Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

SPECIAL ISSUE
Proceedings from a Clinical Investigator Think Tank

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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. 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 program assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care.
- Apply the results of recent clinical research to the evidence-based use of adjuvant intravenous bisphosphonates as bone-protective and/or anticancer agents.
- Recognize the applications and limitations of available diagnostic assays in the reliable discrimination between breast tumor receptor subtypes.
- Compare and contrast the efficacy and safety of trastuzumab in combination with anthracycline- and nonanthracycline-containing chemotherapy.
- Formulate an evidence-based algorithm for the management of HER2-positive localized or metastatic breast cancer.
- Appraise the role of lapatinib and other novel HER2-targeted agents in the treatment of trastuzumab-resistant metastatic disease.
- Educate patients with HER2-negative advanced breast cancer about the individualized risks and benefits of combining bevacizumab with front-line or subsequent chemotherapy.
- Recount the role of poly(ADP-ribose) polymerase (PARP) in the DNA repair pathway, and review the efficacy and safety of investigational PARP inhibitors for patients with BRCA-deficient and/or triple-negative breast cancer.
- Identify ongoing breast cancer clinical trial opportunities and counsel appropriately selected patients about study participation.

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SELECT EXCERPTS FROM THE DISCUSSION

DR LOVE: Jenny, can you discuss Dr Tutt's presentation at ASCO 2009 evaluating the oral poly(ADP-ribose) polymerase (PARP) inhibitor olaparib for metastatic breast cancer?

DR CHANG: This study evaluated two cohorts of patients with refractory metastatic breast cancer who were BRCA1/BRCA2 carriers. Approximately 50 patients were enrolled and received olaparib at a dose of either 400 milligrams or 100 milligrams twice daily. It is stunning that, in the intent-to-treat cohort of patients with heavily pretreated disease, 400 milligrams of olaparib twice a day had an overall response rate of about 40 percent and a median progression-free survival of about six months (Tutt 2009; [1.1]).

DR LOVE: What were the side effects or toxicities?

DR CHANG: Nothing unmanageable. I believe it's tolerable.

DR LOVE: What are your thoughts on Joyce O'Shaughnessy's presentation evaluating another PARP inhibitor, BSI-201, in combination with chemotherapy for triple-negative breast cancer?

DR CHANG: This study evaluated the addition of BSI-201 to gemcitabine/carboplatin. The addition of BSI-201 to chemotherapy increased the overall response rate from 16 to 48 percent and the median progression-free survival from 3.3 months to 6.9 months with a hazard ratio of 0.34. Although it is rarely seen in clinical trials in metastatic disease, the addition of BSI-201 to gemcitabine/carboplatin also increased the median overall survival from 5.7 months to 9.2 months (O'Shaughnessy 2009; [1.2]).

1.1

Phase II Trial of the PARP Inhibitor Olaparib for BRCA1/BCRA2 Carriers with Refractory Advanced Breast Cancer

	Intent-to-treat cohort	
	Olaparib 400 mg BID (n = 27)	Olaparib 100 mg BID (n = 27)
Overall response rate	41%	22%
Complete response rate	4%	0%
Partial response rate	37%	22%
Median progression-free survival	5.7 months	3.8 months

"Olaparib at 400 mg bd [BID] is well tolerated and highly active in advanced chemotherapy-refractory BRCA-deficient breast cancer. Toxicity in BRCA1/BRCA2 carriers was similar to that reported previously in non-carriers. This first study with olaparib in BRCA-deficient breast cancers provides positive proof of concept for high activity and tolerability of a genetically defined targeted therapy."

SOURCE: Tutt A et al. *Proc ASCO* 2009;**Abstract CRA501**.

DR LOVE: One difference in these agents is that BSI-201 is administered intravenously, and olaparib is administered orally.

Has BSI-201 been evaluated in combination with other chemotherapy agents, such as the taxanes?

DR CHANG: I have not seen reports of other combinations.

DR GRADISHAR: One of the issues that has been discussed, which I believe is reasonable, is to evaluate how the PARP inhibitors combine with radiation therapy. That would apply not only to breast cancer but also to lung cancer, head and neck cancer and others. The underlying rationale for using radiation therapy is to induce DNA damage, the effect of which may be significantly enhanced by a PARP inhibitor. ■

1.2

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 (95% CI)	*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 (0.200-0.584)	<0.0001
Median overall survival (n = 59, 57)	5.7 mo	9.2 mo	0.348 (0.189-0.649)	0.0005

Incidence of select Grade III/IV toxicities

	GC (n = 59)	GC + BSI-201 (n = 57)
Anemia	11.9%	12.3%
Thrombocytopenia	20.4%	22.8%
Neutropenia	52.5%	43.9%
Febrile neutropenia	6.8%	0%
Nausea	3.4%	0%

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

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

SELECT PUBLICATIONS

O'Shaughnessy J et al. **Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial.** *Proc ASCO* 2009;**Abstract 3**.

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

NOVEL ANTI-HER2 AGENTS BEING EVALUATED FOR METASTATIC DISEASE

DR LOVE: Cliff, would you discuss the Phase II trial with trastuzumab-DM1 (T-DM1) presented at ASCO 2009 by Chuck Vogel?

DR HUDIS: Chuck's data showed that T-DM1 is active in trastuzumab-refractory breast cancer. Under independent review, the rate of response, confirmed complete or partial response, was about 25 percent (Vogel 2009; [2.1]).

What is striking is that 100 percent of the patients were pretreated with trastuzumab and 60 percent were pretreated with lapatinib (Vogel 2009). This suggests, as have other experiences, that continuing to target HER2 in one form or another can be beneficial.

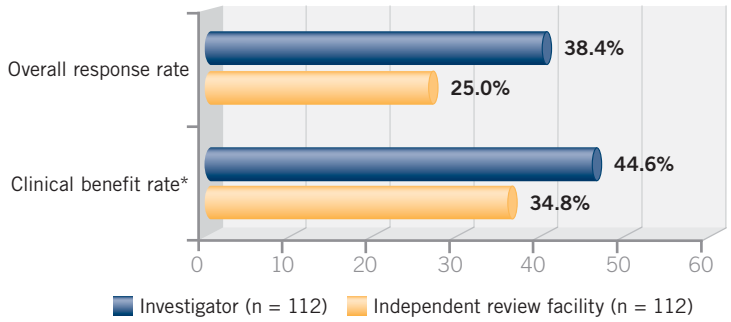
DR BURSTEIN: We've evaluated T-DM1 in several Phase I and Phase II trials, and I believe the responses have been impressive. These responses have been robust and durable in patients who have received multiple lines of trastuzumab-based therapy and, frequently, also lapatinib-based therapy. I believe it's a notably active drug.

DR SLAMON: T-DM1 must be compared head to head against its parent molecule, trastuzumab, and also against lapatinib. Preliminary data suggest that T-DM1 is better, but that's according to cross-trial comparisons.

DR BLACKWELL: The good news, at least in the United States, is that our patients have multiple options for trials

2.1

Phase II Trial of T-DM1 for Patients with HER2-Positive Metastatic Breast Cancer Who Experience Disease Progression while Receiving HER2-Directed Therapy



* Complete response, partial response or stable disease for six or more months

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

with HER2 inhibitors. They can go from one trial of an exciting agent to the next trial of an exciting agent to a third trial of an exciting agent, without feeling that they are compromising their anti-HER2 therapy.

DR LOVE: Cliff, what about the Phase II trial with pertuzumab that was presented at ASCO?

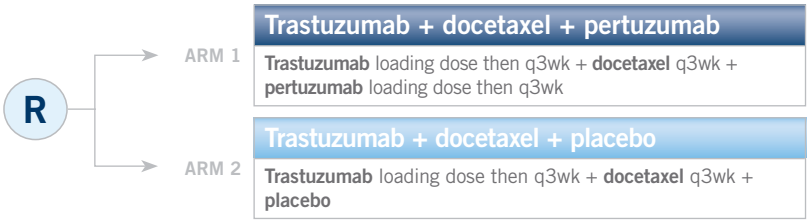
DR HUDIS: This key clinical trial has been reported several times because it has involved multiple stages. They initially combined pertuzumab with trastuzumab and described almost a 25 percent response rate among patients with trastuzumab-pretreated metastatic breast cancer who had received up to three lines of prior treatment (Gelmon 2008).

Then they added another stage to the trial, in which a small number of patients received pertuzumab alone with the proviso that at disease progression they could receive trastuzumab. Although an indirect comparison, the single-agent activity of pertuzumab appeared to be far less than the single-agent activity of T-DM1 — certainly it appeared to be less than the activity of pertuzumab/trastuzumab. The partial response rate was seven percent, with no complete responses (Cortés 2009).

A pivotal trial, CLEOPATRA — CLinical Evaluation Of Pertu-

2.2

CLEOPATRA: A Phase III, Double-Blind Trial to Evaluate the Efficacy and Safety of Trastuzumab and Docetaxel with or without Pertuzumab in Previously Untreated HER2-Positive Metastatic Breast Cancer



Treatment continues in both arms until disease progression or unmanageable toxicity.

Key Facts

Select Eligibility Criteria

- Locally recurrent or metastatic HER2-positive (FISH-positive or IHC 3+) breast cancer
- Baseline LVEF ≥ 50% within 42 days of randomization
- No prior therapy with tyrosine kinase/HER inhibitors for breast cancer, except neoadjuvant or adjuvant trastuzumab
- No CNS metastases
- No uncontrolled hypertension or unstable angina
- No myocardial infarction within six months of randomization or clinically relevant cardiovascular disease

Target Accrual: 800

Date Activated: February 2008

Estimated Completion Date: March 2012

ClinicalTrials.gov Identifier: NCT00567190

SOURCES: NCI Physician Data Query, October 2009; **www.clinicaltrials.gov**; Roche Clinical Trials Registry, October 2009.

zumab And TRAstuzumab — is evaluating docetaxel/trastuzumab versus docetaxel/trastuzumab and pertuzumab as first-line therapy for HER2-positive metastatic disease (2.2). This trial has the potential to change the standard approach for the first-line treatment of HER2-positive metastatic disease.

ADJUVANT TRASTUZUMAB IN PATIENTS WITH HER2-NEGATIVE TUMORS

DR LOVE: Chuck, can you update us on the work by Soon Paik and the NSABP evaluating adjuvant trastuzumab for patients with HER2-negative breast cancer?

DR GEYER: What generated the notion of possible benefit with adjuvant trastuzumab for patients with HER2-normal/HER2-negative disease was the central review that Soon and his lab conducted on our specimens from the NSABP-B-31 trial. They found that 9.7 percent of the patients enrolled in NSABP-B-31 who received HER2-positive test results with IHC or FISH at a local laboratory were negative for FISH amplification and also had IHC scores less than three when tested at a central laboratory (Paik 2008).

Among the patients with HER2-positive breast cancer, the relative risk for disease-free survival associated with adjuvant trastuzumab was 0.47, and it was 0.66 for overall survival, which is consistent with the overall trial data. Of note, for the cohort of 174 patients with HER2-negative disease, the relative risk for disease-free survival was 0.34 and there was a remarkable relative risk of 0.08 for overall survival. Only one patient in the group who had received trastuzumab died (Paik 2008; [2.3]), a totally unexpected finding.

This clearly runs counter to everything we understand about HER2-positive breast cancer, particularly in the metastatic setting. One of the criticisms was that perhaps this result was related to heterogeneity, suggesting that the tissue block that was sent for testing to the local laboratory was not the block that was sent to the central lab. We had axillary nodal disease samples from 67 of these patients with HER2-negative disease, and Soon tested the nodal disease. Only two of the 67 patients had HER2-positive disease in the axillary nodes. So we felt that heterogeneity didn't explain this.

We became convinced that this information might reflect some new biology, and we proposed conducting an adjuvant trial — NSABP-B-47. The Cancer Therapy Evaluation Program (CTEP) did not approve it but indicated that if we conducted an independent validation study, then it probably would be worth exploring.

DR LOVE: This was the round-robin evaluation of the specimens. Is it done yet?

DR GEYER: It was recently completed, and Soon's results have been validated. We also hope to have the NSABP-B-47 proposal back to CTEP within a few weeks.

DR LOVE: What are the eligibility criteria for that trial?

DR GEYER: It'll be for patients with

a HER2 IHC score of zero, one or two.

DR LOVE: Which chemotherapy will be used?

DR GEYER: We had initially proposed six cycles of docetaxel/cyclophosphamide (TC) with or without trastuzumab. CTEP was concerned that we weren't allowing an anthracycline, so we are proposing a dealer's choice design, in which oncologists choose between six cycles of TC with trastuzumab or AC → TH. ■

2.3 HER2 Status and the Efficacy of Adjuvant Trastuzumab in NSABP-B-31

Endpoint	ACT	ACTH	Relative risk (95% CI)	*p*-value	*p*-value for the interaction
	Number of events/ total number of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37-0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14-0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43-0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01-0.64)	0.017	

"Since our findings are based on an exploratory analysis, they should not alter current criteria used for selecting patients for adjuvant trastuzumab. Validation of the findings from central testing would justify a phase 3 trial of adjuvant trastuzumab in women with breast cancers that do not meet established criteria for therapy."

SOURCE: Paik S et al. *N Engl J Med* 2008;358(13):1409-11.

SELECT PUBLICATIONS

Baselga J et al. **Pertuzumab and trastuzumab: Re-responses to 2 biological agents in patients with HER2-positive breast cancer which had previously progressed during therapy with each agent given separately: A new biological and clinical observation.** San Antonio Breast Cancer Symposium 2009;**Abstract 5114**.

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

Gelmon KA et al. **Results of a phase II trial of trastuzumab (H) and pertuzumab (P) in patients (pts) with HER2-positive metastatic breast cancer (MBC) who had progressed during trastuzumab therapy**. *Proc ASCO* 2008;**Abstract 1026**.

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**.

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

Portera CC et al. **Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer.** *Clin Cancer Res* 2008;14(9):2710-6.

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**.

NOVEL STRATEGIES FOR EXTENDED ADJUVANT ENDOCRINE THERAPY

DR LOVE: Cliff, what are some of the new clinical research strategies with adjuvant endocrine therapy?

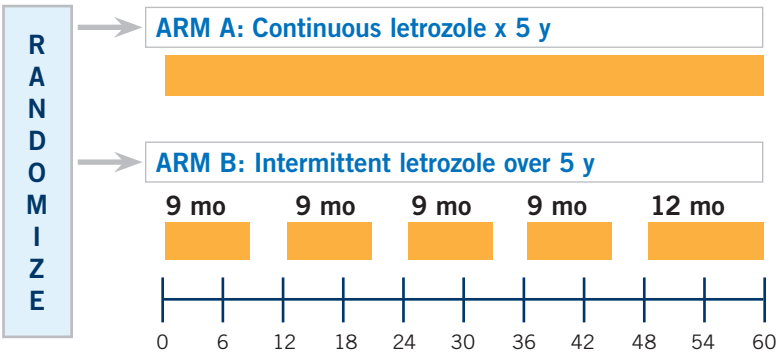
DR HUDIS: One study evaluating a novel approach to endocrine therapy is called SOLE (3.1). It is a randomized trial of continuous versus intermittent exposure to letrozole for patients who have already completed four to six years of standard adjuvant endocrine therapy.

DR GRADISHAR: It's nine months on and three months off.

DR CHLEBOWSKI: What's also interesting about that trial is that patients receive four to six years of baseline adjuvant hormonal therapy and then five years of an aromatase inhibitor (AI) versus the intermittent AI. The standard therapy in that trial could be up to 10 years of an AI.

3.1

Study of Letrozole Extension (SOLE): A Phase III Trial Evaluating the Role of Continuous Letrozole versus Intermittent Letrozole After Four to Six Years of Adjuvant Endocrine Therapy for Postmenopausal Women with ER-Positive and/or PR-Positive, Node-Positive Early Breast Cancer



Key Facts

Select Eligibility Criteria

- Postmenopausal women
- ER-positive and/or PR-positive, node-positive breast cancer
- Completed four to six years of adjuvant endocrine therapy with a selective estrogen receptor modulator, aromatase inhibitor or the sequence

Target Accrual: 4,800

Accrual: 714 (September 2009)

Date Activated: August 2007

Estimated Completion Date: December 2021

ClinicalTrials.gov Identifier: NCT00553410

SOURCE: **www.clinicaltrials.gov**, October 21, 2009.

DR LOVE: This is something Paul Goss has talked about. Is the strategy to allow estrogen levels to come back up after prolonged suppression — providing high-dose estrogen therapy?

DR HUDIS: Precisely. The trial is being conducted by the Breast International Group (BIG 1-07).

DR BLACKWELL: Postmenopausal women with hormone-sensitive breast cancer are at risk for relapse for decades, and the MA17 trial, especially for patients with node-positive disease, demonstrated that 10 years of endocrine therapy is better than five years.

It makes me nervous to decrease the endocrine therapy, and I would only do so in the context of a clinical trial.

RECENT AND ONGOING CLINICAL TRIALS WITH FULVESTRANT

DR LOVE: Bill, what do we know about doubling the dose of fulvestrant to 500 milligrams monthly?

DR GRADISHAR: Steve Come and colleagues conducted a Phase II trial with about 30 postmenopausal patients with previously untreated, ER-positive metastatic breast cancer. About 40 percent of the patients had received adjuvant endocrine therapy.

As opposed to administering fulvestrant 250 milligrams monthly, they used fulvestrant 500 milligrams on days one, 15, 28 and then monthly. They doubled the dose of fulvestrant that was administered (Come 2009).

They recorded a clinical benefit rate of 86 percent and an objective response rate of 33 percent. The median progression-free survival was impressive at about 22 months, which is an outlier from what we typically see with endocrine therapy. Also, despite more frequent and higher doses, no excess toxicity was apparent (Come 2009).

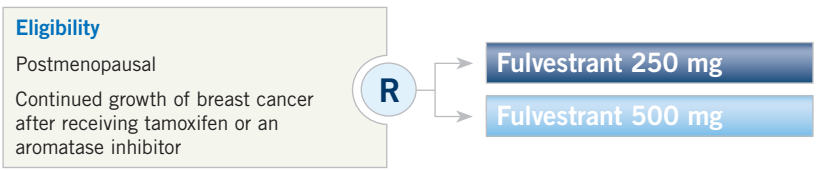
This is an intriguing but small study. To determine whether the results are a major step forward, we need to examine this more critically in a larger population of patients.

DR CHLEBOWSKI: I agree that we need further confirmation, and I believe that the proof will be forthcoming.

3.2

CONFIRM: A Phase III Randomized Trial Evaluating Fulvestrant 250 Milligrams versus 500 Milligrams for ER-Positive Advanced Breast Cancer Failing Prior Hormonal Therapy

Accrual: 736 (Closed)



SOURCES: NCI Physician Data Query, October 2009; **www.clinicaltrials.gov**.

A Phase III randomized trial, CONFIRM (3.2) — comparing 500 milligrams to 250 milligrams of fulvestrant for postmenopausal women with ER-positive, advanced breast cancer relapsing after prior endocrine therapy — has completed accrual. The data are being evaluated.

If CONFIRM results were positive, fulvestrant would by default become first-line hormonal therapy after failure of an AI, because EFECT, comparing a standard dose of fulvestrant to exemestane for patients after failure of an AI, demonstrated equivalence between the two drugs (Chia 2008). ■

SELECT PUBLICATIONS

Bergh J et al. **First results from FACT — An open-label, randomized phase III study investigating loading dose of fulvestrant combined with anastrozole versus anastrozole at first relapse in hormone receptor positive breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 24**.

Chia S et al. **Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT.** *J Clin Oncol* 2008;26(10):1664-70.

Come SE et al. **Tolerability and efficacy of 500 mg fulvestrant in postmenopausal women with estrogen receptor (ER)+ advanced breast cancer.** *Proc ASCO* 2009;**Abstract 1050**.

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**.

ADJUVANT CHEMOTHERAPY: ROLE OF GENOMIC TESTING

Case discussion

A 77-year-old woman presents with a mammographically detected 1.4-cm, ER-positive (80 to 90 percent), PR-positive, HER2-negative, invasive ductal carcinoma (IDC) with three positive nodes.

She has a medical history of well-controlled hypertension and a TIA without any long-term sequelae. She opts for a lumpectomy and prefers not to receive adjuvant chemotherapy but will accept it if necessary (from the practice of Clifford Hudis, MD).

DR LOVE: Chuck, would you order an Onco*type* DX® assay for this patient?

DR GEYER: I'd like to have the results from an Onco*type* DX assay in a patient like this if it would help the discussion.

If she says, "I'll take chemotherapy, but I need to understand more about its benefits," then I would order an Onco*type* DX assay.

If she's sure she doesn't want chemotherapy, then I would administer adjuvant endocrine therapy and not order an Onco*type* DX assay.

DR LOVE: What did you do, Cliff?

DR HUDIS: In this case it was a question of anatomy versus biology. Kathy Albain reported results from SWOG-8814 (Albain 2007; [4.1]) that opened the door to at least considering an Onco*type* DX assay for node-positive disease.

This patient would clearly have been a candidate for SWOG-8814, comparing tamoxifen to CAF/tamoxifen, a study that was positive overall for chemotherapy. My normal approach for such patients is to use chemotherapy, but she didn't want it. So we ordered an Onco*type* DX assay, and it returned a Recurrence Score® of 11.

DR LOVE: With this score, you were more comfortable, and she was more comfortable?

DR HUDIS: She certainly didn't want chemotherapy. It allowed me to sleep at night because I suspect that her benefit from chemotherapy, notwithstanding her substantial risk of recurrence, was fairly modest.

DR BURSTEIN: By historical experience, the benefits from chemotherapy for a 77-year-old woman with comorbid conditions, including a TIA and hypertension, are modest, especially with ER-positive, PR-positive, HER2-negative breast cancer. I believe it would have required a lot to make me strongly consider adjuvant chemotherapy for such a patient. If you were to use the Adjuvant! Online model for this patient, no effect on survival would be expected from adjuvant chemotherapy.

We've known all along that older women are more likely to have HER2-negative tumors, lower proliferative indices and higher quantitative levels of ER. Now we also know that they're likely to have lower Onco*type* DX Recurrence Scores. Everything we know to predict benefit from chemotherapy tracks the opposite way with older patients.

For a 77-year-old woman with average comorbidities for her age and a Grade II, 1- to 2-cm breast tumor with one to three positive nodes, the benefit of adding chemotherapy to adjuvant endocrine therapy is less than 0.5 percent. With recurrence-free survival, you would extend that by 1.4 percent on average. ■

4.1

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

	10-year disease-free survival point estimates (95% CI)	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low Recurrence Score (<18)	60% (40%, 76%)	64% (50%, 75%)
Intermediate Recurrence Score (18-30)	49% (32%, 63%)	63% (48%, 74%)
High Recurrence Score (≥31)	43% (28%, 57%)	55% (40%, 67%)

CI = confidence interval

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

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**.

Cuzick J et al. **Prognostic value of a combined ER, PgR, Ki67, HER2 immunohistochemical (IHC4) score and comparison with the GHI recurrence score — Results from transATAC.** San Antonio Breast Cancer Symposium 2009;**Abstract 74**.

Goldstein LJ et al. **Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features.** *J Clin Oncol* 2008;26(25):4063-71.

Wolf I et al. **Association between standard clinical and pathologic characteristics and the 21-gene recurrence score in breast cancer patients: A population-based study.** *Cancer* 2008;112(4):731-6.

ANTI-ANGIOGENIC THERAPY

Case discussion

A 47-year-old postmenopausal woman underwent a right modified mastectomy seven years ago for a 1.5-cm, node-negative, Grade III, ER-positive, PR-positive, HER2-negative IDC. She did not have health insurance and because of the costs, she declined adjuvant chemotherapy, but she did complete five years of adjuvant tamoxifen.

She was subsequently found to have asymptomatic, small-volume bone, lung and liver metastases for which she received anastrozole for four months. At that time, a CT scan demonstrated disease progression (from the practice of Jenny C Chang, MD).

DR LOVE: Bill, would you recommend another hormonal therapy or chemotherapy for this patient at this point?

DR GRADISHAR: You could make the case for trying another endocrine maneuver, but I wouldn't be overly optimistic.

Her volume of disease is still relatively limited, and she's asymptomatic. You could try that approach, and I would be better persuaded to proceed if she were reluctant to receive chemotherapy.

My natural instinct would be to go with chemotherapy, not because she has liver disease but rather because she didn't respond to hormonal therapy.

DR LOVE: Which chemotherapy would you use, and what about combining it with bevacizumab?

DR GRADISHAR: If you consider ECOG-E2100 (Miller 2007), paclitaxel/bevacizumab would be reasonable in light of the fact that she's never received chemotherapy and certainly not a taxane. With RIBBON 1 (Robert 2009) and the AVADO trial (Miles 2008), I believe you have other partners that you could combine with bevacizumab.

DR CHLEBOWSKI: I'd proceed in the same way. Capecitabine used to be the most common chemotherapy I would administer. However, the adjuvant trial comparing CMF to capecitabine (Muss 2009) raised the question, what agent has capecitabine ever bested in a Phase III trial in advanced disease? Taking that into consideration, I have better data for paclitaxel/bevacizumab (Miller 2007).

DR LOVE: Chuck, what would you be thinking for this patient?

DR GEYER: Paclitaxel/bevacizumab. I didn't hear anyone mention zoledronic acid, but that's a given in this situation.

DR BURSTEIN: I believe that many choices exist. You could try an endocrine treatment or consider enrolling her in the CALGB-40502 study, evaluating fulvestrant with or without lapatinib.

Chemotherapy is perfectly reasonable in this setting. We know from your surveys, Neil, that this patient is likely to receive five to seven lines of chemotherapy as palliation for her advanced disease.

Relatively few compelling data suggest that the individual selection of agents or the sequencing of those agents affects overall survival, as long as she receives reasonably standard drugs.

To my knowledge, no data suggest that adding bevacizumab would affect her overall survival. It may, however, improve her time to disease progression modestly.

I believe adding bevacizumab would be perfectly reasonable, but it would mean receiving IV medication once every week for three out of every four weeks, and substantial toxicities exist with that.

For that reason many patients prefer an oral agent such as capecitabine, which is reasonably well tolerated and convenient. Patients only come to the office once every four weeks for a bisphosphonate.

She would also be a candidate for CALGB-40502, evaluating bevacizumab with either weekly ixabepilone, paclitaxel or *nab* paclitaxel. Any one of those treatment approaches would be reasonable.

DR LOVE: If you treated with capecitabine, would you likely use bevacizumab?

DR BURSTEIN: I believe you could. I'm not sure it's a compelling intervention. In the first trial evaluating capecitabine with or without bevacizumab for women who had received anthracyclines and taxanes, no benefit was found with the addition of bevacizumab (Miller 2005).

In the more recent RIBBON 1 trial, approximately a three-month improvement in progression-free survival was found compared to capecitabine alone (Robert 2009; [5.1]).

She's not experiencing symptoms, so you won't improve her symptom control. I believe it is an option, but it's probably not my first choice. If I use bevacizumab, I often administer it with weekly paclitaxel.

DR LOVE: Jenny, what happened with this patient?

DR CHANG: We used capecitabine, and she fared well for about 18 months. She had an objective

response. In fact, her liver metastases decreased in size.

DR LOVE: Cliff, would you comment on the RIBBON 1 trial?

DR HUDIS: I was the Chair of the Data Safety Monitoring Board for RIBBON 1. This was a trial with more than 1,100 patients, designed to obtain a real world experience with bevacizumab. It was partly fueled by the disparate results from the first two studies reported.

ECOG-E2100 achieved positive results with paclitaxel/bevacizumab (Miller 2007), and the other trial with capecitabine/bevacizumab had results that were perceived as negative (Miller 2005).

The patients in RIBBON 1 had previously untreated metastatic breast cancer. They were allowed to receive capecitabine on a 14-day schedule, a taxane — docetaxel or *nab* paclitaxel — or an anthracycline.

The taxane and anthracycline groups were powered together, and the capecitabine group was powered separately. The patients were randomly assigned two to one to bevacizumab or placebo (Robert 2009).

Investigator-assessed progression-free survival was the primary endpoint of the trial. Numerically, the results appeared to be slightly better than some of the components of the AVADO trial (Miles 2008). They were nothing like the results from ECOG-E2100 (Miller 2007). Overall the study results were positive, met the endpoint and demonstrated a progression-free survival advantage (Robert 2009; [5.1]).

From a practical point of view, the fact that the benefit was clearly seen in the capecitabine subset as much as in the taxane and anthracycline subset provided comfort to oncologists who have been using capecitabine and bevacizumab for years.

Toxicity-wise, not a single surprise emerged. A few more of the expected problems of hypertension and proteinuria occurred with bevacizumab. ■

5.1

RIBBON 1: A Phase III Randomized Trial of Chemotherapy with Bevacizumab (BEV) or Placebo (PL) as First-Line Therapy for HER2-Negative, Locally Recurrent or Metastatic Breast Cancer

	Capecitabine		Taxane or 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	

* Only includes patients with measurable disease at baseline

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

SELECT PUBLICATIONS

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

Miles DW et al. **Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC).** San Antonio Breast Cancer Symposium 2009;**Abstract 41**.

Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

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

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9.

Muss HB et al. **Adjuvant chemotherapy in older women with early-stage breast cancer.** *N Engl J Med* 2009;360(20):2055-65.

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**.

ROLE OF BISPHOSPHONATES FOR EARLY BREAST CANCER

DR LOVE: Rowan, would you review the ABCSG-12 trial data?

DR CHLEBOWSKI: The trial enrolled 1,803 premenopausal patients who were treated with goserelin monthly and either tamoxifen or anastrozole with or without zoledronic acid four milligrams every six months. The patients who received zoledronic acid had a 36 percent improvement in disease-free survival with a *p*-value of 0.01. The hazard ratio for the risk of death was 0.6 with borderline statistical significance (Gnant 2009; [6.1]).

Disease-free survival wasn't much different between anastrozole and tamoxifen, and for overall survival the hazard ratio was 1.80 with a *p*-value of 0.7 (Gnant 2009).

DR LOVE: Kim, what is the role of adjuvant bisphosphonates for premenopausal women not participating in a clinical trial?

DR BLACKWELL: I have been using a twice-a-year bisphosphonate for the prevention of bone loss in premenopausal women. Charlie Shapiro has generated some solid data suggesting that young women lose bone in the setting of adjuvant chemotherapy (Shapiro 2001). We had data from ABCSG-12 suggesting that one dose of zoledronic acid every six months for a total of six doses would eliminate the bone loss associated with ovarian suppression (Gnant 2007). The fact that zoledronic acid might

have anticancer activity is "the icing on the cake."

DR LOVE: Do you offer adjuvant zoledronic acid to your postmenopausal patients?

DR BLACKWELL: I offer it to my postmenopausal patients with documented bone loss or osteoporosis.

DR BURSTEIN: ABCSG-12 included a special population of young, premenopausal women who did not receive adjuvant chemotherapy and had hormone receptor–positive tumors. I believe the results from ABCSG-12 are provocative findings, but they are not influencing my ordinary practice in the adjuvant setting.

We are waiting for the results from NSABP-B-34 and the AZURE trial, which are large, robust adjuvant studies of bisphosphonate therapy. We've been enrolling many patients on the SWOG-S0307 trial, randomizing among zoledronic acid, ibandronate and clodronate, which is a valuable vehicle for providing access to bisphosphonates, but I believe the jury is still out. ■

6.1

ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Prolongs Disease-Free Survival (DFS) for Premenopausal Patients with ER-Positive Early Breast Cancer

	First DFS event per patient, n	
	ZDA (n = 899)	No ZDA (n = 904)
Locoregional recurrence	10	20
Distant recurrence	29	41
Contralateral breast cancer	6	10
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS versus no ZDA = 0.64 (0.46-0.91), $p = 0.01$

"The significant benefit of zoledronic acid with respect to disease-free survival may be explained by several antitumor mechanisms. In preclinical studies, zoledronic acid inhibited tumor-cell adhesion, invasion, and proliferation and induced apoptosis in a variety of human tumor cell lines. It also delayed disease progression in animal models of human cancers and acted synergistically with many chemotherapy agents. Early data suggest that zoledronic acid can stimulate antitumor immune reactions and exert antiangiogenic effects."

SOURCE: Gnant M et al. *N Engl J Med* 2009;360(7):679-91.

SELECT PUBLICATIONS

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

Gnant MF et al. **Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: A report from the Austrian Breast and Colorectal Cancer Study Group.** *J Clin Oncol* 2007;25(7):820-8.

Shapiro CL et al. **Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer.** *J Clin Oncol* 2001;19(14):3306-11.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **For patients with heavily pretreated metastatic breast cancer who were BRCA1/BRCA2 carriers, olaparib 400 milligrams twice daily had an overall response rate of about _____.**
   a. 80 percent
   b. 60 percent
   c. 40 percent
   d. 20 percent

2. **The addition of BSI-201 to gemcitabine/carboplatin improved the _____ for patients with triple-negative, metastatic breast cancer treated with zero to two chemotherapy regimens.**
   a. Objective response rate
   b. Median progression-free survival
   c. Median overall survival
   d. Both a and b
   e. All of the above

3. **An independent review confirmed an overall response rate of about _____ with T-DM1 for patients with trastuzumab-refractory metastatic breast cancer.**
   a. 75 percent
   b. 50 percent
   c. 25 percent
   d. 10 percent

4. **CLEOPATRA, a Phase III randomized trial, is evaluating docetaxel/trastuzumab with or without _____ as first-line therapy for HER2-positive, metastatic breast cancer.**
   a. Lapatinib
   b. Pertuzumab
   c. T-DM1
   d. Neratinib
   e. None of the above

5. **In NSABP-B-31, patients with HER2-negative breast cancer by central laboratory testing derived a similar benefit from adjuvant trastuzumab to patients with HER2-positive disease.**
   a. True
   b. False

6. **CONFIRM, a Phase III randomized trial, is comparing 500 milligrams to 250 milligrams of fulvestrant for postmenopausal women with ER-positive advanced breast cancer as second-line therapy after relapse on tamoxifen or an aromatase inhibitor.**
   a. True
   b. False

7. **A retrospective analysis of _____ evaluated the effect of adjuvant chemotherapy according to the Onco*type* DX Recurrence Score for postmenopausal women with ER-positive, node-positive breast cancer.**
   a. NSABP-B-14
   b. NSABP-B-21
   c. SWOG-8814
   d. None of the above

8. **In the RIBBON 1 trial, the addition of bevacizumab to _____ improved median progression-free survival by approximately three months for patients with previously untreated metastatic breast cancer.**
   a. An anthracycline-containing regimen
   b. A taxane
   c. Capecitabine
   d. All of the above
   e. None of the above

9. **For premenopausal women with ER-positive and/or PR-positive breast cancer, ABCSG-12 demonstrated that the addition of zoledronic acid to adjuvant hormonal therapy, consisting of goserelin with either tamoxifen or anastrozole, _____.**
   a. Improved disease-free survival
   b. Reduced bone loss
   c. Both a and b
   d. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Think Tank Issue 1, 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
Phase II efficacy of PARP inhibitors in advanced breast cancer (BC)	4 3 2 1	4 3 2 1
Mechanism of action and early clinical findings with trastuzumab-DM1 (T-DM1)	4 3 2 1	4 3 2 1
Proposed NSABP-B-47 study of adjuvant chemotherapy with or without trastuzumab for patients with HER2-negative tumors	4 3 2 1	4 3 2 1
High-dose fulvestrant versus anastrozole for advanced BC	4 3 2 1	4 3 2 1
Results of RIBBON 1: A Phase III study of chemotherapy with bevacizumab or placebo as first-line therapy for HER2-negative, locally recurrent or metastatic BC	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:

- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care . . . . . 4 3 2 1 N/M N/A
- Apply the results of recent clinical research to the evidence-based use of adjuvant intravenous bisphosphonates as bone-protective and/or anticancer agents . . . . . 4 3 2 1 N/M N/A
- Recognize the applications and limitations of available diagnostic assays in the reliable discrimination between breast tumor receptor subtypes . . . . . 4 3 2 1 N/M N/A
- Compare and contrast the efficacy and safety of trastuzumab in combination with anthracycline- and nonanthracycline-containing chemotherapy . . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based algorithm for the management of HER2-positive localized or metastatic breast cancer. . . . . 4 3 2 1 N/M N/A
- Appraise the role of lapatinib and other novel HER2-targeted agents in the treatment of trastuzumab-resistant metastatic disease . . . . . 4 3 2 1 N/M N/A
- Educate patients with HER2-negative advanced breast cancer about the individualized risks and benefits of combining bevacizumab with front-line or subsequent chemotherapy . . . . . 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 investigational PARP inhibitors for patients with BRCA-deficient and/or triple-negative breast cancer. . . . . 4 3 2 1 N/M N/A
- Identify ongoing breast cancer clinical trial opportunities and counsel appropriately selected patients about study participation. . . . . 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?

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

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Harold J Burstein, MD, PhD	4	3	2	1	4	3	2	1
Jenny C Chang, MD	4	3	2	1	4	3	2	1
Rowan T Chlebowski, MD, PhD	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
Clifford Hudis, MD	4	3	2	1	4	3	2	1
Dennis J Slamon, MD, PhD	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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