Avastin for Breast Cancer, 2005–2011: Requiescat in Pacem?

In November, the FDA withdrew its accelerated approval of Avastin as treatment for metastatic breast cancer. The decision was highly anticipated since the vote by the Oncology Drug Advisory Committee (ODAC) last summer voiced near unanimous sentiment against full approval. The 70-page decision from FDA commissioner Dr. Margaret Hamburg (available at http://www.fda.gov/downloads/NewsEvents/Newsroom/UCM280546.pdf) was a detailed account of the initial accelerated approval in 2008, the expectations for full approval, and the several studies whose outcomes determined the fate of Avastin. The FDA deemed the analysis sufficiently important that the decision was written in the first-person by Dr. Hamburg, a clear signal of personal accountability and authority on this. Despite this authoritative review, the Avastin story continues to stir discussion and seems unlikely to go peacefully into the night, with several areas of controversy that remain unsettled.

Study End Points

The Avastin data forced a debate on the most important end points for trials in advanced breast cancer. Accelerated approval was based on improvement in progression-free survival (PFS) seen in E2100, without an overall survival difference. Confirmatory trials were expected to show, at a minimum, similar improvement in PFS in both magnitude and hazard ratio. However, neither the AVADO nor the RIBBON-1 studies showed a clinically compelling difference for Avastin with regard to PFS, despite a statistically significant P value. Furthermore, a survival benefit never emerged.

Was a survival benefit asking too much? The Avastin trials prompted biostatisticians to model outcomes in advanced breast cancer that focus on how post-progression treatment might affect survival results. The models implied that identifying a survival difference in first-line treatment, when most patients receive multiple lines of therapy, would require studies so large as to be prohibitive.

Unfortunately, none of the key questions for end point selection raised by the Avastin experience have been settled. Although there is no argument over survival difference, defining a meaningful benefit in PFS remains elusive. Response rates in first-line therapy have not historically been accepted for regulatory approval in breast cancer. The impact on quality of life was not seriously quantified in the Avastin trials, and it is uncertain whether measurable gains in quality of life could lead to a drug approval. One is hard-pressed to review the Avastin experience and figure out just how much benefit—short of overall survival—would have been needed to cement a full drug approval. The controversy over surrogate end points for approval in breast cancer will fester.

Cooperative Groups

The first trial designed for registration of Avastin was a Genentech-led study of capecitabine +/- Avastin for refractory breast cancer, a study that was overtly negative. The subsequent study, E2100, was run through NCI cooperative groups and developed at a time when leaner, simpler data collection and study designs were encouraged as an efficient strategy. E2100 was not a placebo-controlled phase III study and did not initially require independent radiology review. In the end, a separate radiology review was required, and the confirmatory studies (AVADO, RIBBON-1) were company-led and placebo-controlled.
Cooperative groups continue to mount critical phase III studies, but the Avastin experience in breast cancer may ultimately contribute to a chilling effect for using the groups for registration studies. Those who favor the group approach may argue that E2100 remains the most important data for Avastin and a success for cooperative group research. However, subsequent controversies may stem, in part, from the lack of a placebo in E2100, and it seems likely that the resources demanded of phase III studies for approval may outpace the resources and designs available within NCI groups.

**Accelerated Approval**

The Avastin story became a test case for the accelerated approval process for many on different sides. Accelerated approval is designed to hasten delivery of important drugs to the clinic, allowing quicker approval based on end points such as PFS or response rate while awaiting confirmatory trials to justify full approval.

Accelerated approval has a mixed record. Clearly, it has brought important products to the market early. However, a Government Accounting Office report chastised the FDA for not paying enough attention to timely completion of confirmatory studies, and recommended that the “Commissioner of FDA should clarify the conditions under which the agency would utilize its authority to expedite the withdrawal of drugs approved based on surrogate end-points under the accelerated approval process if sponsors either fail to complete required confirmatory studies with due diligence, or if studies are completed, but fail to demonstrate the clinical effectiveness of the drugs.”

Many commentators have viewed the Avastin process as a “test case” for accelerated approval. Those favoring more liberal approval greeted the withdrawal with frustration, citing the completion of confirmatory studies with significant $P$ values, and worry that the decision will stifle entrepreneurial innovation. Others believe that the FDA was practically compelled to withdraw approval to demonstrate a vigorous and robust ongoing review process and as a reminder to other drug developers of the importance of those efforts.

**The Media**

To an extraordinary degree, the Avastin story has engendered attention in major media outlets, not just the health or business pages but also editorials. In particular, the discourse pitted *The Wall Street Journal* against *The New York Times*. *The Wall Street Journal* memorably referred to the “Avastin mugging” after the 2010 ODAC vote against Avastin, and called this week’s approval withdrawal a “chillingly blunt assertion of regulatory power.” *The New York Times* praised the FDA for following the evidence and making a “reasonable” decision.

The stakes were high—millions in annual U.S. sales and a standard treatment for thousands of women with advanced breast cancer. Still, seeing breast cancer care negotiated on the editorial page of our nation’s most influential newspapers is an odd development.

**Guidelines, Panels, and Compendia Coverage**

Based on the E2100 data, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer had included Avastin and chemotherapy, and that endorsement remains, despite the negative data emerging since then. Genentech, in rebutting the anticipated FDA withdrawal, cited the NCCN Guidelines in support of Avastin for breast cancer. The FDA commissioner’s decision, however, pointedly dismissed the importance of the panel recommendation, noting that NCCN received money from Genentech/Roche and that a third of the panel membership had a potential conflict of interest with the company. These critiques of panel structure
and membership are important for NCCN, ASCO, and other guidelines developers to digest, as they suggest that not everyone believes the current system is optimized.

To date, most insurers and Medicare have indicated they will continue to cover Avastin for breast cancer, in part because it is listed in the NCCN Drugs & Biologics Compendium, but that seems unsustainable long term. These circumstances are unique, but whether third-party payers will continue to support use of a drug that has specifically had approval withdrawn by the FDA remains to be seen.

**Cost**

For a while, it seemed that Avastin for breast cancer would prompt a serious assessment of cost in cancer treatment. As Joe Nocera wrote in the *The New York Times*, “If we’re not willing to say no to a drug like Avastin, then what drug will we say no to?” Surely, the high cost and arguable benefits made this a good situation for debate. That dialogue, however, never really materialized. The FDA commissioner went to great effort to point out that the FDA’s role is to approve drugs based solely on safety and efficacy. Despite soft mutterings that cost somehow influenced the Avastin decisions, and *The Wall Street Journal*’s raging against Federal control of the doctor–patient–pharma relationship, it seems that a long overdue national discussion on the cost of cancer therapies will wait. That is an unfortunate lost opportunity for a serious review of whether and how cost consideration should affect approval and use of cancer drugs.

**Data Yet to Come**

Although this chapter of Avastin for breast cancer has closed, potential for controversy has not. Extant trials for Avastin for metastatic breast cancer and as adjuvant and neoadjuvant therapy for earlier-stage disease are still accumulating patients and data. Investigators, manufacturers, and regulatory agencies have all suggested that biomarker analyses may yet identify which patients truly benefit from Avastin. Whether clinically robust biomarkers exist is by no means clear, as they have yet to be spotted in 5 randomized trials in breast cancer and dozens of studies in other malignancies, but there is always the chance.

However, the argument that we have yet to find the right subset is both a platitude and a cop-out. None of the prospective, definitive studies—studies in which innumerable investigators participated—were designed to find a subset in which Avastin is particularly valuable. At best, such retrospective work now would be only of value to generate a hypothesis that might merit future study. And besides, the fundamental tenet of targeting angiogenesis was that this is the universal approach to cancer, effective because all tumors need a blood supply. To suggest it is important to define subsets where Avastin really works in breast cancer seems disingenuous at this point in the game.

To stakeholders across the spectrum of interests in oncology, the saga of Avastin for breast cancer had emerged as a kind of Rorschach test, an ambiguous blot onto which we project our own impressions and personal feelings. The Avastin era in breast cancer may be officially over, but the lingering questions surrounding it are likely to persist for years to come.

**References**
