

Breast Cancer[®]

U P D A T E

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

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Results from numerous ongoing clinical trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic/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 the latest research developments, ongoing clinical trials and expert perspectives, this CME program is designed to assist medical oncologists with the formulation of up-to-date clinical management strategies for patients with localized and metastatic breast cancer.

LEARNING OBJECTIVES

- Identify and use prognostic and predictive biomarkers to enhance the delivery of individualized breast cancer care.
- Review the long-term risk of recurrence for patients with ER-positive early breast cancer, and consider on- and off-protocol extended adjuvant endocrine therapy for appropriately selected patients.
- Counsel patients about skeletal complications associated with aromatase inhibitors and the impact of bisphosphonates on maintaining bone mineral density and reducing the risk of breast cancer recurrence.
- Assess patients' vitamin D status and provide recommendations for vitamin D replacement and/or supplementation.
- Formulate an evidence-based algorithm for the management of HER2-positive localized or previously treated metastatic breast cancer.
- Apply the results from recent clinical trials when recommending first-line chemotherapy in combination with bevacizumab for women with HER2-negative metastatic breast cancer.
- Summarize the anti-angiogenic agents being evaluated in clinical trials for HER2-negative localized or 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 design and eligibility criteria for clinical trials evaluating new treatment strategies in early and advanced breast cancer, and screen appropriate patients for study participation.

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INTERVIEW

Joyce O'Shaughnessy, MD

Dr O'Shaughnessy is Co-Director of the Breast Cancer Research Program at Baylor-Charles A Sammons Cancer Center in Dallas, Texas and is affiliated with Texas Oncology, PA and US Oncology.

Tracks 1-16

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|--|---|
| Track 1 Poly(ADP-ribose) polymerase (PARP) and the DNA repair pathway | Track 8 Updated results from the Phase II trial of T-DM1 for heavily pretreated, HER2-positive mBC |
| Track 2 Mechanism of action of PARP inhibitors | Track 9 Pertuzumab in combination with trastuzumab for HER2-positive mBC with disease progression on trastuzumab |
| Track 3 BRCA1/BRCA2 mutations and triple-negative breast cancer (BC) | Track 10 Overview of HER binding targets and clinical activity of neratinib versus lapatinib |
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| Track 6 Case discussion: A 36-year-old woman with a BRCA1 mutation and triple-negative BC who received gemcitabine/carboplatin and BSI-201 for lung and brain metastases | Track 13 Identification of novel targeted therapies in oncology |
| Track 7 PARP inhibitors for patients who carry BRCA1/BRCA2 mutations | Track 14 ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial |
| | Track 15 Duration of therapy with adjuvant anti-HER2 agents |
| | Track 16 Clinical use of lapatinib/capecitabine |

Select Excerpts from the Interview

Tracks 4-5

▶ **DR LOVE:** Would you summarize the data presented at ASCO 2009 on the poly(ADP-ribose) polymerase (PARP) inhibitors?

▶ **DR O'SHAUGHNESSY:** One presentation on the oral PARP inhibitor olaparib in BRCA1/BRCA2 carriers with metastatic ovarian cancer heavily pretreated with chemotherapy demonstrated around a 50 percent clinical benefit rate (Audeh 2009). Approximately half were objective responses and half were prolonged stable disease, which is remarkable.

In another presentation by Dr Tutt, BRCA1/BRCA2 carriers with refractory metastatic breast cancer had an impressive overall response rate of approximately 40 percent with olaparib 400 milligrams twice daily (Tutt 2009; [1.1]). The waterfall plot is fascinating because nearly all patients demonstrated reductions in tumor volume, and olaparib was well tolerated.

► **DR LOVE:** Would you review your ASCO 2009 plenary presentation evaluating the PARP1 inhibitor BSI-201?

► **DR O'SHAUGHNESSY:** US Oncology conducted a Phase II randomized trial for women with measurable triple-negative breast cancer who had received zero to two chemotherapy regimens for metastatic disease but no platinum agent, gemcitabine or PARP inhibitor. The patients were randomly assigned to gemcitabine/carboplatin with or without BSI-201.

We chose to administer gemcitabine/carboplatin on a schedule that's not commonly used: 1,000 mg/m² on days one and eight, carboplatin at an AUC of 2 mg/mL x min on days one and eight and BSI-201 intravenously on days one, four, eight and 11 (O'Shaughnessy 2009).

► **DR LOVE:** What were the results?

► **DR O'SHAUGHNESSY:** We treated 116 patients on the protocol. The primary endpoint was the clinical benefit rate, defined as an objective response by RECIST or stable disease for at least six months. The clinical benefit rate increased from 21 percent for gemcitabine/carboplatin alone to 62 percent with the addition of BSI-201, and the response rate tripled from 16 percent to 48 percent (O'Shaughnessy 2009; [1.2]).

These are preliminary objective responses and clinical benefit rates because not all patients have been on the study for six months to determine whether they've derived a clinical benefit.

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%

"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.**

Progression-free survival and overall survival were secondary endpoints, and these two parameters included all treated patients. Median progression-free survival increased from 3.3 months with gemcitabine/carboplatin alone, which is typical for chemotherapy in triple-negative disease, to 6.9 months with the addition of BSI-201.

The hazard ratio was 0.342. Hence, we had a 66 percent reduction in disease progression with a *p*-value of <0.0001. Median overall survival increased from 5.7 months with gemcitabine/carboplatin alone to 9.2 months with the addition of BSI-201, with a hazard ratio of 0.348 and a *p*-value of 0.0005 (O’Shaughnessy 2009; [1.2]).

Although the *p*-values for progression-free and overall survival were highly robust, these were not the prespecified primary endpoints around which the statistics were built.

These *p*-values are encouraging, but they’re simply descriptive indicators of the differences between the two arms. We don’t want to interpret them as definitive *p*-values on a prespecified endpoint.

► **DR LOVE:** What about the safety?

► **DR O’SHAUGHNESSY:** It was superb. We could not discern any additional toxicity, either hematologic or nonhematologic, with the addition of BSI-201. It did not potentiate chemotherapy-related toxicity (O’Shaughnessy 2009).

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)	<i>p</i> -value
Objective response rate (n = 44, 42)	16%	48%	—	0.002
Clinical benefit rate (CR + PR + SD ≥ 6mo) (n = 44, 42)	21%	62%	—	0.0002
Median progression-free survival (n = 59, 57)	3.3mo	6.9mo	0.342 (0.200-0.584)	<0.0001
Median overall survival (n = 59, 57)	5.7mo	9.2mo	0.348 (0.189-0.649)	0.0005

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

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

 **Track 8**

► **DR LOVE:** Can you bring us up to date on T-DM1?

► **DR O'SHAUGHNESSY:** An update was presented at ASCO 2009 of the Phase II trial evaluating T-DM1 in patients with breast cancer that was confirmed as HER2-positive by a central laboratory. Unfortunately, approximately 20 to 25 percent of patients still have disease that is FISH-positive by local laboratories but not confirmed by a central laboratory (Krop 2009).

The Independent Radiology Review Committee reported a clinical benefit rate of 34 percent, and the investigators reported a 44 percent clinical benefit rate with T-DM1. The median progression-free survival for these patients with heavily pretreated disease was 7.4 months (Krop 2009).

T-DM1 is a fascinating agent because of its extremely good safety and tolerability profile. It doesn't cause hair loss or neutropenia. It causes modest fatigue and transient thrombocytopenia that occurs on day eight.

Track 9

► **DR LOVE:** Would you review the findings on pertuzumab that were presented at ASCO?

► **DR O'SHAUGHNESSY:** We saw data demonstrating that pertuzumab monotherapy has a low objective response rate of less than 10 percent, but when it is combined with trastuzumab for patients with heavily pretreated disease, the objective response rate is in the high 20s (Cortés 2009), which is impressive for two antibodies in patients with trastuzumab-refractory disease.

The CLinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) trial is evaluating docetaxel/trastuzumab with or without pertuzumab as first-line therapy for HER2-positive metastatic breast cancer. ■

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Audeh MW et al. **Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer.** *Proc ASCO* 2009; **Abstract 5500.**

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.**

Krop IE et al. **Quantitative assessment of HER2 status and correlation with efficacy for patients (pts) with metastatic breast cancer (MBC) in a phase II study of trastuzumab-DM1 (T-DM1).** *Proc ASCO* 2009; **Abstract 1003.**

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.**

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Rottenberg S et al. **High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs.** *Proc Natl Acad Sci USA* 2008;105(44):17079-84.

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



INTERVIEW

John Mackey, MD

Dr Mackey is Medical Oncologist at the Cross Cancer Institute, Professor of Medical and Experimental Oncology at the University of Alberta, Chair of Research at the Northern Alberta Breast Cancer Program and Executive Director of the Cancer International Research Group in Edmonton, Canada.

Tracks 1-11

- Track 1** Phase II randomized trial of paclitaxel with placebo, bevacizumab or motesanib as first-line therapy for HER2-negative mBC
- Track 2** Phase II trial data with motesanib, an orally administered small-molecule antagonist of VEGFR-1,2,3, PDGFR and c-Kit
- Track 3** Predictors of response to anti-angiogenic agents
- Track 4** BETH: A Phase III randomized trial of adjuvant chemotherapy/ trastuzumab with or without bevacizumab for HER2-positive BC
- Track 5** ToGA: A Phase III randomized trial of chemotherapy with or without trastuzumab as first-line therapy for HER2-positive advanced gastric cancer
- Track 6** TRIO/CIRG 013: A Phase III randomized trial of capecitabine/ oxaliplatin with or without lapatinib for HER2-positive metastatic gastric cancer
- Track 7** BEATRICE: A Phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for triple-negative BC
- Track 8** Phase III randomized trial of trastuzumab and paclitaxel with or without everolimus as first-line therapy for HER2-positive, locally recurrent or metastatic BC
- Track 9** **Case discussion:** A 32-year-old woman with T2N1, HER2-positive, ER-negative, PR-negative BC who wishes to preserve her fertility
- Track 10** **Case discussion:** A 51-year-old woman with T2N1M0, HER2-positive, ER-negative, PR-negative BC that recurred shortly after treatment with AC → docetaxel/ trastuzumab who experienced a prolonged complete response to first-line capecitabine/lapatinib
- Track 11** Treatment options for refractory HER2-positive mBC

Select Excerpts from the Interview

Track 4

► **DR LOVE:** Would you discuss the NSABP/CIRG collaborative adjuvant BETH trial for patients with HER2-positive breast cancer?

► **DR MACKEY:** We know from Phase II experience that the combination of trastuzumab and bevacizumab is highly active for women with HER2-ampli-

fied breast cancer — response rates of 53 percent and a clinical benefit rate exceeding 80 percent have been recorded (Pegram 2006). That means that more than 80 percent of the patients will have their disease under control at the six-month period with the combination of two monoclonal antibodies alone, no chemotherapy.

This observation with the two antibodies together along with preclinical observations and Phase I experience triggered the design of a large, adjuvant Phase III registration clinical trial — BETH (2.1). The CIRG and TRIO teamed up with the NSABP and have launched this trial in more than 40 countries.

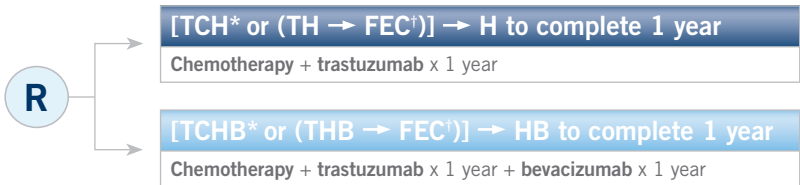
It has been accruing well, with the majority of patients entering the cohort in which the backbone chemotherapy is docetaxel/carboplatin and trastuzumab — the TCH regimen pioneered by the BCIRG 006 study (Slamon 2006) — alone or in combination with bevacizumab.

The IDMCs have been evaluating safety signals, and at present we’ve seen no indication that we need to change any of the trial procedures as a result of safety issues.

2.1

BETH: NSABP/CIRG Trial of Chemotherapy and Trastuzumab with or without Bevacizumab in Patients with HER2-Positive Early Breast Cancer

Protocol IDs: NSABP-B-44-I, CIRG (TRIO) 011, BETH; **Target Accrual:** 3,500



Eligibility

- Node-positive or high-risk, node-negative early breast cancer
- HER2-positive by central FISH testing

Stratification

- Nodal status
- Hormone receptor status

T = docetaxel; C = carboplatin; H = trastuzumab; F = 5-FU; E = epirubicin; C[†] = cyclophosphamide; B = bevacizumab; * Chemotherapy used by NSABP/CIRG investigators (Cohort 1); [†] Chemotherapy used by independent investigators (Cohort 2)

SOURCE: NCI Physician Data Query, August 2009.

Track 7

▶ **DR LOVE:** Would you discuss the adjuvant Phase III BEATRICE study evaluating chemotherapy with or without bevacizumab for patients with triple-negative breast cancer?

► **DR MACKEY:** BEATRICE is a multinational adjuvant trial. After surgery, patients receive “dealer’s choice” chemotherapy. Essentially, any of the active chemotherapy regimens that might be used around the globe are allowed as the backbone chemotherapy. After the investigator selects the chemotherapy regimen, the patient is randomly assigned to either bevacizumab for one year beginning with day one of chemotherapy or not (2.2).

Accrual is well ahead of the anticipated schedule — more than 1,800 patients are being treated. We anticipate completing accrual well before the end of this calendar year.

2.2

BEATRICE: A Study of Bevacizumab Adjuvant Therapy in Triple-Negative Breast Cancer

Protocol IDs: BEATRICE, B020289; Target Accrual: 2,992 (Open)



Eligibility

- Age ≥ 18 years
- Operable primary invasive breast cancer
- Completed definitive locoregional surgery
- Primary tumor centrally confirmed as triple-negative
- No locally advanced breast cancer
- No breast cancer history
- No clinically significant cardiovascular disease

* Anthracycline with or without taxane or taxane only

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

Track 10

Case discussion

A 51-year-old woman initially presented in 2004 with a T2N1M0, HER2-positive, ER-negative, PR-negative infiltrating ductal carcinoma and underwent mastectomy and locoregional radiation therapy followed by adjuvant AC → docetaxel/trastuzumab on BCIRG 006 (Slamon 2006). Three months after completion of trastuzumab, she presented with a 20- x 30-cm erythematous rash on her chest wall and palpable nodules, which were biopsy proven to be consistent with her primary cancer.

► **DR MACKEY:** She was absolutely devastated by this news. She had a new grandchild that she wanted to see graduate from high school, which was a daunting goal for me.

We had a new trial open that was evaluating capecitabine 1,000 mg/m² BID, which I would have offered her anyway, in combination with lapatinib 1,250

milligrams daily. This trial ended up being the registrational trial for lapatinib and was subsequently published in *The New England Journal* (Geyer 2006).

To my continued surprise and amazement, this has been an ideal treatment for this woman. She demonstrated a complete clinical response and remains completely free of any signs of breast cancer after four and a half years.

She has mild hand-foot syndrome but is otherwise tolerating the combination well, and I have promised to maintain her on this regimen as long as this run lasts.

► **DR LOVE:** What a dramatic situation that she walks right through chemotherapy and trastuzumab but has this incredible response to capecitabine/lapatinib. Do you have any guesses what you might see if you could study her tumor?

► **DR MACKAY:** It's interesting that you ask because in our lab we're investigating trastuzumab resistance mechanisms and have found one that looks intriguing. Patients with HER2-positive metastatic breast cancer include a subgroup with high levels of a protein called beta1 integrin, which is a cell-surface molecule involved in cellular adhesion. Approximately one third of HER2-positive breast cancer cases have high levels of this cell adhesion molecule on their surface.

Why would a cell adhesion molecule be important to trastuzumab resistance? It turns out that beta1 integrin is a bit like the epidermal growth factor receptor superfamily in that it can turn on both the AKT pathway and the PI3K pathway. So essentially it can mimic in some ways and provide a redundant stimulation of the postreceptor pathways that trastuzumab can inhibit.

In our hands, this is the number one factor associated with a short time to disease progression with chemotherapy/trastuzumab. In theory, beta1 integrin may circumvent the efficacy of lapatinib, which is an intracellular inhibitor of the HER2 protein that inhibits downstream signaling. However, we have no data to suggest that's the case. ■

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INTERVIEW

Nicholas J Robert, MD

Dr Robert is Co-Chair of the Breast Cancer Committee for the US Oncology Research Network and Chairman of the Cancer Committee at Inova Fairfax Hospital's Cancer Center in Fairfax, Virginia.

Tracks 1-17

- Track 1** RIBBON 1: A Phase III randomized trial of chemotherapy with bevacizumab or placebo as first-line therapy for HER2-negative, locally recurrent or metastatic BC
- Track 2** Clinical implications of the RIBBON 1 trial results
- Track 3** **Case discussion:** A 68-year-old woman with multiple comorbid conditions and symptomatic, triple-negative mBC
- Track 4** CALGB-40502: A Phase III trial of weekly paclitaxel, weekly *nab* paclitaxel or ixabepilone combined with bevacizumab as first-line therapy for locally recurrent or metastatic BC
- Track 5** Lack of steroid premedication with *nab* paclitaxel
- Track 6** Correlation between SPARC and response to *nab* paclitaxel
- Track 7** Ongoing US Oncology adjuvant clinical trials evaluating nonanthracycline-containing regimens in HER2-negative and HER2-positive BC
- Track 8** Incorporating capecitabine into adjuvant chemotherapy clinical trials
- Track 9** TAILORx: A Phase III randomized trial of adjuvant hormonal therapy with or without chemotherapy for resected, node-negative, ER-positive and/or PR-positive BC with various levels of risk for recurrence
- Track 10** TransATAC: Risk of distant recurrence using the *Oncotype DX*[®] assay for postmenopausal patients with ER-positive BC treated with anastrozole or tamoxifen
- Track 11** Concomitant administration of CYP2D6 inhibitors and tamoxifen
- Track 12** Duration of adjuvant hormonal therapy for ER-positive BC
- Track 13** ABCSG-12: Adjuvant ovarian suppression in combination with either tamoxifen or anastrozole, with or without zoledronic acid, for premenopausal women with ER-positive BC
- Track 14** Clinical use of adjuvant bisphosphonates for BC
- Track 15** Clinical benefits associated with the bisphosphonates
- Track 16** Correlation between side effects of adjuvant hormonal therapy and risk of recurrence
- Track 17** Clinical recommendation for vitamin D supplementation in patients with BC

Select Excerpts from the Interview

Tracks 1-2

► **DR LOVE:** Would you review the background of the RIBBON 1 trial and the findings you reported at ASCO 2009?

► **DR ROBERT:** The RIBBON 1 trial evolved from two Phase III trials — ECOG-E2100 (Miller 2007) and AVADO (Miles 2008) — in the first-line setting for metastatic breast cancer. ECOG-E2100 evaluated weekly paclitaxel, and AVADO evaluated docetaxel. Both trials demonstrated a benefit in progression-free survival with the addition of bevacizumab to a taxane.

Patients with metastatic breast cancer are candidates for treatment with agents other than taxanes, so it was important to determine if other drugs would produce the same improvement in progression-free survival when administered with bevacizumab. RIBBON 1 was designed to address this question, and we enrolled more than 1,200 patients with metastatic breast cancer not previously treated with chemotherapy (Robert 2009).

The investigators selected the chemotherapy — capecitabine, a taxane or an anthracycline-containing regimen. The patients were then randomly assigned in a two-to-one fashion to receive chemotherapy with bevacizumab or with placebo. At the time of disease progression, patients had the opportunity to receive bevacizumab with second-line chemotherapy (Robert 2009; [3.1]).

The capecitabine cohort was independently evaluated, and we found that the addition of bevacizumab to capecitabine produced an improvement in median progression-free survival of approximately three months and an improvement in the response rate (Robert 2009; [3.1]).

The other cohort of patients in RIBBON 1, which was powered independently of the capecitabine cohort, showed an improvement in median progression-free survival of one month with the addition of bevacizumab (3.1). In an exploratory analysis, the taxane and an anthracycline-containing regimen demonstrated similar results, each with a one-month improvement in progression-free survival (Robert 2009).

► **DR LOVE:** What is your clinical interpretation of the results from RIBBON 1?

► **DR ROBERT:** I believe it was a proof of principle trial, and we've now demonstrated with different drugs the advantage of adding bevacizumab in terms of progression-free survival. Tomorrow, when facing a patient with metastatic breast cancer who is a candidate for chemotherapy in the first-line setting, I believe we can be confident that adding bevacizumab to whatever drug we choose will produce an advantage.

An approach many of us use, especially for patients with hormone receptor-positive disease, is to start capecitabine when the disease progresses and we've exhausted oral hormonal therapy options. With the capecitabine/bevacizumab

data from RIBBON 1 (Robert 2009), I believe that will be a natural option. Considering that we're palliating and trying to maintain control of the disease without significant toxicity, I also value the fact that capecitabine/bevacizumab doesn't produce alopecia.

Depending on the prior therapy, situations may exist in which you want to use a taxane or an anthracycline-based regimen, especially if the patient is in visceral crisis, because the response rate was higher with bevacizumab in combination with a taxane or an anthracycline-containing regimen.

3.1

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/anthracycline	
	BEV (n = 409)	PL (n = 206)	BEV (n = 415)	PL (n = 207)
Median progression-free survival	8.6mo	5.7mo	9.2mo	8.0mo
Hazard ratio (p-value)	0.69 (p = 0.0002)		0.64 (p < 0.0001)	
Median overall survival	29.0mo	21.2mo	25.2mo	23.8mo
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**.

 **Track 4**

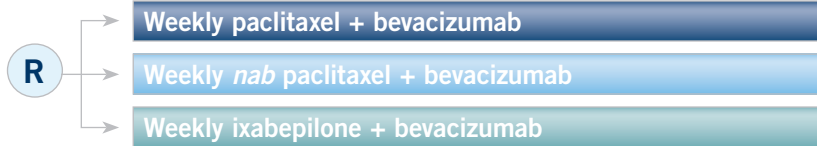
▶ **DR LOVE:** Would you discuss the US Oncology experience with nanoparticle albumin-bound (*nab*) paclitaxel and bevacizumab?

▶ **DR ROBERT:** We conducted a Phase II study with *nab* paclitaxel in combination with bevacizumab (Danso 2008). The results were encouraging, with an objective response rate of 30 percent and a median progression-free survival of 9.2 months, so this is a reasonable regimen to consider and is worth pursuing further in larger clinical trials. In fact, the CALGB has a Phase III trial of bevacizumab in combination with weekly paclitaxel, *nab* paclitaxel or ixabepilone as first-line therapy (3.2).

I believe that *nab* paclitaxel is an exciting platform for the administration of a drug, and anecdotally I have observed some nice responses in patients treated with *nab* paclitaxel/bevacizumab. The CALGB trial is a great idea because weekly paclitaxel is an effective way to administer a taxane and we need to demonstrate whether these other approaches with weekly *nab* paclitaxel or ixabepilone are better.

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 \geq 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 August 2009.

Track 9

► **DR LOVE:** Would you discuss the TAILOR_x trial?

► **DR ROBERT:** It's a well-designed study that identifies patients with node-negative, ER-positive and/or PR-positive breast cancer who are at low, intermediate or high risk of recurrence according to the *Oncotype DX* assay. Those with an intermediate Recurrence Score[®] are randomly assigned to endocrine therapy alone or with chemotherapy. The hope is that the results of this trial will allow us to be smarter about treatment.

► **DR LOVE:** Are you using the assay for patients with node-positive disease?

► **DR ROBERT:** For postmenopausal patients with ER-positive, HER2-negative disease, especially if they're older and have fewer than four positive nodes, we obtain an *Oncotype DX* assay. If the Recurrence Score is low, we have a discussion about chemotherapy. The thinking is that this test is not only a predictor of prognosis but also a predictor of response to chemotherapy. ■

SELECT PUBLICATIONS

Danso MA et al. Phase II trial of weekly *nab*-paclitaxel in combination with bevacizumab as first-line treatment in metastatic breast cancer. *Proc ASCO* 2008; **Abstract 1075**.

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

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**.



INTERVIEW

Catherine H Van Poznak, MD

Dr Van Poznak is Assistant Professor in Internal Medicine for the division of Hematology/Oncology at the University of Michigan Comprehensive Cancer Center in Ann Arbor, Michigan.

Tracks 1-9

- Track 1** Vitamin D status in the general population
- Track 2** Recommendations for vitamin D supplementation and replacement
- Track 3** Influence of vitamin D and bisphosphonates on BC recurrence
- Track 4** Clinical use of adjuvant bisphosphonates for the prevention of BC recurrence
- Track 5** Risk of osteonecrosis of the jaw associated with the bisphosphonates
- Track 6** Denosumab: Mechanism of action and clinical trial data
- Track 7** **Case discussion:** A 69-year-old woman with osteopenia was diagnosed with T1N0, ER-positive, HER2-positive BC and received ibandronate with adjuvant anastrozole
- Track 8** **Case discussion:** A 53-year-old postmenopausal woman with a history of hepatitis B and alcoholism fell and incurred a traumatic bone fracture while receiving adjuvant AC → paclitaxel/trastuzumab for T2N0, ER-positive, PR-positive, HER2-positive BC
- Track 9** **Case discussion:** A 43-year-old premenopausal woman with locally advanced, ER-positive, PR-positive, HER2-positive BC underwent prophylactic oophorectomy after receiving neoadjuvant dose-dense AC → paclitaxel/trastuzumab

Select Excerpts from the Interview

Track 3

► **DR LOVE:** Would you discuss data by Pam Goodwin evaluating vitamin D level and breast cancer recurrence (Goodwin 2009)?

► **DR VAN POZNAK:** It was a beautiful presentation at the 2008 ASCO meeting and then the *JCO* paper. At this point, however, I don't believe that sufficient data exist for us to define how vitamin D might affect breast cancer in terms of risk of recurrence and overall survival or how factors associated with vitamin D insufficiency, such as obesity, inactivity and poor nutrition, might interplay with breast cancer risk.

► **DR LOVE:** What are your thoughts on the research evaluating the effect of bisphosphonates on the risk of breast cancer recurrence?

► **DR VAN POZNAK:** A series of clinical trials is indicating a potential for the bisphosphonates to reduce the risk of breast cancer recurrence.

The initial data provide a rationale to support the ongoing clinical trial SWOG-S0307, evaluating adjuvant therapy with clodronate versus ibandronate versus zoledronic acid (4.1). NSABP-B-34 is evaluating adjuvant clodronate versus placebo, and the AZURE trial is assessing zoledronic acid versus nil. The German Adjuvant Intergroup Node-positive (GAIN) study is evaluating ibandronate. We hope that when we have a larger series of studies to examine, we'll have a sense of whether the bisphosphonates have an effect in the adjuvant setting.

Track 5

► **DR LOVE:** The Austrian study reported a 36 percent relative reduction in the risk of disease progression with zoledronic acid, and no cases of osteonecrosis of the jaw (ONJ) were confirmed. In this ABCSG-12 study, zoledronic acid was administered every six months (Grant 2009). What are your thoughts?

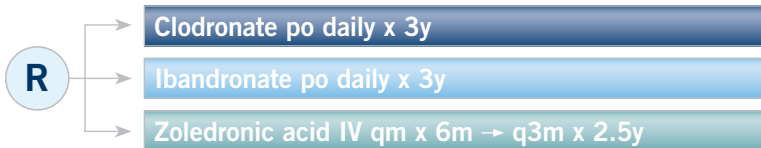
► **DR VAN POZNAK:** For patients with osteoporosis, to whom bisphosphonates are typically administered chronically at low doses, the incidence of ONJ tends to be one in 10,000 to one in 100,000. For patients with metastatic

4.1

Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer

Protocol IDs: SWOG-S0307, CTSU; **Target Accrual:** 4,500 (Open)

Date Activated: July 2005



Eligibility

Stage I to Stage III breast cancer treated with standard adjuvant therapy

Study Contacts

SWOG

Julie R Gralow, MD and Robert Livingston, MD, Tel: 205-288-7722

Other participating cooperative groups: NCCTG, ECOG, NSABP, CALGB and NCIC CTG

SOURCE: NCI Physician Data Query, August 2009.

disease, the incidence appears to be between one and 10 percent (Khosla 2007), although one report from a prospective clinical trial for patients with prostate cancer demonstrated an incidence of approximately 17 percent (Aragon-Ching 2009).

In the adjuvant setting, we have data from the AZURE study. I believe that of the 1,500 patients receiving zoledronic acid, seven cases of ONJ were reported (Coleman 2006). The dosing schedule for zoledronic acid used in AZURE, however, is different from the one used in ABCSG-12.

Track 6

▶ **DR LOVE:** Would you review what we know about denosumab?

▶ **DR VAN POZNAK:** It's a monoclonal antibody to the receptor activator of nuclear factor- κ B (RANK) ligand. RANK ligand and osteoprotegerin are critical to setting the balance between bone resorption and bone deposition. A monoclonal antibody to RANK ligand will ultimately suppress bone resorption.

Denosumab has been investigated in a number of disease processes, including osteoporosis. A few studies have matured and demonstrated a decreased risk of fracture with denosumab (Cummings 2009; Miller 2009).

Denosumab has also been studied in the HALT trial, which enrolled postmenopausal women with osteopenia who were receiving adjuvant aromatase inhibitors. These patients were randomly assigned to placebo or denosumab, which was administered every six months subcutaneously. An improvement in bone mineral density was reported with denosumab (Ellis 2008). ■

SELECT PUBLICATIONS

Aragon-Ching JB et al. **Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents.** *Cancer Invest* 2009;27(2):221-6.

Coleman R et al. **Zoledronic acid is well tolerated and can be safely administered with adjuvant chemotherapy — First safety data from the AZURE trial (BIG01/04).** San Antonio Breast Cancer Symposium 2006; **Abstract 2080.**

Cummings SR et al. **Denosumab for prevention of fractures in postmenopausal women with osteoporosis.** *N Engl J Med* 2009;361(8):756-65.

Ellis GK et al. **Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer.** *J Clin Oncol* 2008;26(30):4875-82.

Gnant M et al; ABCSG-12 Trial Investigators. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91.

Goodwin PJ et al. **Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer.** *J Clin Oncol* 2009;27(23):3757-63.

Khosla S et al; American Society for Bone and Mineral Research. **Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research.** *J Bone Miner Res* 2007;22(10):1479-91.

Miller PD. **Denosumab: Anti-RANKL antibody.** *Curr Osteoporos Rep* 2009;7(1):18-22.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The PARP inhibitor olaparib has been evaluated in BRCA1/BRCA2 carriers with _____ cancer.
 - a. Ovarian
 - b. Breast
 - c. Either a or b
 - d. None of the above
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. Clinical benefit rate
 - b. Median progression-free survival rate
 - c. Median overall survival rate
 - d. Both a and b
 - e. All of the above
3. The CLEOPATRA 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
4. Everolimus is being evaluated for _____ breast cancer.
 - a. HER2-positive
 - b. HER2-negative
 - c. Both a and b
 - d. None of the above
5. 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
6. Which of the following trials evaluated the efficacy of bevacizumab in combination with docetaxel for metastatic breast cancer?
 - a. ECOG-E2100
 - b. AVADO
 - c. RIBBON 1
 - d. Both a and b
 - e. Both b and c
7. In the TAILORx trial, the patient's risk of recurrence is assessed by the _____.
 - a. Oncotype DX assay
 - b. MammaPrint® assay
 - c. Either a or b
 - d. None of the above
8. The BETH trial is evaluating adjuvant chemotherapy/trastuzumab with or without _____ for patients with HER2-positive breast cancer.
 - a. Lapatinib
 - b. Bevacizumab
 - c. T-DM1
 - d. Pertuzumab
9. The trial design for BETH includes two cohorts for the chemotherapy backbone, allowing investigator discretion in the use of an anthracycline or nonanthracycline chemotherapeutic regimen.
 - a. True
 - b. False
10. In the BEATRICE trial of standard adjuvant chemotherapy (anthracycline with or without a taxane or a taxane only) with or without bevacizumab for patients with triple-negative breast cancer, what is the duration of administration for the anti-angiogenic agent?
 - a. One month
 - b. Three months
 - c. Six months
 - d. 12 months

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 4, 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
RIBBON 1 trial: Chemotherapy with bevacizumab or placebo as first-line therapy for HER2-negative metastatic breast cancer (mBC)	4 3 2 1	4 3 2 1
CALGB-40502: Bevacizumab with paclitaxel, nab paclitaxel or ixabepilone for mBC	4 3 2 1	4 3 2 1
Activity of BSI-201 in combination with gemcitabine/carboplatin for triple-negative mBC	4 3 2 1	4 3 2 1
Mechanism of action of denosumab	4 3 2 1	4 3 2 1
Randomization arms for the BETH and BEATRICE trials	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
- Review the long-term risk of recurrence for patients with ER-positive early breast cancer, and consider on- and off-protocol extended adjuvant endocrine therapy for appropriately selected patients. 4 3 2 1 N/M N/A
- Counsel patients about skeletal complications associated with aromatase inhibitors and the impact of bisphosphonates on maintaining bone mineral density and reducing the risk of breast cancer recurrence. 4 3 2 1 N/M N/A
- Assess patients' vitamin D status and provide recommendations for vitamin D replacement and/or supplementation. 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
- Apply the results from recent clinical trials when recommending first-line chemotherapy in combination with bevacizumab for women with HER2-negative metastatic breast cancer. 4 3 2 1 N/M N/A
- Summarize the anti-angiogenic agents being evaluated in clinical trials for HER2-negative localized or 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 design and eligibility criteria for clinical trials evaluating new treatment strategies in early and advanced breast cancer, and screen appropriate patients for study participation. 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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			
Joyce O'Shaughnessy, MD	4	3	2	1	4	3	2	1
John Mackey, MD	4	3	2	1	4	3	2	1
Nicholas J Robert, MD	4	3	2	1	4	3	2	1
Catherine H Van Poznak, 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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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: Date:

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U P D A T E

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