



**RIBBON 2 – A Phase III Trial  
of Second-Line Bevacizumab in  
Combination with Chemotherapy  
for HER2-Negative Metastatic  
Breast Cancer**

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## 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 efficacy and safety of bevacizumab in combination with chemotherapy as second-line treatment for patients with HER2-negative metastatic breast cancer.

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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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Advisory Committee: AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Novartis Pharmaceuticals Corporation;  
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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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# **RIBBON 2 — A Phase III Trial of Second-Line Bevacizumab in Combination with Chemotherapy for HER2-Negative Metastatic Breast Cancer**

## **Presentation discussed in this issue**

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

**Editor's comment:** At the end of this slide set are several graphics with results from a recent Patterns of Care study of 100 US-based medical oncologists.

**Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Adam M Brufsky, MD, PhD (12/23/09)**

## **RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab In Combination with Chemotherapy for Second-Line Treatment of HER2-Negative Metastatic Breast Cancer**

**Brufsky A et al.**  
SABCS 2009;Abstract 42.

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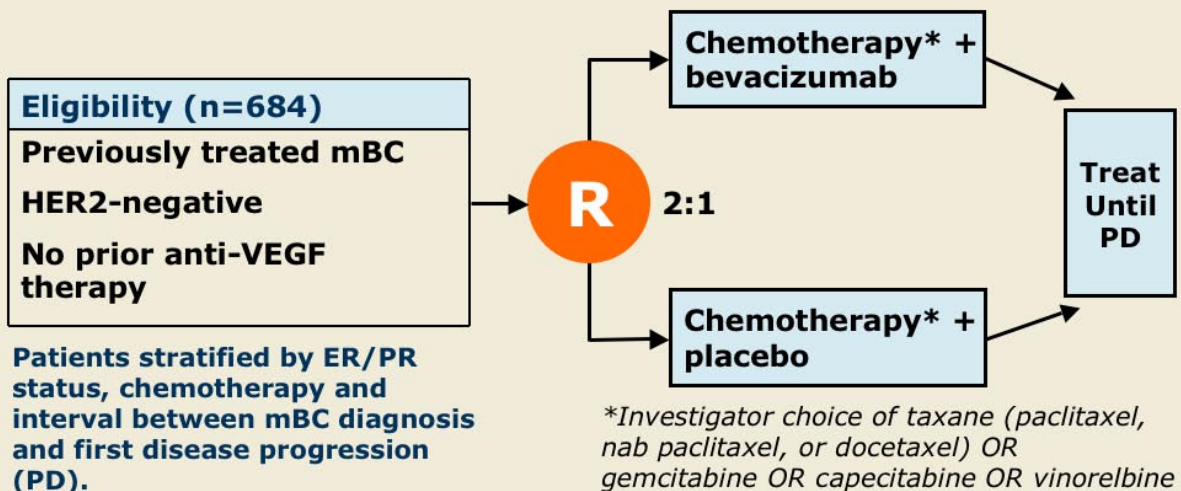
# Introduction

- Phase III trials have reported improved progression-free survival (PFS) with 1<sup>st</sup>-line bevacizumab (bev) combined with chemotherapy versus chemotherapy alone in the metastatic breast cancer (mBC) setting.
  - ECOG-E2100 PFS: 11.8 mos vs. 5.9 mos (*NEJM* 2007;357:2666)
  - AVADO PFS: 8.8 mos vs. 8.0 mos (SABCS 2009;Abstract 41)
- Phase III AVF2119g trial of bev combined with capecitabine in patients with heavily pretreated mBC did not meet its primary PFS endpoint, but reported a significant increase in the objective response rate (*JCO* 2005;23:792).
- **Current study objectives:**
  - Evaluate the clinical benefit of combining bev with various chemotherapy regimens used to treat patients with mBC in the second-line setting.

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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# RIBBON-2 Study Design



Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## Efficacy Analysis (Intent-to-treat Population)

	Chemo + bev (n = 459)	Chemo (n = 225)	Hazard ratio	p-value
Median PFS	7.2 mos	5.1 mos	0.78	0.0072
Median overall survival *	18.0 mos	16.4 mos	0.90	0.3741
1-year survival rate	69.5%	66.2%	—	—

\*Interim analysis at 57% information (315 events).

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## PFS: Cohort Specific Analyses (Intent-to-treat Population)

Cohort	Chemo + bev (n = 459)		Chemo (n = 225)		Hazard ratio
	Events	Median (mos)	Events	Median (mos)	
All subjects (n=684)	372/459	7.2	184/225	5.1	0.78
<b>Chemotherapy</b>					
Taxanes (n=304)	151/201	8.0	84/103	5.8	0.64
Gemcitabine (n=160)	84/108	6.0	43/52	5.5	0.90
Capecitabine (n=144)	87/97	6.9	39/47	4.1	0.73
Vinorelbine (n=76)	50/53	5.7	18/23	7.0	1.42

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## Efficacy Analysis (continued)

	Chemo + bev	Chemo	p value
Objective response rate*	39.5%	29.6%	0.0193 <sup>†</sup>
Complete response	2.2%	1.1%	
Partial response	37.3%	28.5%	
Duration of response	7.3 mos	7.5 mos	—

\* Includes only patients with measurable disease at baseline.

<sup>†</sup> p-value for ORR was not significant according to pre-specified limit of 0.01.

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## Select Adverse Events $\geq$ Grade 3 (Safety Population)

Adverse Event*	Chemo + bev (n = 458)	Chemo (n = 221)
Neutropenia	17.7%	14.5%
Hypertension	9.0%	0.5%
Sensory neuropathy	6.3%	5.9%
Proteinuria	3.1%	0.5%
Febrile neutropenia	2.2%	2.7%
Bleeding events	1.7%	0%
Arterial thrombotic event	0.7%	1.4%

\*Shown are only those adverse events with an incidence of  $\geq 1\%$ .

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## Conclusions

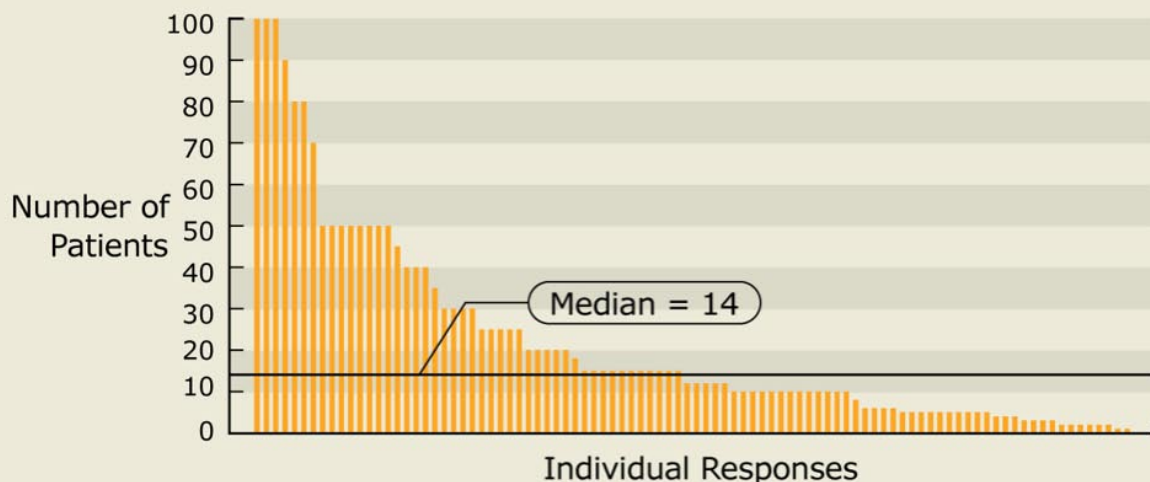
- RIBBON-2 is the first randomized Phase III study demonstrating an advantage for adding bevacizumab to chemotherapy in the second-line metastatic setting.
- RIBBON-2 demonstrated benefit for the combination of bevacizumab with standard second-line chemotherapy versus chemotherapy alone.
  - PFS: 7.2 mos vs 5.1 mos ( $p = 0.0072$ )
- PFS results were generally consistent across all chemotherapy cohorts with the exception of a small vinorelbine sub-group.
- Adverse event profile of bevacizumab was consistent with that of previous studies in mBC.

Source: Brufsky A et al. SABCS 2009;Abstract 42.

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## How many cases of breast cancer have you treated with bevacizumab?

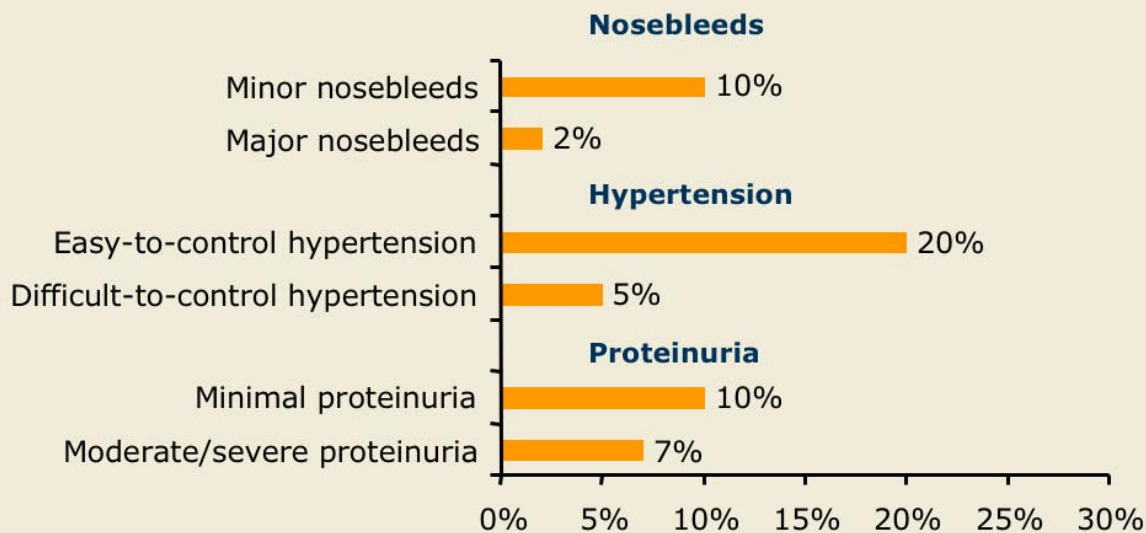
Responses from the 96 physicians who have used bevacizumab to treat breast cancer



Source: Patterns of Care in Breast Cancer — Survey of 100 US-Based Medical Oncologists®

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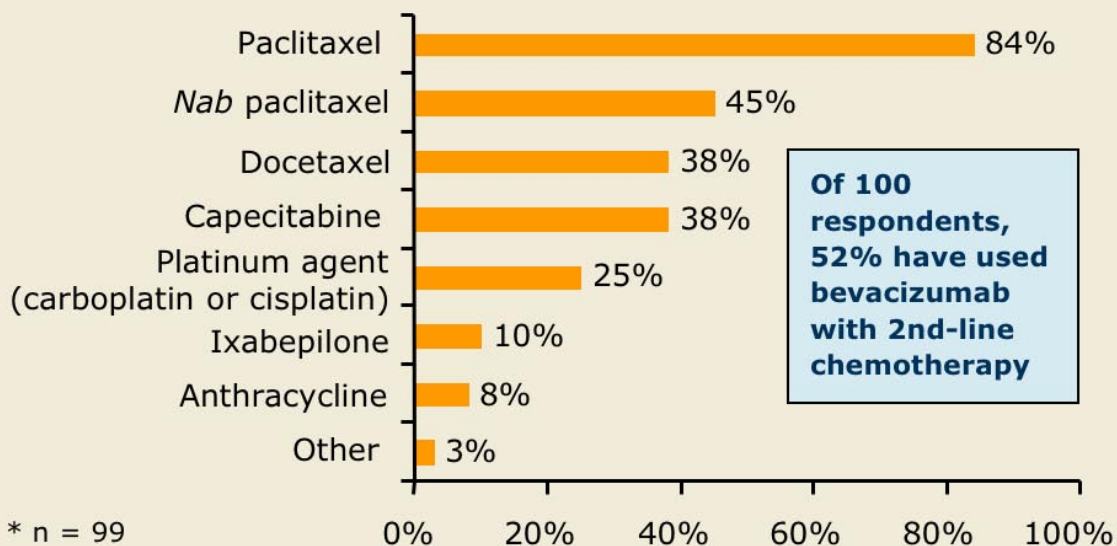
## What proportion of your patients who receive bevacizumab develop the following complications? (Median)



Source: Patterns of Care in Breast Cancer — Survey of 100 US-Based Medical Oncologists

## Which chemotherapy agents have you combined with bevacizumab?\*

(Check all that apply)



\* n = 99

Source: Patterns of Care in Breast Cancer — Survey of 100 US-Based Medical Oncologists

**ADAM M BRUFISKY, MD, PhD:** We know from trials in the first-line metastatic setting — ECOG-E2100, AVADO and RIBBON 1 — that the addition of bevacizumab to chemotherapy provides benefit. The idea behind RIBBON 2 was to ascertain whether the addition of bevacizumab to second-line chemotherapy was of benefit.

We evaluated four different second-line chemotherapy regimens — taxanes, specifically paclitaxel, nanoparticle albumin-bound (*nab*) paclitaxel or docetaxel, capecitabine, gemcitabine or vinorelbine — in a two-to-one randomization with or without bevacizumab. Chemotherapy was administered at standard dosages, with the exception of vinorelbine, in which the dose was a bit higher than the typical dose.

The bottom line for this trial is that there was a substantial progression-free survival benefit for the chemotherapy/bevacizumab combination — 7.2 months versus 5.1 months. We reported about a two-month improvement in overall survival with the combination, though this value only currently represents a bit more than 50 percent of the patient population on trial and has not yet reached statistical significance.

As far as safety goes, side effects were as expected — hypertension, proteinuria and three wound dehiscences on the trial in the bevacizumab arm — and no new toxicities were reported.

Also of note when analyzing the RIBBON 2 data is an exploratory analysis we performed of chemotherapy endpoints stratified by regimen. The addition of bevacizumab to a taxane regimen and to capecitabine provided a statistically significant benefit. The addition of bevacizumab to gemcitabine also provided a benefit — about 10 to 12 percent — though not statistically significant. The addition of bevacizumab to the vinorelbine arm of the study, however, did not provide a benefit and showed a detriment, which is bizarre.

We discussed this facet for a couple of months before the data were published, and I am not sure why that is. It was a limited analysis, with only 23 patients on the vinorelbine/placebo arm. It's likely that many of the patients on the placebo arm were treated at other institutions. And it's really a subset of a subset, so I'm not sure we should read too much into it.

I believe the take-home message for practicing oncologists is you can safely administer bevacizumab in the second-line setting. It's as safe as it is in the first-line setting. You still have to watch out for the usual side effects. I think the chemotherapy/bevacizumab combination is something that will be added to the armamentarium of therapies that we utilize for second-line metastatic breast cancer.

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