



**Analysis of the Incidence of
Osteonecrosis of the Jaw and
Surgical Complications with
Neoadjuvant Therapy in Patients
Receiving Bevacizumab**

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 where 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 OBJECTIVE

- Assess the risk of osteonecrosis of the jaw and surgical complications from neoadjuvant therapy associated with the inclusion of bevacizumab in the treatment of breast cancer.

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IN THIS ISSUE:

- **RIBBON 2 trial:** Bev/chemo meets primary PFS endpoint in the second-line metastatic setting
- **AVADO trial** (bev plus docetaxel versus docetaxel alone) — Same story, different day: Benefit in PFS but not in OS in the first-line metastatic setting
- **Green flag on bev/bisphosphonates with lack of increased risk of ONJ** but red flag on breast reconstruction in patients recently receiving bev

On a chilly San Antonio evening in December 2002, I sat down for an interview with the usually exuberant but then pretty bummed out investigator Dr Kathy Miller, just minutes after she had presented the first randomized trial data in any cancer evaluating the anti-VEGF antibody bevacizumab, in this case combined with capecitabine in patients with metastatic breast cancer and multiple prior lines of chemotherapy. Kathy, and her mentor George Sledge, had been telling our audio audiences for several years about encouraging early findings with this agent that at that time was thought to somehow “choke off” tumor blood supply. Dr Miller’s depressive mood was engendered by the data, which revealed a not inconsequential increase in objective response rate but no effect on the primary endpoint of time to progression.

Speaking with George later in the meeting, I learned that he wasn’t as down on the findings as Kathy was and adamantly stated that he wanted to see more studies, including the results from the ECOG-E2100 first-line trial Kathy was running at that time. In his unique Prairie Home Companion manner, he quipped, “Bad things happen to drugs that hang out in the wrong neighborhood,” suggesting bev would do better with less advanced-stage disease.

As usual George was right, and six months after Kathy’s disappointing talk, Herb Hurwitz stood up at ASCO and started a new era in oncology by presenting the IFL/bev colon cancer data. Over the next few years, we saw the presentation of a number of randomized trials in metastatic breast cancer evaluating bev plus chemo that demonstrated a significant improvement in PFS, including Kathy’s memorable 2005 ASCO data set from ECOG-E2100 (paclitaxel/bev) providing the greatest improvement (5.9 to 11.8 months). At San Antonio this year, we finally heard positive bev findings from the second-line setting in the RIBBON 2 trial — even with capecitabine — and

we'll see what the NSABP/BCIRG BETH trial shows about trastuzumab/chemo/bev in the adjuvant setting for HER2-positive disease.

The weird thing is, I have now interviewed some of the best translational minds in the field — Lee Ellis, John Heymach, Ron Bukowski, Ursula Matulonis, Jim Vredenburgh, Rakesh Jain and even the legendary father of the field, the late Judah Folkman (one of our listeners) — and no one seems to really know how bev works. The mystery deepened at the 2009 ASCO plenary session when Norm Wolmark presented the “negative” results from the NSABP-C-08 study evaluating bev/FOLFOX as adjuvant therapy for colon cancer. Interestingly, and shrouded in controversy, that data set also revealed a 40 percent reduction in recurrences in the first year while bev was on board. So, while this unique agent may be costly, the truth is we need to invest even more research resources in order to determine who to treat and how, and why this mysterious agent is actually effective.

Next up on 5MJC: Other anti-angiogenic data sets from San Antonio — this time working from the inside — the TKIs sorafenib and sunitinib.

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Analysis of the Incidence of Osteonecrosis of the Jaw and Surgical Complications with Neoadjuvant Therapy in Patients Receiving Bevacizumab

Presentations discussed in this issue

Guarneri V et al. **Analysis of bevacizumab therapy, bisphosphonate use, and osteonecrosis of the jaw in >3500 patients treated in three large clinical trials.** San Antonio Breast Cancer Symposium 2009; **Abstract 208**.

Golshan M et al. **Surgical complications and the use of neoadjuvant bevacizumab.** San Antonio Breast Cancer Symposium 2009; **Abstract 43**.

Slides from presentations at SABCS 2009 and transcribed comments from recent interviews with Ian E Smith, MD (12/11/09) and Adam M Brufsky, MD, PhD (12/23/09)

Analysis of Bevacizumab Therapy, Bisphosphonate Use, and Osteonecrosis of the Jaw in >3500 Patients Treated in Three Large Clinical Trials

Guarneri V et al.
SABCS 2009; Abstract 208.

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Introduction

- Osteonecrosis of the jaw (ONJ) is a serious complication typically associated with intravenous bisphosphonate therapy.
- Cases of ONJ have been reported among patients receiving bevacizumab (bev).
 - A small retrospective analysis of patients receiving bev or sunitinib reported 16% incidence of ONJ (*Oncology* 2009;76:209).
- **Current study objectives**
 - Determine the incidence of ONJ in a large population of patients receiving bev-containing regimens as first-line therapy for locally recurrent (LR) or metastatic breast cancer (MBC) in prospective clinical trials
 - Assess whether bev administration increases risk of ONJ

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Methods

- Case reviews were performed of ONJ from clinical trials of bev-containing first-line treatment regimens for LR/MBC.
 - AVADO:
 - Randomized, placebo-controlled trial of docetaxel with bev, 7.5 or 15 mg/kg, every three weeks
 - RIBBON-1:
 - Randomized, placebo-controlled trial of chemotherapy with 15 mg/kg bev every three weeks
 - ATHENA:
 - Single-arm safety study of bev with standard, first-line non-anthracycline-containing chemotherapy conducted in the context of general oncology practice
- Comparison of ONJ incidence carried out between:
 - Bev versus placebo (PL) arms
 - Patients with and without exposure to bisphosphonates in AVADO and RIBBON-1 trials

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Study Population

- A total of 3,650 patients treated with bev were included in the analysis.
 - Randomized trials: n=1,309
 - Open-label ATHENA: n=2,251
- Median follow-up in the data sets used in this analysis:
 - Randomized trials:
 - AVADO: 10.2 mos
 - RIBBON-1 taxane/anthracycline cohort: 19.2 mos
 - RIBBON-1 capecitabine cohort: 15.6 mos
 - Open-label, non-randomized trial:
 - ATHENA: 12.7 mos

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Incidence of ONJ in Placebo-Controlled Randomized Bev Trials

Patients with ONJ/total patients	AVADO*		RIBBON-1†		Total	
	Bev	PL	Bev	PL	Bev	PL
Overall population	3/492 (0.6%)	0/238 (0%)	1/817 (0.1%)	0/412 (0%)	4/1309 (0.3%)	0/650 (0%)
Bisphosphonate exposure	1/77 (1.3%)	0/33 (0%)	1/156 (0.6%)	0/66 (0%)	2/233 (0.9%)	0/99 (0%)
No bisphosphonate exposure	2/415 (0.5%)	0/205 (0%)	0/661 (0%)	0/346 (0%)	2/1076 (0.2%)	0/551 (0%)

*Bev 7.5 and 15 mg/kg arms pooled.

†Taxane/anthracycline and capecitabine cohorts pooled

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Incidence of ONJ in the ATHENA Non-Randomized Study

	ONJ Incidence
Overall population (n=2,251)	0.4%
Bisphosphonate exposure (n=425)	2.4%*
No bisphosphonate exposure (n=1,826)	0%

*Additional risk factors for ONJ: previous dental extractions (n=2); maxillary surgery (n=1)

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Conclusions

- This analysis of the largest population of patients treated with bev for LR/MBC suggests an incidence of <1% of ONJ with bev.
 - ONJ incidence was higher among patients exposed to bisphosphonates.
 - ONJ incidence of 0.9-2.4% in bisphosphonate-exposed patients receiving bev is within the range reported with bisphosphonates alone (1-6%).
 - ONJ incidence of 0-0.2% among patients without bisphosphonate exposure is consistent with previous analysis (investigator's experience, not reported).
- Good oral hygiene, dental examination and avoidance of invasive dental procedures remain important in patients receiving bisphosphonates, irrespective of treatment with bev.

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Surgical Complications and the Use of Neoadjuvant Bevacizumab

Golshan M et al.
SABCS 2009;Abstract 43.

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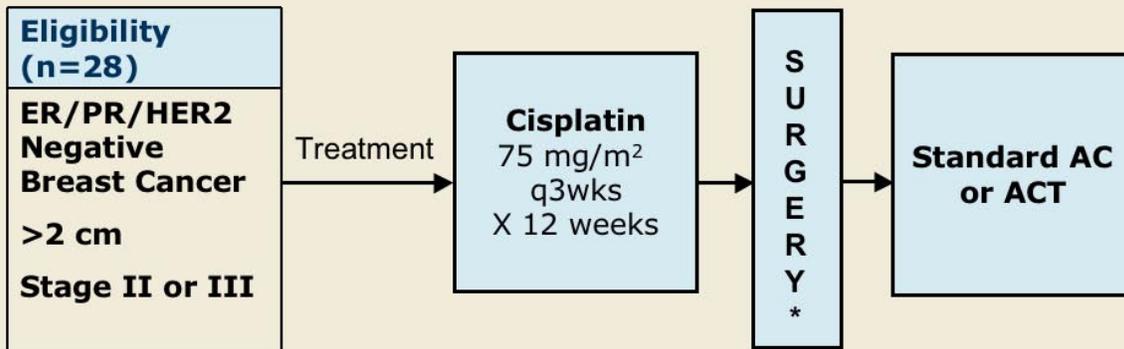
Introduction

- BRCA1-deficient cells and BRCA-deficient tumors have shown susceptibility to cisplatin-based therapy in preclinical studies.
- Sporadic triple-negative breast cancer (TNBC) and BRCA1-associated breast cancers share many histopathologic features, therefore TNBC may also be susceptible to cisplatin-based therapy.
- Neoadjuvant chemotherapy is increasingly being used in operable breast cancer, but data on the safety of bevacizumab in combination with chemotherapy in this setting is limited.
- **Current study objectives:**
 - Assess the incidence of surgical complications in two sequential phase II trials for patients with TNBC evaluating neoadjuvant cisplatin and neoadjuvant cisplatin plus bevacizumab.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Trial #1: Neoadjuvant Cisplatin for TNBC



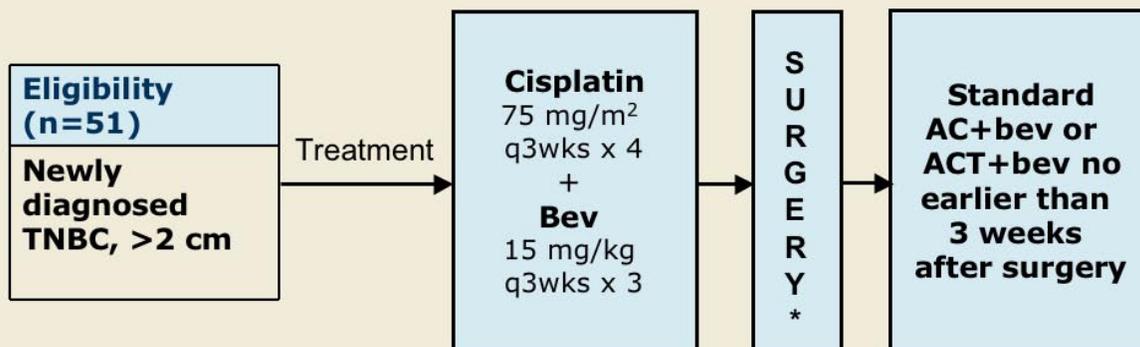
A= doxorubicin
C= cyclophosphamide
T= paclitaxel

*4 weeks following last chemotherapy

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Trial #2: Neoadjuvant Cisplatin Plus Bevacizumab for TNBC



*No earlier than 6 weeks from last cycle of neoadjuvant bevacizumab

Research biopsies were obtained before treatment and at surgery.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Clinical Response and Surgical Procedures

Clinical response	Trial #1: Cisplatin alone (n = 28)	Trial #2: Cisplatin + bev (n = 51)
Complete response	14%	27%
Partial response	35%	53%
Stable disease	35%	18%
Progressive disease	14%	2%
Surgical response		
Breast conserving therapy	46%	57%
Mastectomy	54%	43%
No reconstruction (n)	10	14
Expander (n)	3	6
TRAM (n)	2	2

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Surgical Complications

	Trial #1: Cisplatin alone (n = 28)	Trial #2: Cisplatin + bev (n = 51)	p-value
All complications	39%	43%	0.82
Seromas requiring multiple aspirations	18%	10%	NS
Wound breakdown*	7%	16%	NS
Progressive disease	14%	2%	NS
Hematoma	7%	10%	NS
Abscess	7%	0%	NS
Loss of reconstruction (n)	0% (0/5)	50% (4/8 ⁺)	0.10

* All of the patients with wound breakdown on Trial #2 required surgical debridement and/or wound vac placement, though the same was not required in any of the patients on Trial #1 with wound breakdown; + three patients with saline expanders and one with silicone implant; NS = not significant.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Summary and Conclusions

- Surgical complications were common in both preoperative cisplatin therapy single arm trials.
- Addition of bevacizumab did not increase the overall risk of surgical complications.
- Reconstruction-related complications trended higher on Trial #2 (cisplatin + bev) but did not reach statistical significance.
 - Four patients required removal of expanders or implants due to infection and/or wound healing failure.
 - Data suggests the use of tissue expanders could be problematic in patients treated with neoadjuvant bev.
- Evaluation in a randomized trial is necessary to determine the safest approach(es) to bev usage in the timing of BC surgery.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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GUARNERI PAPER

IAN E SMITH, MD: From anecdotal statements, the story was emerging that if you were on bevacizumab therapy along with bisphosphonates, then there was an increased risk of osteonecrosis of the jaw. Given the mechanism of action of bevacizumab, that was a plausible hypothesis.

What we have done in our study is to examine two randomized trials that I am not involved in and a large safety study of about 2,200 patients called ATHENA, which I've been leading. The three trials examined patients with breast cancer who were receiving bevacizumab. We've pooled the different study populations so there's a database now of well over 3,000 patients. Our results show that there is no increased risk of developing osteonecrosis of the jaw in patients receiving bevacizumab and bisphosphonates compared to patients receiving bisphosphonates alone. This is a story that didn't stand up. Whatever the cons of bevacizumab may be, increased risk of osteonecrosis of the jaw is not one of them.

GOLSHAN PAPER

DR BRUFISKY: This report came from a partnership of surgeons and medical oncologists at Dana-Farber. The authors reported on two separate Phase II trials — one evaluating neoadjuvant chemotherapy and the other evaluating neoadjuvant chemotherapy with bevacizumab — for patients with triple-negative breast cancer.

This was an interesting idea, though I was a bit concerned that it was not a randomized comparison. The response rate in the trial in which patients received a platinum agent alone was about 49 percent, and the response rate in the trial in which patients received a platinum agent and bevacizumab was about 80 percent. Though pathologic complete response rates were not reported, that's a very high response rate with the addition of bevacizumab.

Additionally, there appeared to be more downstaging and more breast-conserving surgery — 57 percent in the platinum/bevacizumab trial versus 46 in the platinum-only trial. Of concern in the platinum/bevacizumab trial was the fact that of eight women who underwent reconstructions, four actually lost their reconstructions — three saline expanders and one silicone implant. Clearly wound dehiscence occurred in four of the eight women.

This was not a statistically significant difference as these were two separate Phase II trials and not one randomized Phase II analysis, but nonetheless, I believe this paper is important because it is almost a "shot across the bow" to let us know that we have to be careful if we're going to administer bevacizumab in the neoadjuvant setting. I believe that's something we need to strongly consider.

Prof Smith is Professor of Cancer Medicine in the Breast Unit of the Department of Medicine of The Royal Marsden Hospital in London and Surrey, United Kingdom.

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