Avastin’s Uncertain Future in Breast Cancer Treatment

By Renee Twombly

At the December 2010 San Antonio Breast Cancer Symposium, more than 600 attendees voted on whether the Oncologic Drugs Advisory Committee (ODAC) of the U.S. Food and Drug Administration was right when it voted 12–1 last July to revoke approval of Avastin (bevacizumab) for first-line use in metastatic breast cancer.

The outcome reflected the divisions in the oncology community at large over whether the world’s top-selling cancer drug should be approved for late-stage breast cancer: 37% of attendees agreed with revoking approval, 42% disagreed, and 21% were undecided.

The vote came just 1 week before the FDA started to officially revoke Avastin’s approval. According to Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research, “The limited effects of Avastin combined with the significant risks led us to this difficult decision.”

Genentech, Avastin’s manufacturer, has appealed the decision, citing the roughly 15,000 American women annually who are diagnosed with metastatic HER-2-negative breast cancer use the drug. The FDA has set a hearing on the appeal for June 28-29. The company has proposed a new clinical trial to retest Avastin in combination with weekly paclitaxel—which would essentially mimic the trial that led to initial FDA approval of the drug. Genentech also recommends that patients who have been using Avastin with paclitaxel continue to take Avastin.

Continental Divide

The same day the FDA decided to revoke Avastin’s approval, the agency’s European counterpart, the European Medicines Agency, judged the drug to be beneficial in combination with weekly paclitaxel. But the European agency also stated that Avastin in combination with other chemotherapies showed no benefit and that its use should not be expanded.

Some leading oncologists, however, defend Avastin. They say that the drug delays recurrence more than other drugs do. Furthermore, they argue, chemotherapy drugs have been approved that show even shorter progression-free survival (PFS) times and greater toxicity than has occurred with Avastin.

“If they pull it, patients will have one [fewer] option to discuss with their physicians, an option of an agent that has been demonstrated to improve response, delay tumor progression, and improve 1-year survival,” said oncologist Edith Perez, M.D., of the Mayo Clinic in Jacksonville, Fla. (Perez was an investigator in two of the three trials testing Avastin as first-line treatment in metastatic breast cancer.)

Other oncologists suggest that the high cost of the drug, $88,000 per year, influenced the FDA’s decision, especially against the backdrop of a national health care debate that has underscored the high cost of cancer drugs—even though by law, the FDA cannot consider cost in the drug approval process. As Eric Winer, M.D., director of the Breast Oncology Center at Boston’s Dana–Farber Cancer Institute, said, “What would have happened if the drug costs $6,000? There are benefits associated with Avastin, and the risks are fairly modest. But some argue that the net benefit is not worth the cost of this expensive drug.”

Some breast cancer advocacy groups are also wary of the high cost of drugs compared with the drugs’ relative benefit. “Unfortunately, we seem to be moving toward higher drug prices and diminishing benefit. Cancer therapies are becoming increasingly expensive and a drain on health care resources, without necessarily providing meaningful benefit,” said Fran Visco, president of the National Breast Cancer Coalition. The coalition applauded the FDA’s decision to revoke approval of Avastin.

Changing the Rules Midgame?

Genentech applied for accelerated approval for Avastin on the basis of findings from the phase III E2100 Eastern Cooperative Oncology Group study of 722 patients, which the New England Journal of Medicine published in 2007. The study found that patients treated with Avastin and paclitaxel had a PFS time of 11.8 months, compared with 5.9 months for patients treated with chemotherapy alone. One-year survival rates increased, whereas overall survival rates did not. Although the ODAC voted then 5–4 not to grant accelerated approval, the FDA approved the drug in 2008, under the condition that two other ongoing trials confirm the PFS benefit reported in E2100.

The two trials did confirm that Avastin improved PFS, but only modestly compared with the effect in E2100. The findings showed no statistically significant increase in overall survival rate. The disappointing results ultimately led to the ODAC’s 12–1 vote last July to revoke approval for Avastin.

Both trials were phase III, multicenter international trials that Genentech sponsored. The Avado trial tested different...
doses of Avastin with docetaxel compared to women receiving docetaxel alone. In results presented at the 2008 American Society of Clinical Oncology meeting—findings that the FDA already knew when it granted approval—researchers found that a higher dose of Avastin with docetaxel improved PFS by 24 days: 9 months compared with 8.2 months for the docetaxel group alone. A later analysis published May 24, 2010, in the *Journal of Clinical Oncology* showed a PFS difference of almost 2 months but no increase in overall survival.

The RIBBON-1 study tested Avastin with an investigator-chosen chemotherapy in 1,237 women. The findings, presented at the 2009 American Society of Clinical Oncology meeting, showed that Avastin improved PFS by 2.9 months when added to capecitabine and by 1.2 months when added to anthracycline-based chemotherapy. Overall survival did not increase, but the investigators said that was not a primary endpoint—even if overall survival is normally the “gold standard” measure in clinical trials. FDA representatives cited lack of overall survival in the Avastin studies in the agency’s decision to revoke the drug last December.

“None of the studies demonstrated that patients receiving Avastin lived longer, and patients receiving Avastin experienced a significant increase in serious side effects,” said FDA’s Woodcock.

But according to Genentech, the only basis for full approval was improved PFS. Phillepe Bishop, M.D., global head of clinical development for Avastin, said drug approval was contingent on proof that “Avastin continues to provide an effect on PFS, with adequate safety information coming from those studies, and no detriment on overall survival. We’re very mindful that none of those studies were designed to adequately assess an effect on overall survival.” He added that Avastin was approved for kidney cancer on the basis of PFS. (See sidebar for Avastin’s approval for other tumor types.)

In its written response to the FDA decision, Genentech reiterated that “FDA still has not articulated clearly what magnitude of improvement in median PFS or risk reduction in disease progression it will consider adequate to establish clinical benefit, thereby creating uncertainty for sponsors and potentially discouraging oncology innovation.”

**Mixed Reactions**

Some oncologists argue against overall survival as a measure of drug efficacy in diseases such as metastatic breast cancer. They say that few drugs used today in this setting show an overall survival benefit. Furthermore, they say so many drugs are used in advanced cancers that the effect of a single drug is diluted. “Gauging overall survival in studies like Avado and RIBBON-1 would have been impossible because patients were allowed to cross over to use of Avastin,” said Perez.

The degree of toxicity that occurred in the Avastin trials was also a point of contention. The FDA argued that patients using Avastin were at greater risk of experiencing severe side effects, including high blood pressure; bleeding; perforations of the stomach and intestines; organ damage and failure; swelling of the brain; and heart attack or heart failure.

But some oncologists say cancer patients with many types of tumors have tolerated the drug well. Gabriel Hortobagyi, M.D., chair of the department of breast medical oncology at the University of Texas M. D. Anderson Cancer Center in Houston, said that almost 90,000 patients have tolerated the drug in the past few years. “Why is it all just sounding much more toxic for breast cancer than for anything else?” he asked.

“Despite all the hullabaloo about severe toxicity, it is a very well-tolerated agent, and what you see on paper has been largely blown out of proportion—mostly by people who have never used the drug.”

Others surmise that the FDA didn’t agree with the design of the Avastin studies. “The problem is that the FDA, as far as I can tell, didn’t like those study designs, which were based on the idea that if Avastin works for one cancer, maybe it will work for others,” said oncologist Hope Rugo, M.D., director of the breast oncology clinical trials program at the University of California, San Francisco.

“They didn’t like the way the approval was originally obtained, and then it’s a really expensive drug that didn’t improve survival,” she said. “So the thinking overall was, well, do we really need this drug?”

**Assigning Blame**

ODAC member Gary Lyman, M.D., director of comparative effectiveness and outcomes research at the Duke Comprehensive Cancer Center, said that

---

**Avastin’s Steep Trajectory of Approval**

Avastin, a monoclonal antibody, blocks VEGF-A (vascular endothelial growth factor A), which contributes to the growth of new blood vessels that feed tumors.

- **2004:** Approved as first-line therapy for advanced colorectal cancer. A study showed a 52% approval in overall survival. Median survival was 20.3 months in patients who received it in combination with chemotherapy, compared with 15.6 months in patients treated with chemotherapy alone. Both groups had previously untreated metastatic colorectal cancer.
- **2006:** Approved as second-line therapy for colon cancer and first-line therapy for nonsquamous, non-small-cell lung cancer.
- **2008:** Granted accelerated approval for metastatic breast cancer.
- **2009:** Approved as first line therapy for metastatic renal cell carcinoma (kidney cancer). A trial showed a 67% improvement in progression-free survival (PFS; 10.2 vs. 5.4 months) in previously untreated patients treated with the drug in combination with interferon α versus interferon α alone. Also in 2009, Avastin was given accelerated approval for glioblastoma that had progressed following prior therapy, on the basis of a study showing a 25.9% response rate.
- **2010:** FDA retracted approval for metastatic breast cancer. Genentech has appealed the decision.
- **2013:** Expected results from a phase III clinical trial for glioblastoma with co-primary endpoints of both PFS and overall survival.
legitimate concerns about FDA’s decision have emerged. “This was probably the most difficult series of votes and actions since I have been a member of ODAC,” he said.

Lyman was the only ODAC member to vote against revoking approval in July. “My preference was to extend the conditional approval pending more data and more time. I think we all recognize this drug does have activity,” Lyman said. “The question is of magnitude and balance of benefit and harm. With longer follow-up, the hope was that [PFS] might translate into overall survival.”

Looking at the decision from Genentech’s standpoint, Lyman said, “the FDA does tend to change the rule a little bit along the path,” adding that the changing membership of ODAC means “different eyes and minds may view things differently.”

Genentech, in its official complaint to the FDA, is asking for “an objective advisory committee with substantial breast cancer expertise,” saying that the previous ODAC group had only modest breast cancer expertise.

“This saga is a great example of the unpredictability of the FDA drug approval process,” said Hortobagyi. “I hope this event is going to lead to a more open discussion about what the FDA’s role should be in drug development and approval, what should be the expectations, and what can be a transparent and predictable system that sponsors and the FDA can follow so that there are no surprises at the end.”

Root of the Problem?
Some oncologists fault the underlying science behind drug development. Without a way to identify who will benefit from targeted therapies such as Avastin, overall benefit will always be murky, they say, and attempts to develop a predictive biomarker test for Avastin have failed.

“Where much of this controversy is leading is [that] here we have a drug that is clearly effective but it is clearly not effective on all patients. And the major problem is that none of us—including the sponsor, including the FDA—have a marker that helps us select whom we should give it to and whom we should not give it to,” Hortobagyi said, adding that every new targeted agent should be developed in parallel with a molecular diagnostic to predict benefit.

Martine Piccart-Gebhart, M.D., Ph.D., of the Institute Jules Bordet in Brussels, Belgium, agrees. She was one of the moderators at the San Antonio meeting where the audience voted on Avastin. “We are responsible for this situation,” she said after the split vote was revealed. “A lot of money and a waste of energy have been spent on nothing, and unless we revise fundamentally the way we do our work, we will be nowhere in 10 years.”

Avastin will continue to be available for use in metastatic breast cancer while the appeals process is under way.

Dr. Piccart-Gebhart has served in an advisory or consulting capacity to Roche.