

# NBCCF

NATIONAL BREAST CANCER COALITION FUND

*grassroots advocacy in action*

February 19, 2008

Dr. Richard Pazdur  
Director  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammandale Road  
Beltsville, MD 20705-1266

## COMMENTS TO THE FOOD AND DRUG ADMINISTRATION ON ITS EVALUATION OF AVASTIN AS FIRST-LINE TREATMENT IN METASTATIC BREAST CANCER

Dear Dr. Pazdur,

The National Breast Cancer Coalition Fund (NBCCF) urges the FDA not to weaken the standard for approval of drugs in first-line treatment of metastatic breast cancer. We believe a demonstration of statistically significant improvement in overall survival is fundamental to achieving meaningful progress in the treatment of breast cancer and should be the cornerstone of drug approval in this and most other settings.

In its May 2007 "Guidance for Industry – Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," the FDA enumerates the advantages and numerous limitations of Progression Free Survival (PFS) as an endpoint to support drug approval. The Guidance document indicates that PFS can offer regulatory evidence when it is a proven surrogate for overall survival. It is therefore necessary to establish such proof before granting approval on this basis. The Guidance document further states: "whether an improvement in PFS represents a direct clinical benefit of a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies."

On December 5, 2007, the FDA asked ODAC to discuss, in the context of E2100, whether PFS alone without a demonstrated survival advantage should be considered a measure of direct clinical benefit in the initial treatment of metastatic breast cancer. This question must be addressed in the context of the safety profile of the treatments offered in E2100, their impact on quality of life, and the design and conduct of the trial, and also in a larger context, considering the consequences such a decision would have in our understanding of the true impact of new treatments for advanced breast cancer. In either context, our ultimate goal should be to make meaningful progress towards finding cures and saving patients' lives while minimizing toxicities and protecting the quality of their lives.

Any discussion and determination of adoption or change of guidelines should not be done in relation to a specific product. Rather the agency should make these determinations with input from all stakeholders and free from influence of any one company, investigator, group, or trial, and as a separate process.

### **Reported outcomes for E2100**

Like many in the breast cancer community, we are very disappointed that in E2100 the combination of Avastin and Taxol did not result in an improvement in overall survival over Taxol alone, despite improvement in PFS. We have serious concerns about the safety of the combination treatment:

- There were 5-6 deaths attributed to the experimental treatment and none attributed to the control arm
- In addition to treatment-associated deaths, there were significantly more severe toxicities in the experimental treatment arm
- There was no demonstrated improvement in the quality of life of patients in the experimental arm over the control arm

We are also concerned about reported methodological shortcomings in the design and conduct of E2100. These undermine the community's confidence in the trial's findings. Given all these, we believe a favorable benefit/harm profile has not been established for this combination treatment.

Lastly, recent media reports indicate that the AVADO trial met its primary endpoint of PFS for a combination treatment with Avastin at two different doses. We urge the agency to consider the full data set of this trial before making an approval decision on Avastin, particularly as one of the experimental arms in the AVADO trial used a lower dose of Avastin than that used in E2100. We believe the question of dose is of critical importance.

There are other ongoing trials looking at Avastin in first-line treatment of metastatic breast cancer. Data for these trials and the AVADO trial will mature over the next couple of years. There is no patient imperative to rush approval before that time. In fact, given the number of trials, FDA should at some point consider analyzing all quality data sets in their entirety and eliminate those of lower quality.

### **Standard for drug approval**

Since its inception in 1991, the National Breast Cancer Coalition Fund has fought for federal funding for research aimed at eradicating breast cancer. From the start we insisted on the involvement of trained consumer advocates at all levels of the research process to ensure impact, accountability and scientific rigor. We have always insisted on high standards for research in order to generate high levels of evidence for health care. The FDA plays a critical role in protecting the public health by setting high evidentiary standards for clinical utility. In the first-line metastatic setting, it is the hope of consumer advocates that the research effort aims to improve survival and eventually lead to cures. We believe that lowering the standard for drug approval will undermine the quest for advancement in treatment and for cures, as we will lose the ability to determine whether new treatments truly save lives.

On the broader question of whether PFS is an adequate endpoint for drug approval in first-line treatment of metastatic breast cancer, as stated earlier, we believe this may only be appropriate when PFS is a demonstrated surrogate for OS. In the absence of such evidence, PFS may be an adequate endpoint in more advanced disease settings provided that the treatment is safer relative to evidence-based alternatives and offers a significant improvement in the patient's quality of life. There are, however, strong limitations to both the assessment of progression and to the assessment of quality of life itself which must be addressed.

Sincerely,

A handwritten signature in cursive script that reads "Fran Visco".

Fran Visco  
President  
National Breast Cancer Coalition Fund

cc: Janet Woodcock