



Key SABCS Presentations
Issue 8, 2011

**Efficacy and Safety of
Bevacizumab-Containing
Chemotherapy Regimens in
Metastatic Breast Cancer**

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVES

- Educate patients with metastatic breast cancer about the relative risk of clinically significant cardiac toxicity with the combination of bevacizumab and chemotherapy.
- Assess the efficacy and safety of the combination of bevacizumab and 75-mg/m² docetaxel with or without trastuzumab for the first-line treatment of HER2-negative and HER2-positive metastatic breast cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

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

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

William J Gradishar, MD
Director, Breast Medical Oncology
Professor of Medicine

Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc,

Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium — The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

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

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

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

Last review date: March 2011
Expiration date: March 2012

[Click here for SABCS papers on metastatic breast cancer](#)

The use of tissue assays to identify patients most likely to respond to specific therapies has markedly increased following a series of reports on genomic alterations in EGFR and EML4-ALK in lung cancer, K-ras in colorectal cancer, B-raf in melanoma and a host of factors in hematologic cancers, including and most recently CD30 in Hodgkin lymphoma and anaplastic large cell lymphoma.

Of course, the grandmother of “personalized oncology” is breast cancer, and while ER and HER2 testing are classic models of tissue predictors, we have seen reams of data over the years to shake our confidence in almost every ER/HER2 result obtained. [An intriguing new data set from Sweden](#) raises even more concern, demonstrating again that it is not uncommon for ER and to a lesser extent HER2 to be different in a biopsied metastasis than in the previous primary tumor. In this study discordance was observed in approximately one third of patients. However, what this means exactly in terms of treatment decision-making is uncertain and under active debate.

It seems plausible that patients with a prior negative assay might respond to targeted treatment if the marker is detected in the met, but it’s not clear if the reverse (which is more common) is true. With few data to go on, many clinicians follow the “Cliff Hudis Rule” — if a patient with breast cancer has ever had a positive ER or HER2 result, she likely should receive at least one course of the appropriate targeted treatment in the relapsed disease setting, regardless of the most recent assay result.

Another critical issue related to rebiopsy is ruling out another cause of what seems to be recurrence. Many groups, including the Swedes, have shown that things are not always as they appear, and my favorite example of this phenomenon relates to a case presented at one of our CME symposia several years ago by Bill Reeves, an oncologist from Youngstown, Ohio. The patient had received chemotherapy for node-positive breast cancer three years earlier and presented with early satiety and several space-occupying lesions in the liver. Rather than assume the obvious, Bill had a needle placed and discovered that the hepatic disease was in fact GIST (with an occult gastric primary tumor later detected). Dr Reeves quickly altered his clinical thinking, and the patient went on to have an excellent response to imatinib.

Clearly the decision to rebiopsy any patient with apparent metastatic disease is multifactorial with a critical issue being the ease or difficulty of accessing tissue, but our Patterns of Care surveys have demonstrated frequent use of rebiopsy in clinical practice both for accurate diagnosis and repeat tissue biomarker assays. In addition to this thought-provoking Swedish study, the following interesting papers on metastatic breast cancer were presented in San Antonio:

1. **Denosumab (D-mab)**

A randomized, Phase III placebo-controlled trial demonstrated an 18 percent relative risk reduction in skeletal events with this RANK ligand inhibitor compared to zoledronic acid (ZA) with the risk of pathologic fracture decreasing from 28.1 percent to 23.5 percent and the risk of radiation to the bone dropping from 17.2 percent to 13.5 percent. Rates of osteonecrosis of the jaw (ONJ) were similar with D-mab (26 patients — 2.5%) and ZA (18 patients — 1.8%), but Grade 3/4 hypocalcemia was seen in 18 patients on D-mab (1.8%) versus 12 (1.2%) on ZA. In another bone-related study that followed a series of case reports, the group from Roswell Park presented their experience with ONJ in patients on bisphosphonates versus those on bisphosphonates/bevacizumab, and the severity and dental outcome appeared quite similar in the two groups, which is reassuring given the issue of wound healing with bev.

2. **Endocrine treatment combined with targeted therapy**

For years, investigators have been proposing the combined use of biologic and hormonal agents to subvert endocrine resistance, but two recent randomized studies provided lukewarm or no support for the concept. One small trial seemed to show a modest benefit when the mTOR inhibitor everolimus was combined with tamoxifen, while another study of fulvestrant plus lapatinib was flat-out negative, although there was a suggestion of benefit in patients with HER2-positive tumors.

3. **More on bevacizumab**

A meta-analysis focusing on cardiovascular events in randomized studies of chemotherapy with or without bevacizumab in the metastatic disease setting demonstrated the expected risk of hypertension but also a modest but statistically significant increase in left ventricular dysfunction. Rates of arteriothrombotic events were not statistically different. Another Phase II study demonstrated good tolerability and encouraging efficacy when docetaxel 75 mg/m² was combined with bevacizumab in HER2-negative disease, as well as when trastuzumab was added to the regimen in patients with HER2-positive tumors.

This concludes our brief series on the happenings in San Antonio. Stay tuned for another experiment in CME as we are set to launch a new four-part series on GI cancers using what we think is an innovative, interesting and different web-based platform.

Neil Love, MD

Research To Practice

Miami, FL

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

Research To Practice designates each educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in each activity.

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

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

This email was sent to you by Dr Neil Love and Research To Practice. To unsubscribe to future email requests and announcements, **[click here](#)**. To unsubscribe from all email communications, including CME/CNE activities sent by Research To Practice, **[click here](#)**. To update your information on our current distribution lists, **[click here](#)**.

Efficacy and Safety of Bevacizumab-Containing Chemotherapy Regimens in Metastatic Breast Cancer

Presentations discussed in this issue

Nasim S et al. **A meta-analysis of risk of cardiovascular events in patients with metastatic breast cancer (MBC) treated with anti vascular endothelial growth factor (VEGF) therapy — Bevacizumab.** San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-01.**

Schwartzberg LS et al. **Phase II multicenter study of docetaxel and bevacizumab +/- trastuzumab as first-line treatment of patients with metastatic breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-08.**

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with William J Gradishar, MD (1/4/11)

A Meta Analysis of Risk of Cardiovascular Events in Patients with Metastatic Breast Cancer (MBC) Treated with Anti Vascular Endothelial Growth Factor (VEGF) Therapy — Bevacizumab¹

Phase II Multicenter Study of Docetaxel and Bevacizumab (Bev) +/- Trastuzumab as First-Line Treatment of Patients with Metastatic Breast Cancer (MBC)²

¹Nasim S et al.

Proc SABCS 2010;Abstract P6-12-01.

²Schwartzberg LS et al.

Proc SABCS 2010;Abstract P6-12-08.

Research
To Practice®

A Meta Analysis of Risk of Cardiovascular Events in Patients with Metastatic Breast Cancer (MBC) Treated with Anti Vascular Endothelial Growth Factor (VEGF) Therapy – Bevacizumab

Nasim S et al.

Proc SABCS 2010;Abstract P6-12-01.

Research
To Practice®

Methods

- Randomized Phase III trials that evaluated chemotherapy with or without bevacizumab in MBC as first- or second-line therapy were identified.
- Data extraction was carried out from results published in the literature or from conference proceedings of the selected studies.
 - ECOG-E2100, AVADO, RIBBON 1, RIBBON 2 and a Phase III trial of capecitabine with or without bevacizumab in MBC (*JCO* 2005;23:792)
- All Grade 3 and 4 cardiovascular events in these trials were collected.
 - Hypertension, left ventricular dysfunction, congestive heart failure, cardiomyopathy, venous and arterial thromboembolic events

Nasim S et al. *Proc SABCS 2010;Abstract P6-12-01.*

Research
To Practice®

Relative Risk with Bevacizumab-Containing Regimens

Grade 3-4 events	Relative risk	p-value
Hypertension	10.32	<0.0001
Left ventricular dysfunction	2.58	0.04
Venous/arterial thromboembolism	1.71	0.16

Nasim S et al. *Proc SABCS 2010*;Abstract P6-12-01.

Research
To Practice®

Author Conclusions

- Bevacizumab administered in combination with chemotherapy for patients with MBC is associated with significant cardiotoxicity:
 - Hypertension
 - Left ventricular dysfunction
- Careful monitoring of cardiac function is warranted in trials combining chemotherapy with bevacizumab:
 - To assess long-term cardiac sequelae
 - To better understand the mechanism underlying bevacizumab-induced cardiac damage

Nasim S et al. *Proc SABCS 2010*;Abstract P6-12-01.

Research
To Practice®

Phase II Multicenter Study of Docetaxel and Bevacizumab (Bev) +/- Trastuzumab as First-Line Treatment of Patients with Metastatic Breast Cancer (MBC)

Schwartzberg LS et al.

Proc SABCS 2010;Abstract P6-12-08.

Research
To Practice®

Background

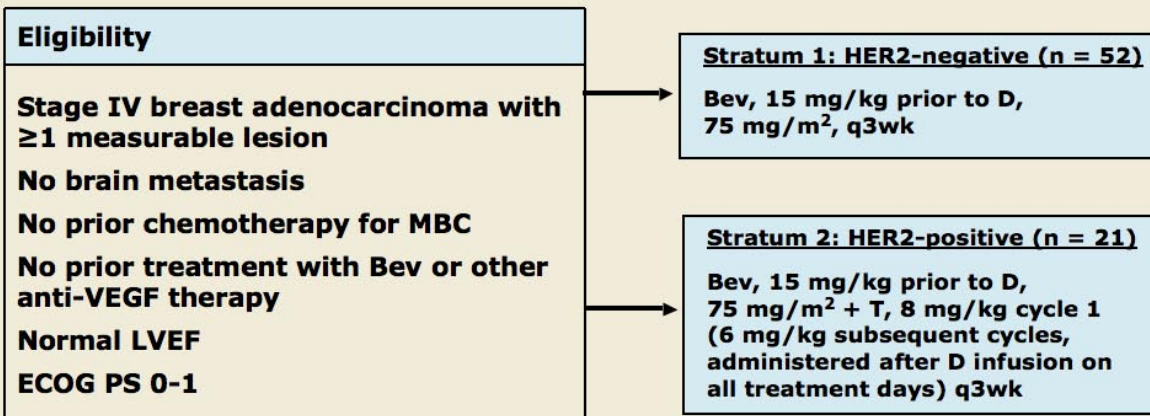
- Progression-free survival (PFS) is improved with the addition of Bev to docetaxel or paclitaxel for first-line treatment of HER2-negative MBC.
- There are limited data on Bev combined with docetaxel at the dosage of 75 mg/m² in patients with HER2-negative MBC, and no data on Bev plus docetaxel at any dosage in patients with HER2-positive MBC.
- **Primary objective:** Evaluate PFS with docetaxel (D) and Bev plus trastuzumab (T) for the first-line treatment of patients with MBC.
- **Secondary objectives:** Response; overall survival (OS); safety and toxicity

Schwartzberg LS et al. *Proc SABCS 2010;Abstract P6-12-08.*

Research
To Practice®

Study Design

Phase II, nonrandomized, parallel-group, prospective, multicenter study
Accrual: 73 (Closed)



G-CSF prophylaxis was administered to all patients
 Treatment until unacceptable toxicity, progression or death

Schwartzberg LS et al. *Proc SABCS 2010*;Abstract P6-12-08.

Research
To Practice®

Efficacy Results (Intent to Treat)

Outcome	Stratum1, HER2-neg Bev+D (n = 52)	Stratum2, HER2-pos Bev+D+T (n = 21)
Median PFS	8.5 mos	13.43 mos
Overall response rate	57.7%	81.0%
- Complete response	5.8%	28.6%
- Partial response	51.9%	52.4%
- Stable disease	26.9%	4.8%
- Progressive disease	11.5%	4.8%
Median response duration	8.57 mos	12.2 mos
Overall survival (OS)	61.5%	76.2%

OS measured at the time of data cutoff (patient accrual August 2006 to March 2009;
 data cutoff April 5, 2010)

Schwartzberg LS et al. *Proc SABCS 2010*;Abstract P6-12-08.

Research
To Practice®

Selected Adverse Events (AE)

All Grades; Grade 3/4 AEs	Stratum1, HER2-neg Bev+D (n = 52)	Stratum2, HER2-pos Bev+D+T (n = 20)
Fatigue	71.2%; 11.5%	65.0%; 10.0%
Alopecia	67.3%; 0%	75.0%; 0%
Nausea	53.8%; 0%	55.0%; 0%
Diarrhea	44.2%; 1.9%	35.0%; 0%
Dysgeusia	40.4%; 0%	40.0%; 5.0%
Headache	30.8%; 0%	40.0%; 0%
Epistaxis	28.8%; 0%	40.0%; 0%
Arthralgia	28.8%; 3.8%	25.0%; 0%
Vomiting	23.1%; 1.9%	25.0%; 0%
Hypertension	15.4%; 3.8%	35.0%; 0%

Schwartzberg LS et al. *Proc SABCS 2010*;Abstract P6-12-08.

Research
To Practice®

Author Conclusions

- In first-line treatment of MBC, docetaxel at 75 mg/m² plus Bev in HER2-negative disease or docetaxel at 75 mg/m² plus trastuzumab plus Bev in HER2-positive disease was safe and feasible.
- Response and PFS for patients with HER2-negative disease were similar to previous reports, confirming the benefit of adding Bev to docetaxel.
- Overall toxicity was less with Bev combined with docetaxel at 75 mg/m², compared to higher doses.
- Response rates with docetaxel/trastuzumab/Bev are among the highest reported for HER2-positive disease, and median PFS of 13.4 months with low incidence of Grade 3/4 toxicity suggest the addition of Bev is a promising strategy for patients with HER2-positive disease.

Schwartzberg LS et al. *Proc SABCS 2010*;Abstract P6-12-08.

Research
To Practice®

Investigator Commentary: Effect of Bevacizumab on the Development of Rare Adverse Events

Evidence from multiple trials indicates that bevacizumab is associated with a higher risk of hypertension, although serious hypertension is relatively rare.

In the pooled analysis of several trials — ECOG-E2100, AVADO, RIBBON 1, RIBBON 2 and an earlier study of capecitabine with or without bevacizumab — an increased incidence was observed, predictably, of hypertension and more left ventricular dysfunction.

These findings underscore the prudence of carefully monitoring patients receiving bevacizumab for hypertension and overall cardiac function.

Interview with William J Gradishar, MD, January 4, 2011

Research
To Practice®