

The logo features a white stopwatch icon with the number '5' inside the circular face. To the right of the icon, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

5 Minute Journal Club

Key SABCS Presentations
Issue 8, 2011

Efficacy of Denosumab vs Zoledronic Acid in Patients with BC and Bone Mets and Safety Analysis of Bev Plus Bisphosphonates in Met BC

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

- Compare and contrast the time to onset of ONJ and subsequent dental outcomes in patients with BC who received bisphosphonates either alone or in combination with bevacizumab.
- Counsel patients with BC and bone metastases about the benefits and risks of treatment with denosumab relative to zoledronic acid.

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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:

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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

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Efficacy of Denosumab vs Zoledronic Acid in Patients with BC and Bone Mets and Safety Analysis of Bev Plus Bisphosphonates in Met BC

Presentations discussed in this issue

Ngamphaiboon N et al. **Osteonecrosis of the jaw: Dental outcomes in metastatic breast cancer patients treated with bisphosphonates with/without bevacizumab at Roswell Park Cancer Institute.** San Antonio Breast Cancer Symposium 2010; **Abstract P2-13-03**.

Stopeck A et al. **Effect of denosumab versus zoledronic acid treatment in patients with breast cancer and bone metastases: Results from the extended blinded treatment phase.** San Antonio Breast Cancer Symposium 2010; **Abstract P6-14-01**.

Slides from presentations at SABCS 2010 and transcribed comments from Lisa A Carey, MD (12/12/10) and a recent interview with William J Gradishar, MD (1/4/11)

Effect of Denosumab versus Zoledronic Acid Treatment in Patients with Breast Cancer and Bone Metastases: Results from the Extended Blinded Treatment Phase¹

Osteonecrosis of the Jaw: Dental Outcomes in Metastatic Breast Cancer Patients Treated with Bisphosphonates with/without Bevacizumab at Roswell Park Cancer Institute²

¹Stopeck A et al.

Proc SABCS 2010;Abstract P6-14-01.

²Ngamphaiboon N et al.

Proc SABCS 2010;Abstract P2-13-03.

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Effect of Denosumab versus Zoledronic Acid Treatment in Patients with Breast Cancer and Bone Metastases: Results from the Extended Blinded Treatment Phase

Stopeck A et al.

Proc SABCS 2010;Abstract P6-14-01.

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Phase III Study Design

Accrual: 2,046 (Closed)

Eligibility

Advanced breast cancer

Bone metastasis

No prior bisphosphonates



Denosumab + Placebo IV

q 4 weeks
(n = 1,026)

Supplemental calcium and vitamin D in both arms

Zoledronic acid + Placebo SC

q 4 weeks
(n = 1,020)

*Denosumab 120 mg subcutaneously (SC)
Zoledronic acid (ZA) 4 mg intravenously (IV)*

Primary Endpoint: Time to first on-study skeletal related event (SRE) (predefined as pathologic fracture, radiation or surgery to bone, or spinal cord compression) – Noninferiority

Secondary Endpoints: Time to first and subsequent on-study SRE (superiority), safety

Stopeck A et al. *Proc SABCS 2010;Abstract P6-14-01.*

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Primary Endpoint: Estimated Time to First On-Study SRE (Noninferiority)

Denosumab n = 1,026	Zoledronic acid n = 1,020	Hazard ratio (HR) (95% CI)	p-value*
32.4 months	27.4 months	0.82 (0.71 – 0.95)	< 0.0001

- Denosumab therapy resulted in an 18% reduction in risk of time to first on-study SRE in comparison to treatment with zoledronic acid

* Superiority analysis, $p = 0.0096$

Stopeck A et al. *Proc SABCS 2010*;Abstract P6-14-01.

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Secondary Endpoints

	Denosumab	ZA	HR, p-value	Risk reduction
Time to first on-study SRE or hypercalcemia (superiority)	32.4 mos	25.1 mos	0.82; 0.0076	18%
Time to first and subsequent on-study SREs*, events	526 events	669 events	0.76; 0.0008	22%
Skeletal morbidity rate	0.46	0.58	—; 0.0039	—
Overall survival	NR	NR	0.96; 0.5605	—
Time to overall disease progression	NR	NR	0.98; 0.7295	—

* Multiple event analysis

NR, not reported

Stopeck A et al. *Proc SABCS 2010*;Abstract P6-14-01.

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SRE Types and Adverse Events

Types of SREs by Treatment Group			
	Denosumab	ZA	p-value
Pathologic fracture	23.5%	28.1%	0.0354
Radiation to bone	13.5%	17.2%	0.0184
Surgery to bone	2.9%	2.8%	NR
Spinal cord compression	1.4%	1.4%	NR
Adverse Events, n (%)			
	Denosumab (n = 1,020)	ZA (n = 1,013)	p-value
Serious adverse events	489 (47.9%)	509 (50.2%)	NR
AEs related to renal toxicity	55 (5.4%)	95 (9.4%)	NR
Osteonecrosis of the jaw (ONJ)	26 (2.5%)	18 (1.8%)	0.2861
Hypocalcemia (any; Grade 3/4)	62 (6.1%); 18 (1.8%)	37 (3.7%); 12 (1.2%)	NR
Acute-phase reactions	109 (10.7%)	286 (28.2%)	NR

Stopeck A et al. *Proc SABCS 2010*;Abstract P6-14-01.

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Hypocalcemia and ONJ

Hypocalcemia

- Approximately half of the events occurred within the first 6 months after the first dose (denosumab 57%, ZA 46%).
- The majority of patients who experienced hypocalcemia had a single hypocalcemia event (denosumab 71%, ZA 70%).

ONJ

- Most patients had a history of tooth extraction, poor oral hygiene and/or use of a dental appliance (denosumab, 24/26 patients [92%]; ZA, 15/18 patients [83%]).
- Most patients were current or past recipients of chemotherapy (denosumab, 19/26 patients [73%]; ZA, 14/18 patients [78%]).
- 69% of patients in the denosumab group and 44% in the ZA group discontinued treatment due to ONJ.
- As of data cutoff (October 1, 2010), ONJ was considered resolved by the investigator for 12/26 (46%) patients in the denosumab group and 9/18 (50%) patients in the ZA group.

Stopeck A et al. *Proc SABCS 2010*;Abstract P6-14-01.

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Author Conclusions

- In this extended data analysis of denosumab in patients with breast cancer and bone metastases, denosumab was superior to ZA in preventing SREs.
- Continued denosumab treatment resulted in a median time to first SRE that was 5 months longer than treatment with ZA.
- Continued denosumab treatment significantly reduced the proportion of patients who experienced pathologic fractures or radiation to bone compared with ZA.
- Patients treated with denosumab had a higher incidence of hypocalcemia.
- Patients treated with ZA had a higher incidence of renal adverse events and acute-phase reactions.
- Incidence of ONJ was low and similar in both groups.
- Denosumab represents a new treatment option for patients with breast cancer and bone metastases without the need for dose adjustment or renal monitoring.

Stopeck A et al. *Proc SABCS 2010*;Abstract P6-14-01.

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Osteonecrosis of the Jaw: Dental Outcomes in Metastatic Breast Cancer Patients Treated with Bisphosphonates with/without Bevacizumab at Roswell Park Cancer Institute

Ngamphaiboon N et al.

Proc SABCS 2010;Abstract P2-13-03.

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Methods

- All cases of osteonecrosis of the jaw (ONJ) in metastatic breast cancer, while receiving bevacizumab (Bev) + bisphosphonates (BP) or bisphosphonates alone, and diagnosed between October 2002 and April 2010 were reviewed.
- ONJ was diagnosed and staged in the department of dentistry according to the American Association of Oral and Maxillofacial Surgeons position paper (*J Oral Maxillofac Surg* 2009;67(5 Suppl):2-12).

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

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Clinical Manifestations, Time and Dose of Bisphosphonates Prior to Diagnosis of ONJ

Presentations	All (n = 27)	Bev + BP (n = 7)	BP (n = 20)
Necrotic bone	85%	86%	85%
Purulence	48%	57%	45%
Swelling	33%	29%	35%
Pain	67%	86%	60%
Paraesthesia	15%	0%	20%
Tooth mobility	33%	57%	25%
Edentulous	19%	14%	20%
Treatments	(n = 27)	(n = 7)	(n = 20)
Median time to ONJ	34.0 mo	32.6 mo	34.6 mo
Median number of BP doses	32.0	32.0	36.5

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

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Dental Outcomes of Treatments for ONJ

Dental responses*	All (n = 27*)	Bev + BP (n = 7)	BP (n = 20)	Year of diagnosis 2007-2010 (n = 13)	Year of diagnosis <2007 (n = 14)
Complete resolution	24%	33%	21%	33%	15%
Partial resolution	28%	50%	21%	33%	23%
Stable disease	28%	0%	37%	25%	31%
Progressive disease	20%	17%	21%	8%	31%

* n = 25; Two patients (one from each arm) lost to follow-up were excluded from response analysis

Ngamphaiboon N et al. *Proc SABCS 2010*;Abstract P2-13-03.

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Author Conclusions

- The addition of bevacizumab to bisphosphonates does not appear to alter the time to development of ONJ.
 - 32.6 months versus 34.6 months
- The number of bisphosphonate treatments administered prior to the diagnosis of ONJ was similar between bevacizumab + bisphosphonates and bisphosphonates.
- Patients who were diagnosed with ONJ in 2007-2010 presented with lower stages and had improved outcomes.
- Since dental management of ONJ has not changed over time, early recognition and screening may account for the improvement in dental outcomes.

Ngamphaiboon N et al. *Proc SABCS 2010*;Abstract P2-13-03.

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Investigator Commentary:

Effect of Bevacizumab on the Development of Rare Adverse Events

Osteonecrosis of the jaw (ONJ) is a real phenomenon but a relatively rare consequence of bisphosphonate therapy and denosumab. The Roswell Park study demonstrated that the risk of ONJ did not appear to increase for patients receiving bisphosphonates and bevacizumab, nor did the consequences of ONJ appear to increase when it did develop.

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

Impact of Bisphosphonates on Skeletal-Related Events in Patients with Breast Cancer and Bone Metastases

The randomized, placebo-controlled study of denosumab versus zoledronic acid for patients with advanced breast cancer and bone metastasis reported an 18 percent reduction in risk with the primary study endpoint of time to first on-study SRE with denosumab compared to zoledronic acid.

Tolerability was favorable with this agent. Denosumab appears to be at least as well tolerated and more effective at preventing SREs than monthly zoledronic acid and can be used in patients with renal insufficiency, which was an area in which we previously had no options to offer patients.

Presentation by Lisa A Carey, MD, SABCS December 12, 2010

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