Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY

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SPECIAL ISSUE

Proceedings from a Clinical Investigator Think Tank

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Breast Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — clinicians must be well informed of these advances. To bridge the gap between research and practice, this program features leading oncology investigators debating the merits, applications and limitations of emerging data sets. By providing access to the latest research developments and expert perspectives, this CME activity aims to assist medical oncologists, hematologist/oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Use genomic assays to quantify recurrence risk and aid in individualized recommendations for systemic therapy.
- Communicate the benefit-risk profile of bevacizumab and its evidence-based therapeutic partners to appropriate patients with HER2-negative metastatic breast cancer.
- Apply the results of emerging research with targeted agents to optimize outcomes for patients with HER2-positive breast cancer.
- For patients with advanced BRCA mutation-associated or triple-negative breast cancer, discuss the preliminary clinical activity and safety of PARP inhibitors, alone or with chemotherapy, and provide guidance about available ongoing clinical trials.
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic role of bisphosphonates and other bone-targeted agents in disease management.
- Educate postmenopausal patients with ER-positive advanced breast cancer about the sequential use of evidence-based treatment options that facilitate quality and quantity of life.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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This program is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

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

TABLE OF CONTENTS

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FACULTY — **Drs Burstein**, **Geyer** and **Wolff** 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 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. **Dr Gradishar** — Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi. **Dr Robson** — Advisory Committee: Abbott Laboratories, Pfizer Inc, Sanofi; Research Trial Funding: KuDOS Pharmaceuticals. **Dr Rugo** — Paid Research: Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Sanofi; Speakers Bureau: Genomic Health Inc.

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USE OF GENOMIC ASSAYS IN EARLY BREAST CANCER (BC)

SELECT EXCERPTS FROM THE DISCUSSION

DR LOVE: What are your thoughts about the Onco*type* DX® assay and its use in ER/PR-positive, HER2-negative, node-positive disease?

DR WOLFF: I may consider ordering Onco*type* DX in such a situation, or I would enroll the patient on the recently activated RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) study (1.1), which is the follow-up of the TAILORx trial. This study is trying to recapitulate the data observed in SWOG-8814 for women with ER-positive, node-positive disease treated with tamoxifen with or without CAF. In the publication in *Lancet Oncology*, patients with a low Recurrence Score® (RS) appeared to derive little benefit from chemotherapy (Albain 2010).

DR LOVE: Would you likely offer chemotherapy in the case of an intermediate RS? And if so, would you change your choice of chemotherapy in any situation, based on the RS?

DR BURSTEIN: For patients with node-positive disease and intermediate RS, the SWOG data do appear to show some benefit for chemotherapy, so I would use chemotherapy for these patients.

DR GEYER: For patients with node-negative disease I suppose I might change my choice of adjuvant chemotherapy because I view Onco*type* DX as also providing information on relative risk reduction with endocrine therapy. In the NSABP-B-20 results, for example, patients with intermediate RS did benefit from endocrine therapy, whereas for patients with high RS, relative risk reduction seems to result largely from chemotherapy (Mamounas 2010).

For patients with intermediate RS, I believe the mainstay of treatment is still endocrine therapy. The nuances of chemotherapy probably don't have absolute consequences. Therefore, for these patients I may shorten the duration or stay away from anthracyclines, so I do use the RS to select chemotherapy in that regard.

DR ROBSON: We're asking Onco*type* DX, which is a relatively primitive indicator of tumor biology, to

1.1

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

Eligibility
- Node-positive (1-3 nodes) breast cancer
- ER/PR-positive, HER2-negative
- Recurrence Score by Onco*type* DX ≤ 25

R

- Endocrine therapy x 5 to 10 years
- Adjuvant chemotherapy based on patient and/or physician preference
- Endocrine therapy x 5 to 10 years

www.clinicaltrials.gov. Identifier NCT01272037, May 2011.

carry an awful lot of weight in a situation for which it wasn't originally designed or validated. With a low-grade tumor, assuming that it is the source of what's going on in the node, ordering Onco*type* DX may not reflect the biology of that node. My bias is that putting too much weight on RS to parse out what to do in the face of the biologic or clinical data regarding node-positive breast cancer is anxiety provoking.

DR LOVE: This relates to the Tang presentation from San Antonio with regard to the Recurrence Score-Pathology-Clinical (RSPC), an attempt to address this issue. Hope, would you discuss what came out of that presentation?

DR RUGO: In the trans-ATAC data, the RS and the clinicopathologic variables each had prognostic effect. What Dr Tang first presented at ASCO was that if you included the clinicopathologic criteria, the combined score (RSPC) had an even greater effect on prognosis (Tang 2010b). The number of patients with intermediate RS changed, which is useful. We came away from that saying, "This may change prognosis, but we need to know if it also changes prediction of benefit from chemotherapy."

At the San Antonio Breast Cancer Symposium (SABCS), the data on the prediction of benefit from chemotherapy indicated that RS was superior to RSPC in terms of the prediction of benefit from chemotherapy (Tang 2010a).

DR LOVE: Do you believe that the RSPC has any clinical utility?

DR GEYER: I'm not using RSPC at this point. I'm still awaiting the day when I can bring it into the clinic and it can truly help me with some difficult treatment decisions. ■

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.

Auerbach J et al. **Can features evaluated in the routine pathologic assessment of lymph node-negative estrogen receptor-positive stage I or II invasive breast cancer be used to predict the Onco*type* DX Recurrence Score?** *Arch Pathol Lab Med* 2010;134(11):1697-701.

Mamounas EP et al. **Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** *J Clin Oncol* 2010;28(10):1677-83.

Parisi F et al. **Benefits of biomarker selection and clinico-pathological covariate inclusion in breast cancer prognostic models.** *Breast Cancer Res* 2010;12(5):R66;[Epub ahead of print].

Tang G et al. **Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** *Breast Cancer Res Treat* 2011;127(1):133-42.

Tang G et al. **Comparing the prediction of chemotherapy benefit in patients with node-negative, ER-positive breast cancer using the Recurrence Score and a new measure that integrates clinical and pathologic factors with the Recurrence Score.** San Antonio Breast Cancer Symposium 2010a;**Abstract S4-9**.

Tang G et al. **Recurrence risk of node-negative and ER-positive early-stage breast cancer patients by combining recurrence score, pathologic, and clinical information: A meta-analysis approach.** *Proc ASCO* 2010b;**Abstract 509**.

DURATION OF ADJUVANT ENDOCRINE THERAPY

DR LOVE: An ongoing issue in the treatment of ER-positive disease in the adjuvant setting is duration of endocrine therapy. How do you approach these decisions today outside a protocol setting?

DR GEYER: For patients with node-positive disease, I encourage continuation of adjuvant endocrine therapy unless the patient is having trouble with the treatment. In the node-negative setting, I believe it depends on how they're faring with therapy.

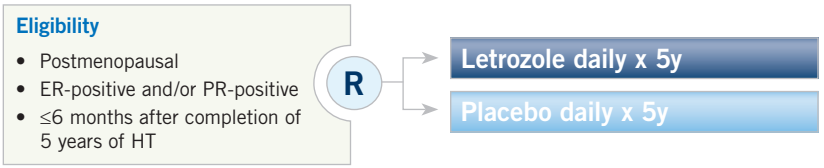
I try to help them get a sense of their residual risk of recurrence and what we're trying to accomplish with continued therapy.

The specific conversation I have with patients is that NSABP-B-42 has completed accrual and what we're doing is deciding whether to continue endocrine therapy until the study reports within a few years (2.1). I don't tell them, "Do it for five more years." Rather, I tell them, "This is what's going on. We don't know yet." Generally, most of the women who are faring well opt to continue endocrine therapy until those results are available.

2.1

NSABP-B-42: Adjuvant Letrozole After Completion of Five Years of Hormonal Therapy (HT) with Either an Aromatase Inhibitor or Tamoxifen Followed by an Aromatase Inhibitor

Protocol IDs: NSABP-B-42; NCT00382070



NCI Physician Data Query, May 2011.

NEW DEVELOPMENTS IN ER-POSITIVE METASTATIC BC (mBC)

DR LOVE: What about choice of endocrine therapy in the metastatic setting?

DR GRADISHAR: In the past, you could basically use any endocrine agent and the sequence didn't make much of a difference with regard to changing outcomes. Fulvestrant was pushed toward the end of the algorithm for endocrine therapy.

Recent studies have shown that as you escalate the fulvestrant dose or administer an increased dose up front, you not only reach steady state levels more quickly, but you also have more likelihood of obtaining a response. The FIRST trial evaluated a higher

2.2

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

	Fulvestrant 500 mg (n = 102)	Anastrozole 1 mg (n = 103)	Hazard ratio	*p*-value
Median time to progression	23.4 mo	13.1 mo	0.66	0.01

Robertson JFR et al. San Antonio Breast Cancer Symposium 2010;**Abstract S1-3**.

dose of fulvestrant — 500 mg — compared to anastrozole in the first-line setting. The 500-mg dose was significantly better in terms of time to disease progression (Robertson 2009, 2010; [2.2]).

I believe data support the idea of using the higher 500-mg dose, and the FDA has changed the recommendations for fulvestrant dosing.

DR BRUFSKY: Based on the FIRST and CONFIRM trial data (Di Leo 2009), the higher dose is clearly the way to go, but from a practical standpoint, it's tough. In my practice, we want to administer 500 mg, but some patients we've had on 250 mg who then attempt to switch over don't like two shots.

DR RUGO: We've had some patients ask, if they are stable on 250 mg, why should they receive two shots instead of one? It's a little hard to argue with. But you could presumably always increase the dosage if they experience disease progression.

DR LOVE: What are your thoughts on the TAMRAD study presented at the 2010 SABCS?

2.3

TAMRAD: Efficacy of Tamoxifen with or without Everolimus for ER-Positive, HER2-Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors (AIs)

	Tamoxifen	Tamoxifen + everolimus	Hazard ratio	*p*-value
Clinical benefit rate (n = 57; 54)	42.1%	61.1%	—	—
Median time to progression (TTP) (n = 57; 54)	4.5 mo	8.6 mo	0.53	0.0026
TTP, all patients with **primary** hormone resistance[1] (n = 28; 26)	3.9 mo	5.4 mo	0.74	—
TTP, all patients with **secondary** hormone resistance[2] (n = 29; 27)	5.0 mo	17.4 mo	0.38	—

[1] Patients who received no benefit from hormone therapy, experiencing either relapse during adjuvant AI or progression within six months of starting AI in the metastatic setting
[2] Patients who relapsed later (≥6 months), either after AI discontinuation in the adjuvant setting or, after responding, experiencing progression in the metastatic setting

Bachelot T et al. San Antonio Breast Cancer Symposium 2010;**Abstract S1-6**.

DR GRADISHAR: This Phase II study accrued 111 patients — about half of whom received tamoxifen and about half of whom received everolimus and tamoxifen. What was striking was that patients who received the doublet had a much greater clinical benefit, an enhanced response rate and marked improvement in time to disease progression (Bachelot 2010; [2.3]). These results suggest that using a doublet of a biologic agent and an endocrine agent may enhance the antitumor effect. ■

SELECT PUBLICATIONS

Bachelot T et al. **TAMRAD: A GINECO randomized Phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast cancer (MBC) with prior exposure to aromatase inhibitors (AI).** San Antonio Breast Cancer Symposium 2010;**Abstract S1-6**.

Di Leo A et al. **CONFIRM: A Phase III, randomized, parallel-group trial comparing fulvestrant 250 mg vs fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 25**.

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

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

MANAGEMENT OF HER2-POSITIVE BC

NEOADJUVANT THERAPY

DR LOVE: Among the most discussed data sets at the recent 2010 SABCS were three neoadjuvant studies for patients with HER2-positive disease. Could you comment on the German GEPARQUINTO study of chemotherapy with either trastuzumab or lapatinib?

DR COBLEIGH: The hypothesis for the German study was that the lapatinib arm would be better, yet the results indicated that the trastuzumab arm was better (Untch 2010; [3.1]).

Patients who received lapatinib experienced more toxicity and their discontinuation rate was higher. That's an important aspect to consider — how people are feeling while they're on this treatment, especially if we're moving into the adjuvant setting and patients are receiving therapy for a year.

DR LOVE: Another presentation, the Neo-ALTTO trial, also evaluated these two agents. What was reported?

DR BURSTEIN: Neo-ALTTO, which was designed to parallel the adjuvant ALTTO trial, evaluated lapatinib versus trastuzumab versus the combination of the two. The excitement out of that study was that the combination of the two agents led to a higher pathologic complete response (pCR) rate (Baselga 2010; [3.2]).

DR GEYER: The bottom line is lapatinib needed to show superi-

3.1

GEPARQUINTO (GBG 44) Trial: Neoadjuvant Trastuzumab (T) versus Lapatinib (L) with Epirubicin/Cyclophosphamide/Docetaxel (EC-Doc) in HER2-Positive Early Breast Cancer

	T + EC-doc	L + EC-doc	*p*-value
Pathologic complete response[1]	50.4%	35.2%	<0.05
Pathologic complete response[2]	45.0%	29.9%	<0.05
Pathologic complete response[3]	31.3%	21.7%	<0.05
Breast conservation rate	65.6%	56.0%	—

[1] No residual invasive cancer in breast only; [2] No residual invasive cancer in breast and nodes; [3] No residual invasive or noninvasive cancer in breast and nodes based on central pathology report review

Untch M et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-1**.

ority to make it worth considering as a single agent because it does have a greater toxicity. So it appears that lapatinib as a substitute for trastuzumab probably isn't the way forward. Clearly the combination is intriguing.

DR LOVE: Should this type of approach be considered outside a protocol setting, and what do these results mean in terms of ongoing and future trials in the adjuvant setting?

DR BURSTEIN: The goals of neoadjuvant therapy are to facilitate breast surgery and to provide a patient effective adjuvant treatment. At the moment, adding lapatinib to the mix to change either of those clinical goals is not supported by data. So, outside of a clinical study, I don't believe it's something we would regularly recommend. Having said that, this approach clearly has implications because pairing these drugs can result in some greater biological activity.

The hope is that the Neo-ALTTO pCR rate, which was better with the combination, foreshadows the results of the ongoing ALTTO trial, which has nearly completed accrual of approximately 8,000 patients. Hopefully, in a couple of years we'll know whether adding lapatinib does help prevent the cancer from coming back, which is ultimately the goal and helps women live longer and fare better.

DR LOVE: What about NeoSphere, the other big neoadjuvant study reported at SABCS 2010, which evaluated yet another anti-HER2 treatment, pertuzumab? Can you talk about this agent and the study?

DR COBLEIGH: Pertuzumab is a monoclonal antibody that prevents dimerization of the HER2 receptor with other members of the HER2 family, so it has a different mechanism of action compared to trastuzumab. The NeoSphere trial evaluated typical chemotherapy with trastuzumab versus chemotherapy with pertuzumab versus the combination of all three versus targeted therapy alone. The winner was the combination of all three. However, a 17 percent pCR rate was reported for the targeted therapy alone (Gianni 2010; [3.3]).

3.2

Neo-ALTTO: Pathologic Complete Response (pCR) Rates in a Phase III Neoadjuvant Trial of Lapatinib (L), Trastuzumab (T) or 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**.

3.3

Efficacy of Neoadjuvant Trastuzumab and Pertuzumab by Breast and Lymph Node Status During the NeoSphere Study

	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; pCR = pathologic complete response

* *p*-value was significant for THP versus all other arms.

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

LONG-TERM/INDEFINITE ANTI-HER2 TREATMENT OF METASTATIC DISEASE

DR LOVE: What do these neoadjuvant data mean in terms of choice of anti-HER therapy in the metastatic setting, whether or not trastuzumab has a greater antitumor effect than lapatinib and whether some type of anti-HER2 treatment should be continued indefinitely in the metastatic setting?

DR WOLFF: I don't believe we know the answer for sure in the metastatic setting. One of the important questions we had from the beginning was how long to continue anti-HER2 therapy at the time of disease progression. I believe patients should remain on some anti-HER2 therapy in the metastatic setting.

The trial that led to the approval of lapatinib by the FDA in many ways wasn't truly answering the question (Geyer 2006). So with regard to administering the drugs individually, it's not clear to me that one is necessarily better than the other. For many patients whom I start with first-line

trastuzumab, I tend to continue administering various trastuzumab/chemotherapy combinations for a while.

An important question is whether you should consider combination anti-HER2 therapy in the metastatic setting because of the data we have seen with the combination of lapatinib and trastuzumab. I've used this combination rarely, but it's intriguing.

DR GRADISHAR: We also have administered the combination of trastuzumab and lapatinib to patients in the metastatic disease setting. It's reasonably well tolerated. I believe the data are intriguing because we have seen a couple of trials — in the metastatic setting and now in the neoadjuvant setting — suggesting that dual targeting enhances antitumor effect. A cautionary note has to be that the combination of chemotherapy and dual anti-HER2 targeting should not yet be viewed as a standard approach for patients with HER2-positive disease.

NOVEL AGENTS UNDER INVESTIGATION

DR LOVE: What are some of the exciting novel agents currently under investigation in advanced HER2-positive breast cancer?

DR BURSTEIN: Trastuzumab-DM1 (T-DM1) is an antibody-drug conjugate with trastuzumab chemically linked to the maytansinoid chemotherapy DM1. It's interesting — people are calling it "nonchemotherapy" because it doesn't have the side effects of chemotherapy in that patients do not experience nausea, dramatically lower blood counts or hair loss.

T-DM1 has been studied in both Phase I and now a couple of Phase II studies evaluating patients with multiply refractory HER2-positive disease, including a study of approximately 100 patients who'd received anthracycline, taxanes, trastuzumab, capecitabine and lapatinib, and it is clearly associated with robust responses of about 30 to 40 percent in that patient population (Krop 2009). The worldwide Phase III EMILIA study is now evaluating T-DM1 versus capecitabine/lapatinib for patients with HER2-positive locally advanced or metastatic breast cancer (NCT00829166).

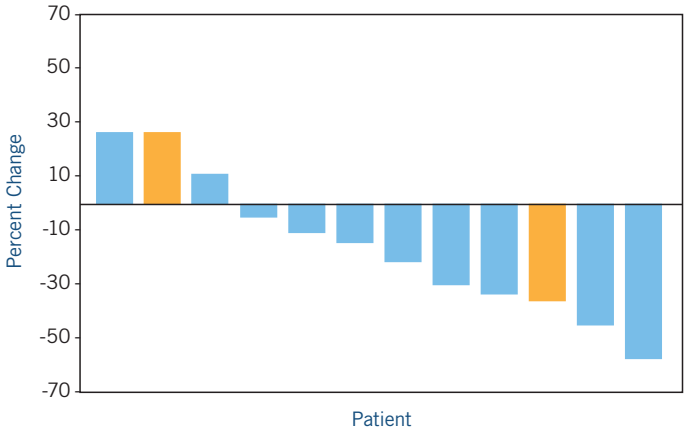
We have also treated a number of patients on T-DM1 protocols at our institution, and we recently presented data on outcomes for about 20 patients with mBC who discontinued T-DM1, mainly because of disease progression. Most of these patients went on to receive more anti-HER2 therapy with chemotherapy, and the response rate with the next line of treatment was approximately 30 percent (Olson 2010; [3.4]).

The take-away point here is that there seems to be no exhaustion to the potential benefits of ongoing anti-HER2 therapy, even after a number of anti-HER2 treatments, including novel agents.

DR LOVE: Would you also discuss tyrosine kinase inhibitors (TKIs) under investigation? We've heard a lot in our lung cancer programs about BIBW 2992, now called afatinib, particularly in EGFR-mutant non-small cell lung cancer, and I know objective responses to single-agent afatinib have been observed in HER2-

3.4

Response to Anti-HER2 Therapy After Treatment with T-DM1 in Women with HER2-Positive Metastatic Breast Cancer



Best response to first or second line of subsequent therapy after treatment with T-DM1. Blue bars indicate patients who received trastuzumab- and/or lapatinib-based regimens; orange bars indicate patients who received nontrastuzumab- and nonlapatinib-based regimens only.

With permission from Olson EM et al. San Antonio Breast Cancer Symposium 2010;**Abstract P3-14-08**.

3.5

Efficacy of Afatinib (BIBW 2992): A Novel Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor for Patients with HER2-Positive Metastatic Breast Cancer After Failure of Treatment with Trastuzumab

Overall investigator assessment (best response)	Response, n (%)
Clinical benefit (complete response + PR + SD)	18 (53%)
Partial response (PR)	4 (12%)
Stable disease (SD)	14 (41%)
Progressive disease	16 (47%)

Hickish T et al. *Proc ASCO* 2009;**Abstract 1023**.

positive breast cancer. A Phase II study recently presented with 34 evaluable patients whose disease progressed on trastuzumab reported a disease stabilization rate of 53 percent with single-agent afatinib (Hickish 2009; [3.5]).

DR BURSTEIN: It's a great time for drug discovery in HER2-positive breast cancer because once you know a target, it's easy to go after it. In addition to those already discussed, we also have lapatinib, which is the dual kinase inhibitor that inhibits the EGFR and HER2 tyrosine kinases. The irreversible TKIs neratinib and afatinib are competing products in the sense that they are also dual kinase inhibitors that are orally available and may have a similar niche. ■

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**.

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43.

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**.

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**.

Krop I et al. **A Phase II study of trastuzumab-DM1 (T-DM1), a novel HER2 antibody-drug conjugate, in patients previously treated with lapatinib, trastuzumab, and chemotherapy.** San Antonio Breast Cancer Symposium 2009;**Abstract 5090**.

Olson EM et al. **Responses to subsequent anti-HER2 therapy after treatment with trastuzumab-DM1 in women with HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract P3-14-08**.

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**.

EMERGING THERAPEUTIC APPROACHES IN TRIPLE-NEGATIVE BC (TNBC)

ANTI-ANGIOGENIC THERAPY

DR LOVE: Where are we right now in understanding the benefit of bevacizumab in triple-negative disease versus ER-positive, HER2-negative disease?

DR GEYER: I believe that bevacizumab is important in the triple-negative population, even if it does not clearly show greater activity than in the ER-positive setting, simply because we have fewer options in the triple-negative population — we "work through our toolbox" more quickly. When I am attempting to provide palliation to a woman with TNBC, I view bevacizumab's contribution as having greater absolute value for that patient than it would have for a patient with HER2-positive or ER-positive disease, simply because my options are so much more limited.

DR LOVE: What are your thoughts on how the results of the neoadjuvant German GEPARQUINTO study, which evaluated chemotherapy with or without bevacizumab for patients with HER2-negative early breast cancer, tie into this discussion?

DR WOLFF: On the GEPAR-QUINTO study, patients received conventional anthracycline and docetaxel preoperative therapy and were randomly assigned to receive bevacizumab or not. The study was a dud in terms of the outcome of pathologic changes at time of surgery. But these data are coming on the heels of much discussion in the last year about the true clinical utility

of bevacizumab in patients with metastatic disease, and I believe this is an important theme.

This study did show that the hazard ratio was more favorable for patients with triple-negative disease than for patients with ER-positive disease in terms of achieving the pCR endpoint (von Minckwitz 2010; [4.1]).

DR BRUFSKY: RIBBON 2 reported a modest progression-free survival (PFS) benefit of about two months with the addition of bevacizumab to chemotherapy for patients with HER2-negative metastatic disease. I might add that it is the same progression-free survival benefit that one sees with ixabepilone and capecitabine versus capecitabine alone, which was approved by the FDA. A substantial PFS benefit of three to four months was also observed in a prespecified subset of about 100 patients with triple-negative disease (Brufsky 2010).

I believe that by combining that sort of finding with some of these outcome data, we may be evolving. We may be moving toward a state in which we can identify a subset of patients who gain benefit from bevacizumab in the metastatic setting.

4.1

GEPARQUINTO GBG 44: Subset Analysis of Benefit for Patients with HER2-Negative Early Breast Cancer Receiving Neoadjuvant Chemotherapy with Bevacizumab (Bev)

Subtype	Odds ratio[1]
Overall	1.21
ER/PR-negative	**1.42**
ER/PR-positive	1.05
T1-3 and N0-2	1.17
T4 or N3	1.70

[1] Odds ratio >1 favors more patients with pCR on the EC-Doc + Bev arm.

Von Minckwitz G et al. San Antonio Breast Cancer Symposium 2010;**Abstract S4-6**.

EMERGING ROLE OF PARP INHIBITORS

DR LOVE: Can you summarize the data recently reported in *The New England Journal of Medicine* on the randomized Phase II study of carboplatin/gemcitabine with or without iniparib in metastatic TNBC?

DR GEYER: This randomized Phase II study was a straight one-to-one randomization of carboplatin/gemcitabine on day one and day eight with and without iniparib. Endpoints included response rate, overall survival (OS) and PFS. The primary endpoint of clinical benefit rate was improved from about 35 to 55 percent with iniparib, but of course the stunning results were that PFS and OS were also much better (O'Shaughnessy 2011; [4.2]). This resulted in the development of a Phase III study with a similar randomization and design.

DR LOVE: Speaking of the Phase III metastatic trial, could you discuss the

recent press release regarding results from this trial?

DR GEYER: The press release is carefully worded to say that the trial did not meet its prespecified criteria for significance for the coprimary endpoints of OS and PFS, so the results did not clear that high bar. It did say, however, that a planned subset analysis of patients treated in the second- and third-line setting demonstrated an improvement in OS and PFS. It's clear from the report that there was activity, but we'll have to wait until the data are presented at ASCO to know what that means.

For me, the press release has not raised any serious doubt that iniparib is an active drug. The drug may not be the home run the Phase II trial suggested, but in terms of changing interest in the compound, I don't see that happening. ■

4.2

Gemcitabine/Carboplatin with or without Iniparib (BSI-201) in Metastatic Triple-Negative Breast Cancer

	Gemcitabine/ carboplatin (n = 62)	Gemcitabine/ carboplatin + iniparib (n = 61)	Hazard ratio	*p*-value
ORR	32%	52%	—	0.02
PFS	3.6 months	5.9 months	0.59	0.01
OS	7.7 months	12.3 months	0.57	0.01

ORR = overall response rate; PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. *N Engl J Med* 2011;364(3):205-14.

SELECT PUBLICATIONS

Brufsky A et al. **Progression-free survival (PFS) in patient subgroups in RIBBON-2, a phase III trial of chemotherapy (chemo) plus or minus bevacizumab (BV) for second-line treatment of HER2-negative, locally recurrent or metastatic breast cancer (MBC).** *Proc ASCO* 2010;**Abstract 1021**.

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

Sanofi-Aventis reports top-line results from Phase III study with iniparib (BSI-201) in metastatic triple-negative breast cancer [press release]. January 27, 2011.

Von Minckwitz G et al. **Neoadjuvant chemotherapy with or without bevacizumab: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-6**.

BONE-TARGETED THERAPY IN BC

USE OF ADJUVANT BISPHOSPHONATE THERAPY

DR LOVE: Would you talk about recent data on the use of adjuvant bisphosphonates?

DR BRUFSKY: Michael Gnant's ABCSG-12 trial — presented about two years ago in an ASCO plenary

session and now published in *The New England Journal of Medicine* — reported that administration of an LHRH agonist and zoledronic acid with tamoxifen or anastrozole provided a significant disease-free survival benefit for premenopausal patients (Gnant 2009).

That brings us to AZURE, which is a large trial with approximately 3,000 women who received standard chemotherapy for Stage II or III breast cancer with or without zoledronic acid at a fairly substantial dose.

AZURE was presented at SABCS 2010, and overall the results were negative. The primary endpoint was five-year disease-free survival (DFS), and basically no difference in DFS was observed for patients who received adjuvant bisphosphonate versus those who did not, with a hazard ratio of 0.98 (Coleman 2010). Rob Coleman also presented a subset analysis. Postmenopausal women experienced not only a DFS benefit but also an OS benefit (Coleman 2010; [5.1]).

You could create a model now when you combine these results with Michael Gnant's study in which premenopausal patients receiving an LHRH agonist also had a DFS benefit — you could argue that a subset of patients may derive benefit from this approach.

DR BURSTEIN: We have to be cautious when thinking about a role for bisphosphonates in the adjuvant setting. It was a great idea, and it's been tested now in randomized trials. We still have data yet to come from NSABP-B-34 and SWOG-S0307, which may resolve the matter, but for the moment it's a strategy with no proven anticancer activity.

DR BRUFSKY: The SWOG-S0307 trial has now completed accrual, and we're waiting for the data. The trial is similar to the AZURE design, although patients with Stages I, II or III breast cancer were eligible. Patients received standard chemotherapy/hormonal therapy and then were randomly assigned to a fairly intensive dose of zoledronic acid monthly for six months then every three months for two and a half years or oral ibandronate or oral clodronate daily.

5.1

AZURE Trial: Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer — Subset Analysis of Overall Survival by Menopausal Status

	Control group	Zoledronic acid group	Adjusted HR	*p*-value
Pre/peri/unknown menopausal status (n = 1,127; 1,131)	156 deaths	157 deaths	1.01	0.93
>5 years postmenopausal or age >60 (n = 551; 550)	120 deaths	86 deaths	0.71	0.017

Coleman RE et al. San Antonio Breast Cancer Symposium 2010;**Abstract S4-5**.

DURATION OF USE, ADMINISTRATION INTERVAL AND CHOICE OF BONE-TARGETED THERAPY IN mBC

DR LOVE: How do you approach the issues of duration of use, interval of administration and choice of bone-targeted therapy for a patient who

has been receiving two years of an aromatase inhibitor and zoledronic acid for mBC?

DR GRADISHAR: The honest answer is we have no data to guide us. The ongoing OPTIMIZE 2 trial (NCT00320710) is evaluating zoledronic acid every four weeks versus every 12 weeks but is having difficulty accruing patients.

The issue with continuing zoledronic acid on a monthly basis is whether more toxicity accrues with more exposure. What a number of clinicians have done, even in the absence of data, is to spread out the intervals anywhere from every two to three months to every six months, rather than administering it monthly.

With respect to switching such a patient to denosumab, we probably wouldn't do that, but it would be a consideration.

DR COBLEIGH: I have been switching simply because denosumab is more convenient for patients — it's an injection instead of a 30-minute infusion and you don't have to evaluate kidney function before you administer it to the patient.

DR BRUFSKY: If patients receiving zoledronic acid begin experiencing renal insufficiency, switching to an every three-month or every six-month approach is reasonable and denosumab is also a rational alternative. We don't have any data beyond two years to guide us one way or the other.

DR LOVE: What are your thoughts about denosumab? Is it something that in the near future we'll be using up front before zoledronic acid?

DR WOLFF: My understanding from the data that I have seen is that the major advantage of denosumab is convenience more than any other factor. I have not run into problems with renal dysfunction in the patients to whom I administer zoledronic acid.

A big question that remains unanswered is the optimal schedule for all of these agents. When should you start spacing out the dosing of zoledronic acid? I start spacing it out quickly and early — within a couple of months — as soon as I get a sense that the patient's disease has stabilized, especially patients with bone disease on endocrine therapy.

DR GEYER: I gauge my zoledronic acid administration according to how the patient's disease is doing and start backing off as quickly as six months.

I've started using some denosumab, but I've been administering it to patients who have been receiving zoledronic acid and have active skeletal disease, for whom I've not felt comfortable backing off. ■

SELECT PUBLICATIONS

Aapro MS. **Denosumab for bone metastases from breast cancer: A new therapy option?** *J Clin Oncol* 2011;29(14):e419-20.

Coleman RE et al. **Adjuvant treatment with zoledronic acid in Stage II/III breast cancer. The AZURE trial (BIG 01/04).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-5**.

Gnant M et al. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91.

Van Poznak CH et al. **American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer.** *J Clin Oncol* 2011;29(9):1221-7.

CURRENT INVESTIGATIONAL APPROACHES WITH ANTI-ANGIOGENIC AGENTS IN EARLY HER2-NEGATIVE BC

DR LOVE: How is bevacizumab currently being investigated in HER2-negative breast cancer?

DR WOLFF: In the ongoing adjuvant ECOG-E5103 trial, patients are randomly assigned to receive AC followed by paclitaxel versus the same chemotherapy administered concurrently with bevacizumab for the duration of chemotherapy versus the same chemotherapy administered concurrently followed by six months of bevacizumab alone. This study will be closing relatively soon, so the question of the clinical utility of bevacizumab in this setting will be answered.

The Irish group recently presented a pilot study of bevacizumab with docetaxel and cyclophosphamide in the adjuvant setting for patients with early-stage breast cancer (Crown 2010). This was a study in a relatively healthy population of approximately 100 patients, and the investigators reported a significant frequency of changes in cardiac function, with drops in ejection fraction of 10 to 15 percent from baseline in approximately 20 percent of the patients. They were not receiving an anthracycline, suggesting a cardiac toxicity signal from the use of bevacizumab.

DR RUGO: What was most concerning in that trial — and I agree that the cardiac abnormalities were intriguing — was that two patients out of 100 experienced intestinal perforations. It may be the steroids, but nonetheless, this is a real toxicity that I find concerning.

DR LOVE: What are your thoughts on the NSABP-B-40 neoadjuvant trial, which also studied chemotherapy with or without bevacizumab?

DR GEYER: We will be analyzing the pCR data from B-40 at the end of March. It's a complicated design, but effectively it's a three-by-two trial. All patients received four cycles of docetaxel followed by AC. One third of the patients received gemcitabine and one third received capecitabine along with the docetaxel. So it asked a chemotherapy question and a bevacizumab question, with 1,200 patients to study with regard to bevacizumab and pCR.

We also have the randomized NSABP-B-46-I trial with US Oncology, which is evaluating TAC versus TC versus TC/bevacizumab. We've accrued approximately 1,250 patients to the trial thus far. ■

SELECT PUBLICATIONS

Crown JP et al. **Bevacizumab (bev) in combination with docetaxel (T) and cyclophosphamide (C) as adjuvant treatment (AdjRx) for patients (pts) with early stage (ES) breast cancer (BrCa) and normal HER-2 status. A pilot evaluation.** San Antonio Breast Cancer Symposium 2010;**Abstract P5-10-17**.

Pierga VP et al. **BEVERLY2, a phase II study evaluating bevacizumab (BEV) combined with chemotherapy (CT) and trastuzumab (H) as neoadjuvant therapy for HER2-positive inflammatory breast cancer (IBC): First efficacy results.** San Antonio Breast Cancer Symposium 2010;**Abstract P2-16-05**.

QUESTIONS (PLEASE CIRCLE ANSWER):

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

2. **A recent presentation by Tang and colleagues at the San Antonio Breast Cancer Symposium demonstrated that the RSPC score was a better predictor of benefit from chemotherapy than the Onco*type* DX Recurrence Score.**
   a. True
   b. False

3. **NSABP-B-42 is evaluating the duration of adjuvant _____ for early breast cancer.**
   a. Hormonal therapy
   b. Trastuzumab
   c. Chemotherapy
   d. All of the above

4. **The FIRST study demonstrated that an improved response to fulvestrant in patients with advanced breast cancer could be obtained by administering the drug at a higher, _____ dose.**
   a. 500-mg
   b. 250-mg
   c. 750-mg

5. **In the GEPARQUINTO GBG 44 study, among patients with HER2-positive early breast cancer, the pCR rate was higher with chemotherapy/trastuzumab than with chemotherapy/lapatinib.**
   a. True
   b. False

6. **Afatinib is an oral inhibitor of _____.**
   a. HER2 receptor
   b. EGF receptor
   c. Both a and b

7. **The NeoSphere trial found that the combination of pertuzumab, trastuzumab and docetaxel was associated with an in-breast pCR rate of approximately 20 percent.**
   a. True
   b. False

8. **In the GEPARQUINTO GBG 44 study, among patients with HER2-negative breast cancer receiving neoadjuvant chemotherapy with bevacizumab, the hazard ratio for pCR was more favorable for patients in which of the following subsets?**
   a. ER/PR-negative
   b. ER/PR-positive
   c. Neither a nor b

9. **Which of the following outcomes was improved in the randomized Phase II study of the addition of iniparib to carboplatin/gemcitabine in previously treated metastatic triple-negative breast cancer?**
   a. Overall response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above

10. **In ABCSG-12, which of the following bisphosphonates was found to reduce the risk of breast cancer recurrence in premenopausal women treated with adjuvant ovarian suppression combined with hormonal therapy?**
    a. Clodronate
    b. Ibandronate
    c. Zoledronic acid
    d. All of the above
    e. None of the above

11. **Which of the following bisphosphonates is being evaluated in SWOG-S0307?**
    a. Clodronate
    b. Ibandronate
    c. Zoledronic acid
    d. All of the above
    e. None of the above

Post-test answer key: 1a, 2b, 3a, 4a, 5a, 6c, 7b, 8a, 9d, 10c, 11d

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Think Tank Issue 1, 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
Contribution of clinicopathologic data to the Onco*type* DX RS relative to the RS alone	4 3 2 1	4 3 2 1
EMILIA: A Phase III study of T-DM1 versus capecitabine/lapatinib in HER2-positive locally advanced or metastatic BC	4 3 2 1	4 3 2 1
Pathologic complete response rate with the addition of pertuzumab to neoadjuvant chemotherapy/trastuzumab in HER2-positive early BC	4 3 2 1	4 3 2 1
Duration of use and administration interval of bisphosphonates in mBC	4 3 2 1	4 3 2 1
Benefit of bevacizumab-based therapy for patients with TNBC versus those with ER-positive, HER2-negative BC on the GEPARQUINTO GBG 44 study	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:

- Use genomic assays to quantify recurrence risk and aid in individualized recommendations for systemic therapy . . . . . 4 3 2 1 N/M N/A
- Communicate the benefit-risk profile of bevacizumab and its evidence-based therapeutic partners to appropriate patients with HER2-negative metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging research with targeted agents to optimize outcomes for patients with HER2-positive breast cancer . . . . . 4 3 2 1 N/M N/A
- For patients with advanced BRCA mutation-associated or triple-negative breast cancer, discuss the preliminary clinical activity and safety of PARP inhibitors, alone or with chemotherapy, and provide guidance about available ongoing clinical trials . . . . . 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
- Educate postmenopausal patients with ER-positive advanced breast cancer about the sequential use of evidence-based treatment options that facilitate quality and quantity of life . . . . . 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 TWO — Please tell us about the faculty and moderator for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
Adam M Brufsky, MD, PhD	4	3	2	1	4	3	2	1
Harold J Burstein, MD, PhD	4	3	2	1	4	3	2	1
Melody A Cobleigh, MD	4	3	2	1	4	3	2	1
Charles E Geyer Jr, MD	4	3	2	1	4	3	2	1
William J Gradishar, MD	4	3	2	1	4	3	2	1
Mark Robson, MD	4	3	2	1	4	3	2	1
Hope S Rugo, MD	4	3	2	1	4	3	2	1
Antonio C Wolff, MD	4	3	2	1	4	3	2	1
Moderator	**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:

.....

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Breast Cancer® UPDATE

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Breast Cancer® UPDATE

This program is supported by educational grants from
Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology,
Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

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Sponsored by Research To Practice.

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