780	Afatinib/vinorelbine Trastuzumab/vinorelbine
NCT00829166	III	980	T-DM1 Capecitabine/lapatinib
NCT00777101	II	233	Neratinib Capecitabine/lapatinib
NCT01026142	II	450	Capecitabine/trastuzumab/pertuzumab Capecitabine/trastuzumab

www.clinicaltrials.gov, July 2011.

Track 16

DR LOVE: What are your thoughts on T-DM1, the trastuzumab-chemotherapy conjugate?

DR BURSTEIN: T-DM1 is an exciting agent. Robust responses occur in patients who've received prior trastuzumab- and lapatinib-based therapy. The response rate is approximately 30 percent (Burris 2011; [2.3]), and it's now in definitive Phase III trials. T-DM1 is composed of trastuzumab conjugated to a maytansinoid chemotherapy agent called DM1. In the past, by the time investigators reached sufficient cytotoxic doses of DM1 to kill the tumor, the patient was often moribund.

What the researchers have done now is to chemically link DM1 to trastuzumab, creating T-DM1. Each molecule of trastuzumab has three or four molecules of DM1, which enables a more targeted delivery of the chemotherapy directly to the cancerous cell while avoiding the severe toxicities seen in the past.

2.3

Phase II Study of T-DM1 for the Treatment of HER2-Positive Metastatic Breast Cancer After Prior HER2-Directed Therapy

	T-DM1 (n = 112)	
	Independent review facility	Investigator assessment
Objective response rate	25.9%	37.5%
Median progression-free survival	4.6 months	4.6 months
Median duration of response	Not reached	9.4 months

Burris HA et al. *J Clin Oncol* 2011;29(4):398-405.

Track 20

DR LOVE: Would you discuss the current trial of Onco*type* DX in node-positive disease?

DR BURSTEIN: The RxPONDER trial is a re-creation of the TAILORx study with node-positive disease instead of node-negative disease (2.4). The stakes are higher in node-positive disease. My threshold for offering chemotherapy is different. If I know I will be administering chemotherapy or if the patient is younger or premenopausal and has multiple positive nodes, then I don't order the assay. We don't have data for premenopausal patients with node-positive disease. In those cases, I don't lean too hard on the test.

However, it has become increasingly clear in recent years that a small amount of nodal disease is not a bad prognostic factor. In NSABP studies, nodal metastases up to two millimeters were not prognostically significant if patients received adjuvant therapy. For those patients, the biological principles of Onco*type* DX are likely relevant and a low Recurrence Score probably means that the benefit from chemotherapy is negligible.

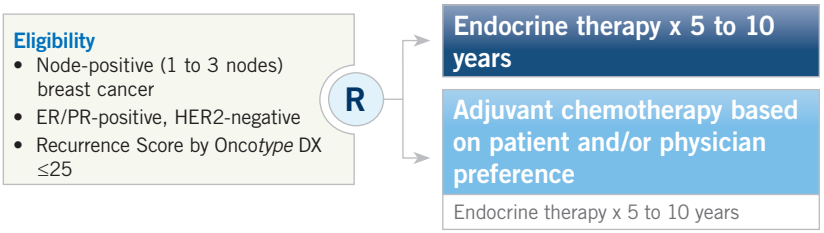
DR LOVE: You have commented that the issue is not about prognosis but about whether a benefit is obtained from treatment. Theoretically, some patients with 10 positive nodes may have chemotherapy-unresponsive tumors.

2.4

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, June 2011.

DR BURSTEIN: I don't mind administering chemotherapy to a patient with 10 positive nodes because that patient has high-risk cancer and it is reasonable to do everything possible to help the patient.

On the other end of the spectrum, a patient with a 1.5-mm focus of cancer in the lymph node probably has a prognosis similar to a patient with node-negative disease, and it's much more reasonable to consider the value of adjuvant chemotherapy. I reiterate that the important issue is not about prognosis. Patients need to know whether or not a treatment will change their risk of recurrence. ■

SELECT PUBLICATIONS

Brufsky A et al. **RIBBON-2: A randomized, double-blind, placebo-controlled, Phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 42**.

Burris HA et al. **Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy.** *J Clin Oncol* 2011;29(4):398-405.

Hickish T et al. **Use of BIBW 2992, a novel irreversible EGFR/HER2 tyrosine kinase inhibitor (TKI), to treat patients with HER2-positive metastatic breast cancer after failure of treatment with trastuzumab.** *Proc ASCO* 2009;**Abstract 1023**.

Miles DW et al. **Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer.** *J Clin Oncol* 2010;28(20):3239-47.

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

O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011a;364(3):205-14.

O'Shaughnessy J et al. **A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ASCO* 2011b;**Abstract 1007**.

Robert NJ et al. **RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer.** *J Clin Oncol* 2011;29(10):1252-60.

INTERVIEW

Adam M Brufsky, MD, PhD

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

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on your recent update on the RIBBON 2 study evaluating chemotherapy with bevacizumab in the second-line setting presented at ASCO 2011 and the trend that was revealed toward an overall survival benefit for patients with triple-negative disease?

DR BRUFSKY: Based on the RIBBON 2 data (Brufsky 2010; [3.1]), I administer bevacizumab in the second-line setting for triple-negative disease even though it's not the approved setting.

The question is whether a signal for continued first-, second- and third-line therapy with bevacizumab exists, as it does with trastuzumab.

Bevacizumab has rare but severe side effects, such as pulmonary embolus and bowel perforation, which we must be mindful of. Other serious side effects can also occur, such as hypertension and proteinuria. In clinical practice we're struggling with where to place this agent. The ODAC has one perspective and the NCCN has another.

DR LOVE: In general, for what kind of patient would you likely administer chemotherapy and bevacizumab?

DR BRUFSKY: I consider it for patients with aggressive tumors for whom you would normally administer combination chemotherapy. If you're considering two cytotoxic agents, it's also reasonable to consider a cytotoxic agent with bevacizumab. Although I'm one of the principal investigators on one of the trials, I'm somewhat ambivalent because we're not convinced which patient subsets will experience a benefit.

Would I administer chemotherapy with bevacizumab in the first line? I may consider it in some situations. For a patient with bulkier disease, someone who is not at risk for hemorrhage or thrombosis and who has a decent performance status — for example, a young woman with bulky triple-negative disease that progresses within 12 to 18 months after adjuvant therapy — I would consider chemotherapy with bevacizumab in the first-line setting.

As I mentioned, I would also consider it for a patient with triple-negative disease who has completed first-line therapy — whether on a PARP trial, through the PARP expanded-access program or with another therapy. I would seriously consider second-line chemotherapy with bevacizumab in that setting.

The one setting in which I would not administer bevacizumab is in the case of a patient with ER-positive, slowly progressive disease with a long disease-free interval before metastasis. For a 65- or 68-year-old woman with a few

3.1

RIBBON 2 Study: Effect of Bevacizumab (Bev) on Efficacy of Second-Line Chemotherapy (CT)* in the Subset of Patients with Triple-Negative Breast Cancer

Efficacy	CT + bev (n = 112)	CT + placebo (n = 47)	Hazard ratio	*p*-value
Overall response rate	41%	18%	—	0.0078
Median progression-free survival	6.0 mo	2.7 mo	0.494	0.0006
Median interim overall survival	17.9 mo	12.6 mo	0.624	0.0534
Select adverse events†				
Neutropenia	18.8%	10.6%	—	—
Hypertension	10.7%	0%	—	—
Proteinuria	5.4%	0%	—	—

* Capecitabine, gemcitabine, paclitaxel, docetaxel, *nab* paclitaxel or vinorelbine
† No unanticipated side effects were observed except neutropenia.

Brufsky A et al. *Proc ASCO* 2011;**Abstract 1010**.

bony metastatic lesions who's experienced disease progression on one to three hormone therapies, I would administer chemotherapy — probably capecitabine — but not bevacizumab.

DR LOVE: What typical dose and schedule of capecitabine do you use?

DR BRUFSKY: It's interesting to note that nowadays a number of options are available for different doses and schedules. The label-indicated dose is too high, so many of us will start a patient like the one just described on three to four 500-mg tablets twice daily, which works out to a little less than 2 g/m^2 per day and is under the recommended dose. Additionally, the one-week-on, one-week-off schedule that was popularized in an unpublished abstract by investigators at Memorial Sloan-Kettering is becoming a more widely adopted practice.

Track 12

DR LOVE: Are you currently using the Onco*type* DX assay for patients with node-positive disease?

DR BRUFSKY: Yes. I use Onco*type* DX for postmenopausal patients with node-positive disease. Data from both ASCO and San Antonio suggest that certain subsets behave like node-negative disease (Dowsett 2010; Albain 2010). So for a patient with IHC-positive nodes or even simply one to three positive nodes, a strong estrogen receptor and a low Ki-67 level — five to 10 percent — I order an Onco*type* DX assay. It is reimbursed for postmenopausal women in my practice.

The challenge is for a premenopausal woman who receives an LHRH agonist and no chemotherapy for node-positive breast cancer. Suppose the patient is 45 years old and prefers not to go through chemotherapy. For premenopausal women with one to three positive nodes, no data exist with Onco*type* DX. However, one could argue that biology trumps anatomy so if you make her postmenopausal by administering an LHRH agonist, the Onco*type* DX assay should be predictive of her response to chemotherapy and/or hormone therapy. ■

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.

Brufsky A et al. **Impact of bevacizumab (bev) on efficacy of second-line chemotherapy (CT) for triple-negative breast cancer: Analysis of RIBBON-2.** *Proc ASCO* 2011;**Abstract 1010**.

Cortazar J et al. **Relationship between OS and PFS in metastatic breast cancer (MBC): Review of FDA submission data.** *Proc ASCO* 2011;**Abstract 1035**.

Dowsett M et al. **Prediction of risk of distant recurrence using the 21-gene Recurrence Score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A TransATAC study.** *J Clin Oncol* 2010;28(11):1829-34.

Hayes DF. **Bevacizumab treatment for solid tumors: Boon or bust?** *JAMA* 2011;305(5):506-8.

INTERVIEW

Melody A Cobleigh, MD

Dr Cobleigh is Professor of Medicine and Director of the Section of Medical Oncology at Rush University Medical Center in Chicago, Illinois.

Tracks 1-8

Track 1 **Case discussion:** A 53-year-old woman who developed liver, lung and chest wall metastases seven years ago and subsequently underwent treatment for CNS metastases is currently receiving sixth-line therapy with metronomic cyclophosphamide/methotrexate 12 years after treatment for node-negative TNBC

Track 2 **Case discussion:** A 59-year-old woman with ER-positive, HER2-positive mBC whose disease has progressed through multiple lines of anti-HER2 therapy during the past five years has a significant response to T-DM1 on protocol

Track 3 Clinical experience with T-DM1 in patients with HER2-positive mBC

Track 4 Treatment options for patients who experience relapse during or after adjuvant chemotherapy/trastuzumab

Track 5 NSABP-B-47: A Phase III trial of adjuvant chemotherapy with or without trastuzumab in HER2-normal BC

Track 6 Clinical utility of the Onco*type* DX assay

Track 7 NSABP-B-43 trial: Radiation therapy with or without trastuzumab in HER2-positive ductal carcinoma in situ

Track 8 Perspective on community BC practice

Select Excerpts from the Interview

Tracks 2-4

Case discussion

A 59-year-old woman with ER-positive, HER2-positive mBC whose disease has progressed through multiple lines of anti-HER2 therapy during the past five years is treated with T-DM1 on protocol.

DR COBLEIGH: Since diagnosis, this patient's disease has progressed through multiple lines of treatment, including dose-dense AC/paclitaxel followed by radiation therapy, capecitabine/trastuzumab, trastuzumab alone, vinorelbine/trastuzumab, lapatinib with and without trastuzumab, trastuzumab/bevacizumab, trastuzumab/letrozole and trastuzumab with metronomic therapy.

She became eligible for the expanded-access T-DM1 protocol and experienced a dramatic response and was transformed from someone who was unable to work into a person who was able to hike seven miles during a recent vacation in Arizona. Her tumor measurements markedly decreased — this was interesting because previously her liver disease was so extensive that it was impossible to measure. Using volumetric measurements, we found that her tumor had shrunk by approximately 66 percent. She remains on the study.

DR LOVE: Did she experience any side effects?

DR COBLEIGH: The only side effects she had were bleeding gums and transient thrombocytopenia, which most patients experience after about a week of therapy with this agent. Otherwise she felt terrific.

DR LOVE: How do you believe T-DM1 will fit into the future treatment algorithm for breast cancer?

DR COBLEIGH: Most clinicians would like to see this agent used in the adjuvant setting in place of chemotherapy. Although T-DM1 contains trastuzumab bound to a chemotherapeutic agent, it doesn't cause the toxicity associated with chemotherapy.

DR LOVE: You mentioned that this patient experienced a response to the combination of trastuzumab and bevacizumab. What has been your experience with this regimen for metastatic disease?

DR COBLEIGH: I believe it to be an active combination. I've administered it to patients who, like this one, were responding to trastuzumab and then experienced disease progression and subsequently responded when bevacizumab was added back in.

DR LOVE: What is your approach for patients who experience relapse after previous adjuvant chemotherapy/trastuzumab?

DR COBLEIGH: Thankfully, that is not a common scenario, so I don't have a specific algorithm. I don't believe lapatinib is as well tolerated or as active as trastuzumab. Information from neoadjuvant trials confirms that lapatinib is not as active an agent (Baselga 2010; [1.1, page 4]; Untch 2010). I administer lapatinib to patients for whom a number of trastuzumab-containing regimens have failed. I have also used the combination of trastuzumab with lapatinib, which is associated with less toxicity than combinations of trastuzumab with chemotherapy drugs.

Tracks 5, 7

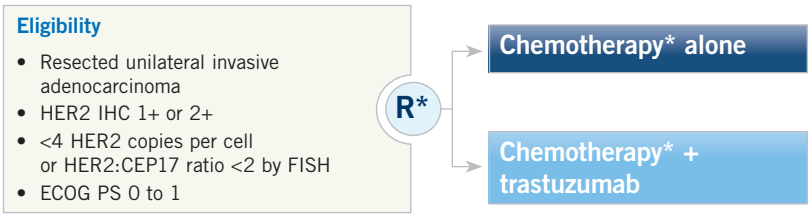
DR LOVE: What are your thoughts on the NSABP-B-47 trial, which is evaluating adjuvant chemotherapy with or without trastuzumab for patients with HER2-normal breast cancer?

DR COBLEIGH: The first time Dr Soon Paik presented information on the purported benefit of adjuvant trastuzumab for patients with HER2-normal

4.1

NSABP-B-47: A Phase III Trial of Adjuvant Chemotherapy with or without Trastuzumab for Patients with Node-Positive or High-Risk Node-Negative, HER2-Normal Invasive Breast Cancer

Protocol IDs: CDR0000692574; NCT01275677 **Target Accrual:** 3,260 (Open)



* Investigator preference: Docetaxel/cyclophosphamide OR doxorubicin/cyclophosphamide → paclitaxel

www.clinicaltrials.gov, June 2011.

breast cancer at an NSABP meeting, I was skeptical, as were most of the people sitting around the table. As a result, he conducted more research and his hypothesis became more robust (Paik 2008) and is definitely worthy of testing in a clinical trial (4.1).

DR LOVE: Would you describe your NSABP-B-43 study of trastuzumab in ductal carcinoma in situ (DCIS)?

DR COBLEIGH: The B-43 trial is enrolling patients with HER2-positive DCIS resected by lumpectomy. Patients receive two doses of trastuzumab during radiation therapy as a radiosensitizer. The primary endpoint is breast tumor recurrence, and one of the secondary endpoints is the effect of trastuzumab on the contralateral breast tumor.

An interesting study of neoadjuvant trastuzumab for patients with DCIS was recently published by Dr Kuerer from MD Anderson (Kuerer 2011). The study focused on the underlying immunologic effects of trastuzumab and demonstrated that antibody-dependent cell-mediated cytotoxicity skyrocketed within two weeks of a single dose of trastuzumab. ■

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 HER2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Kuerer HM et al. **Biologic and immunologic effects of preoperative trastuzumab for ductal carcinoma in situ of the breast.** *Cancer* 2011;117(1):39-47.

Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11.

Untch M et al. **Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S3-1**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Neo-ALTTO study of neoadjuvant treatment with paclitaxel and lapatinib, trastuzumab or their combination, the three-drug regimen was associated with a pathologic complete response rate in the breast of approximately _____.**
   a. 20 percent
   b. 35 percent
   c. 51 percent
   d. None of the above

2. **The mechanism of action of pertuzumab _____.**
   a. Is the same as that of trastuzumab
   b. Is unique from that of trastuzumab because pertuzumab binds to the dimerization domain of HER2
   c. Allows for its potential use in combination with trastuzumab
   d. Both b and c

3. **Retrospective analysis of data from the ATAC and BIG 1-98 trials has shown that CYP2D6 _____ predict response to tamoxifen.**
   a. Did
   b. Did not

4. **The Phase III EMBRACE trial of eribulin versus treatment of physician's choice for previously treated metastatic breast cancer has shown that eribulin results in improvement in _____.**
   a. Objective response rate
   b. Overall survival
   c. Progression-free survival
   d. Both a and b
   e. All of the above

5. **Updated data from ASCO 2011 on a Phase III trial of gemcitabine/carboplatin with or without iniparib in triple-negative breast cancer demonstrated a statistically significant improvement in both overall survival and progression-free survival.**
   a. True
   b. False

6. **The Phase III SWOG-S1007 (RxPONDER) study randomly assigns women with ER/PR-positive, HER2-negative, node-positive disease and an Onco*type* DX Recurrence Score of less than or equal to 25 to endocrine therapy with or without adjuvant chemotherapy.**
   a. True
   b. False

7. **Data from the RIBBON 2 study of bevacizumab in the second-line metastatic setting revealed a trend toward an overall survival benefit for patients with triple-negative disease.**
   a. True
   b. False

8. **The NSABP-B-47 trial is comparing the effects of chemotherapy with and without trastuzumab in patients with _____.**
   a. HER2-positive, high-risk, node-negative breast cancer
   b. HER2-positive, low-risk, node-negative breast cancer
   c. HER2-positive, node-positive breast cancer
   d. HER2-normal, high-risk, node-negative breast cancer

9. **The NSABP-B-43 trial is evaluating the effect of T-DM1 as a radiosensitizer in patients with HER2-positive DCIS.**
   a. True
   b. False

10. **A commonly reported side effect during treatment with T-DM1 is _____.**
    a. Alopecia
    b. Nausea
    c. Transient thrombocytopenia
    d. Transient neuropathy

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 2011

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
Ongoing clinical trials of Onco*type* DX in node-negative (TAILORx) and node-positive (RxPONDER) breast cancer	4 3 2 1	4 3 2 1
Results of major neoadjuvant trials of anti-HER2-based therapy (NEOSPHERE, Neo-ALTTO)	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
RIBBON 2 study: Effect of bevacizumab on efficacy of second-line therapy for triple-negative breast cancer (TNBC)	4 3 2 1	4 3 2 1
Efficacy of the PARP inhibitor iniparib with gemcitabine/carboplatin in metastatic triple-negative breast cancer	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; no changes will be made
☐ 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:

- Determine the utility of genomic assays in counseling patients with ER-positive early breast cancer about their risk of recurrence and the potential benefits of adjuvant chemotherapy..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic role of bisphosphonates and other bone-targeted agents in disease management..... 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
- Evaluate the unique mechanisms of action and the emerging clinical data with novel anti-HER2 agents under investigation in 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
- 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)

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 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
Clifford Hudis, MD	4 3 2 1	4 3 2 1
Harold J Burstein, MD, PhD	4 3 2 1	4 3 2 1
Adam M Brufsky, MD, PhD	4 3 2 1	4 3 2 1
Melody A Cobleigh, 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

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

Professional Designation:

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

Street Address:..... Box/Suite:.....

City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/BCU211/CME.

BCU211

Breast Cancer® UPDATE

Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

Breast Cancer® UPDATE

This activity is supported by educational grants from
Boehringer Ingelheim Pharmaceuticals Inc, Eisai Inc,
Genentech BioOncology, Genomic Health Inc and Sanofi.

Research
To Practice®

Sponsored by Research To Practice.

Last review date: August 2011
Release date: August 2011
Expiration date: August 2012
Estimated time to complete: 3 hours