BREAST CANCER ACTION

July 6, 2010

Nicole Vesely, Pharm.D.
c/o Melanie Whelan
10903 New Hampshire Avenue
WO51-6100
Silver Spring, MD 20993-0002

RE: Comments on Supplemental Biologics License Applications (sBLSs) 125085 and 192 for AVASTIN (bevacizumab), manufactured by Genentech, Inc.

Dear Dr. Vesely:

Please provide a copy of this letter to members of the ODAC who will be meeting on July 20, 2010 to discuss the above-referenced application.

Breast Cancer Action (BCA) opposes full approval for Avastin for the treatment of metastatic breast cancer, for the reasons explained in this letter.

In 2007, when accelerated approval for Avastin was granted there were several other trials underway in the metastatic breast cancer setting: AVADO, RIBBON 1, and RIBBON 2.

At the time that accelerated approval was granted, the data that the sponsor submitted showed improvements in progression free survival (PFS), but no overall survival (OS) advantage with Avastin. It was hoped that the subsequently completed trials would illuminate the overall survival picture with Avastin.

The three trials that were underway when Avastin was given accelerated approval have now been completed. Though all the trials showed improvement in PFS, there was still no improvement in OS with Avastin.

As Dr. Pazdur noted in his comments to ODAC in July 2009, "The approval process is not merely a screening process for drug activity. The goal of a registration trial is not merely to obtain a statistically significant result. The primary goal is to obtain a statistically reliable evaluation of the drug that represents a clinically meaningful result that yields a favorable benefit/risk evaluation." BCA agrees with Dr. Pazdur that a clinically meaningful result that can be objectively measured must exist before the FDA approves a drug.

"Clinical benefit rate" – a combination of complete response, partial response, and stable disease – is the new measure of effectiveness most often cited to the FDA. Yet the measure is not an objective one. As acknowledged by many researchers in the field, including during presentation of the data from the RIBBON 2 trial at the San Antonio Breast Cancer Symposium in December, 2009, "clinical benefit rate" is "somewhat subjective." At a meeting that Genentech representatives held with advocates on December 11, 2009 in San Antonio, Sandra J. Horning, M.D., Senior Vice President and Global Head of Clinical Development Hematology/Oncology for the company agreed that the term is "somewhat subjective."

The farther we move from objective measures of drug efficacy, the more difficult it will become to know whether drugs are effective in a way that is truly meaningful for patients with metastatic disease.

Despite multiple trials of Avastin in metastatic breast cancer, there is no evidence that the drug improves either overall survival or patients' quality of life. In light of this, it is inappropriate to continue to rely on PFS as the indicator of Avastin's effectiveness in metastatic breast cancer patients. As Dr. Pazdur has noted in comments to ODAC, "[a]n improvement in overall survival has repeatedly been viewed as a direct clinical benefit and is very reliably assessed," while "PFS is primarily considered either a surrogate or a surrogate reasonably likely to predict for clinical benefit."

In the case of Avastin, PFS was the surrogate on which accelerated approval was extended. Based on the data now available, it is clear that, despite best hopes, PFS is not a true surrogate for overall survival or other clinical benefit.

Breast Cancer Action is deeply troubled by the prospect that Avastin may now receive full approval, even though the drug has not been shown to improve survival of breast cancer patients, nor to improve their quality of life. We strongly believe that no new drug should be approved for breast cancer that has not been shown to (1) improve overall survival and/or (2) improve the quality of patients' lives.

We urge you to reconsider the standards for drug approval in settings, such as breast cancer, where there are already many options. Increased overall survival or improved quality of life should be the goal.

If full approval is given to Avastin despite the lack of survival advantage, we urge you to require the sponsor to conduct a prompt and thorough confirming Phase IV review of Avastin's use.

Sincerely,

Barbara A. Brenner
Executive Director

Note: As a matter of policy, in order to avoid the fact or appearance of a conflict of interest, Breast Cancer Action does not accept funding from Genentech or from any other pharmaceutical or biotech company.

cc: Joshua Sharfstein