FDA Briefing Document
Oncology Drug Advisory Committee Meeting

July 20, 2010

BLA STN 125085/191 and 192
Avastin® (bevacizumab)

Applicant: Genentech Inc.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought supplemental biologics license applications for Avastin (bevacizumab), STN BL 125085/191 and STN BL 125084/192 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

I. EXECUTIVE SUMMARY

Genentech, Inc submitted two efficacy supplements to the Biologics License Application (BLA) for Avastin (bevacizumab), STN BL 125085/191 (AVADO trial), and STN BL 125084/192 (RIBBON1 trial) to support label expansion for Avastin for first-line treatment of metastatic breast cancer (MBC) in combination with docetaxel, anthracycline, or capecitabine and to support conversion from accelerated approval to regular approval for first-line treatment of metastatic breast cancer.

Avastin in combination with paclitaxel received accelerated approval for first-line treatment of patients with MBC on February 22, 2008 based on the results of the E2100 study, a randomized, multicenter, open-labeled trial of bevacizumab with paclitaxel or paclitaxel alone that enrolled patients with HER-2 neu negative breast cancer who received no previous chemotherapy for metastatic disease. The addition of bevacizumab to paclitaxel resulted in a 52% increase in progression-free survival (HR 0.48, 95% CI 0.39, 0.61; $p< 0.0001$) with an observed 5.5-month difference in median PFS, based on an independent radiographic review. There was no significant difference in overall survival, a secondary endpoint, between the two treatment arms. The tumor response rate was higher with bevacizumab plus paclitaxel as compared to paclitaxel alone (48.9% versus 22.2%).

As a condition of the accelerated approval, Genentech was required to submit data from two ongoing, placebo-controlled trials (AVADO and RIBBON1) to provide verification of the treatment effect on PFS and to provide additional information on the effects on overall survival.

AVADO (STN BL 125085/19) was a double-blind, placebo-controlled, three-arm trial of docetaxel plus placebo, docetaxel plus bevacizumab 7.5mg/kg, and docetaxel plus bevacizumab 15 mg/kg. A total of 736 patients with HER-2 neu negative tumors who had not received prior chemotherapy for metastatic breast cancer were enrolled. The addition of bevacizumab 7.5 mg/kg to docetaxel resulted in 30% increase in progression free survival [HR 0.70 (95% CI 0.55, 0.90)] with an observed 0.8-month difference in median PFS while the addition of bevacizumab 15 gm/kg to docetaxel resulted in 39% increase in progression-free survival [HR 0.62 (95% CI 0.48, 0.79)] with an observed 0.88-month difference in median PFS. Objective responses were observed in 44% of patients in the placebo arm, 55% in the bevacizumab 7.5 mg/kg arm (p-value 0.0295) and 63% in the bevacizumab 15 mg/kg arm (p -value 0.0001). Mature survival data showed a HR of 1.103 (95% CI 0.84, 1.45) favoring the placebo arm over the 7.5mg/kg bevacizumab arm. The HR for overall survival was 1.003 (95% CI 0.76, 1.32) for the 15 mg/kg bevacizumab arm compared to the placebo arm.

Safety data showed an increase of grade 3-5 adverse events, serious adverse events and study drug discontinuation with the addition of bevacizumab to docetaxel. More patients in the bevacizumab-containing arms required interruption/dose reduction or discontinuation of docetaxel due to an adverse event.

RIBBON 1 (STN BL 125084/192) was a double-blind, randomized, parallel group study conducted in women with metastatic or locally recurrent HER 2- neu negative adenocarcinoma of the breast, who had not received prior chemotherapy for their advanced or metastatic cancer. A total of 1237 patients were randomized (2:1) to receive anthracycline- or taxane-based chemotherapy (n=622) or capecitabine (n=615) in combination with bevacizumab or placebo. The taxane/anthracycline cohort and capecitabine cohort were analyzed as separately with the alpha split equally (1-sided α 0.025) for comparisons of PFS within each subgroup.

The addition of bevacizumab to taxane/anthracycline-based chemotherapy resulted in 36% increase in progression free survival [HR 0.64 (95% CI 0.52, 0.80)], with an observed 1.2-month difference in median PFS. Objective response rate was higher in the bevacizumab containing arm, with an absolute increase of 13.5 % (95% CI 4.6, 22.3%) with the addition of bevacizumab to anthracycline/taxane-based chemotherapy. Mature survival analysis yielded a HR of 1.11 (95% CI 0.86, 1.43) favoring the placebo arm.

The addition of bevacizumab to capecitabine resulted in 31% increase in progression free survival [HR 0.69 (95% CI 0.56, 0.84)], with an observed difference of 2.9 months in median PFS. Objective response rate was higher in the bevacizumab containing arm, with an absolute increase of 11.8 % (95% CI 3.4, 20.2 %) observed with the addition of bevacizumab to capecitabine. A comparison of the mature survival data for the capecitabine cohort showed a HR of 0.88 (95% CI 0.69, 1.13) favoring the bevacizumab-containing arm.

Overall, the incidence of grade 3-5 AEs and serious AEs were almost twice as high in the bevacizumab arms compared to placebo arms in both cohorts. In the taxane/anthracycline cohort, taxane subgroup, there was slightly more deaths in the bevacizumab containing arm than placebo arm (49.8 % versus 43.1 %). The vast majority of the deaths were attributed to breast cancer. Adverse events known to be caused by bevacizumab were, as expected, increased in the bevacizumab containing arms in both cohorts. The most common AEs associated with bevacizumab were hypertension, bleeding/hemorrhage and febrile neutropenia. The incidence of AEs is not significantly different than currently described in the Avastin® package insert.

The key issue for discussion is the balance of benefit versus risks. AVADO and RIBBON 1 are well conducted, double-blinded trials. The magnitude of the improvement in PFS observed in these two studies failed to confirm the magnitude of PFS improvement observed in the E2100 trial, the basis for the accelerated approval. The magnitude of treatment effect is clinically important because it is really a measure of delaying symptoms from tumor progression, which has to be weighed against drug toxicity that is present for the duration of treatment. The addition of bevacizumab to chemotherapy resulted in an increased rate of serious adverse events, of grade 3-5 adverse events and of adverse events attributable to bevacizumab in both studies. Overall survival data showed hazard ratios favoring the placebo arms in both the AVADO study and the taxane/anthracycline cohort of the RIBBON1 study.

ODAC advice is requested.

II. BACKGROUND

Regulatory Standards for Approval

Based on advice from two Oncologic Drugs Advisory Committee meetings over the past 15 years, FDA has recommended that sponsors seeking regular approval for initial treatment of metastatic breast cancer demonstrate an improvement in overall survival as compared to available (standard) therapy. In 2007, the final version of the "Guidance to Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" was published. In that document, FDA noted that progression-free survival may be considered a surrogate endpoint or a direct clinical benefit; the determination is based on factors such as effect size, effect duration, and benefits of other available therapy. The Guidance notes that tumor-based efficacy endpoints may not be acceptable in diseases where tumors cannot be measured accurately (e.g., malignant mesothelioma, pancreatic cancers, brain tumors). The Guidance further states that, for cancer types where tumors can be accurately measured, the outcome should be evaluated for the potential for bias and studies that rely on tumor measurement-based endpoints as sole evidence of efficacy may need confirmatory evidence from a second trial.

In February 2008, Avastin received accelerated approval for use in combination with chemotherapy for the initial treatment of metastatic breast cancer based on demonstration of a large treatment effect (52% improvement) on progression-free survival in a single, randomized, open-label, multicenter trial. Since this trial also demonstrated that there was no significant treatment effect on overall survival (note that the study was adequately powered to detect a 16% improvement in overall survival), preliminary summary results from a second trial were submitted informally as evidence that the effect on PFS was "confirmed". The accelerated approval for Avastin required submission of two ongoing, placebo-controlled to provide verification of the treatment effect on PFS and to provide additional information on the effects on overall survival.

Metastatic Breast Cancer (MBC) and Available Therapies

Breast cancer is the number one cause of cancer in women in the United States. In 2009, an estimated 192,300 new cases of breast cancer and 40,000 deaths related to breast cancer occurred. Approximately 10% of the patients will have metastatic disease at the time of the diagnosis and nearly half of all patients treated with apparently localized breast cancer develop metastatic disease. The median survival of breast cancer patients with metastatic disease is 18 -24 months.

Metastatic breast cancer is essentially incurable. The main goals of therapy are palliation of symptoms and prolongation of overall survival time without negatively impacting quality of life.

There is no single standard of care for MBC and treatment requires an individualized approach based on multiple factors. For ER/PR positive tumors, endocrine therapy, alone or in combination with chemotherapy, is the treatment of choice. For HER-2-neu

expressing tumors, trastuzumab or lapatinib, in combination with chemotherapy, are indicated.

Chemotherapy alone or in combination with hormonal agents or anti-HER2 therapy, is an initial treatment option for many patients with MBC. Several cytotoxic agents have established single-agent activity (Table 1). Anthracycline and taxanes are considered to be the most active. Although combination chemotherapy generally results in higher objective response rates than single-agent therapy, it does not result in superior survival outcome and the higher response rate comes at a cost of increased toxicity. In the absence of rapid clinical progression, life-threatening visceral metastasis, or the need for rapid symptom and/or disease control, sequential single-agent chemotherapy is preferred to combination chemotherapy

The following table lists the agents approved by the FDA for use in MBC since 1953.

Table 1 - Agents Approved by the FDA for use in Metastatic Breast Cancer

Indication: MBC	Agent	Year of Approval
MBC	Methotrexate, Cyclophosphamide Thiotepa, Vinblastine 5-fluorouracil Doxorubicin	1953 1959 1959 1961 1962 1974
2nd and 3rd line	Paclitaxel Docetaxel Trastuzumab Capecitabine Capecitabine + Docetaxel Abraxane Lapatinib Ixabepilone	1994 1996 1998 1998 2001 2005 2006 2007
1st line	Trastuzumab +Paclitaxel Gemcitabine + Paclitaxel	1998 2004
1st line (Accelerated Approval)	Bevacizumab + Paclitaxel	2008

Avastin (bevacizumab)

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and subsequent tumor growth.

Bevacizumab is currently approved in the United States for the following indications:

- 1st and 2nd line metastatic color-rectal cancer in combination with oxaliplatin and 5-fluorouracil (5-FU)-based chemotherapy
- 1st line metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel
- 1st line advanced renal cell carcinoma in combination with interferon alpha
- 2nd/3rd line glioblastoma multiforme (accelerated approval)
- 1st line metastatic breast cancer in combination with paclitaxel (accelerated approval) - See Regulatory History below.

Since the initial marketing approval in February 2004, the Avastin package insert has been revised four times to add safety information regarding: arterial thromboembolic events and infusion reactions (December 2004), gastrointestinal perforation (April 2006), reversible posterior leukoencephalopathy syndrome (RPLS) and nasal septum perforation (September, 2006) and non-gastrointestinal fistula formation (October, 2007).

Regulatory History

Prior to the 2008 approval of Avastin, FDA approvals for first line MBC were based on evidence of improvement in overall survival (OS). Approvals were granted for trastuzumab plus paclitaxel and gemcitabine plus paclitaxel based on statistically significant improvements in survival in the treatment arm compared to the control arm.

Accelerated approval was granted on February 2009 for bevacizumab, in combination with paclitaxel, for the first- line treatment of MBC based on evidence of improvement in progression free survival (PFS). Approval was based on the result of one, randomized, open-labeled study of paclitaxel with or without bevacizumab (E2100). The study was conducted by the Eastern Cooperative Oncology Group (ECOG), under an IND sponsored by the National Cancer Institute.

E2100 enrolled 722 patients (368 women randomized to bevacizumab plus paclitaxel and 354 women to paclitaxel alone) with recurrent or metastatic, HER2 negative breast cancer who had not received prior chemotherapy for metastatic disease. The median age was 55 years-old (range 27 to 85), 76% were white, and 76% post-menopausal.

The pre-specified primary endpoint of the study was progression-free survival (PFS), as determined by investigators with overall response rate and overall survival as secondary endpoints. Given FDA's concerns with the subjective nature of the endpoint, PFS was also determined by a retrospective review conducted by an independent radiology review committee (IRRC) masked to treatment assignment. The IRRC results demonstrated a 52% prolongation in PFS (HR 0.48, 95% CI 0.39, 0.61) for bevacizumab plus paclitaxel compared to paclitaxel alone. Based on a mature analysis, there was no improvement in overall survival. Efficacy results are summarized in Table 2.

Table 2 - E2100 Efficacy Results

	Paclitaxel N = 354	**Bevacizumab + Paclitaxel N = 368**
Progression Free Survival		
# PFS events (%)	184 (52%)	173 (47%)
Median (month)	5.8 months	11.3 months
Hazard ratio (95% CI)	0.48 (0.39, 0.61)	
p–value (stratified log-rank)	< 0.0001	
Overall Survival		
# Deaths (%)	238 (67.2%)	243 (66.0%)
Median (month)	24.8	26.5
Hazard ratio (95% CI)	0.87 (0.72, 1.05)	
p-value (log rank)	0.14	
Objective Response		
# pts w/ measurable disease	243	229
Objective response rate (%)	22.2 %	48.9%
Between-arm difference in ORR	26.7%	
p-value	< 0.001	

The review division had several issues with the design of the E2100 study. Chiefly, this was open-labeled study with deficient collection of primary efficacy and safety data. Although the addition of bevacizumab to paclitaxel resulted in a significant improvement in PFS, this did not translate into an improvement in overall survival. The review team did not have confidence in the PFS results because baseline or PFS-determining radiographic scans were missing in 10% of the patients and 34% of the patients were not followed until an IRRC-determined PFS event or the end of the study. In addition, there was a high rate of discordance (50%) between investigator and independent review determined PFS events. Toxicity was increased with the addition of bevacizumab to paclitaxel. There was a 20% higher incidence of grade 3-5 toxicity, including unique toxicities attributed to bevacizumab, and a 1.7% treatment related death in the bevacizumab plus paclitaxel arm.

Results from E2100 were presented to the Oncologic Drugs Advisory Committee (ODAC) on December 15, 2007. The following is a summary of the comments from ODAC members:

- The committee expressed concerns that the E2100 study had shortcomings (selective safety data collection) and inconsistencies (high rate of inter-reader discordance in interpretation of imaging)
- Some members raised the concern that, given the uncertainties in the PFS effect size due to missing data, patients could be offered false hope.

- The committee expressed concerns over the toxicity of Avastin and the fact that other agents are available in this setting.
- Many committee members agreed that PFS is a clinically meaningful endpoint but had issues with how best to measure this endpoint. The committee also reaffirmed that if PFS is to be used, the study must be powered for survival to ensure that benefit outweigh the risks.

ODAC voted 5 versus 4 against approval.

On February 22, 2008, FDA granted accelerated approval to bevacizumab based on the magnitude of the effect on PFS demonstrated in the E2100 study and supported by sensitivity analyses of E2100 which supported the presence (if not the magnitude) of the treatment effect and by the preliminary results for a second study, AVADO, reporting a statistically significant improvement in PFS. Final results from two ongoing, double-blind, placebo-controlled, randomized studies being conducted by Genentech/Roche for 1st line MBC (AVADO and RIBBON 1 studies) were required to provide confirmatory evidence of benefit as post-marketing requirements.

PFS is the protocol-specified primary endpoint for both AVADO and RIBBON 1 studies. Overall survival is a secondary endpoint in both studies. Under a post-marketing requirement for the accelerated approval based on the E2100 trial, Genentech must collect and submit mature survival data assessing whether the addition of bevacizumab to chemotherapy results in a deleterious effect on survival.

The sBLAs 125085/191 and 125084/192, containing the results of the AVADO and RIBBON 1 trials, were submitted on November 16, 2009. The data from these trials are the subject of this advisory meeting.

III. OVERVIEW OF CLINICAL STUDIES

AVADO TRIAL (STN 125081/191)

AVADO Trial has been submitted to support the following proposed indication (revisions to current indication underlined) for bevacizumab:

Metastatic breast cancer, with paclitaxel <u>or docetaxel</u> for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer

AVADO is a randomized, double-blinded, international study conducted in women with metastatic or locally recurrent HER 2- neu negative adenocarcinoma of the breast who had not received prior chemotherapy for advanced or metastatic cancer. Eligible patients were randomized (1:1:1) to one of the following treatment regimens:

- Docetaxel 100mg/kg plus placebo every 3 weeks
- Docetaxel 100mg/kg plus bevacizumab 7.5mg/kg every 3 weeks
- Docetaxel 100mg/kg plus bevacizumab 15.0 mg/kg every 3 weeks

Randomization was stratified by region, prior adjuvant/neo-adjuvant taxane/time to relapse since last dose of adjuvant/neoadjuvant chemotherapy, measurable disease, and hormone receptor status.

Treatment continued until disease progression or unacceptable toxicity. The protocol allowed for unblinded treatment with bevacizumab plus chemotherapy of choice by the investigator for patients who experienced disease progression.

Tumor assessment was performed at baseline, every 9 weeks up to week 36, and every 12 weeks thereafter until disease progression. Upon disease progression, patients were followed for survival every 3 months.

The primary efficacy endpoint was investigator-assessed PFS. Key secondary endpoints were overall response rate and overall survival.

Summary Results

Between March 2006 and October 2007, the study enrolled 736 patients (241: 248: 247) in Western Europe, Australia, Canada, Eastern Europe, East Asia, Central and South America. The demographic and baseline characteristics in the intent-to-treat (ITT) population were balanced among treatment arms. The median age was 55 years, 83% of subjects were white, 62% postmenopausal, and 79 % had a median disease-free interval ≥ 12 months. Sixty-six percent of the patients received prior adjuvant therapy and 16% received a prior taxane as adjuvant or neo-adjuvant therapy.

The efficacy results are shown in the following table and figures.

Table 3 - AVADO Trial: Efficacy Results

	Placebo + Docetaxel N=241	**Bev 7.5 + Docetaxel N=248**	**Bev 15.0 + Docetaxel N=247**
Progression Free Survival			
No. of Events (%) PD Death	152 (63.1) 144 8	135 (54.4) 125 10	134 (54.3) 126 8
Median (months) (95% CI)	7.89 (6.74, 8.25)	8.71 (8.18, 9.72)	8.77 (8.41, 10.22)
Stratified HR (95% CI)		0.704 (0.55, 0.90)	0.616 (0.48, 0.79)
Log-rank p-value* (Adj)		0.0054	0.0003
Overall Survival			
No. of Events (%)	108 (44.8)	118 (47.6)	116 (47.0)
Median (Months)	31.9	30.8	30.2
Stratified HR (95% CI)		1.103 (0.84, 1.45)	1.003 (0.76, 1.32)
Log-rank p-value*		0.4827	0.9830
Objective Response Rate			
No. of ORR (%) CR PR	92 (44.4%) 2 (1.0%) 90 (43.5%)	111 (55.2%) 6 (3.0%) 105 (52.2%)	130 (63.1%) 2 (1.0%) 128 (62.1%)
Difference in ORR (95% CI)		10.8% (0.55, 0.90)	18.7% (0.48, 0.79)
P-value (χ^2)*		0.0295	0.0001

* treatment arm compared to placebo-control arm

Figure 1. Kaplan-Meier Curve for Progression-Free Survival
AVADO trial: Docetaxel + Placebo vs. Docetaxel + Bevacizumab 7.5mg/kg

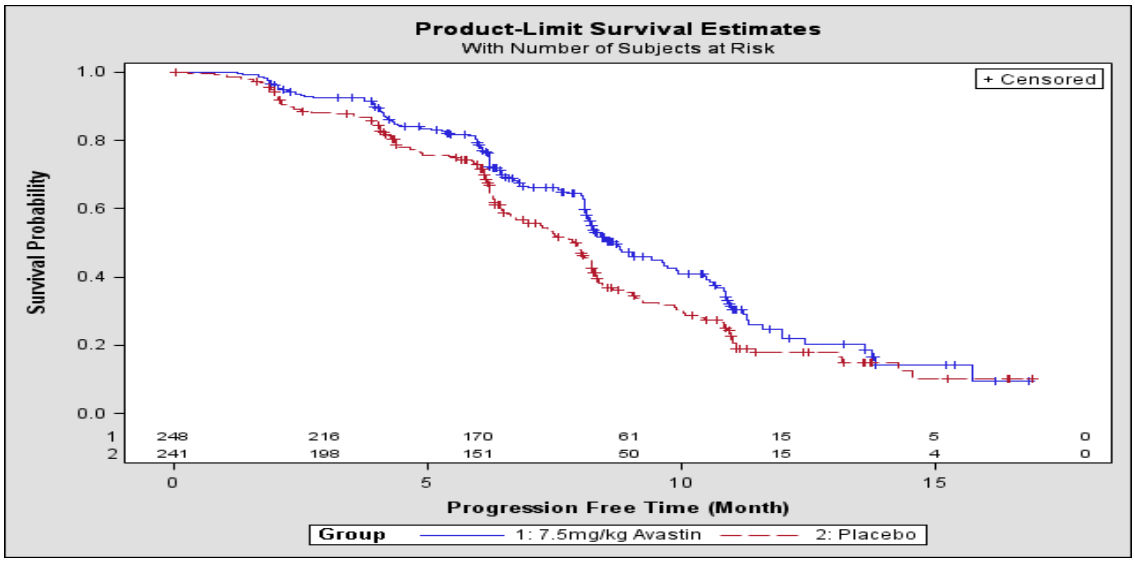
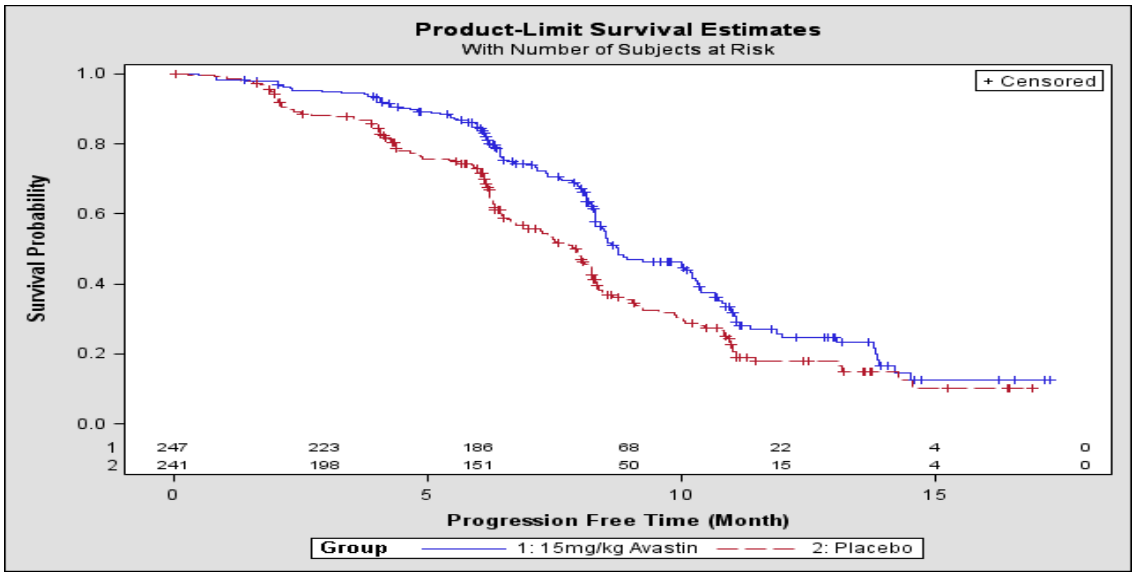


Figure 2. Kaplan-Meier Curve for Progression-Free Survival
AVADO trial: Docetaxel + Placebo vs. Docetaxel + Bevacizumab 15mg/kg



As shown above, AVADO showed a statistically significant improvement in PFS for the bevacizumab-containing arms, with a HR of 0.70 (95% CI 0.55, 0.90) for 7.5 mg/kg bevacizumab arm and HR of 0.62 (95% CI 0.48, 0.79) for the 15 mg/kg bevacizumab arm. The magnitude of treatment effect, as commonly assessed by clinicians based on differences in median PFS, was marginal. The difference in median PFS was 0.82 months for the 7.5 mg/kg bevacizumab arm and 0.88 months for 15mg/kg bevacizumab arm as compared to the placebo arm, both favoring the bevacizumab-containing arms.

Objective responses were observed in 44% of patients in the placebo arm, 55% in the bevacizumab 7.5 mg/kg arm (p-value 0.0295) and 63% in the bevacizumab 15 mg/kg arm (p -value 0.0001)

Overall survival is both an efficacy and safety endpoint. There was no survival benefit with the addition of bevacizumab to docetaxel at either bevacizumab dose level. Mature survival data showed a HR of 1.103 (95% CI 0.84, 1.45) favoring the placebo arm over the 7.5mg/kg bevacizumab arm. Similarly, the hazard ratio for overall survival data was 1.003 (95% CI 0.76, 1.32) favoring the placebo arm over the 15 mg/kg bevacizumab arm.

Figure 3. Kaplan-Meier Curve for Overall Survival
AVADO trial: Docetaxel + Placebo vs. Docetaxel + Bevacizumab 7.5mg

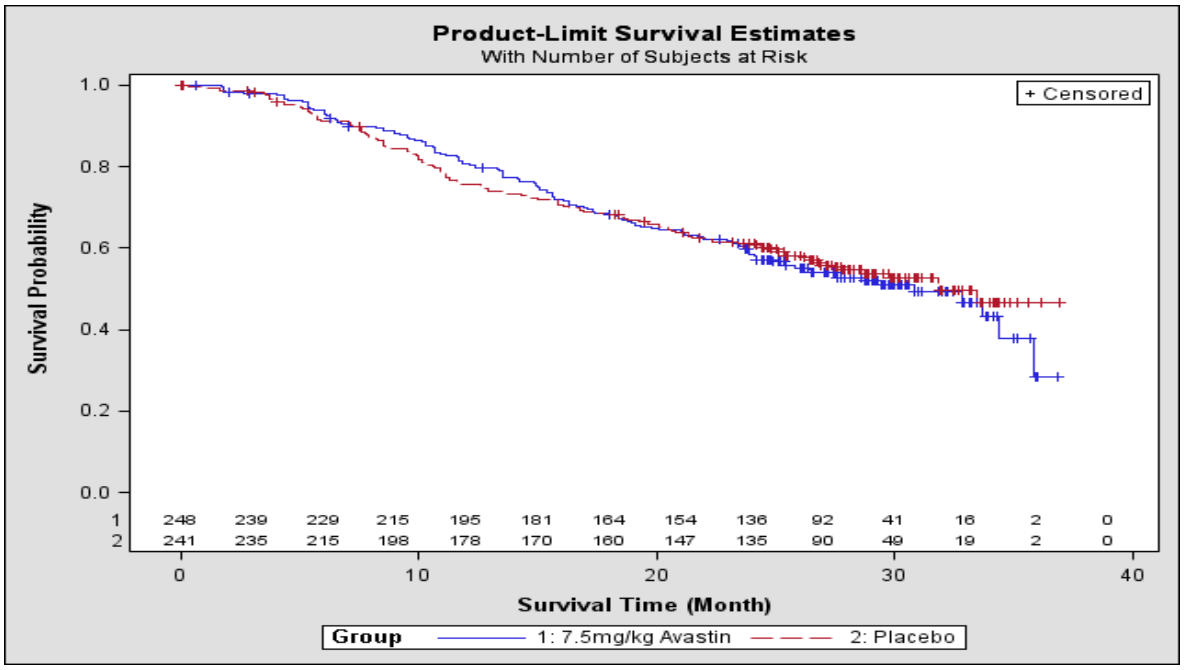
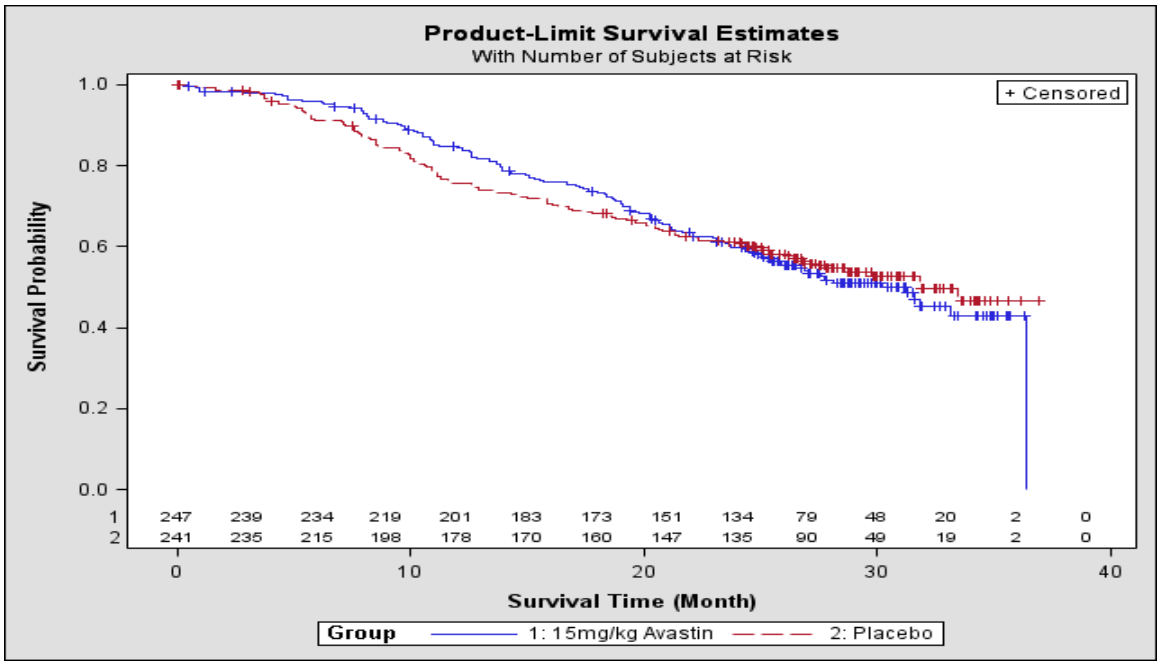


Figure 4. Kaplan-Meier Curve for Overall Survival
AVADO trial: Docetaxel + Placebo vs. Docetaxel + Bevacizumab 15mg



Analysis of the safety data showed an increase in the incidence of grade 3-5 adverse events, of serious adverse events and of study drug discontinuation with the addition of bevacizumab to docetaxel. More patients in the bevacizumab-containing arms required interruption/dose reduction or discontinuation of docetaxel due to an adverse event. Common adverse events leading to discontinuation of docetaxel were neutropenia/febrile neutropenia, asthenia/fatigue, mucosal inflammation, diarrhea and peripheral neuropathy. Common adverse events leading to discontinuation of bevacizumab were hypertension, fatigue/asthenia and neutropenia. Results are shown in tables 4 and 5.

Table 4 - AVADO Trial - Overall Safety

	Pl+ Doc N = 231 (%)	Bev 7.5 + Doc N = 252 (%)	Bev 15 +Doc N = 247 (%)
Grade 3-5 AE*	156 (68)	**196 (78)**	**186 (75)**
Serious AE*	75 (33)	**94 (37)**	**106 (43)**
AE leading to interruption of Bevacizumab/placebo^	24 %	**29%**	**35%**
AE leading to interruption/dose reduction docetaxel^	49 %	**56 %**	**59 %**
All deaths* • Disease Progression • AE leading to death	108 (45) 101 (42) 7 (3)	**118 (48)** 108 (44) 10 (4)	**116 (47)** 109 (44) 7 (3)

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bo17708.CRF: ^ae11modb_s001; ae11modd_s001

Selected clinically important adverse events are shown in table 5.

Table 5 - AVADO Trial - Clinically Significant Adverse Events

	Pl+ Doc N = 233 (%)		Bev 7.5 + Doc N = 250 (%)		Bev 15 +Doc N = 247 (%)	
	All Gr*	**Gr 3-4^**	**All Gr***	**Gr3-4^**	**All Gr***	**Gr3-4^**
Bleeding/Hemorr	67 (29)	2 (1)	**137 (54)**	3 (1)	**136 (55)**	3 (1)
Fever/neutropenia	27 (12)	27 (12)	**39 (16)**	**38 (15)**	**45 (18)**	**41 (17)**
Hypertension	23 (10)	3 (1)	**36 (14)**	2 (1)	**54 (22)**	**11 (5)**
Fatigue	97 (41)	12 (5)	103 (41)	**24 (10)**	96 (39)	**16 (7)**
Diarrhea	108 (46)	9 (4)	**137 (55)**	**17 (7)**	**125 (51)**	**17 (7)**
Wound healing complications	3 (1)	2 (1)	**8 (3)**	1 (< 1)	**12 (5)**	1 (< 1)
Fistula/GI perforation	3 (1)	3 (1)	**7 (3)**	3 (1)	**8 (3)**	3 (1)
Proteinuria	4 (2)	0	5 (2)	**2 (1)**	**19 (8)**	**5 (2)**
Palmar-Plantar Erythrodysaesthesia	21 (9)	2 (1)	**42 (17)**	**13 (5)**	**35 (14)**	**17 (7)**
Peripheral Sensory neuropathy	60 (26)	5 (2)	64 (26)	**8 (3)**	56 (23)	**11(4.5)**

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The most common AEs attributable to bevacizumab reported in this study were bleeding/hemorrhage (55%), the majority of the cases due to epistaxis (grade 1-2); hypertension (22%), with 4% grade 3-4, fever/neutropenia 17% grade 3-4. Other clinically significant events attributable to bevacizumab that were reported in this study were wound healing complications, fistula, gastrointestinal perforation and proteinuria.

Adverse events associated with docetaxel were also increased in incidence and severity in the bevacizumab containing arms (diarrhea, palmar-plantar erythrodysesthesia and peripheral sensory neuropathy)

At the cut off date of April 30, 2009, the number of deaths was numerically higher in the two bevacizumab-containing arms than in the control (48% and 47% compared to 45% in the control arm). The vast majority of the deaths were attributed to breast cancer. Deaths clearly attributed to an adverse event were equal across the three arms. One patient in the 15 mg/kg bevacizumab arm died due to gastrointestinal perforation and one died due to pulmonary hemorrhage, adverse events that are clearly attributable to bevacizumab.

RIBBON 1 TRIAL (STN 125085/192)

RIBBON1 Trial has been submitted to support the following proposed indication (revisions to current indication underlined) for bevacizumab:

Metastatic breast cancer, <u>with taxane-based, anthracycline-based or capecitabine chemotherapy</u> for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

RIBBON 1 was a randomized, double-blinded, international study conducted in women with metastatic or locally recurrent HER 2- neu negative adenocarcinoma of the breast, who had not received prior chemotherapy for their advanced or metastatic cancer. Eligible patients were randomized (2:1) to receive bevacizumab or placebo in combination with either an anthracycline- or taxane-based chemotherapy or in combination with capecitabine. Choice of the chemotherapy was at the discretion of the investigator and was specified prior to randomization for use as a stratification variable.

- Anthracycline or taxane cohort:
  - Anthracycline or taxane plus placebo every 3 weeks
  - Anthracycline/taxane plus bevacizumab 15 mg/kg every 3 weeks
- Capecitabine cohort:
  - Capecitabine plus placebo every 3 weeks
  - Capecitabine plus bevacizumab 15 mg/kg every 3 weeks

Treatment continued until disease progression or unacceptable toxicity. The protocol allowed for unblinded treatment with bevacizumab plus chemotherapy of choice by the investigator for patients who experienced disease progression at the discretion of the investigator.

Randomization was stratified by choice of chemotherapy (taxane and/or anthracycline-based vs. capecitabine-based); disease-free interval (≤ 12 m vs. > 12 m since completion of adjuvant chemotherapy or definitive surgery if no adjuvant therapy), prior adjuvant chemo (yes vs. no) and number of metastatic sites (< 3 vs. ≥ 3).

Tumor assessment was performed at baseline, every 9 weeks up to week 36, and every 12 weeks thereafter until disease progression. Upon disease progression, patients were followed for survival every 3 months.

The primary efficacy endpoint was investigator-assessed PFS. Key secondary endpoints were overall response rate and overall survival. The overall type I error rates for the primary and secondary efficacy analyses were controlled (p 0.05, 2-sided) independently for the taxane and/or anthracycline-based chemotherapy cohort and for the capecitabine-based chemotherapy cohort.

Between December 2005 and July 2008, the study enrolled 1237 patients (622 in the taxane/anthracycline cohort and 615 in the capecitabine cohort) in US, Europe and the rest of the world.

Taxane/Anthracycline Cohort

Patient demographic and baseline characteristics were balanced between the arms. For the anthracycline/taxane cohort, the median age was 55 (range 28 - 88 years), 83 % of the subjects were white, 73% were post-menopausal, 82% had measurable disease at baseline, and 76% had ER or PR positive disease. Forty-five percent of the patients had received adjuvant chemotherapy (15% prior taxane, 30 % prior anthracycline).

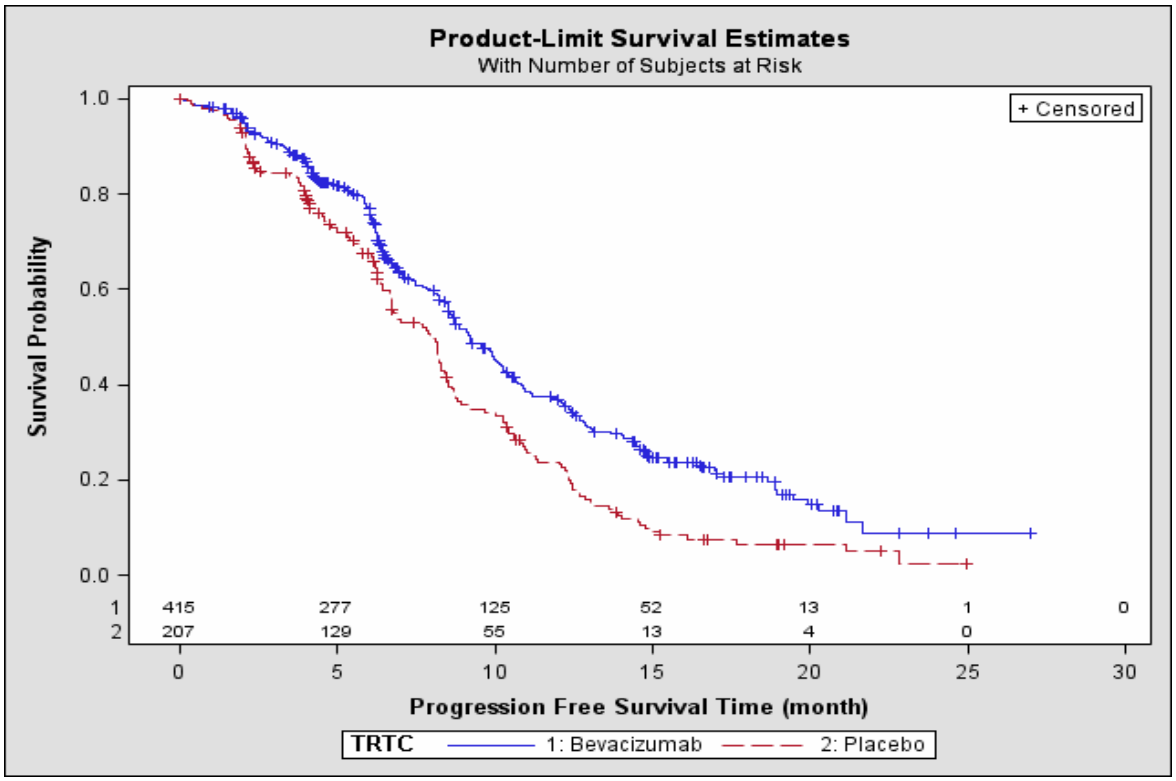
Of the 622 patients enrolled in the taxane/anthracycline cohort, 315 (50.6%) received anthracycline based chemotherapy and 307 (49.4%) received taxane based chemotherapy. Efficacy result for the taxane/anthracycline cohort is shown in the following table.

Table 6 - Ribbon 1 Trial Efficacy Results, Taxane/Anthracycline Cohort

	Taxane/Anthracycline + Placebo (n = 207)	**Taxane/Anthracycline + Bevacizumab (n = 415)**
PROGRESSION FREE SURVIVAL		
N with an event (%) Disease progression Death	160 (77.3) 149 11	249 (60.0) 217 32
Median	8.0 months	9.2 months
Hazard ratio (95% CI)	0.64 (0.52, 0.80)	
p–value (stratified log-rank)	< 0.0001	
OVERALL SURVIVAL		
No. of patients	207	415
No. of death (%)	89 (43.0)	189 (45.5)
Median	-	27.5 months
Hazard ratio (95% CI)	1.11 (0.86, 1.43)	
p-value (log rank)	0.44	
OBJECTIVE RESPONSE RATE		
No. of patients	177	345
N with objective response (%) Complete response Partial response	67 (37.9%) 5 (2.8%) 62 (35.0%)	177 (51.3%) 7 (2.0%) 170 (49.3%)
≠ in ORR (95% CI)	13.5% (4.6%, 22.3%)	
p-value	0.005	

The addition of bevacizumab to anthracycline- or taxane-based chemotherapy showed a statistically significant improvement in PFS with the hazard ratio favoring the bevacizumab-containing arm; the comparison of PFS for the anthracycline/taxane cohort yielded a HR of 0.64 (95% CI 0.52, 0.80). There was a difference of 1.2 months, also favoring the bevacizumab-containing arm at the Kaplan-Meier estimated median PFS.

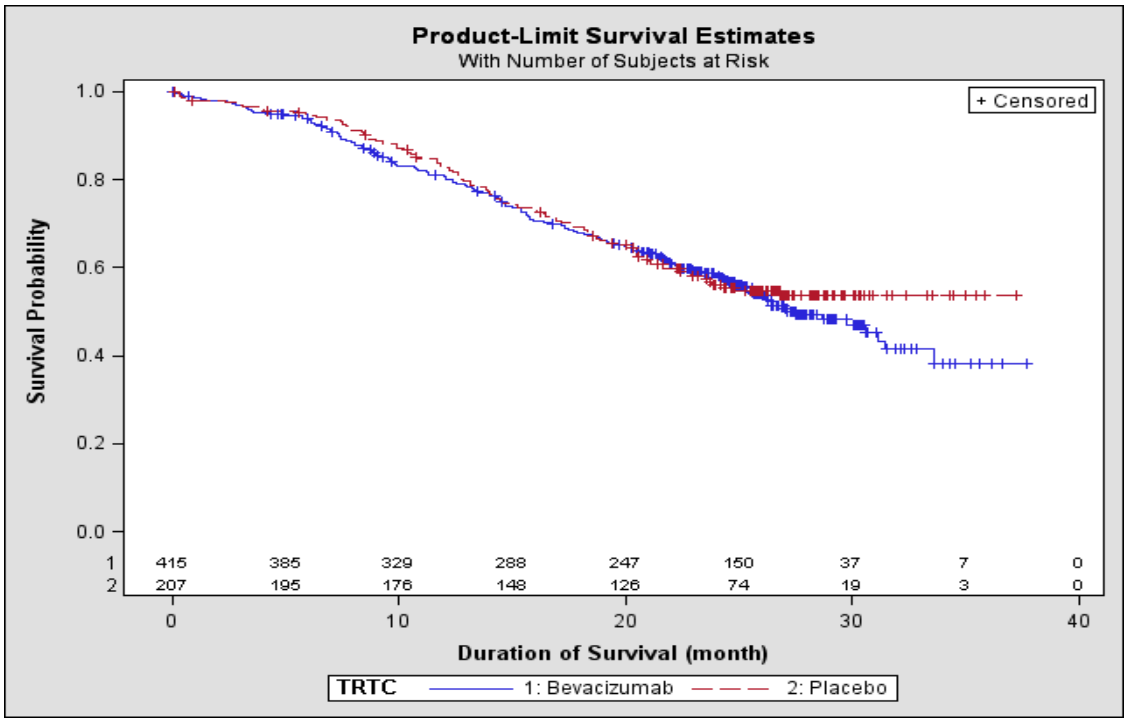
Figure 5. Kaplan-Meier Curve for Progression Free Survival
RIBBON1 Trial - Taxane/Anthracycline Cohort



There was a higher objective response rate, with an absolute increase of 13.5 % (95% CI 4.6, 22.3%) also observed with the addition of bevacizumab to anthracycline/taxane-based chemotherapy.

There was no survival benefit with the addition of bevacizumab to anthracycline or taxane based chemotherapy. Similar to AVADO trial, the mature survival analysis yielded a HR of 1.11 (95% CI 0.86, 1.43) favoring the placebo arm.

Figure 6. Kaplan-Meier Curve for Overall Survival
RIBBON1 Trial - Taxane/Anthracycline Cohort



Capecitabine cohort

Patient demographic and baseline characteristics in the capecitabine cohort were generally balanced between the two arms. The median age for the entire capecitabine cohort was 57 (range 23 - 91 years), 76% of the patients were white, 67% post-menopausal, 82 had measurable disease at baseline, and 76% had either ER and/or PR positive disease. More patients (73%) in the capecitabine cohort received prior adjuvant chemotherapy, with 40 % of the patients receiving taxane and 65% receiving an anthracycline in the adjuvant setting.

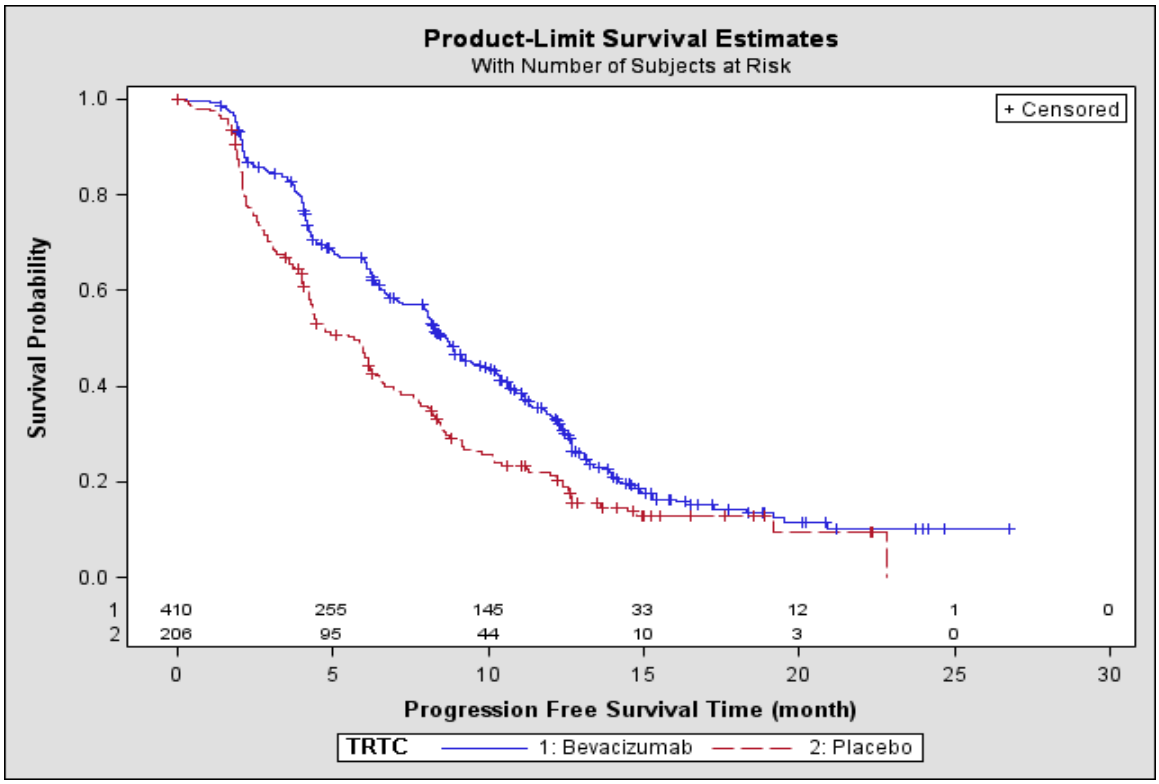
Table 7 shows the efficacy findings for the capecitabine cohort.

Table 7 - Ribbon 1 Trial: Efficacy Results, Capecitabine Cohort

	Placebo + Cap (N=206)	**Bevacizumab + Cap N = 409**
Progression Free Survival		
N with an event (%)	162 (78.6)	291 (71.1)
Disease progression	149	266
Death	13	25
Median (month)	5.7	8.6
Hazard ratio (95% CI)**	0.69 (0.56, 0.84)	
p–value (stratified log-rank)	< 0.0001	
Overall Survival		
No. of patients	206	409
No. of death (%)	99 (48.1%)	186 (45.5%)
Median (month)	22.8	25.7
Hazard ratio (95% CI)	0.88 (0.69, 1.13)	
p-value (log-rank)	0.33	
Objective Response		
No. of patients	161	325
N with objective response (%)	38 (23.6%)	115 (35.4%)
Complete response	1 (0.6%)	7 (2.2%)
Partial response	37 (23.0%)	108 (33.2%)
Difference in objective response rates (95% CI)	11.8% (3.4%, 20.2%)	
p-value	0.0097	

The addition of bevacizumab to capecitabine showed a statistically significant improvement in PFS with the hazard ratio favoring the bevacizumab-containing arm [HR 0.69 (95% CI 0.56, 0.84)].). There was a difference of 2.9 months, also favoring the bevacizumab-containing arm at the Kaplan-Meier estimated median PFS.

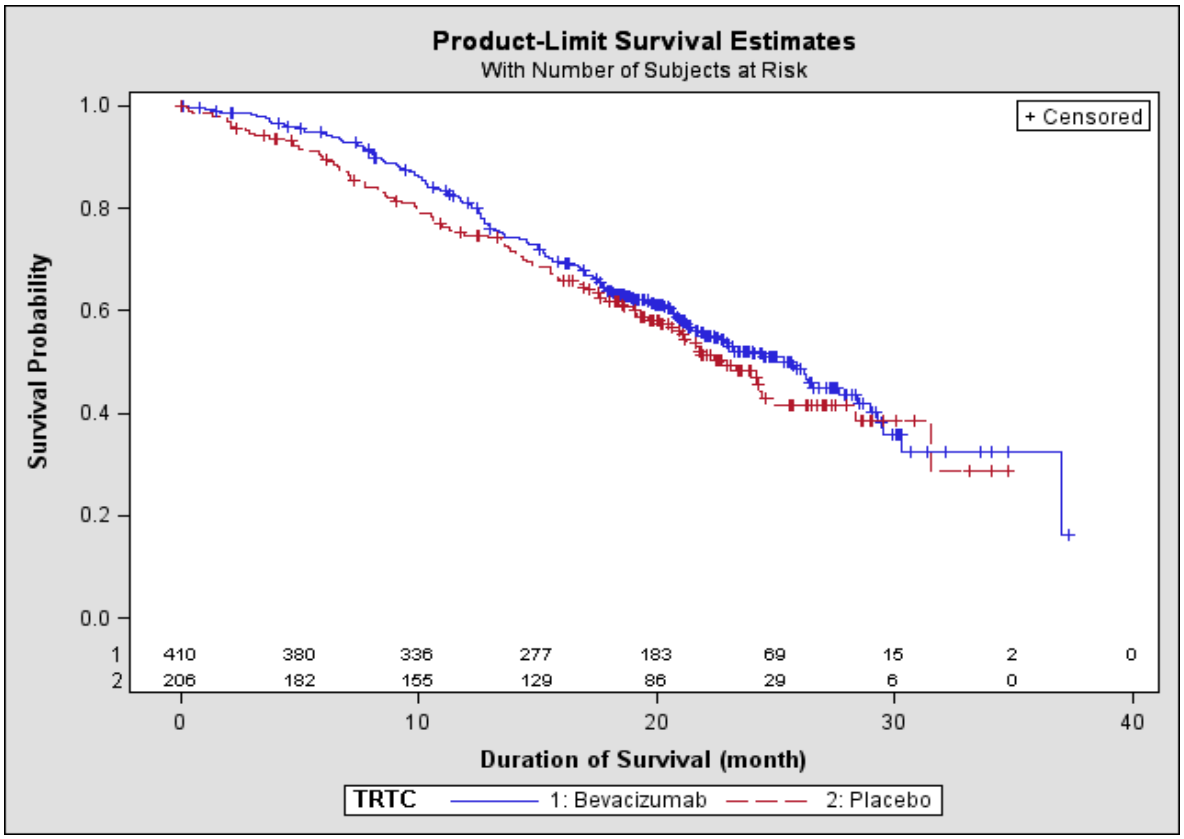
Figure 7. Kaplan-Meier Curve for Progression Free Survival
RIBBON1 Trial - Capecitabine Cohort



There was a higher objective response rate, with an absolute increase of 11.8 % (95% CI 3.4, 20.2 %) also observed with the addition of bevacizumab to capecitabine.

There was no survival benefit with the addition of bevacizumab to capecitabine. A comparison of the mature survival data for the capecitabine cohort showed a HR of 0.88 (95% CI 0.69, 1.13) favoring the bevacizumab-containing arm.

Figure 8. Kaplan-Meier Curve for Overall Survival
RIBBON1 Trial - Capecitabine Cohort



Safety Results

The RIBBON1 trial collected only selected AEs, serious AEs and AEs resulting in discontinuation of bevacizumab/placebo.

Safety overview and clinically significant adverse events are shown in table 8 and 9. The total number of AEs (collected), grade 3-5 AEs were twice as high in the bevacizumab arms compared to placebo arms in both cohorts.

Table 8 - Ribbon 1 Trial Safety Overview (grade ≥ 3)

	TAXANE		ANTHRACYCLINE		CAPECITABINE	
	Placebo N=102	**Bev N=203**	**Placebo N=100**	**Bev N=210**	**Placebo N=201**	**Bev N=404**
	%	**%**	**%**	**%**	**%**	**%**
Any AEs*	41.2	**63.1**	21.0	**39.0**	26.9	**40.1**
Grade 3-5 AE	38.2	**57.1**	15.0	**34.8**	22.9	**36.6**
AE leading to death	2.9	**5.4**	3.0	2.4	3.5	2.5
Serious AEs	26.5	**41.9**	16.0	**22.9**	20.4	**25.2**
AE leading to study drug (Bev/PL) discont.	8.8	**25.1**	4.0	**15.2**	11.9	12.6
All deaths*	43.1	**49.8**	44.0	41.0	48.3	45.8
Due to PD	37.3	**44.3**	40.0	39.0	44.3	41.1
Other	5.9	5.4	4.0	1.9	4.0	4.7

* Only selected AEs, serious AEs, and AE resulting in discontinuation of study drug were collected
* Avf3694g.CSR addendum: Feb 23, 2009 cutoff.; dataset (pat, pa,ae))

In the taxane/anthracycline cohort, taxane subgroup, there was slightly more deaths in the bevacizumab containing arm than placebo arm (49.8 % versus 43.1 %). The vast majority of the deaths were attributed to breast cancer. There was no significant difference in the incidence of deaths associated with adverse events in either cohort (Table 8).

In the taxane/anthracycline cohort, 5/16 deaths in the bevacizumab containing arm was directly or indirectly caused by gastrointestinal perforation, fistula and/or abdominal abscess. One patient died due to massive pulmonary hemorrhage. These AEs are most likely caused by bevacizumab. Other causes of death include sepsis (2) and pneumonia/respiratory failure (4).

In the capecitabine cohort, death due to myocardial infarction and/or cardiogenic shock occurred in 5/19 patients in the bevacizumab containing arm. Other causes of death include sepsis (3), unknown (4).

Table 9 - Ribbon 1 Trial Clinically Significant Adverse Events (grade 3-5)

	TAXANE		ANTHRACYCLINE		CAPECITABINE	
	Placebo N=102	Bev N=203	Placebo N=100	Bev N=210	Placebo N=201	Bev N=404
	%	%	%	%	%	%
Arterial thromboembolic event	0	**0.5**	1	**1.4**	1.5	**2.0**
Bleeding/hemorrhage	0	**5.4**	0	**1.0**	0.5	0.2
Febrile neutropenia	2.0	**8.4**	5.0	3.8	0	0
Fistula/GI perforation	2.0	**3.0**	0	0	0.5	0.2
Hypertension	2.0	**9.4**	0	**10.5**	1.0	**10.6**
LV systolic dysfunction	0	**2.5**	6	**6.2**	1	**1.5**
Neutropenia	4.9	**9.4**	4.0	**4.3**	1.0	**1.2**
Proteinuria	0	**4.4**	0	**2.9**	0	**2.2**
RPLS*	0	**0.5**	0	0	0	0
Venous thromboemb. event	4.9	**2.0**	1.0	**2.9**	3.5	**5.0**
Wound dehiscence	1.0	**1.5**	0	**1.0**	0	**0.7**

*RPLS - reversible posterior leukoencephalopathy syndrome
- Avf3694g.CSR addendum: Feb 23, 2009 cutoff.; dataset (pat, pat,ae))

Adverse events known to be caused by bevacizumab were, as expected, increased in the bevacizumab containing arms in both cohorts (Table 9). The most common AEs associated with bevacizumab were hypertension, bleeding/hemorrhage and febrile neutropenia.

Overall, the incidence of AEs is not significantly different than currently described in the Avastin® package insert.

IV. SUMMARY

The addition of bevacizumab to docetaxel (AVADO study) and to taxane/anthracycline-based chemotherapy or to capecitabine (RIBBON1 study) met the pre-specific primary endpoint, with a statistically significant improvement in PFS, however the magnitude of the PFS improvement is not clinically meaningful. The combination of bevacizumab to chemotherapy resulted in an overall increased in serious adverse events, grade 3-5 adverse events, and adverse events related to bevacizumab in both studies. Overall survival data showed hazard ratios favoring the placebo arms for AVADO study and RIBBON1 (taxane/anthracycline cohort), indicating an inferior outcome with the addition of bevacizumab to these chemotherapies.

AVADO and RIBBON 1 are well-conducted, double-blinded trials, with less missing data compared to E2100. The improvement in PFS observed in these two studies, as measured by the hazard ratio and as more commonly expressed by clinicians as the difference in median PFS between the treatment arms, failed to confirm the magnitude of

PFS improvement observed in the E2100 trial, the basis for the accelerated approval. The magnitude of treatment effect is clinically important because it is really a measure of delaying symptoms from tumor progression, which has to be weighed against drug toxicity that is present for the duration of treatment

The risk-benefit ratio of bevacizumab when added to the standard the chemotherapeutic regimens serving as standard of care in the AVADO and RIBBON1 studies may not be considered favorable. FDA seeks the Committee's advice on whether clinical benefit has been demonstrated in these applications.

PFS and OS results for E2100, AVADO and RIBBON1 are summarized in Table 10.

Table 10 - Key Efficacy Data: E2100, AVADO and RIBBON1

Study	Treatment regimen (s)	HR for PFS (95% CI) log-rank test	Median PFS control Arm (mos)	Difference in Median PFS (mos)	HR for OS (95% CI) log-rank test	Median OS Control Arm (mos)	Difference in Median OS (mos)
E2100	Paclitaxel+/- bevacizumab 15 mg/kg	0.48 (0.39, 0.61) p < 0.0001	5.8	5.5	0.87 (0.72, 1.05) p = 0.14	24.8	+ 1.7
AVADO	Docetaxel+/- bevacizumab 7.5 mg/kg	0.70 (0.55, 0.90) p < 0.005	7.9	0.8	1.103 (0.84, 1.45) p=0.48	31.9	- 1.1
	Docetaxel+/- bevacizumab 15 mg/kg	0.62 (0.48, 0.79) p < 0.0003	7.9	0.9	1.003 (0.76, 1.32) p= 0.98	31.9	-1.7
RIBBON	Taxane/Anthracycline+/- bevacizumab 15 mg/kg	0.64 (0.52, 0.80) p< 0.0001	8.0	1.2	1.1 (0.86, 1.43) p= 0.44	Not Reached	N/A
	Capecitabine+/- bevacizumab 15 mg/kg	0.69 (0.56, 0.84) p < 0.0001	5.7	2.9	0.88 (0.69, 1.13) p= 0.33	22.8	+ 2.9