

## Avastin, ODAC, and the FDA: Are We Drafting the Right Players?

Although the calendar said “summer” and baseball season was in high gear, July seemed to be an early fall for Avastin in breast cancer. The Oncology Drugs Advisory Committee (ODAC) of the FDA voted 12 to 1 that the AVADO and RIBBON1 trials did not provide confirmatory evidence supporting the original ECOG 2100 study that had led to accelerated approval of bevacizumab in combination with paclitaxel for advanced breast cancer. The FDA will decide in September whether to withdraw the label for the agent. A previous ODAC vote, in 2007, was 5 to 4 against approval, a recommendation *not* honored in the subsequent FDA decision.

To date, there have been no fewer than 5 randomized clinical trials of chemotherapy with or without bevacizumab. Of these, the first (capecitabine ± bevacizumab) showed no difference in progression-free survival (PFS). The second (ECOG 2100; paclitaxel ± bevacizumab) showed major improvement in PFS. The next 3 trials—all placebo-controlled—showed changes in PFS that were, though all statistically significant, arguably not clinically compelling, with improvements in PFS of 2 to 3 months. None of these studies, nor a meta-analysis, suggests a survival advantage for adding bevacizumab in advanced breast cancer.

These results leave more questions than answers. The second most common, after the question of bevacizumab itself, is, “what should be the end points for oncology drug approval?” The FDA has offered guidance for clinical trial end points and approval of cancer drugs (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>). A variety of end points can lead to approval, including survival, symptom improvement, response rate in refractory patients, and PFS. Response and PFS have been accepted, though each is acknowledged to be, at best, a weak surrogate for symptom relief, quality of life, duration of tumor control, and overall survival. Considerations of absolute treatment benefit and trade-offs that include adverse effects are also important.

Survival gains in advanced cancer nearly always yield approval, even if the public impression of “survival advantage” vastly exceeds reality. Beyond overall survival, requirements for approval are a *P* value less than 0.05 and a perceived clinical benefit that seems significant. This criterion is ill-defined. We can agree that a 90% response rate is terrific. But is 21% high enough? 37%? Improving PFS by 2.6 months, or 4.9? Supreme Court Justice Potter Stewart famously characterized obscenity by saying “I know it when I see it.” That also appears to reflect the standard for most FDA drug approvals in oncology.

What lessons can bevacizumab in breast cancer teach us? First, it highlights the importance of confirmatory trials, no matter how dramatic the initial findings. Second, it underscores the weak relationship between PFS and survival in advanced breast cancer, particularly in first- and second-line treatment of a disease with a large number of treatment options. Potential explanations for the lack of survival differences are plentiful: inadequate duration of chemotherapy or bevacizumab; ineffective subsequent therapy; accelerated development of resistance. Regardless, there is no survival impact. Third, what about the benefits seen in ECOG 2100? Is this the outlier study, while others are “regression to the mean”? Or does something unique to paclitaxel given on a weekly schedule potentiate bevacizumab’s impact?

Additionally, we have come to expect rational explanations for the effects of targeted therapy. We anticipate that anti-HER2 drugs will work in HER2-expressing breast cancers. We depend on cytogenetics to identify leukemia type and tell us if all-trans retinoic acid is appropriate. For bevacizumab, however, we have no known markers of activity or side



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August 2010

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effects. This *correlative science gap* leaves clinicians wondering which patients might truly benefit from bevacizumab in breast cancer and remains an unresolved challenge.

Finally, there is the elephant in the room—bevacizumab's cost. Neither ODAC nor the FDA is tasked with evaluating drugs by cost or setting prices. Therefore, it took a *New York Times* editorial (on July 25, 2010) to point out that the “cost of Avastin has always seemed outrageously high for the medical benefits it confers.” Cancer care may be costly, and innovative and powerful treatments may be expensive. Cost is not the inherent problem. The problem is that we have no process for weighing costs relative to benefits and too little insight into what drug development and manufacturing actually costs, as opposed to what price the market will bear.

Baseball owner Bill Veeck is credited with saying, “it isn't the high price of stars that is expensive; it's the high price of mediocrity.” Thinking about oncology drugs, we need more stars and fewer minor leaguers. When we “sign” new players, we need to think more about whether they are All-Stars, major league pros, journeymen, or not ready for the big leagues. And we need a review process that offers clear benchmarks for judging that talent and determining how much it is worth. The cancer community needs to engage in a vigorous dialogue to help overhaul a cumbersome and inconsistent drug approval process.