



**AVADO – Final Overall Survival  
Results of First-Line Docetaxel in  
Combination with Escalating Doses  
of Bevacizumab for HER2-Negative  
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 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 of bevacizumab in combination with docetaxel as first-line treatment for patients with HER2-negative locally recurrent or metastatic 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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## **AVADO – Final Overall Survival Results of First-Line Docetaxel in Combination with Escalating Doses of Bevacizumab for HER2-Negative Metastatic Breast Cancer**

**Presentation discussed in this issue**

Miles DW et al. **Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, Phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC).** San Antonio Breast Cancer Symposium 2009;**Abstract 41.**

**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)**

**Final Overall Survival (OS) Results  
from the Randomised, Double-Blind,  
Placebo-Controlled, Phase III AVADO  
Study of Bevacizumab (BV) Plus  
Docetaxel (D) Compared with  
Placebo (PL) Plus D for the First-Line  
Treatment of Locally Recurrent (LR)  
or Metastatic Breast Cancer (mBC)**

**Miles DW et al.**  
SABCS 2009;Abstract 41.

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# Introduction

- Three Phase III trials (AVADO<sup>1</sup>, ECOG-2100<sup>2</sup>, and RIBBON-1<sup>3</sup>) have reported positive results with bevacizumab (BV) in the first-line mBC setting (<sup>1</sup>ASCO 2008;LBA1011, <sup>2</sup>NEJM 2007;357:2666, <sup>3</sup>ASCO 2009;1005).
- AVADO demonstrated significantly improved progression-free survival (PFS) with BV plus docetaxel (D) at 10 months follow-up.
  - Median PFS: 8.7 mos (7.5 mg/kg BV + D), 8.8 mos (15 mg/kg BV + D), and 8.0 mos (D + placebo).
- Final overall survival (OS) and updated results of other study endpoints at 25 months follow-up are presented in the current analysis from the AVADO study.

Source: Miles DW et al. SABCS 2009;Abstract 41.

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# AVADO Study Design

**Accrual: 736 (closed)**

## Eligibility

**1<sup>st</sup>-line locally recurrent or mBC**

**HER2-negative**

**No prior chemotherapy for locally recurrent or mBC, unless relapse is  $\geq 6$  months since last dose ( $\geq 12$  months if taxane-based)**

**R**

**Docetaxel 100 mg/m<sup>2</sup>  
+ Placebo  
q3w x 9 →\***

**Docetaxel 100 mg/m<sup>2</sup>  
+ bevacizumab 7.5 mg/kg  
q3w x 9 →\***

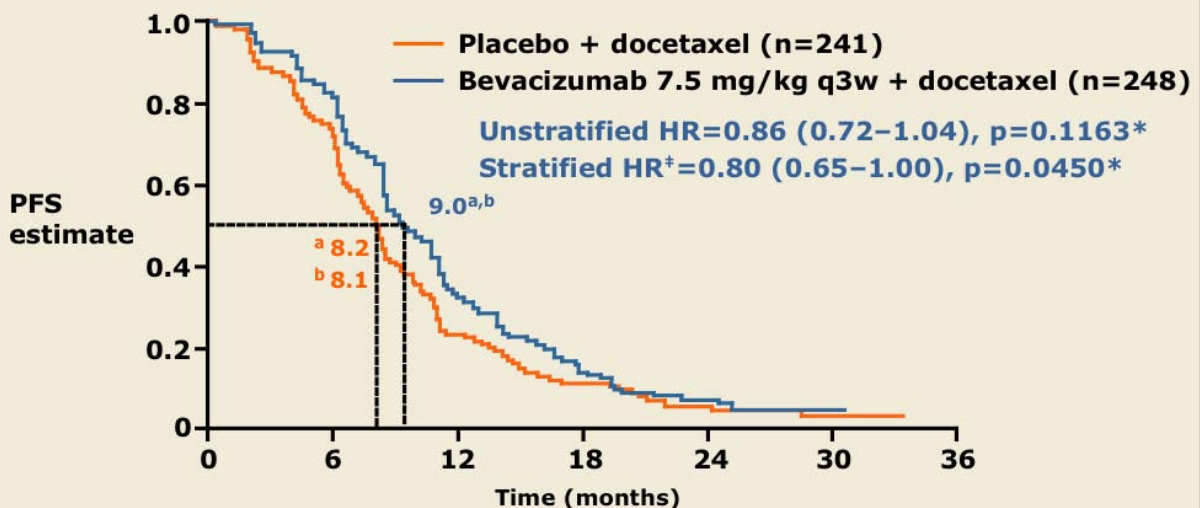
**Docetaxel 100 mg/m<sup>2</sup>  
+ bevacizumab 15 mg/kg  
q3w x 9 →\***

\*Bevacizumab or placebo administered until disease progression

Sources: Miles DW et al. SABCS 2009;Abstract 41; Miles DW et al. ASCO 2008;LBA1011

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## Updated PFS Analysis (Bev 7.5 mg/kg dose)

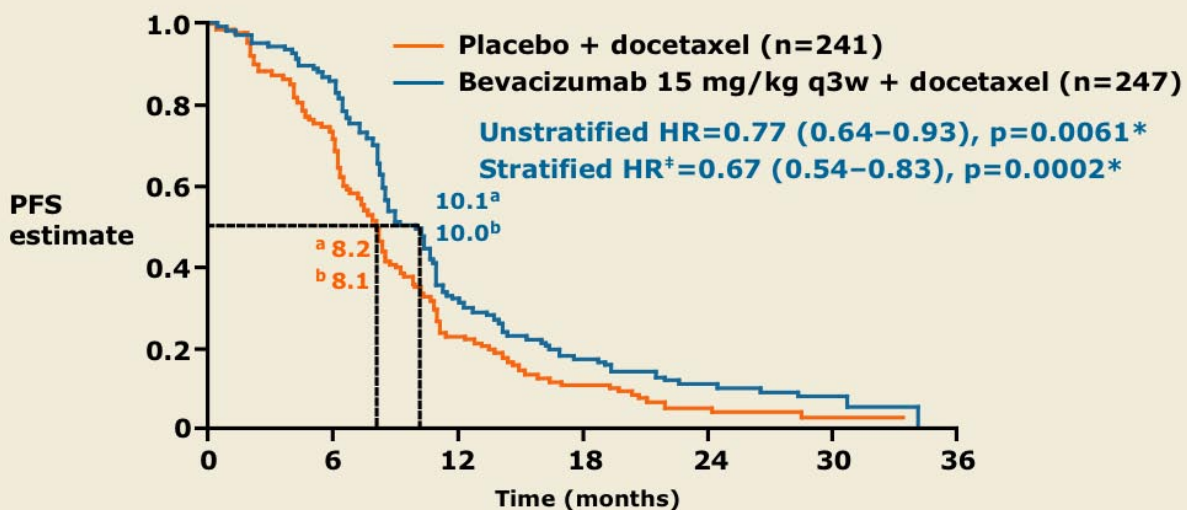


Intent-to-treat analysis; \*p values are of exploratory nature  
 †Censored for non-protocol therapy prior to progressive disease;  
<sup>a</sup> unstratified; <sup>b</sup> stratified

Source: With permission from Miles DW et al. SABCS 2009; Abstract 41.

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## Updated PFS Analysis (Bev 15 mg/kg dose)



Intent-to-treat analysis; \*p values are of exploratory nature  
 †Censored for non-protocol therapy prior to progressive disease;  
<sup>a</sup> unstratified; <sup>b</sup> stratified

Source: With permission from Miles DW et al. SABCS 2009; Abstract 41.

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## Updated Efficacy Analysis

	<b>BV, 7.5 mg/kg + docetaxel (n = 248)</b>	<b>BV, 15 mg/kg + docetaxel (n = 247)</b>	<b>Placebo + docetaxel (n = 241)</b>
<b>Median PFS</b>	9.0 mos	10.0 mos	8.1 mos
HR (vs placebo)	0.80*	0.67*	—
<i>p</i> -value (vs placebo)	0.0450†	0.0002†	—
<b>Median OS</b>	30.8 mos	30.2 mos	31.9 mos
HR (vs placebo)	1.05	1.03	—
<i>p</i> -value (vs placebo)	0.7198†	0.8528†	—

\*Stratified; † *p* values are of exploratory nature.

Source: Miles DW et al. SABCS 2009;Abstract 41.

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## Updated Efficacy Analysis (continued)

<b>Patients with measurable disease at baseline</b>	<b>BV, 7.5 mg/kg + docetaxel (n = 201)</b>	<b>BV, 15 mg/kg + docetaxel (n = 206)</b>	<b>Placebo + docetaxel (n = 207)</b>
Overall response rate (ORR) <i>p</i> -value (vs control)†	55.2% 0.0739	64.1% 0.0003	46.4% —
<b>Intent to treat population</b>	<b>(n = 248)</b>	<b>(n = 247)</b>	<b>(n = 241)</b>
1-year survival rate <i>p</i> -value (vs control)†	81% 0.198	84% 0.02	76% —
Patients still at risk (n)	195	201	178

† *p* values are of exploratory nature.

Source: Miles DW et al. SABCS 2009;Abstract 41.

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## Select Adverse Events $\geq$ Grade 3

	Bev, 7.5 mg/kg + docetaxel (n = 252)	Bev, 15 mg/kg + docetaxel (n = 247)	Placebo + docetaxel (n = 231)
Febrile neutropenia (%)	15.1	16.6	11.7
Hypertension (%)	0.8	4.5	1.3
Bleeding (%)	1.2	1.2	0.9
Wound-healing complications (%)	0.4	0.4	0.9
Venous thromboembolic events (%)	1.6	1.2	3.5
GI perforation (%)	0.4	0.4	0.9

Source: Miles DW et al. SABCS 2009;Abstract 41.

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## Conclusions

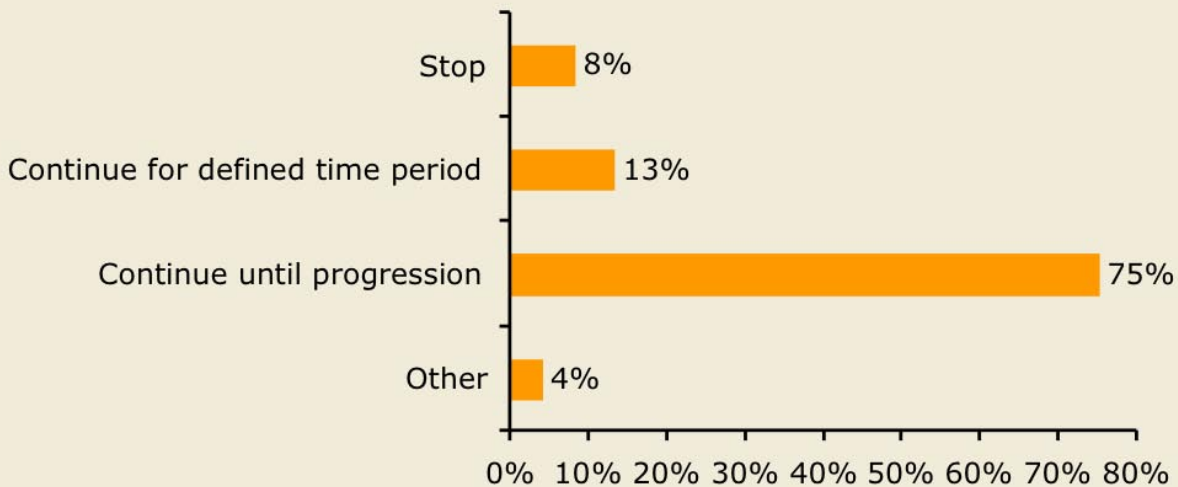
- First-line BV (15 mg/kg) plus docetaxel significantly improves PFS and overall response rate compared to docetaxel alone in patients with HER2- mBC.
  - PFS: 10.0 mos vs 8.1 mos
  - ORR: 64.1% vs 46.4%
- Addition of increasing doses of BV to docetaxel therapy has a limited impact on the existing docetaxel safety profile.
- No difference in OS was observed between the study arms.
- Exploratory analysis in patients receiving post-progression treatment suggests that the use of 2nd-line BV with chemotherapy may influence OS (data not shown).

Source: Miles DW et al. SABCS 2009;Abstract 41.

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## A 45-year-old responds to 1st-line paclitaxel and bevacizumab for mBC. Paclitaxel is discontinued due to toxicity.

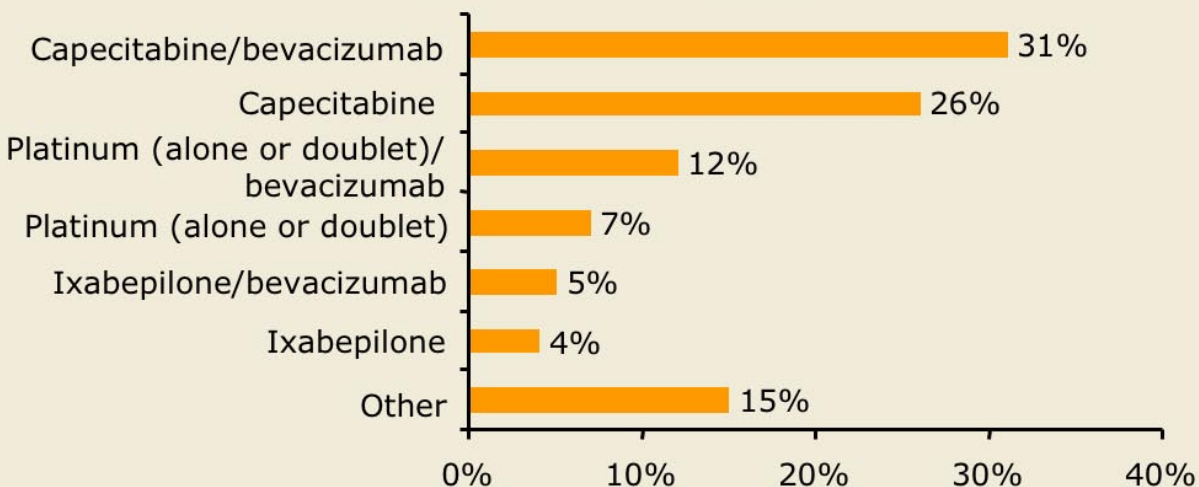
What would you do about the bevacizumab?



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

## A 75-year-old with node+ trip neg BC presents with symptomatic metastases after completion of AC → T 2 years ago.

What would you likely recommend if patient is not eligible for a clinical trial? (Check all that apply)



If the patient were eligible for a Phase III trial randomizing to gem/carbo alone or with a PARP inhibitor (BSI-201) 86% would recommend enrollment.

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

**DR BRUFISKY:** The background for this analysis presented by Miles and colleagues is provided by three trials that reported positive disease-free survival results with first-line bevacizumab on their initial analyses. ECOG-E2100, RIBBON 1 and AVADO all demonstrated that bevacizumab combined with first-line chemotherapy for patients with metastatic breast cancer improves progression-free survival.

This presentation by Dr Miles reported the final, preplanned overall survival analysis at 25 months of the AVADO trial, which evaluated docetaxel in combination with placebo versus docetaxel in combination with two escalating doses of bevacizumab. Patients received treatment until disease progression.

The bottom line in this particular trial was that a substantial increase in progression-free survival was reported with the addition of bevacizumab, particularly the 15-mg dose, with no unexpected toxicity. One of the main complaints about AVADO when it was first reported at ASCO 2008 was that the trial reported a minimal progression-free survival benefit. But these updated results, particularly with the 15-mg/kg dose, are substantial — 10 months versus 8.1 months — and highly statistically significant.

An 18 percent improvement in response rate was also seen — it increased from 46 percent to about 64 percent. But there was no difference in the primary overall survival endpoint at 25 months, which is similar to reports from ECOG-E2100 and RIBBON 1. These trials show a substantial effect, a positive benefit for treatment of patients with metastatic breast cancer with bevacizumab. I believe the take-home message from this trial is that you can feel fairly comfortable administering bevacizumab with docetaxel. These results combined with RIBBON 2 in the second-line setting indicate that taxanes and bevacizumab are a good match.

**DR LOVE:** Do you think that the lack of a survival benefit might have something to do with the duration of bevacizumab administration?

**DR BRUFISKY:** I think that's going to be the answer at the end of the day. Current basic and translational literature have reported in animal models that when you stop administering bevacizumab, or any anti-angiogenic agent for that matter, you get a rebound effect where you actually get more tumor growth when you discontinue the agent.

I think bevacizumab is a drug that's going to need to be used continuously to provide benefit. Many of us who have been involved in these trials are interested in conducting a new study that would be called the RIBBON 3 trial, in which patients go on bevacizumab and are then randomly assigned to stop the bevacizumab at first disease progression or continue through multiple lines. I believe that's the only way we're going to answer this question, which was also raised in evaluating the adjuvant colon data with bevacizumab.

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