Avastin Hearing Leads to More Uncertainty Over Drug’s Future

By Merrill Goozner

In what could evolve into a major challenge to the U.S. Food and Drug Administration’s plans to require improvement in overall survival when confirming the benefit of accelerated-approval cancer-drugs, Genentech plans to conduct a new trial of bevacizumab that will use progression-free survival (PFS) in metastatic breast cancer patients as its primary endpoint, company officials said.

The announcement came shortly before a June 27–28 hearing, at which a six-member subpanel of the Oncology Drugs Advisory Committee (ODAC) unanimously rejected the company’s appeal of last December’s decision to withdraw the drug’s provisional approval for breast cancer. Two follow-up trials and data from three other trials presented at the meeting failed to confirm the level of PFS seen in the original trial that led to accelerated approval. ODAC’s decision now goes to FDA Commissioner Margaret Hamburg for a final decision.

The company’s plans for the new trial, which could take up to 5 years to complete, were revealed near the end of an emotional 2-day hearing that marked the first time a company has challenged an agency decision to withdraw accelerated approval. Other firms have voluntarily withdrawn drugs or label indications when the FDA’s efforts to raise standards after toplially withdrawn drugs or label indications when the FDA was leaning toward issuing similar

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Genentech’s appeal directly challenges the FDA’s efforts to raise standards after giving accelerated approval to new cancer drugs (see News, J. Natl. Cancer Inst. 2011;103:455–7). Many practicing oncologists are also looking for higher standards of final proof because of the escalating cost of new cancer drugs, which for Avastin, can reach $88,000 per year.

ODAC earlier this year backed an agency recommendation that drugs granted accelerated approval for common cancers eventually submit at least two confirmatory trials showing an improvement in overall survival. After that meeting, Richard Pazdur, M.D., director of the oncology drugs division of the Center for Drug Evaluation and Research (CDER), said the agency was leaning toward issuing similar official guidelines for drug developers.

Genentech Plans New Trial

But Genentech, a unit of Roche, said its new trial will seek to replicate only the 5.5 months of PFS that occurred in the original accelerated-approval trial (E2100), which was submitted to the agency in 2006. At the appeal hearing—which was run like a trial and presided over by Karen Midthun, M.D., the director of the Center for Biologics Evaluation and Research—FDA officials repeatedly testified that the E2100 trial was an outlier because the confirmatory trials submitted to the agency last year, dubbed AVADO and RIBBON-1, increased PFS by only 1 and 1.2 months, respectively. None of the trials resulted in a statistically significant change in overall survival, nor was there evidence of improved quality of life.

Company officials said the new trial will seek to reaffirm the results of E2100, which showed that Avastin, an antiangiogenesis drug, prolongs PFS in patients taking it with weekly paclitaxel as their primary chemotherapy agent. The two failed confirmatory trials had coupled the drug with gemcitabine and docetaxel. “The exposure partner may matter,” said Sandra Horning, M.D., Genentech’s global head of clinical development for hematology/oncology, adding, “The clinical data suggest that weekly paclitaxel with Avastin is more effective because of greater exposure and this can be confirmed with additional study.”

Starting in the first quarter of next year, Genentech plans to enroll 480 patients with metastatic breast cancer who have not previously been treated with chemotherapy. They will be randomized by whether they receive Avastin, and then stratified according to whether they have high or low expressions of vascular endothelial growth factor A (VEGF-A), the angiogenesis receptor that Avastin targets. “The purpose is to confirm E2100 in the overall population, and use of VEGF-A to identify those who would have greater benefit,” said James Reimann, Ph.D., chief of oncology biostatistics for Genentech. The company has already begun talks with the Center for Devices and Radiological Health about validating a test for VEGF-A.

The company argued that while the new trial proceeds, the FDA should maintain Avastin’s accelerated-approval status for patients already taking it with paclitaxel. The company claimed that the FDA’s decision to approve gemcitabine (Gemzar) for metastatic breast cancer patients—which in its pivotal trial increased PFS from 2.9 to 5.2 months and had a trend (not statistically significant) toward overall survival—validated using PFS as an endpoint.

“No study has shown an improvement in overall survival in this population,” Reimann said. “A strict requirement for overall survival benefit would greatly affect the study size and its feasibility.” He later estimated that to show a statistically valid increase in survival, a trial would need to include 1,500–2,300 patients.

Every year, about 45,000 women are diagnosed with HER-2-negative metastatic breast cancer. The disease is considered incurable, with an average survival time of 18–24 months.

The FDA’s Defense

The FDA defended its decision by pointing to Avastin’s considerable side effect profile,
saying that those negatives outweighed any benefits because the trials failed to replicate the PFS benefit of the E2100 trial. The drug increases blood pressure and urine protein levels and sometimes causes major adverse events such as bleeding, perforating the stomach or intestines and blood clots. The Avastin arms of the trials registered 5.6% more serious adverse events than the chemotherapy-alone arms, even after excluding hypertension and proteinuria, or excessive protein in the urine, which are both manageable conditions.

“Genentech’s proposed confirmatory study is years from completion. Current data suggest the new trial is unlikely to substantiate clinical benefit and CDER has not overstated the risks of Avastin,” said Patricia Keegan, M.D., director of the biologic products division of the FDA’s Office of Oncology Drug Products. “For metastatic breast cancer patients, the risks outweigh the limited treatment effect.”

The agency also opposed the company’s plea for continuing accelerated approval while it tested its hypothesis that paclitaxel Avastin act synergistically. “Classic pharmacokinetic studies have been designed to test such hypotheses, but such studies have not been done or submitted to CDER,” Keegan said. “The available pharmacokinetic data says there is no interaction between the two drugs.”

Patients Voice Concerns
Unlike most FDA drug advisory committee meetings, which place the public comment period after drug sponsors and agency reviewers have presented their scientific evidence, the review hearing opened with 2 hours of sometimes emotional testimony, mostly from
metastatic breast cancer patients who attributed their survival to Avastin. “I’m a testament that the drug does work,” said Crystal Hannah, 35, a mother of two from Parkersburg, W. Va., whose breast cancer recurred in July 2010. “It is morally and ethically wrong to stop treatment for those who are benefiting.”

And in a theme that many patients echoed, she concluded, “If the approval is removed, it is likely my insurance company will not continue to pay for the drug.”

However, leading insurers, including Medicare and UnitedHealthcare, the nation’s largest private insurer, said after the hearing that they would continue to adhere to NCCN (National Comprehensive Cancer Network) guidelines and its associated compendium when deciding whether to reimburse for cancer drugs. After the FDA announced last year that it planned to remove the breast cancer indication from the Avastin label, NCCN’s 33-member breast cancer committee reaffirmed its earlier decision that the drug was an appropriate choice for patients. After the latest hearing, Medicare and UHC announced that they would continue paying for the drug.

For FDA Commissioner Hamburg, though, the issue now before her represents a major challenge to the integrity of the accelerated-approval process. Granting Genentech’s request that the breast cancer indication remain on the label while the company conducts a new trial is tantamount to proposing “that withdrawal is only appropriate when there is no longer a reasonable likelihood of clinical benefit and no meaningful way to characterize the potential benefit further,” said John Jenkins, M.D., director of the Office of New Drugs. “This would allow the protracted marketing of drugs that have not been shown to be safe and effective while sponsors take numerous bites of the apple to show that the drug is safe and effective. This would undermine the integrity of the accelerated approval program,” he said.

Still, the FDA at one point seemed to suggest that the company’s plans to use PFS as its primary endpoint in the next trial might be acceptable and lead to reinstatement of the breast cancer indication on the label. “What would constitute a win?” the FDA’s Jenkins asked. Genentech’s Reimann replied, “An increase in median PFS and an increase in the hazard ratio.”

After rejecting an improvement in the hazard ratio as a marker, Jenkins asked, “Do you expect it will show a median PFS of 5.5 months?” And Reimann answered, “We’re very confident in the results of E2100.”

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