Overview of the AVADO and RIBBON-1 Clinical Trials

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Author's disclosures of potential conflict of interest are found at the end of this article.

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Breast cancer is the most common female cancer and the second most common cause of female cancer-related death in the United States. Despite advances in the treatment of early-stage breast cancer, approximately one-third of patients will eventually develop metastatic breast cancer (MBC). It is a disease composed of multiple subgroups characterized by their pathophysiologic features, outcomes, and responses to treatment. Advances in the understanding of the biology of breast cancer have led to the classification of breast tumors based on their molecular features and the introduction of targeted therapies for the treatment of MBC (Lorusso, 2008).

Since 2010, there has been considerable debate involving one particular targeted therapy, bevacizumab (Avastin). Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of vascular endothelial growth factor. The role of bevacizumab as first-line metastatic therapy has been evaluated in three randomized phase III clinical trials: E2100, AVADO, and RIBBON-1.

In 2008, the US Food and Drug Administration (FDA) granted conditional, accelerated approval of bevacizumab in combination with paclitaxel for the first-line treatment of HER2-negative MBC. This was granted on the basis of significantly prolonged progression-free survival (PFS) with the addition of bevacizumab to paclitaxel in the randomized, phase III Eastern Cooperative Oncology Group (ECOG) E2100 trial. This trial enrolled 722 patients with MBC who were randomized to receive paclitaxel with or without bevacizumab. Paclitaxel plus bevacizumab significantly prolonged PFS as compared to paclitaxel alone (median 11.8 vs. 5.9 months; hazard ratio [HR] for progression, 0.60; $p < .001$) and increased the objective response rate (36.9% vs. 21.2%, $p < .001$). The median overall survival (OS) was similar in both groups (26.7 and 25.2 months, respectively; HR, 0.88; $p = .16$) (Miller et al., 2007). E2100 was considered a landmark study that demonstrated benefit from the addition of bevacizumab to conventional chemotherapy in MBC.

At the time of the accelerated approval, the manufacturer of bevacizumab agreed to provide further data when they became available. The decision to grant accelerated approval was considered controversial because it was based on PFS and not OS. The FDA justified its decision because PFS had already been utilized as the primary endpoint for the approval of chemotherapy and endocrine therapy for MBC patients (Burstein, 2010).

AVADO

The AVADO (AVAstin and DOcetaxel in Metastatic Breast Cancer) trial investigated docetaxel (100 mg/m^2) alone or with two different doses of bevacizumab (7.5 mg/kg and 15 mg/kg every 3 weeks) as first-line therapy for patients with HER2-negative locally advanced or MBC. This was a randomized, double-blind, placebo-controlled, phase III study that included 736 women. At progression, the patients in the single-agent docetaxel arm could cross over to bevacizumab in combination with a number of other chemotherapy agents. Compared to placebo, PFS was superior in both bevacizumab arms; the 15-mg/kg arm was more favorable than the 10-mg/kg arm (median 10.0 months [15 mg/kg], HR = 0.67; p = .0002 and 9.0 months [7.5 mg/kg], HR = 0.80; p = .0450 vs. 8.1 months in the docetaxel alone arm) (Ocana et al., 2011). There was no difference in OS among the three arms.

RIBBON-1

The RIBBON-1 (Regimens In Bevacizumab for Breast ONcology) study is also a randomized, placebo-controlled, double-blind, phase III clinical trial exploring the efficacy and safety of bevacizumab in combination with capecitabine (Xeloda)-, taxane-, or anthracycline-based chemotherapy as first-line treatment for HER2-negative MBC. This trial enrolled 1,237 patients, with a 2:1 randomization to receive either placebo or bevacizumab at 15 mg/kg, administered every 3 weeks.

Those patients with disease progression in the blinded phase of the study were eligible for bevacizumab in combination with second-line chemotherapy chosen by the investigator. The trial revealed similar results in PFS, as seen in the previous two trials. Compared to the placebo group, the PFS HR with bevacizumab was 0.688 (95% confidence interval [CI] = 0.564 to 0.840) in the capecitabine group and 0.644 (95% CI = 0.522 to 0.795) in the pooled taxane and anthracycline group. As with the E2100 and AVADO trials, the response rate improved by 11.8% (capecitabine), to 12% (anthracyclines) and to 15% (taxanes) (Robert et al., 2009). Again, there was improvement in PFS, but no improvement in OS. Table 1 compares results from all three studies discussed here.

Across the clinical trials listed here, the bevacizumab-related adverse events were similar and included hypertension, proteinuria, thromboembolic events, cardiotoxicity, wound-healing complications, hemorrhage, and gastrointestinal perforation. The adverse events were generally mild to moderate and manageable with standard medications and rarely required discontinuation of therapy. Table 2 compares toxicities across the three trials.

Table 1. Phase III Trials With Bevacizumab in Metastatic Breast Cancer

Trial	Agent(s)	PFS	*p* Value	OS	ORR
E1200	Paclitaxel + bevacizumab	11.8 mo	< .0001	26.7 mo	36.9%
	Paclitaxel	5.9 mo		25.2 mo	21.2%
AVADO	Docetaxel + bevacizumab (15 mg/kg)	10 mo	.0002	30.2 mo	64%
	Docetaxel + bevacizumab (7.5 mg/kg)	9 mo	.0450	30.8 mo	55%
	Docetaxel + placebo	8.1 mo		31.9 mo	46%
RIBBON-1	Capecitabine + placebo	5.7 mo		No difference in OS	23.6%
	Capecitabine + bevacizumab	8.6 mo	< .0002		35.4%
	Taxane/anthracycline + bevacizumab	9.2 mo	< .0001		51.3%
	Taxane/anthracycline + placebo	8.0 mo			37.9%

Note. ORR = overall response rate; OS = overall survival; PFS = progression-free survival. Information from Chan et al. (2010) and Robert et al. (2010).

Clinical Implications

How do we translate these data into clinical practice? In July 2010, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 12 to 1 to remove the metastatic breast cancer indication from bevacizumab's label, stating that the AVADO and RIBBON-1 trials "failed to confirm the magnitude of benefit" in PFS observed in E2100 (Pazdur, 2010).

In December 2010, the FDA announced that it would recommend removing the breast cancer indication from the label for bevacizumab because the drug had not been shown to be safe and effective for that use. The FDA indicated that the drug neither prolonged overall survival in breast cancer patients nor provided a sufficient benefit in slowing disease progression to outweigh the significant risk to patients. These risks include severe hypertension; bleeding and hemorrhage; the development of perforations in the body, including in the nose, stomach, and intestines; and heart attack or heart failure (FDA, 2011).

In January 2011, Genentech submitted its response (and supporting documentation) to the FDA's Notice of Opportunity for a Hearing on the administration's proposal to withdraw approval of the metastatic breast cancer indication for bevacizumab. At this time and until the conclusion of proceedings with the FDA, Avastin remains approved for use in combination with paclitaxel for the first-line treatment of HER2-negative MBC in the United States (Genentech, 2011). Of note, the National Comprehensive Cancer Network (NCCN) has affirmed its existing recommendation of bevacizumab in combination with paclitaxel as a preferred combination, a designation that reflects "balance of efficacy, toxicity, and treatment schedules of the drugs." (NCCN, 2010). Advanced practitioners in oncology should realize that even if the FDA removes its approval, bevacizumab may continue to be used off-label, which could potentially affect third-party reimbursement.

Summary

There have been significant advances in recent years in the treatment of breast cancer. These accomplishments have been led by the introduction of targeted therapies. We need to gain a better understanding of the molecular mechanisms so that personalized decisions about the use of bevacizumab or other targeted agents may be made. Until the FDA's final decision, bevacizumab remains approved for use with paclitaxel

Table 2. Clinically Significant Adverse Events[a]

Trial	Agent(s)	ATE	Bleeding	FN	HTN	Proteinuria
E2100	Paclitaxel + bevacizumab	3.0%	2.3%	0.3% (grade 4)	16%	0.8% (grade 4)
	Paclitaxel	0%	0.3%	0%	1.4%	0%
AVADO	Docetaxel + bevacizumab (15 mg/kg)	0%	55%	18%	22%	8%
	Docetaxel + bevacizumab (7.5 mg/kg)	0%	54%	16%	14%	2%
	Docetaxel + placebo	0.4%	29%	12%	10%	2%
RIBBON-1	Capecitabine + bevacizumab	20%	2.0%	0%	10.6%	2.2%
	Capecitabine + placebo	1.5%	1.5%	0%	1.0%	0%
	Taxane + bevacizumab	0.5%	5.4%	8.4%	9.4%	4.4%
	Taxane + placebo	0%	0%	2%	2.0%	0%
	Anthracycline + bevacizumab	1.4%	1.0%	3.8%	10.5%	2.9%
	Anthracycline + placebo	1.0%	0%	5.0%	0%	0%

Note. ATE = arterial thromboembolic events; FN = febrile neutropenia; HTN = hypertension. Information from Chan et al. (2010), Robert et al. (2010), and Miller et al. (2007).
[a]All grades unless noted.

in first-line treatment of HER2-negative MBC.

Update: As we go to press, the FDA has just held a public hearing to consider an appeal of its December 2010 decision to remove the breast cancer indication for bevacizumab. Following the June 28/29 hearing, ODAC again recommended that the FDA reverse its earlier accelerated approval of bevacizumab in combination with paclitaxel for treatment of HER2-negative metastatic breast cancer. A final decision regarding bevacizumab's indication in metastatic breast cancer will be determined by FDA Commissioner Margaret Hamburg.

DISCLOSURE

The author has no conflicts of interest to disclose.

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