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Pushing the envelope

The US Food and Drug Administration (FDA) should follow its advisory panels and rescind metastatic breast cancer from Avastin's label.

The future of Roche/Genentech's Avastin (bevacizumab) was never at stake at the FDA hearing held in June to discuss use of the drug in metastatic breast cancer. Only a fraction of Avastin's $7 billion in annual sales come from this indication. What was at stake, however, was the credibility of the FDA's accelerated approval pathway.

Accelerated approval was introduced in 1992 to accelerate patient access to drugs. The protocol allows early or surrogate data to be used to assess a drug's effectiveness and in guiding a marketing approval decision. The use of early data permits decisions to be made more quickly. In the case of Avastin in metastatic breast cancer, the original clinical studies showed that the antibody, which targets vascular endothelial growth factor (VEGF-A), gave patients respite from the worsening of their disease: the median gain in progression-free survival (PFS) was 5.5 months.

PFS is often used as a clinical endpoint in trials of cancer drugs. However, PFS is only an intermediate endpoint in the disease. What regulators were really looking for in the case of Avastin was an extension to the lives of cancer patients, rather than an elongation of the time they took to get worse. In clinical terms, the real endpoint for the study is an extension of overall survival, in essence the time it takes for patients to die. Assessing time to death requires a longer clinical study simply because dying takes longer than getting worse. Thus, the accelerated approval process is a means of getting drugs to patients sooner.

Showing that Avastin extended life was data that Genentech could not muster. In July 2010, the FDA advisory committee that considers cancer drugs looked at data from two 'confirmatory' trials that the company had run—AVADO and Ribbon 1—and concluded that there was no evidence to support the continued use of Avastin in metastatic breast cancer. Those trials again showed an extension of PFS, although the extension was much shorter than in the original study. In neither trial, however, did Avastin help patients live longer than those on chemotherapy or provide a better quality of life. In one trial, the control group did better than the treatment group, and in both studies patients on Avastin suffered more serious side effects. Unsurprisingly, the advisory panel concluded that Avastin should no longer be used for metastatic breast cancer.

Unlike other companies who have received conditional accelerated approvals, though, Genentech didn't take the hint. After hearing from FDA last December that Avastin should be withdrawn, the company asked for an additional hearing—in essence an appeal. So 11 months after the initial advisory panel rejected the drug, FDA convened a second panel at the end of June.

The second panel included five of the six experts from last year's panel. No new clinical data were brought by Genentech. Various individual patients and patient advocacy groups were also allowed to present their views, the vast majority claiming their continued vitality as 'evidence' of Avastin's efficacy.

Ultimately, the panel was unmoved. The experts reaffirmed the recommendation of the original panel that the indication be removed from Avastin's label. And now all that remains is for FDA commissioner Margaret Hamburg to determine whether she follows her advisory panels' advice when she announces her decision next month.

It seems fairly clear that the FDA is aware that what is at stake goes beyond Genentech, beyond Avastin and beyond breast cancer. Agency officials have adopted a hard-line response to Genentech's reluctance (or inability) to bring new data in support of its case for full approval. Indeed, the decision to reconstitute in June a virtually identical panel (with no breast cancer specialist) gave little scope for the experts to arrive at a different opinion from the earlier panel, especially as Genentech failed to provide additional clinical evidence (although to be fair, at least it did do the confirmatory trials, unlike many other companies in the past).

In this respect, it's a shame that FDA did not explore how it could work with Genentech in facilitating the next steps for defining the subpopulation of breast cancer patients who might benefit. For example, there are preliminary indications that VEGF-1154 AA and VEGF-2578 AA genotypes correlate with improved median overall survival and VEGF-634 CC and VEGF-1498 TT genotypes show protection from grade 3-4 hypertension, a common side effect of Avastin.

For its part, Genentech did what it had to do. To satisfy its shareholders, the company pushed its blockbuster as hard as it could. Since being notified last December of the FDA's decision to reverse approval in breast cancer, it has continued to generate millions of revenue marketing Avastin as a breast cancer drug. It has also highlighted the debate over efficacy interpretation—whether PFS or overall survival—to both the clinical community and healthcare payers.

On the other hand, the company singularly failed to provide any new data or put together a prospective pharmacogenomic trial that might have identified responders. The appeal was therefore a gambit to gain time on the market, raising the debate over efficacy and fostering a very public (and sometimes acrimonious) debate over a drug withdrawal in a disease of almost unparalleled cultural and social proportions with few treatment options.

It is this journal's view that Commissioner Hamburg should withdraw Avastin's label in metastatic breast cancer. The two advisory groups that looked at the data both concluded that continued registration in this indication is unjustified.

To ignore the advice of both internal and external experts would not only undermine the FDA's scientific credibility, it would also compromise the credibility of the accelerated approval pathway itself—essentially a contract offering companies rapid market access now in return for confirmatory trials of efficacy later. The question is, If lack of efficacy in the face of toxicity is insufficient to reverse an accelerated approval, then what is?