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Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

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Breast Cancer Update
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OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Results from numerous ongoing trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic/prognostic tools. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Evaluate the potential benefits of surgical resection of the primary tumor in patients presenting with de novo metastatic breast cancer.
- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care.
- 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.
- Formulate an evidence-based algorithm for the management of HER2-positive localized or previously treated metastatic breast cancer.
- Recount the role of poly(ADP-ribose) polymerase (PARP) in the DNA repair pathway, and review the efficacy and safety of the PARP inhibitors for BRCA1/BRCA2 carriers with breast cancer or women with triple-negative breast cancer.
- Recall the utility of the "self-seeding hypothesis" to explain cancer growth, behavior and response to therapeutic interventions.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Jenny C Chang, MD

Dr Chang is Dan L Duncan Professor at the Lester and Sue Smith Breast Center at Baylor College of Medicine in Houston, Texas.

Tracks 1-12

Track 1 Mechanisms of action of trastuzumab (survival pathways) and lapatinib (proliferation pathways)

Track 2 Neoadjuvant study of trastuzumab/lapatinib with or without endocrine therapy in HER2-positive locally advanced breast cancer (BC)

Track 3 Novel anti-HER2 investigational agents: T-DM1 and pertuzumab

Track 4 Clinical use of taxane/carboplatin/trastuzumab (TCH) for locally advanced, HER2-positive BC

Track 5 Defining a "BRCA-ness" triple-negative profile of breast cancer and response to PARP inhibitors

Track 6 Development of an RT-PCR-based assay for a "BRCA-ness" DNA-defective signature

Track 7 Ongoing analyses of predictors of response/resistance to docetaxel or anthracyclines

Track 8 **Case discussion:** A 59-year-old postmenopausal woman presents with a 2.5-cm, Grade II, ER-positive, HER2-negative infiltrating ductal carcinoma (IDC) with three positive nodes and lymphovascular invasion with an Onco*type* DX® Recurrence Score® of 9

Track 9 Use of docetaxel/cyclophosphamide (TC) for node-positive BC

Track 10 Selection and duration of adjuvant endocrine therapy for postmenopausal patients with ER-positive BC

Track 11 **Case discussion:** A 39-year-old woman with a BRCA1 mutation presents with a large, fungating, triple-negative contralateral tumor nine years after treatment for a 3-cm, Grade III, node-negative, triple-negative IDC and subsequent chest wall recurrence

Track 12 **Case discussion:** A 43-year-old premenopausal woman with a BRCA1 mutation presents with inflammatory BC six years after treatment for a 1.8-cm, triple-negative, node-negative breast tumor

Select Excerpts from the Interview

Track 1

DR LOVE: What are the mechanisms of action of the two available anti-HER2 agents?

DR CHANG: Cancer grows via two major pathways — the survival or antideath pathway and the proliferation pathway. The major antideath pathway is PI3/AKT, and the major proliferation pathway is MAP kinase.

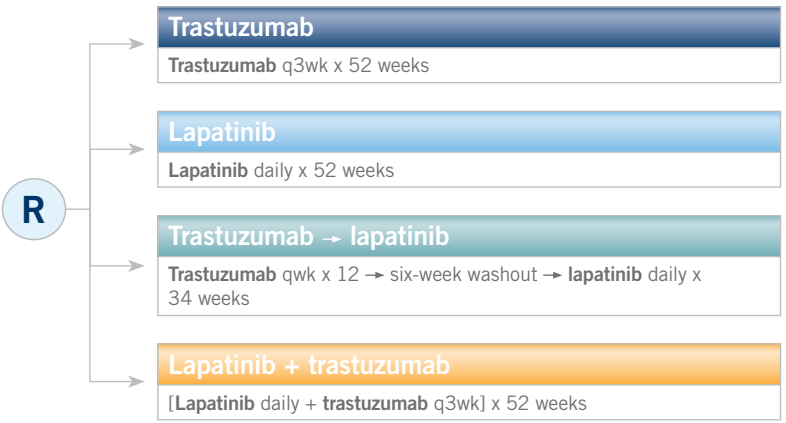
Work by our group and by Carlos Arteaga and José Baselga demonstrated that trastuzumab works through the antideath PI3/AKT pathway and lapatinib may work through the MAP kinase proliferation pathway.

Mutations in the PI3/AKT pathway lead to resistance to trastuzumab but not to lapatinib. In the future, we may have the ability, based on mutations within the tumor, to determine whether a patient should receive trastuzumab or lapatinib.

The ALTTO study evaluating lapatinib and/or trastuzumab is ongoing (1.1), and I predict that sequencing and combining lapatinib and trastuzumab will be superior to either single agent because, although they both affect the HER2 pathway, they work completely differently.

1.1 **Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial**

Protocol ID: BIG 2-06; **Target Accrual:** 8,000



Eligibility

- HER2-positive breast cancer

In Design 1, patients will complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy.

In Design 2, patients will receive weekly paclitaxel concurrently for 12 weeks with targeted therapy after any anthracycline-based (neo)adjuvant chemotherapy.

SOURCES: **www.breastinternationalgroup.org**; **www.alttotrials.com**.

Tracks 2-3

DR LOVE: Would you discuss your study of neoadjuvant trastuzumab in combination with lapatinib?

DR CHANG: We have a neoadjuvant study for women with HER2-overexpressing locally advanced breast cancer evaluating a combination of

trastuzumab and lapatinib. Patients with ER-positive tumors receive endocrine therapy also (NCT00548184). We've recruited 20 of a target of 60 patients, and our pathologic complete response rate is high. These are early, preliminary data, but they are encouraging.

We are trying to eliminate the use of chemotherapy altogether. In the future, I would love to be able to conduct a study using only targeted therapy to achieve a pathologic complete response and then randomly assign patients to receive no chemotherapy versus standard treatment. In five years' time, women with HER2-overexpressing breast cancer may not need chemotherapy.

DR LOVE: Where do T-DM1 and pertuzumab fit into the treatment of HER2-positive disease?

DR CHANG: I believe that T-DM1 is a promising drug (Vogel 2009; [1.2]). Hepatic toxicity has been reported with T-DM1, as it has with lapatinib. So we may not be able to combine those agents because of toxicity.

In terms of pertuzumab, evidence from our group and others shows that blocking other members of the HER family is important for overcoming resistance to anti-HER2 agents. By blocking HER3, pertuzumab overcomes resistance. It is possible that we have to block the HER pathway at multiple points to achieve a complete response.

1.2

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

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

CR = complete response; PR = partial response; SD = stable disease

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

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

Track 5

DR LOVE: Where are we headed in terms of treating triple-negative breast cancer?

DR CHANG: I believe that in the next two to three years, PARP inhibitors will do for triple-negative breast cancer what trastuzumab did for HER2 breast cancer. Joyce O'Shaughnessy and Andy Tutt each presented exciting data on PARP inhibitors at ASCO 2009. Andy Tutt presented data on BRCA1

and BRCA2 germline mutation carriers, showing a high response rate with olaparib monotherapy (Tutt 2009). Joyce O'Shaughnessy demonstrated a high response rate with BSI-201 and chemotherapy for patients with triple-negative breast cancer (O'Shaughnessy 2009; [1.3]). Although pathway similarities exist between germline BRCA1 mutation-carrying and triple-negative breast cancer, they're not the same disease. However, a subset of triple-negative breast cancer behaves like BRCA1 tumors.

Our group has defined a profile for "BRCA-ness" in triple-negative breast cancer (Rodriguez 2008), which accounts for 30 to 40 percent of triple-negative breast cancer cases. Patients with this profile respond extremely well to DNA-damaging agents because, as in BRCA1 tumors, DNA repair is defective. That's why PARP inhibitors, which prevent a form of DNA repair, work so well in these tumors. ■

1.3

Phase II Randomized Trial of Gemcitabine/Carboplatin (GC) with or without BSI-201 — a PARP1 Inhibitor — for Triple-Negative Metastatic Breast Cancer Previously Treated with Zero to Two Chemotherapy Regimens

	GC	GC + BSI-201	HR	*p*-value
Objective response rate (n = 44, 42)	16%	48%	—	0.002
Clinical benefit rate (CR + PR + SD ≥ 6 mo) (n = 44, 42)	21%	62%	—	0.0002
Median progression-free survival (n = 59, 57)	3.3 mo	6.9 mo	0.342	<0.0001
Median overall survival (n = 59, 57)	5.7 mo	9.2 mo	0.348	0.0005

HR = hazard ratio; CR = complete response; PR = partial response; SD = stable disease

SOURCE: O'Shaughnessy J et al. ASCO 2009;**Abstract 3**.

SELECT PUBLICATIONS

Collins D et al. **Lapatinib: A competitor or companion to trastuzumab?** *Cancer Treat Rev* 2009;35(7):574-81.

O'Shaughnessy J et al. **Efficacy of BSI-201, a PARP inhibitor, in combination with gemcitabine/carboplatin (GC) in triple negative metastatic breast cancer (mTNBC): Results of a Phase II study.** ASCO 2009;**Abstract 3**.

Rodriguez AA et al. **BRCA1 gene expression signature predicts for anthracycline-chemosensitivity in triple-negative breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 6039**.

Tomasello G et al. **Jumping higher: Is it still possible? The ALTTO trial challenge.** *Expert Rev Anticancer Ther* 2008;8(12):1883-90.

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

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

INTERVIEW

Kimberly L Blackwell, MD

Dr Blackwell is Associate Professor of Medicine and Assistant Professor of Radiation Oncology at Duke University Medical Center in Durham, North Carolina.

Tracks 1-13

Track 1 **Case discussion:** A 62-year-old woman presents with Grade I, well-differentiated, strongly ER-positive, HER2-negative multifocal BC with clinically positive lymph nodes and de novo extensive bone and liver metastases

Track 2 Central role for HER3 in HER2-positive BC: Implications for therapy with lapatinib or pertuzumab

Track 3 Psychosocial aspects of treatment for patients with metastatic breast cancer (mBC)

Track 4 First-line endocrine therapy versus chemotherapy for patients with multiple, minimally symptomatic metastases

Track 5 Rationale for hormonal therapy in combination with insulin-like growth factor 1 receptor (IGF1R) inhibitors in mBC

Track 6 Role of diet, exercise and lifestyle changes in reducing the risk of cancer recurrence

Track 7 Revisiting the dose of fulvestrant used for postmenopausal patients with ER-positive mBC

Track 8 Transitioning patients with ER-positive mBC from endocrine therapy to capecitabine

Track 9 RIBBON 1: First-line chemotherapy with or without bevacizumab in HER2-negative, locally recurrent or metastatic BC

Track 10 CALGB-40502: Weekly paclitaxel, nanoparticle albumin-bound (*nab*) paclitaxel or ixabepilone with bevacizumab as first-line therapy for locally recurrent or metastatic BC

Track 11 Efficacy of BSI-201, a PARP1 inhibitor, in combination with gemcitabine/carboplatin in triple-negative mBC

Track 12 Therapeutic options for patients with HER2-positive mBC previously treated with trastuzumab

Track 13 Managing the side effects of capecitabine/lapatinib in patients with HER2-positive mBC

Select Excerpts from the Interview

Tracks 4, 7

DR LOVE: What's your approach to first-line therapy for asymptomatic patients with ER-positive, HER2-negative metastatic breast cancer?

DR BLACKWELL: I'm a big believer in endocrine therapy. In this setting, although the response rate is probably higher with first-line chemotherapy and the responses occur more quickly, if a patient responds to hormone therapy, the responses are more durable with much less toxicity than with chemotherapy.

DR LOVE: John Robertson recently presented data from the FIRST trial evaluating front-line anastrozole versus a high-dose fulvestrant regimen in advanced breast cancer. It showed a significantly longer time to disease progression in patients who received the high-dose fulvestrant dose of 500 milligrams per month and 500 milligrams on day 14 of month one (Robertson 2009; [2.1]). How do you dose fulvestrant?

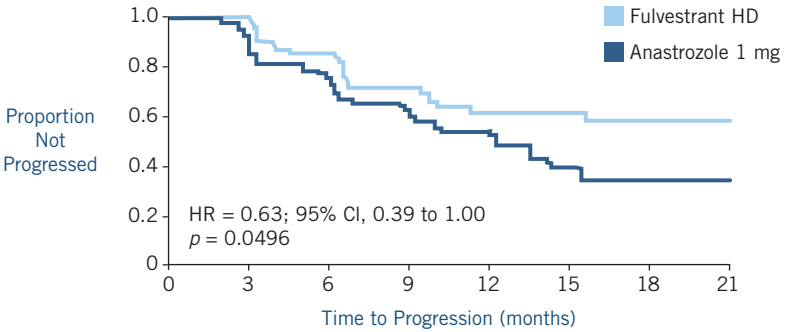
DR BLACKWELL: We've struggled with determining the best dose of fulvestrant. My understanding is that it doesn't reach steady state when administered monthly at the 250-mg dose, so I load it at 500 milligrams and then administer 250 milligrams on day 14.

According to preclinical studies, fulvestrant should work better than the aromatase inhibitors or tamoxifen. We've all seen it work in metastatic breast cancer, but not to the level expected considering that it's the most potent ER inhibitor we know of.

When those of us who've studied ER in the lab for a long time want to block ER signaling, we use fulvestrant. It kills ER-positive cancer cells when used at the correct dose.

2.1

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



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

HR = hazard ratio; CI = confidence interval; DoR = duration of response; DoCB = duration of clinical benefit

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

Track 10

DR LOVE: What are your thoughts on the Intergroup trial CALGB-40502 (2.2), evaluating first-line bevacizumab combined with paclitaxel, *nab* paclitaxel or ixabepilone for locally recurrent or metastatic breast cancer?

DR BLACKWELL: It's a great study and a good opportunity to determine which taxane is better in combination with bevacizumab.

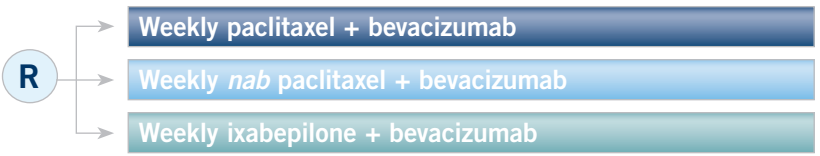
Initially, I wasn't particularly excited about ixabepilone, and even though it's not a taxane, it inhibits microtubules and has a similar mechanism of action. Ixabepilone has been studied in heavily pretreated metastatic breast cancer, and I expected to see a limited response in patients with disease progression after a taxane.

However, I've used it for patients with heavily treated disease who have received all of the usual agents because I didn't know what else to use, and I observed a fair number of good responses to monotherapy. So it's nice to see it being evaluated in the first-line setting in this trial.

2.2

Phase III Trial of Weekly Chemotherapy Combined with Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: CALGB-40502, CTSU; **Target Accrual:** 900



Eligibility: Stage IIIB not amenable to local therapy or Stage IV breast cancer; no preexisting peripheral neuropathy ≥ Grade II; no recent history of abdominal fistula or intra-abdominal abscess, gastrointestinal perforation or significant bleeding; no clinically significant cardiovascular disease; no history of stroke or TIA within previous six months; no CNS metastases

SOURCE: **www.clinicaltrials.gov**. Accessed December 2009.

Track 12

DR LOVE: How do you treat HER2-positive metastatic breast cancer in patients who have and those who have not received adjuvant trastuzumab?

DR BLACKWELL: The good news is that we aren't seeing much disease recurrence in patients who received adjuvant trastuzumab, and when you expect recurrence, I believe that it's critical to recheck the HER2 status.

For patients who did receive adjuvant trastuzumab and experience recurrence, I'm quick to incorporate lapatinib, particularly in combination with

capecitabine. That approved regimen with capecitabine is a good option (Cameron 2008). I also use trastuzumab combined with lapatinib, on which Joyce O'Shaughnessy presented data last year, for patients who haven't received trastuzumab or those who experienced a disease-free interval after trastuzumab (O'Shaughnessy 2008; [2.3]).

I've observed a fair number of durable responses to trastuzumab and lapatinib, and we have seen a 25 percent clinical benefit rate at six months for patients who received trastuzumab/lapatinib versus 12 percent for those who received lapatinib alone. That's a near doubling of response, and many patients crossed over in that trial, so the benefit might be four times as great as what the data show. I enrolled many patients on that study, and several have been on the combination for three or four years, so I'm a big believer that those two biologics can form an active combination for the correct patient. ■

2.3

Lapatinib (L) with or without Trastuzumab (T) for Patients with Heavily Pretreated Metastatic Breast Cancer Who Experience Disease Progression While on Trastuzumab-Containing Therapy

Parameter	L (n = 145)	L + T (n = 146)	Odds ratio	*p*-value
Response rate[1]	6.9%	10.3%	OR 1.5	0.46
Clinical benefit rate[2]	12.4%	24.7%	OR 2.2	0.01
Median progression-free survival	8.1 weeks	12.0 weeks	HR 0.73	0.008
Median overall survival[3]	39.0 weeks	51.6 weeks	HR 0.75	0.106

[1] Confirmed complete responses (CR) + partial responses (PR); [2] CR + PR + stable disease ≥ 6 months; [3] Intent-to-treat population; odds ratio > 1, hazard ratio < 1 favors L + T

SOURCE: O'Shaughnessy J et al. *Proc ASCO* 2008;**Abstract 1015**.

SELECT PUBLICATIONS

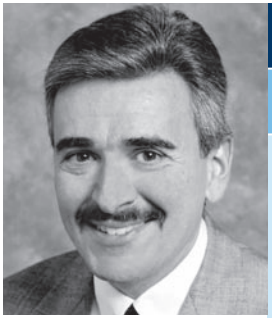
Cameron D et al. **A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: Updated efficacy and biomarker analyses.** *Breast Cancer Res Treat* 2008;112(3):533-43.

Johnston S et al. **Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy.** *J Clin Oncol* 2008;26(7):1066-72.

O'Shaughnessy J et al. **A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1015**.

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

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



INTERVIEW

Joseph A Sparano, MD

Dr Sparano is Professor of Medicine and Women's Health at Albert Einstein College of Medicine, Associate Chairman in the Department of Oncology at Montefiore Medical Center and Director of the Breast Evaluation Center at Montefiore-Einstein Cancer Center in Bronx, New York.

Tracks 1-13

Track 1 **Case discussion:** A 68-year-old woman with a 1.5-cm, high-grade, strongly ER-positive, HER2-negative, multicentric left breast tumor and a 0.9-cm micrometastasis in one lymph node receives an Onco*type* DX Recurrence Score of 19

Track 2 Adjuvant TC for lower-risk, node-positive BC

Track 3 The role of the Onco*type* DX Recurrence Score in clinical decision-making

Track 4 Perspective on results of the NSABP-C-08 adjuvant colon cancer trial and ongoing trials of adjuvant bevacizumab in early BC

Track 5 Validation and clinical utility of the MammaPrint® assay

Track 6 **Case discussion:** A 35-year-old woman with a 0.5-cm, high-grade, ER-negative, HER2-positive, node-negative IDC receives TC in combination with trastuzumab

Track 7 Prognosis for patients with subcentimeter, HER2-positive, node-negative BC

Track 8 **Case discussion:** A 55-year-old woman presents with a locally advanced, ER-negative, HER2-positive, node-positive IDC and de novo lung and liver metastases

Track 9 Removal of the primary breast tumor in patients with de novo mBC

Track 10 **Case discussion:** A 52-year-old woman presents with triple-negative supraclavicular nodal recurrence eight years after receiving adjuvant chemotherapy and endocrine therapy for an ER-positive, HER2-negative mucinous carcinoma with two positive nodes

Track 11 Rationale for CALGB-40502 evaluating bevacizumab in combination with weekly paclitaxel, *nab* paclitaxel or ixabepilone as first-line therapy for mBC

Track 12 Incorporation of *nab* paclitaxel and ixabepilone into clinical practice

Track 13 Implications of the RIBBON 1 trial results for the use of capecitabine and bevacizumab in the treatment of mBC

Select Excerpts from the Interview

Tracks 1-3

Case discussion

A 68-year-old woman presents with a 1.5-cm, high-grade, strongly ER-positive, HER2-negative, multicentric left breast adenocarcinoma and a 0.9-cm micrometastasis in one lymph node

DR LOVE: What was your approach to the decision regarding adjuvant chemotherapy for this patient?

DR SPARANO: I tend to recommend AC followed by weekly paclitaxel in higher-risk cases, such as for patients with four or more positive lymph nodes or other high-risk features. For patients with one to three positive nodes, especially one node or one micrometastasis, I believe that four cycles of docetaxel/cyclophosphamide (TC) or regimens such as AC or CMF are acceptable.

I discussed with this 68-year-old woman the options of four cycles of AC followed by paclitaxel or four cycles of TC. After reviewing the toxicity profiles and the durations of therapy, she decided that if she needed chemotherapy, she preferred TC because of the shorter treatment course and the absence of an anthracycline.

However, we ordered the Onco*type* DX assay, and her Recurrence Score was 19. After reviewing the implications, we both felt comfortable deferring chemotherapy (Albain 2007; [3.1]).

3.1

Effect of Adding Chemotherapy to Tamoxifen According to the Onco*type* DX Recurrence Score for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer

	10-year disease-free survival estimates	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low Recurrence Score (<18)	60%	64%
Intermediate Recurrence Score (18-30)	49%	63%
High Recurrence Score (≥31)	43%	55%

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Tracks 6-7

Case discussion

A 35-year-old woman presents with a 0.5-cm, high-grade, ER-negative, HER2-positive, node-negative IDC

DR LOVE: What are your thoughts on adjuvant therapy for patients with subcentimeter, node-negative, HER2-positive breast cancer?

DR SPARANO: The question is, how small is too small? Is it one millimeter or two millimeters? I'm not sure about the precision of pathology for making that call, nor do I believe that we have enough data to answer that question.

We administered adjuvant therapy to this patient, specifically trastuzumab combined with four cycles of TC. This was a couple of years ago, so at the time our decision wasn't strongly evidence based.

However, since then Gonzalez-Angulo and colleagues have presented data on recurrence rates among patients with small HER2-positive tumors (Gonzalez-Angulo 2009; [3.2]). They examined the risk of recurrence in patients with T1a or T1b node-negative breast cancer who had not received adjuvant therapy, focusing on various subgroups.

Relapse-free survival in the HER2-positive group was significantly inferior to that in the hormone receptor-positive group and the triple-negative group, so I believe there is a benefit for some patients with smaller lesions. I believe that tumor size matters, but biology also matters and probably just as much.

3.2

Recurrence-Free Survival (RFS) and Distant Recurrence-Free Survival (DRFS) in Subgroups of Patients with Small (≤1 cm), Node-Negative Breast Cancer

	Five-year estimate	
Breast cancer subgroup	RFS $p < 0.0001$	DRFS $p < 0.0001$
HER2-positive	77.1%	86.4%
Triple-negative	85.2%	95.6%
ER/PR-positive	95.2%	97.5%

SOURCE: Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.

Tracks 8-9

Case discussion

A 55-year-old woman with a locally advanced, ER-negative, HER2-positive, node-positive IDC and de novo lung and liver metastases receives carboplatin/*nab* paclitaxel and trastuzumab, the chemotherapy is stopped after six cycles and trastuzumab is continued

DR LOVE: How long should the trastuzumab be continued?

DR SPARANO: I don't believe anyone knows that answer, but I would continue it indefinitely.

We all have patients such as this one in our practices. I have one now who presented with cardiac tamponade as her manifestation of metastatic breast cancer. She had widely disseminated disease, and we administered induction carboplatin/paclitaxel with trastuzumab. She is now in her fifth year of maintenance trastuzumab without any evidence of recurrence.

DR LOVE: Should the primary breast tumor be removed in patients who present with de novo metastatic disease?

DR SPARANO: Some evidence indicates that these patients benefit from the removal of the primary tumor (Rapiti 2006; [3.3]). This is based mainly on retrospective data, which are hopelessly flawed because of the selection bias involved in operating on patients who are experiencing favorable responses.

Nonetheless, the evidence suggests a 40 percent reduction in the risk of death for patients who have their primary tumors addressed surgically in a scenario such as this one.

Self-seeding, promulgated by Larry Norton and Joan Massagué, is also an issue (Norton 2006). The concept suggests that distant metastasis can reseed within the circulation, travel back to the primary tumor and be turbocharged, becoming more cancerous, and then seed again.

Data from these laboratory experiments suggest a potential role for the removal of the primary tumor to eliminate the self-seeding that may be occurring.

The Breast Cancer Intergroup is planning a large trial to address this issue. After receiving induction therapy, patients with tumors that exhibit responses will be randomly assigned to immediate versus delayed breast surgery. The trial has a target accrual of 900 patients, so it's powered to detect a survival benefit. ■

3.3

Population-Based Study Evaluating the Removal of the Primary Tumor in Patients with De Novo Metastatic Breast Cancer (N = 300)

	Five-year breast cancer-specific survival	95% confidence interval
Surgery with negative margins	27%	16% to 39%
Surgery with positive margins	16%	3% to 28%
Surgery with unknown margin status	12%	1% to 23%
No surgery	12%	7% to 17%

SOURCE: Rapiti E et al. *J Clin Oncol* 2006;24(18):3743-9.

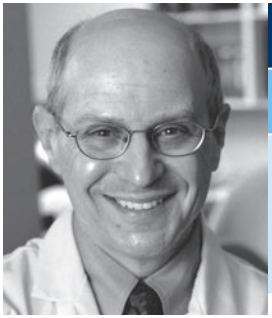
SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Gonzalez-Angulo AM et al. **High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller.** *J Clin Oncol* 2009;27(34):5700-6.

Norton L, Massagué J. **Is cancer a disease of self-seeding?** *Nat Med* 2006;12(8):875-8.

Rapiti E et al. **Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis.** *J Clin Oncol* 2006;24(18):3743-9.



INTERVIEW

Larry Norton, MD

Dr Norton is Deputy Physician-in-Chief at Memorial Hospital, for Breast Cancer Programs and Norna S Sarofim Chair in Clinical Oncology at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-11

Track 1 Optimizing the dosing schedule of capecitabine alone and in combination with biologic agents

Track 2 Beyond mitosis in the development of targeted cancer therapies

Track 3 Application of the "seed and soil" hypothesis to explain the potential benefits of trastuzumab in "HER2-normal" early BC

Track 4 Rationale for targeting Src in ER-positive and ER-negative BC

Track 5 A "self-seeding hypothesis" to explain cancer growth and behavior

Track 6 Efficacy of endocrine therapy in the self-seeding process

Track 7 Implications of the self-seeding hypothesis for removal of the primary tumor in patients with de novo mBC

Track 8 Defining terms in understanding the cancer process: "Tumor-initiating cells" versus stem cells

Track 9 Implications of the self-seeding hypothesis with regard to the antitumor effect of bisphosphonates in ABCSG-12

Track 10 Utility of the Onco*type* DX assay independent of clinicopathologic characteristics and quantitative assessment of individual genes

Track 11 Emergence of PARP inhibitors in the treatment of BRCA-deficient and triple-negative BC

Select Excerpts from the Interview

Track 1

DR LOVE: What do we know about the dosing and scheduling of capecitabine alone and in combination?

DR NORTON: We are in the process of designing an international randomized trial that will compare the conventional capecitabine schedule of 14 days on and seven days off to the novel schedule of seven days on and seven days off. Most people who we are in contact with have evolved toward the seven-on/seven-off schedule because of its greater tolerability.

Patients are often started on the conventional schedule and when toxicities develop, changing the schedule without changing the dosing of the combination is often sufficient to modulate the toxicities without losing efficacy.

Combination schedules, though, must be studied, modeled and tested because of interrelationships between the drugs. The optimal schedule for a single agent is not necessarily the optimal schedule for combination with other agents. For example, capecitabine combined with anti-VEGF therapy may have a different optimal schedule than capecitabine alone.

The RIBBON 1 study (Robert 2009; [4.1]) demonstrated the activity of the bevacizumab/capecitabine combination, and I would like to see optimization of the dose schedule for this combination. I believe that excellent therapeutic ratios and potent anticancer effects can be achieved by using drugs in combination with the proper sequencing and scheduling.

4.1

RIBBON 1: First-Line Chemotherapy with or without Bevacizumab (BEV) for HER2-Negative, Locally Recurrent or Metastatic Breast Cancer

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

* Includes only patients with measurable disease at baseline

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

Tracks 2, 5

DR LOVE: What are some of the new research strategies that you believe are most promising?

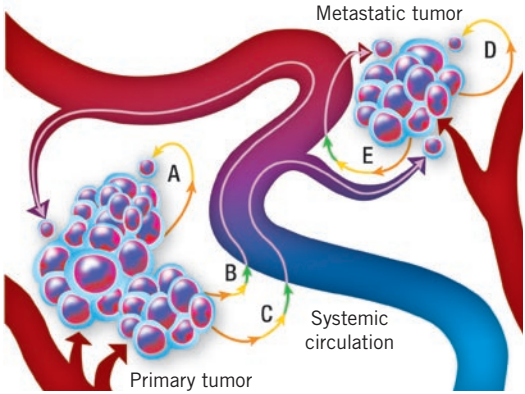
DR NORTON: I am intrigued by the increasing information suggesting that mitosis is only one of the potentially important targets in cancer therapeutics. Cell mobility, invasive capacity, intravasation, extravasation and recruitment of cells are equally important, and many agents that poison cell division can also modulate some of these effects. I'm also interested in anti-HER2 therapies for HER2-dependent tumors because modulation of HER2 affects not only cell division but also cell mobility.

DR LOVE: Would you review and update us on the self-seeding hypothesis?

DR NORTON: Reliable animal models show that a significant proportion of cancer growth occurs because cells leave the primary tumor, circulate, return to the primary site and/or start new areas of growth. We can think of cancer

as a weed bed — a collection of thousands of plants growing together, each starting with an individual seed. If this is true in humans, the knowledge would give us new therapeutic targets and explain the activity of compounds that we couldn't explain before (Norton 2006; [4.2]).

4.2 **Self-Seeding Concept of Cancer Growth and Metastasis**



Self-seeding may take place along the following paths: (A) dislodging and reattachment of a primary tumor cell at the primary site; (B) dislodging, intravasation, circulation, then extravasation back to the primary site; (C) dislodging, intravasation, circulation, then extravasation to a metastatic site; (D or E) self-seeding from a metastatic site following path A or B.

SOURCE: Reprinted by permission from Macmillan Publishers Ltd: *Nature Medicine*. Norton L, Massagué J. **Is cancer a disease of self-seeding?** *Nat Med* 2006;12(8):875-8, copyright 2006.

Track 10

DR LOVE: What is your perspective on the evolution of the Onco*type* DX assay?

DR NORTON: I use Onco*type* DX frequently because it is an approved assay that we find extremely useful for clinical decision-making. In a helpful algorithm, it integrates the complex relationships among estrogen dependence, HER2 status and proliferation with a few housekeeping genes. Some physicians have asked why we don't just quantitatively measure HER2, ER and proliferation rate. First, that may be more expensive, but it's also the relative balance between those factors that seems to be important in the Onco*type* DX Recurrence Score. ■

SELECT PUBLICATIONS

Norton L, Massagué J. **Is cancer a disease of self-seeding?** *Nat Med* 2006;12(8):875-8.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following clinical questions are being evaluated in the international Phase III ALTTO trial for patients with HER2-positive early breast cancer?**
   a. Efficacy and safety of lapatinib versus trastuzumab
   b. Efficacy and safety of lapatinib in combination with trastuzumab
   c. Duration of one versus two years of anti-HER2 treatment
   d. All of the above
   e. Both a and b

2. **An independent review confirmed an overall response rate of approximately _____ with T-DM1 for patients with trastuzumab-refractory metastatic breast cancer.**
   a. 75 percent
   b. 50 percent
   c. 30 percent
   d. 10 percent

3. **The addition of BSI-201 to gemcitabine/carboplatin improved the _____ for patients with previously treated, triple-negative metastatic breast cancer.**
   a. Clinical benefit rate
   b. Median progression-free survival rate
   c. Median overall survival rate
   d. Both a and b
   e. All of the above

4. **A Phase II trial of the PARP inhibitor olaparib demonstrated that the agent was well tolerated and highly active in patients with advanced _____ breast cancer.**
   a. Triple-negative
   b. BRCA-deficient
   c. None of the above

5. **In the FIRST trial for postmenopausal patients with ER-positive advanced breast cancer, the time to progression with first-line fulvestrant was estimated to be approximately _____ longer than in patients who received anastrozole.**
   a. 10 percent
   b. 30 percent
   c. 60 percent

6. **CALGB-40502 is a Phase III trial evaluating _____ in combination with weekly paclitaxel, *nab* paclitaxel or ixabepilone.**
   a. Trastuzumab
   b. Lapatinib
   c. Bevacizumab

7. **In a randomized trial reported by O'Shaughnessy and colleagues, the combination of lapatinib and trastuzumab resulted in equivalent progression-free survival compared to lapatinib alone for patients with heavily pretreated, HER2-positive metastatic breast cancer who experienced disease progression on trastuzumab.**
   a. True
   b. False

8. **A population-based study published by Rapiti and colleagues evaluating the removal of the primary tumor in patients with de novo metastatic breast cancer demonstrated a significant improvement in the five-year breast cancer-specific survival of patients who underwent surgery with negative margins.**
   a. True
   b. False

9. **In the RIBBON 1 trial, the addition of bevacizumab to capecitabine improved the median progression-free survival by approximately three months for patients with previously untreated metastatic breast cancer.**
   a. True
   b. False

10. **According to the self-seeding hypothesis, tumor cells from the primary tumor may leave, circulate and return to start a new growth area.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 6, 2009

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
Efficacy of BSI-201, a PARP1 inhibitor, in combination with gemcitabine/carboplatin in triple-negative metastatic breast cancer (mBC)	4 3 2 1	4 3 2 1
RIBBON 1: First-line chemotherapy with or without bevacizumab in HER2-negative, locally recurrent or metastatic BC	4 3 2 1	4 3 2 1
CALGB-40502: Bevacizumab in combination with weekly paclitaxel, *nab* paclitaxel or ixabepilone as first-line therapy for locally recurrent or metastatic BC	4 3 2 1	4 3 2 1
Role of the Onco*type* DX Recurrence Score in clinical decision-making	4 3 2 1	4 3 2 1
Removal of the primary tumor in patients with de novo mBC	4 3 2 1	4 3 2 1
A "self-seeding hypothesis" to explain cancer growth, behavior and response to therapeutic interventions	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Evaluate the potential benefits of surgical resection of the primary tumor in patients presenting with de novo metastatic breast cancer..... 4 3 2 1 N/M N/A
- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care..... 4 3 2 1 N/M N/A
- 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
- Formulate an evidence-based algorithm for the management of HER2-positive localized or previously treated metastatic breast cancer ..... 4 3 2 1 N/M N/A
- Recount the role of poly(ADP-ribose) polymerase (PARP) in the DNA repair pathway, and review the efficacy and safety of the PARP inhibitors for BRCA1/BRCA2 carriers with breast cancer or women with triple-negative breast cancer ..... 4 3 2 1 N/M N/A
- Recall the utility of the "self-seeding hypothesis" to explain cancer growth, behavior and response to therapeutic interventions..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Jenny C Chang, MD	4 3 2 1	4 3 2 1
Kimberly L Blackwell, MD	4 3 2 1	4 3 2 1
Joseph A Sparano, MD	4 3 2 1	4 3 2 1
Larry Norton, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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