



Lessons and Questions From the E2100 Avastin Breast Cancer Trial

By Robert Erwin

The Food and Drug Administration (FDA) granted accelerated approval this past February to biotech company Genentech to market Avastin (bevacizumab) for the treatment of metastatic breast cancer. The FDA defines “accelerated approval” as “a provisional approval with a written commitment to complete clinical studies that formally demonstrate patient benefit.” The word “accelerated” notwithstanding, the events leading up to this regulatory decision were complex and played out over a long period of time. Here is a simplified chronology of some of the key events prior to this decision:

- ⊗ 2000 – Clinical trial AVF2119g began enrollment (Xeloda with or without Avastin in pretreated metastatic breast cancer).
- ⊗ 2001 – Clinical trial E2100 began enrollment (Taxol with or without Avastin as first-line therapy for locally recurrent or metastatic breast cancer).
- ⊗ 2002 – Failure of Avastin to provide significant benefit to patients in AVF2119g trial reported at San Antonio Breast Cancer Conference.
- ⊗ 2005 – Significant impact of Avastin on progression-free survival of patients in E2100 trial reported at the annual meeting of the American Society of Clinical Oncology. No significant increase in overall survival was reported.
- ⊗ 2006 – Genentech filed a supplemental biologics license application with the FDA seeking approval to market Avastin for first-line treatment of metastatic breast cancer.
- ⊗ 2006 – FDA issued a “complete response” letter requiring Genentech to provide additional data and resubmit its application.
- ⊗ 2007 – Genentech submitted a new application, and the FDA sought input from its Oncologic Drugs Advisory Committee (ODAC). Although an independent review of the E2100 medical records confirmed the significant improvement in progression-free survival, Avastin still had no significant impact on



overall survival. The committee voted 5 to 4 against approval.

The arguments for and against approval of Avastin for treatment of metastatic breast cancer encompass a number of considerations. These include the risks of the drug—which are substantial for some patients—the lack of overall survival as the primary endpoint in a clinical trial, and the wisdom of authorizing the marketing of an expensive drug (approximately \$100,000 a year) that has not been shown to extend survival nor provide an objectively measurable increase in quality of life. However, an important factor in the debate is the fact that in the E2100 trial, Avastin treatment increased progression-

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FROM THE EXECUTIVE DIRECTOR

Putting Patients First

The Need for Better Standards at the FDA

By Barbara A. Brenner

I have written frequently about the Food and Drug Administration for this column. It has never seemed more important than now to spell out in the clearest possible terms what breast cancer patients need from the FDA and why.

The FDA's recent approval of Avastin (bevacizumab) is the latest case in point. In an open letter to the FDA,¹ we pointed out that, with this decision, the agency has lowered the bar on the approval of cancer drugs.

Every day seems to bring a new story either about the dangers of drugs long ago approved by the agency or about the undue influence of the pharmaceutical/biotech industry on FDA decisions. As the only national breast cancer organization that has declared its complete independence from funding by pharmaceutical companies (see BCA's Corporate Contributions Policy),² BCA is in a unique position to articulate a clear standard for approval of new breast cancer drugs.

In addition, as a result of our in-depth strategic planning process, we at BCA have decided to increase our FDA advocacy efforts, so it is critically important that we be clear for ourselves and for our constituents about how we see the drug approval situation and how we would like to transform it.

“BCA is in a unique position to articulate a clear standard for approval of new breast cancer drugs.”

There are many drugs approved for breast cancer. (For a list of breast cancer treatment drugs available free or at discounted rates, see our guide to patient assistance programs.)³ Given this environment, we at BCA believe that any new drug approved for the treatment of breast cancer must be demonstrated to be able to do at least one of the following three things:

- ✦ Extend the life of the patient, i.e., improve overall survival (OS).
- ✦ Improve the patient's quality of life.
- ✦ Cost less than therapies already available.

Improve Overall Survival

Robert Erwin's article in this issue puts in context how the FDA's recent approval of Avastin for breast cancer treatment came about and why the ruling was so controversial. The debate over Avastin centers on whether the drug's ability to improve progression-free survival (PFS) for some patients should justify its approval for the treatment of metastatic breast cancer patients. While PFS is used increasingly in the cancer field as a surrogate for overall survival (OS), this substitute standard is only useful if, in fact, the surrogate standard can be shown to correlate with what it was meant to stand for: overall survival. In the case of Avastin, as presented to the FDA in December, PFS improved but OS did not. So, consistent with the standard enumerated above, BCA opposed approval of Avastin for breast cancer at the time and was gravely disappointed that the FDA commissioner ignored the recommendation of his committee and granted Genentech's application.

Improve Quality of Life

BCA's view is that even if a drug does not improve the chances of survival, it should be approved for breast cancer if it can be demonstrated to improve the quality of life for breast cancer patients. This argument, too, surfaced in the recent Avastin debate. While some patients say that they felt better on Avastin than they have on systemic chemotherapy drugs, these anecdotal reports do not amount to a systematic evaluation of the quality of life for patients on the drug. In trials where patients know that they are receiving the drug that is being evaluated, it is impossible to objectively gauge the impact of the drug on quality of life. Instead, quality of life assessments must be made in blinded trials (where the patients don't know what drug they are receiving) and must use established quality of life criteria to evaluate the results.

Since the Avastin trial that Genentech presented to the FDA was an “open label” trial, where patients knew what drug they were receiving, there was no unbiased information about quality of life available for the FDA to consider. Again, for this reason, BCA opposed approval of Avastin for breast cancer.

Less Expensive Therapies

The FDA's mission statement reads in part that the agency is “responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and *more affordable*” (emphasis added). Despite this statement, the FDA is currently prohibited by law from

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Healthy Job, Healthy Body

A Profile of Women's Action to Gain Economic Security

By Pauli Ojea

Imagine a stable job that pays well, includes benefits, provides opportunities for education and training, and is safe and healthy for workers. (If this describes your own job, you're better off than most people in the U.S. workforce.) Now imagine that at this great job, instead of having a boss, you and your colleagues are in charge.

Welcome to the cooperative business of Natural Home Cleaning (NHC) in Oakland, California.

Natural Home Cleaning is a worker-owned and -operated cooperative that employs low-income Latina women in eco-friendly housecleaning. The cooperative was formed with the help of the nonprofit organization WAGES (Women's Action to Gain Economic Security), which helps form cooperatives like NHC by providing financial support and training.

Worker-owned cooperatives are businesses where the workers are also the owners. In a cooperative, decisions are made democratically by all the worker-owners, and earnings are divided among the group. In addition to promoting democracy in the workplace, WAGES and NHC are also committed to advancing women's health and justice. The jobs they offer not only pay well and include benefits but also take into account the workers' health.



The worker-owners of the cooperative Natural Home Cleaning

WAGES was formed in 1994 to provide jobs to low-income immigrant women. The founders of WAGES knew that housecleaning was a job familiar to many Latinas. But they also recognized that housecleaning could be problematic for women: long hours, unreliable schedules, low pay, no benefits, and an often toxic environment.

Still, the women were convinced that "there had to be something good about this type of work; not all could be bad," says WAGES spokesperson Ivette Meléndez. So believing that housecleaning cooperatives that use safe products were one way of providing

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