FDA CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum to the File
BLA 125085 Avastin (bevacizumab)

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SUBJECT: Regulatory Decision to Withdraw Avastin (bevacizumab) First-line Metastatic Breast Cancer Indication

Summary

The Office of New Drugs (OND) recommends withdrawing approval of the breast cancer indication for bevacizumab (Avastin). This indication was approved on February 22, 2008, under accelerated approval provisions for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

As a condition of the accelerated approval, Genentech was required to submit data from two ongoing trials (AVADO and RIBBON1) to provide verification of the treatment effect on progression-free survival (PFS) and to provide additional information on the effects on overall survival (OS). These two trials failed to confirm the magnitude of benefit originally observed in the E2100 study on which accelerated approval was based. In addition, there was an overall increase in serious adverse events related to bevacizumab.

The modest benefit observed with Avastin together with the substantial adverse reactions observed in breast cancer trials to date fail to provide a favorable risk-benefit profile to support continued marketing of Avastin for a first-line metastatic breast cancer indication. It is the conclusion of OND that the breast cancer indication for Avastin be withdrawn.

Background

The Agency approved Genentech's biologics license application (BLA) for Avastin in February 2004 for first-line metastatic carcinoma of the colon and rectum. The Agency subsequently approved Avastin for second-line metastatic colorectal cancer; first-line unresectable, locally advanced, recurrent, or metastatic non-squamous, non-small cell lung cancer; metastatic renal cell carcinoma; glioblastoma (under accelerated approval); and metastatic HER2-negative breast cancer (under accelerated approval).

In 2009, an estimated 192,300 new cases of breast cancer and 40,000 deaths related to breast cancer occurred. Approximately 10% of patients will have metastatic disease at the time of diagnosis and nearly half of all patients treated for 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.

In 2008, Avastin in combination with paclitaxel received accelerated approval for the first-line treatment of metastatic breast cancer based on the results of study E2100. This trial was a randomized, multicenter, open-labeled trial of Avastin with paclitaxel or paclitaxel alone that enrolled patients with HER2 neu negative breast cancer who had received no previous chemotherapy for metastatic disease. E2100 utilized a prespecified primary endpoint of PFS as determined by investigators with overall response rate (ORR) and OS as secondary endpoints. The addition of Avastin to paclitaxel resulted in a reduction in the risk of disease progression (HR 0.48, 95% CI 0.39, 0.61; $p< 0.0001$) with an estimated 5.5-month difference in median PFS. There was no significant difference in OS between the two treatment arms. The ORR was higher with Avastin plus paclitaxel as compared to paclitaxel alone (48.9% versus 22.2%). The supplement containing the E2100 trial also contained the results of the AVF2119g trial, which was a randomized, open-label trial of capecitabine with or without bevacizumab in patients with disease progression after

both anthracycline- and taxane-based regimens. The AVF2119g trial failed to demonstrate statistically significant effects on PFS or on OS.

Results from the E2100 trial were presented to the Oncologic Drugs Advisory Committee (ODAC) on December 5, 2007. The ODAC expressed concern that the E2100 trial had shortcomings in design and conduct. In addition, ODAC questioned the clinical benefit of PFS without any evidence of an accompanying improvement in OS, symptom benefit or other direct clinical benefit parameter. ODAC voted 5 to 4 against approval. However, the magnitude of benefit attributed to the addition of Avastin to paclitaxel (median PFS difference of 5.5 months, HR 0.48) was considered to be clinical benefit by several of the ODAC discussants. In addition, the hazard ratio for OS in E2100 was 0.87 (95% CI 0.72, 1.05) indicating that a detrimental effect on OS was unlikely with the addition of Avastin to paclitaxel. FDA subsequently granted accelerated approval of the breast cancer indication based on the reported magnitude of the effect on PFS in the E2100 trial with the provision that additional data be provided to verify and describe Avastin's clinical benefit.

Confirmatory Trials

Under accelerated approval Genentech was required to conduct adequate and well-controlled studies (i.e., confirmatory trials) to verify and describe Avastin's clinical benefit. To provide this evidence, Genentech identified the AVADO and RIBBON1 trials. Both trials were in first-line treatment of metastatic breast cancer.

The addition of Avastin to docetaxel (AVADO trial) and to taxane/anthracycline-based chemotherapy or to capecitabine (RIBBON1 trial) showed a statistically significant improvement in PFS. In AVADO, the addition of Avastin 15 mg/kg to docetaxel yielded a reduction in the risk of disease progression (HR 0.62) compared to docetaxel alone with a difference of 0.9 months in estimated median PFS between the two arms. In the RIBBON1 trial, the addition of Avastin 15 mg/kg to taxane/anthracycline chemotherapy yielded a reduction in the risk of disease progression (HR 0.64) compared to docetaxel alone, with a difference of 1.2 months in the estimated median PFS between the two arms. In the capecitabine cohort of the RIBBON1 trial, the addition of Avastin 15 mg/kg to capecitabine yielded a reduction in the risk of disease progression (HR 0.69) compared to docetaxel alone, with a difference of 2.9 months in the estimated median PFS between the two arms. The differences in PFS observed in these trials, as measured by the hazard ratio or median PFS differences, failed to confirm the magnitude of the PFS treatment effect observed in the E2100 trial.

On July 20, 2010, the ODAC reviewed the results of the AVADO and RIBBON1 trials and voted 12 to 1 to recommend against the use of Avastin in combination with chemotherapy for first-line treatment of metastatic breast cancer and also recommended the withdrawal of the accelerated approval of the first-line breast cancer indication.

All four breast cancer trials (E2100, AVADO, RIBBON1, AVF2119g) using Avastin have failed to demonstrate a statistically significant prolongation of OS (please refer to Appendix A for survival curves). There has been a modest improvement in ORR (10-19%). In addition, claims of improvement in patient reported outcomes (e.g., improvement in disease-related symptoms, delay of symptom progression, health-related quality of life) are not supported by data submitted by the Sponsor. Clinical symptoms attributable to disease progression were not collected in the trials. Patients who entered the first-line metastatic disease trial (per eligibility criteria) were either

asymptomatic or had minimal symptoms providing little support to claims that the addition of Avastin improves disease-related symptoms in this population.

The addition of Avastin to standard chemotherapy regimens resulted in an overall increase in serious adverse events, grade 3 through 5 adverse events, and adverse events related to Avastin. Avastin-related toxicities include hypertension, bleeding/hemorrhage, wound healing complications including wound dehiscence, perforation and fistula/abscess formation. Other Avastin-related toxicities include arterial thromboembolic events (stroke, myocardial infarction), venous embolic events, febrile neutropenia, left ventricular dysfunction, and reversible posterior leukoencephalopathy. Avastin-related deaths were observed in 0.8 to 1.2% of patients entered on breast cancer trials. An analysis of toxicities from E2100 disclosed a 26% increase of grade 3 to 5 toxicities (i.e., severe adverse event, life-threatening adverse event, drug-related death) known to be associated with Avastin.

Conclusion

Accelerated approval was granted with the provision that the magnitude of improvement in PFS observed in E2100 would be verified in subsequent first-line breast cancer trials. At the time of accelerated approval, Genentech identified two trials (AVADO and RIBBON1) to provide this confirmation. These two trials failed to confirm the magnitude of benefit originally observed in E2100. The modest benefit observed in breast cancer trials to-date with the substantial adverse reactions observed in breast cancer trials fail to provide a favorable risk-benefit profile to support continued marketing of Avastin in a first-line metastatic breast cancer indication. The following issues are pertinent to the decision.

1. Presently, Avastin has been studied in four large randomized trials in breast cancer. No trial to date has demonstrated an improvement in OS. Based on consultation with ODAC in 1999, FDA has recommended that an improvement in OS be the regulatory endpoint for applications evaluating drugs and biological agents in the first-line setting in metastatic breast cancer. An improvement in OS is considered direct clinical benefit. None of the trials for initial treatment of metastatic disease (E2100, AVADO, RIBBON1) were reviewed by the Agency under a special protocol assessment and the Agency did not agree with the primary endpoint (PFS) prior to trial initiation. Recent approvals in the first-line setting of metastatic breast cancer, including trastuzumab plus chemotherapy (1998) and gemcitabine plus paclitaxel (2004), were supported by data indicating both OS and PFS improvements.

FDA has considered PFS as a surrogate endpoint of clinical benefit rather than a direct measure of clinical benefit. In granting accelerated approval for Avastin as a first-line treatment in metastatic breast cancer in the absence of an OS improvement, FDA demonstrated regulatory flexibility in its desire to make available promising drugs to patients with serious and life-threatening disease. As noted above, several ODAC consultants believed that the magnitude of improvement in this disease setting could be considered clinical benefit. The continued marketing of Avastin for the metastatic breast cancer indication was contingent upon either an improvement in PFS of a similar magnitude as noted in E2100 or an improvement in OS in the AVADO and RIBBON1 trials.

2. FDA considers additional measures of direct clinical benefit to include amelioration of disease-related symptoms, a delay in symptoms or improvement in patient-reported outcomes, including health-related quality of life measures. No evidence has been provided by Genentech that Avastin improves patient symptoms or patient-related outcomes. Genentech has not provided

evidence that the addition of Avastin delays progression of disease-related symptoms in breast cancer.

3. FDA has received numerous testimonials from patients and families attesting to the benefit of Avastin in the treatment of individual patients with breast cancer. For the indication under consideration, Avastin is added to conventional chemotherapy, which makes it very difficult to isolate the effect of Avastin outside of a controlled setting. While it is possible that some patients may receive clinical benefit from Avastin for treatment of breast cancer, the available data are not sufficient to demonstrate that such a subgroup exists and, if so, how to identify the patients in advance.

4. FDA has accepted regulatory endpoints using radiographic measures to approve drugs in other disease settings, including refractory (second and third-line) metastatic breast cancer. These endpoints include PFS and ORR. Approximately 80% of events used in the determination of progression in the first-line breast cancer trials (E2100, RIBBON1, AVADO) were on the basis of measurable disease determined primarily by radiographic examinations. Since these changes in radiographic endpoints are indirect measures of clinical benefit, an improvement in PFS must be robust, and be of sufficient magnitude to demonstrate a favorable risk/benefit analysis in relation to the observed adverse event profile, disease setting, and available therapies.

5. Due to the indirect relationship of an improvement in PFS to clinical benefit and the subjectivity in evaluating radiographs, FDA informed Genentech that the magnitude of improvement noted in the E2100 trial would need to be confirmed in additional trials. FDA had previously evaluated the AVF2119g trial in second and third-line metastatic breast cancer and was aware that this trial did not demonstrate an improvement in PFS or OS.

6. The evaluation of PFS in E2100 was based on an interim analysis. E2100 was stopped early when 65% (357/546 of the planned events had occurred). Stopping a trial early for efficacy based on an event-driven, pre-planned analysis with pre-specified allocation of type I error ensures that a valid statistically significant result has been obtained. However, the estimate of the treatment effect based on an interim analysis is more variable than at the study completion and may represent a “random high” estimate of the true effect size of Avastin in that trial. In contrast, nearly all the planned events were observed in the AVADO and RIBBON1 trials and the trials were not stopped early. Although all three trials demonstrate a statistically significant result for PFS, it is possible that the magnitude of effect observed in the E2100 based on the interim analysis represents a random high and that the true effect is more consistent with the smaller effect seen in the other trials.

7. The randomized “add on” design of the four trials in breast cancer allowed the evaluation (isolation) of Avastin effect from the chemotherapy regimens. These chemotherapy regimens included anthracycline or taxane-based chemotherapy, gemcitabine, vinorelbine, and capecitabine. In 2008, Genentech proposed the AVADO and RIBBON1 be used to confirm the observed 5.5 month improvement in PFS noted in E2100 with the expectation that the observed effect of Avastin on PFS would be consistent irrespective of the chemotherapy regimen. Assertions that there is a unique interaction between Avastin and paclitaxel providing a rationale for the magnitude of PFS change observed only in E2100 has not been substantiated by either clinical or non-clinical evidence.

8. Genentech is encouraged to further develop Avastin in breast cancer to identify patient subsets who are likely to benefit in a risk/benefit evaluation. No current subgroup analyses have

demonstrated this evidence. We strongly urge Genentech to submit future trials under special protocol assessments to ensure agreement with the Agency.

9. A comprehensive understanding of Avastin's effect on PFS, ORR, OS, toxicity, and risk/benefit analysis in breast cancer has become evident since the accelerated approval in 2008. Excluding the PFS results of E2100, the results of the remaining three trials of Avastin (first and second-third line breast cancer populations) are consistent and indicate that when Avastin is used with chemotherapy in breast cancer there is a modest effect on PFS and ORR with substantial increases in toxicity without a demonstrated improvement in OS or symptom benefit.

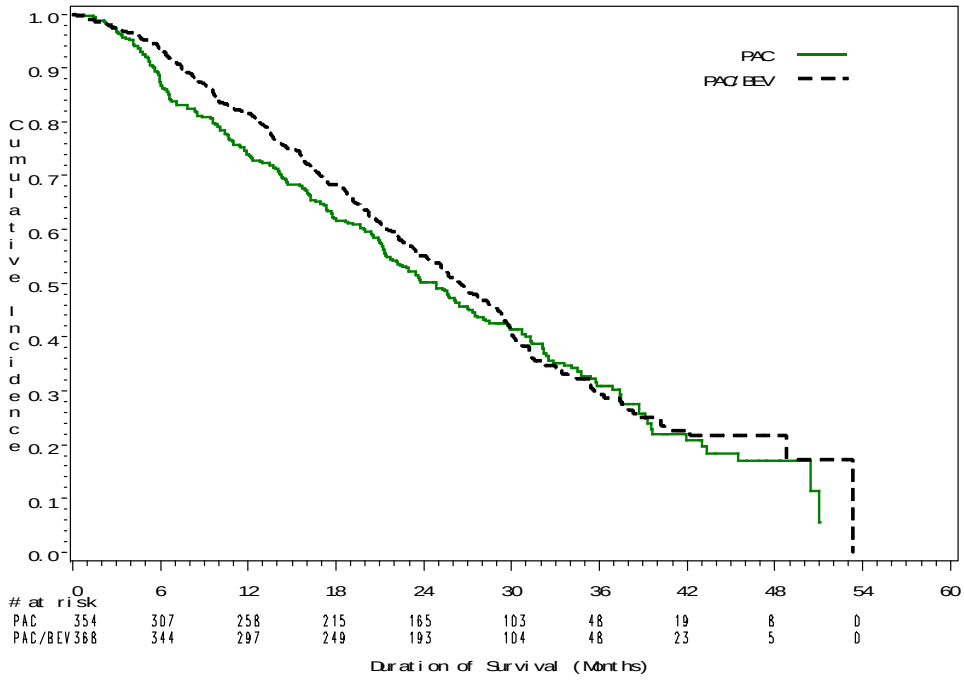
No trial in breast cancer using Avastin provides evidence of direct clinical benefit. Modest effects on primarily radiographic outcomes were demonstrated. These modest indirect measures of clinical benefit must be weighed against a marked increase in clinically serious, life-threatening and disabling adverse events and therapy-related deaths. Deaths attributed to Avastin ranged between 0.8 to 1.2%.

The main goals of therapy for breast cancer are palliation of symptoms and prolongation of overall survival time without negatively impacting quality of life. After reviewing data from the four studies described above, the Agency concluded that women who took Avastin did not live any longer than women who did not receive the drug, and yet were at risk of experiencing severe side effects, including side effects that are unique to this drug and death.

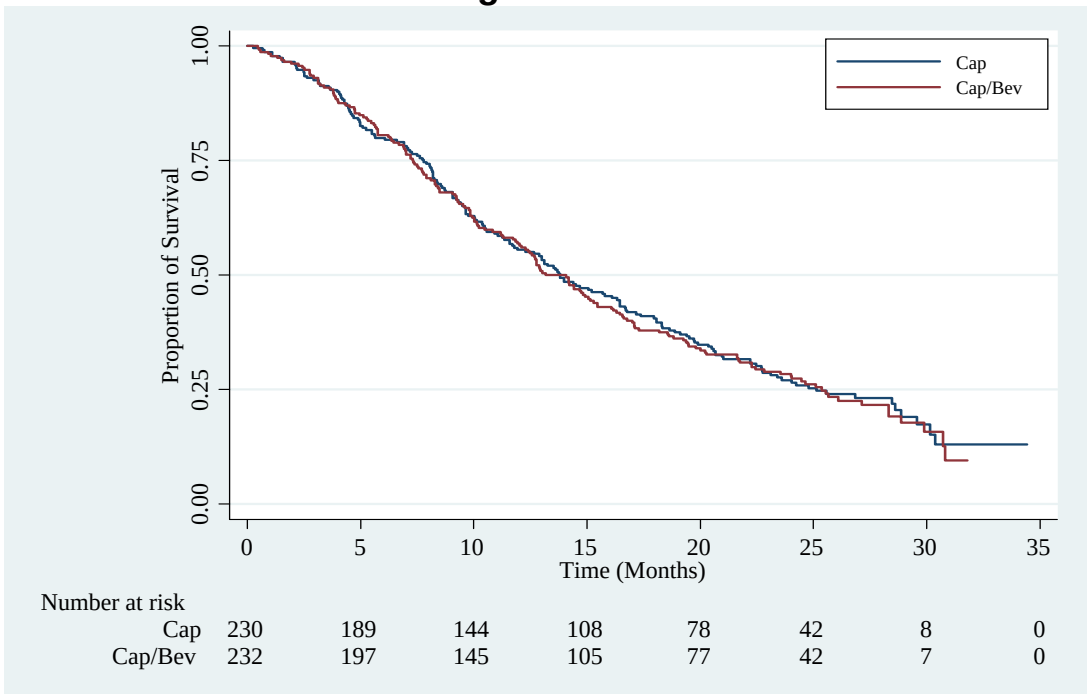
Given the increase in toxicity, lack of direct clinical benefit, and failure to confirm the initial magnitude of PFS improvement noted in E2100, a favorable risk/benefit has not been demonstrated. Accordingly, OND proposes to withdraw approval of Avastin's breast cancer indication.

APPENDIX A. Survival Curves for Avastin Clinical Trials

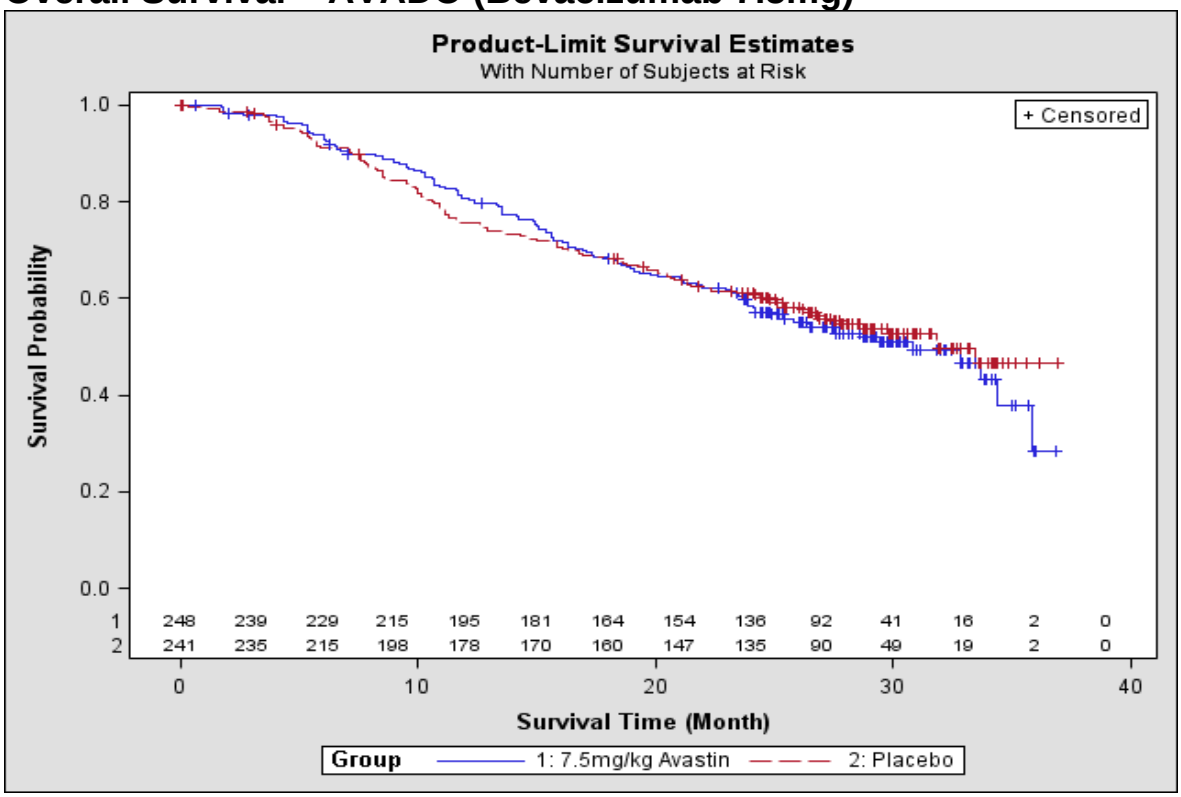
Overall Survival - E2100



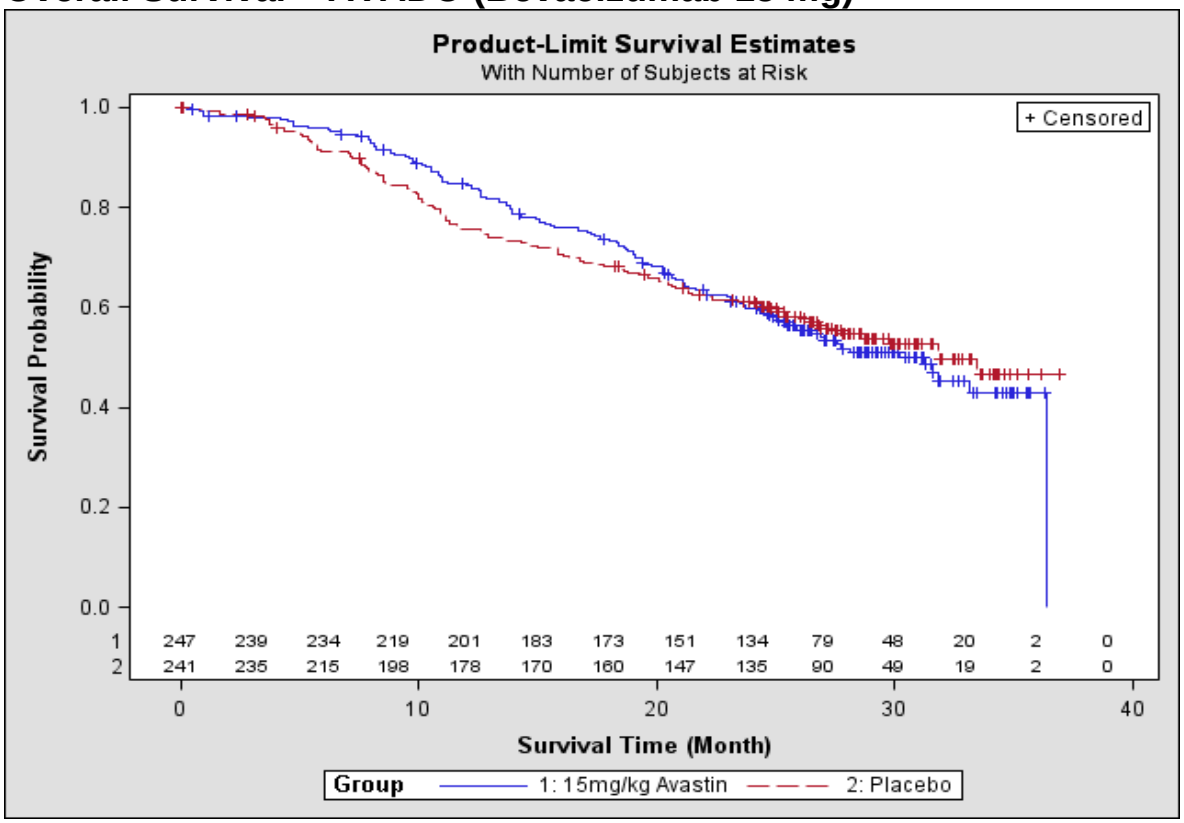
Overall Survival - AVF2119g



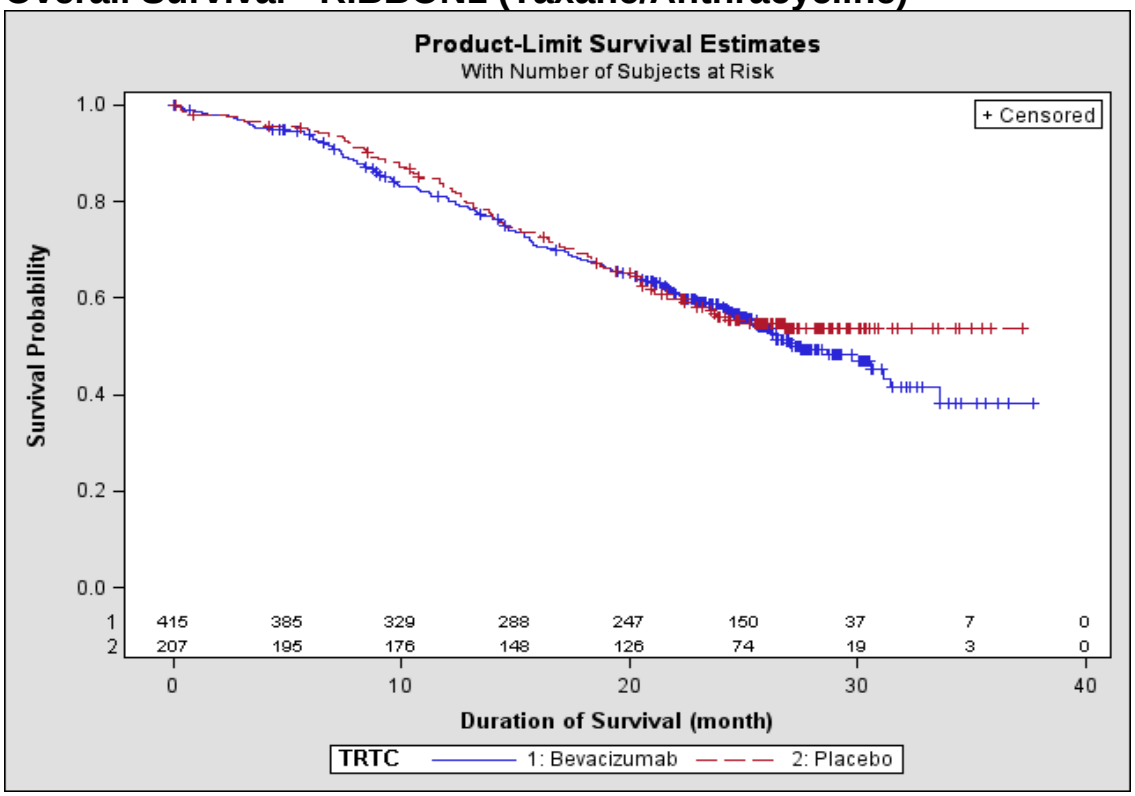
Overall Survival – AVADO (Bevacizumab 7.5mg)



Overall Survival – AVADO (Bevacizumab 15 mg)



Overall Survival - RIBBON1 (Taxane/Anthracycline)



Overall Survival - RIBBON1 (Capecitabine cohort)