THE CANCER LETTER

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As Avastin Decision Nears, Patient Groups Split On PFS In Front Line Breast Cancer

By Paul Goldberg

Sometime before Feb. 23, FDA will likely announce its decision on the Genentech drug Avastin (bevacizumab), but no matter what the agency does, the regulatory questions raised during the drug's review will continue to shape development of cancer therapies.

The Avastin controversy hinges on the acceptability of progression-free survival as a criterion for drug approval. The setting is important: historically, front-line metastatic breast cancer has been an indication where historically survival trumped all other metrics.

The disputes over Avastin have caused rifts within patient advocacy groups and among drug developers. Opponents argue that acceptance of PFS for this indication would lower the bar for drug approval. Proponents

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FDA News:

FDA Proposes To Drop Specific Requirements For Reprint Distribution On Off-Label Uses

By Paul Goldberg

FDA earlier this week issued a draft guidance on distribution of reprinted articles describing off-label uses of approved drugs and devices.

The guidance, which spells out the circumstances where distribution of such materials would be permitted, replaces a provision of an FDA law that expired in 2006.

Under that law, companies were allowed to distribute reprints if they met a number of conditions that included submitting reprints to review by the agency 60 days before proceeding with such distribution.

The new guidance drops these specific requirements, replacing them with general principles that must be met by companies seeking to distribute materials.

"Articles that discuss unapproved uses of FDA-approved drugs and devices can contribute to the practice of medicine and may even constitute a medically recognized standard of care," Randall Lutter, FDA deputy commissioner for policy said in a statement. "This guidance also safeguards against off-label promotion."

The proposed guidelines are particularly significant in oncology, where drugs are routinely used off-label.

The FDA proposal is likely to face challenges both from the industry factions that see off-label promotion as an exercise of First Amendment

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Patient Groups Write To FDA On Acceptability Of PFS

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counter that a highly statistically significant delay in progression of disease is a tangible benefit, and studies measuring survival would be too large and take too long to complete.

As decision time approached, FDA received two letters that represented two sides of the controversy. One letter, from the National Breast Cancer Coalition, argues against approval. "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," NBCC President Fran Visco wrote in a letter dated Feb. 19 and addressed to Richard Pazdur, director of the agency's Office of Oncology Drug Products.

Taking the opposing view, Robert Erwin, president of the Marti Nelson Cancer Foundation, wrote that he believes that a significant PFS improvement is clinically important. He urged FDA and Genentech to agree to extend the regulatory deadline long enough to review the results of AVADO, a Roche study similar to the Genentech's registration trial for Avastin.

"If all other considerations are in good order and AVADO confirms the results of E2100 [the Avastin registration trial], the FDA would approve the sBLA based on a summary review of the data rather than the requisite review of all the primary AVADO data, which I would hope would reduce the review time from months to weeks," Erwin wrote in the letter dated Jan. 31.

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The NBCC Letter

The text of the NBCC letter follows:

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.

The Marti Nelson Foundation Letter

Erwin's letter was addressed to FDA's Pazdur and David Schenkein, senior vice president for clinical hematology and oncology at Genentech.

The text of the letter follows:

Since the December 5 ODAC meeting, I have had extensive discussions with a variety of physicians, patients, patient advocates, and others both in favor of and opposed to approval of Genentech's sBLA for bevacizumab for the initial treatment of metastatic breast cancer. I have also reviewed much publicly available information relevant to the question. I would like to offer a few brief observations and then a specific suggestion for your consideration.

1. I believe that demonstration of a significant PFS improvement is clinically important for metastatic breast cancer patients even with equivocal survival results. In my view, the magnitude of the PFS extension demonstrated by the E2100 trial, with the p-values obtained by both the investigators and the independent review facility, does represent a significant PFS improvement and a clinically important improvement in quality of life.

2. Although it is unfortunate that bevacizumab can be a dangerous drug for some patients, the E2100 trail did not produce any surprises about toxicity. As unfortunate as any individual death is, especially when caused by a drug that is used in the hope of prolonging life, taken as a whole, the E2100 data suggest a balance of the risks and potential benefits. With very clear and complete disclosure in the label of the risks of bevacizumab along with a description of the factors that may increase an individual's risk, I believe that the toxicity of bevacizumab becomes a neutral factor in making a decision about this sBLA.

3. A serious concern of many, and an important question to consider is whether a single trial such as the E2100 trial with PFS as the primary end point and data review concordance issues should be acceptable as an approval standard without independent confirmation of that end point by another clinical trial. This concern arises both from the theoretical subjectivity that may be inherent in the evaluation of PFS in metastatic breast cancer, and also, specific to this case, the lack of concordance between the investigator and IRF assessment of a significant number of individual patients in the E2100 study

However, we are now aware that such a confirmatory trial—the AVADO trial—will soon be completed and, according to Roche, the data will be released during the first quarter 2008. If that projection is still correct, we could have at least the summary results within days or weeks.

Given the very low p-value obtained by both the IRF and investigators in the E2100 trial, it is easy to have confidence that the AVADO study will demonstrate a similar PFS benefit. However, without the results of AVADO, FDA approval of the sBLA on the basis of E2100 alone could be viewed as setting an undesirable precedent for future applications for other drugs based on single trials where the magnitude of PFS benefit may be substantially smaller than that of the current application and with no confirmatory studies completed or underway.

However, despite my misgivings about the problems that would be created by setting a regulatory precedent that could cause problems in the future, I also have serious concern about a potentially lengthy delay in approval of the E2100 sBLA if the AVADO study is positive.

I assume that a new submission by Genentech, and review of primary data from the AVADO trial by the FDA, would take many months to complete. If AVADO confirms the benefits demonstrated by E2100, then a lengthy delay in approval would result in a very difficult situation for patients who might stand to benefit from bevacizumab but whose insurance will not cover off-label uses of drugs.

Although I do not know the extent of flexibility in the relevant regulations, my suggestion is this:

Genentech and the FDA mutually agree to extend the PDUFA deadline for this sBLA to a date soon after release of the AVADO results; and, if all other considerations are in good order and AVADO confirms the results of E2100, the FDA would approve the sBLA based on a summary review of the data rather than the requiste review of all the primary AVADO data which I would hope could reduce the review time from months to weeks.

Please let me know your response to my proposal.

FDA News:

Proposed Reprint Policy Likely To Face Challenges

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rights, and from Congress and consumer protection groups that accuse the agency of trying to benefit the pharmaceutical industry.

In a letter to FDA Commissioner Andrew von Eschenbach, Rep. Henry Waxman, who obtained a leaked copy of the guidance late last year, described the document as "ill-advised" and urged the agency to refrain from issuing it.

"The draft guidance that I have obtained would, in effect, allow drug and device companies to short-circuit FDA review and approval by sponsoring drug trials that are carefully constructed to deliver positive results and then using the results to influence prescribing patterns," Waxman write in a Nov. 30, 2007, letter to von Eschenbach. "This undercuts the prohibition on marketing of unapproved uses of drugs and devices and puts the public at risk for ineffective and dangerous uses of drugs."

Richard Samp, chief counsel of the Washington Legal Foundation, the group that consistently challenges FDA's authority on constitutional grounds, said the guidance document is vaguely worded.

Samp said WLF plans to ask the agency to clarify its standard for determining which treatments would be covered by the new guidance. The document refers to treatments shown to be effective in "well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device."

"The 'well-controlled clinical investigations' language sounds as though FDA is demanding that the studies be the equivalent of studies used to get new product approval," Samp said. "One can be pretty sure that no manufacturer will use this option to disseminate information if FDA interprets the 'well-controlled' language in the strict manner suggested above."

The guidance describes the following characteristics of medical journal articles that could be distributed:

—Materials should be published by an organization that has an editorial board that uses experts who have

demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles, and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization.

—Publications should be peer-reviewed and published in accordance with the peer-review procedures of the organization.

—Special supplements and publications that have been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article would be excluded.

The following types of scientific or medical reference publication would be excluded:

—Publications primarily distributed by a drug or device manufacturer, but should be generally available in bookstores or other independent distribution channels where medical textbooks are sold.

—Publications edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer.

—Publications edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The information contained in the above scientific or medical journal article or reference publications should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device.

Also excluded would be:

—False or misleading information, such as a journal article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (e.g., where a significant number of other studies contradict the article or reference text's conclusions), that has been withdrawn by the journal or disclaimed by the author, or that discusses a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled.

—Interventions that pose a significant risk to the public health.

The following publications are examples of publications that would not be considered consistent with the Good Reprint Practices outlined in this draft guidance:

—Letters to the editor.

—Abstracts of a publication.

—Reports of Phase 1 trials in healthy subjects.

—Reference publications that contain little or no substantive discussion of the relevant investigation or data.

Scientific or medical information that is distributed should be in the form of an unabridged reprint, copy of an article, or reference publication.

—Also, it should not be marked, highlighted, summarized, or characterized by the manufacturer in any way. Approved labeling for the drug or medical device should be included in the package.

—A comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal should also be included.

—In cases where the conclusions of article or text to be disseminated have been specifically called into question by another article or text, the articles in questions should be disseminated with a representative publication that reaches contrary or different conclusions regarding the unapproved use.

—Reprints should be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.

—Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs.

The journal reprint or reference publication should be accompanied by a prominently displayed and permanently affixed statement disclosing.

—That the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device.

—The manufacturer's interest in the drug or medical device that is the subject of the journal reprint or reference text.

—Any author known to the manufacturer as having a financial interest in the product or manufacturer or receiving compensation from the manufacturer.

—Any person known to the manufacturer who has provided funding for the study.

—Any significant risks or safety concerns known

to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text.

The document is posted at www.fda.gov/oc/op/goodreprint.html.

Cancer Statistics:

Cancer Deaths Rise Slightly Due To Aging Population

The American Cancer Society's annual cancer statistics report finds that death rates from cancer in the U.S. have decreased by 18.4 percent among men and by 10.5 percent among women since mortality rates began to decline in the early 1990s, which translates to the avoidance of more than half a million actual cancer deaths (534,500).

Society epidemiologists predict that in the U.S. in 2008 there will be 1,437,180 new cancer cases (745,180 in men and 692,000 in women) and 565,650 cancer deaths (294,120 among men and 271,530 among women).

The findings come from Cancer Statistics 2008, published in the March/April issue of CA: A Cancer Journal for Clinicians, as well as in the 57th edition of its companion publication, Cancer Facts & Figures 2008.

Despite a continuing decline in the cancer death rate from 2004 to 2005, there was an increase of 5,424 actual deaths (559,312 cancer deaths in 2005 compared to 553,888 cancer deaths in 2004). This increase follows a decrease in the number of cancer deaths in the two previous years.

The change is largely due to a smaller decline in the cancer death rate between 2004 and 2005 compared with that in the two previous time periods. From 2004 to 2005, overall cancer mortality dropped about 1 percent, compared to a 2 percent drop from both 2002 to 2003 and 2003 to 2004.

With respect to the four major cancer sites, colorectal cancer death rates decreased by about 3 percent from 2004 to 2005, compared to about 6 percent from 2003 to 2004. The decrease in death rates for cancers of the lung and bronchus and prostate in men and breast in women was also smaller from 2004 to 2005 than from 2003 to 2004.

For the number of cancer deaths to decrease, the decline in the overall cancer mortality rate must be large enough to offset the increasing numbers due to growth and aging of the population.

"The increase in the number of cancer deaths in 2005 after two years of historic declines should not obscure the fact that cancer death rates continue to drop, reflecting the enormous progress that has been made against cancer during the past 15 years," said John Seffrin, ACS chief executive officer. "While in 2005 the rate of decline was not enough to overtake other population factors, the fact remains that cancer mortality rates continue to drop, and they're doing so at a rate fast enough that over a half million deaths from cancer were averted between 1990-1991 and 2004."

The cancer incidence and mortality data were collected by the Centers for Disease Control, NCI, the North American Association of Central Cancer Registries, state and local health agencies, and thousands of cancer registrars throughout the country.

Highlights from this year's publications:

•Among men, cancers of the prostate, lung and bronchus, and colon and rectum account for one in two (50 percent) of all newly diagnosed cancers. Prostate cancer alone accounts for one in four (25 percent) of the total cases in men.

•The three most commonly diagnosed types of cancer among women in 2008 will be cancers of the breast, lung and bronchus, and colon and rectum, accounting for 50 percent of estimated cancer cases in women. Breast cancer alone is expected to account for one in four (26 percent) new cancer cases among women.

•Lung cancer surpassed breast cancer as the leading cause of cancer death in women in 1987. Lung cancer is expected to account for 26 percent of all female cancer deaths in 2008.

•Cancer incidence rates stabilized in men from 1995 to 2004 and in women from 1999 to 2004. Between 2002 and 2004, death rates for all cancer sites combined decreased by 2.6 percent per year in males and by 1.8 percent per year in females.

•Mortality rates have continued to decrease across all four major cancer sites in men and in women except for female lung cancer, in which rates continued to increase by 0.2 percent per year from 1995 to 2004.

•Death rates from all cancers combined peaked in 1990 for men and in 1991 for women. Between 1990/1991 and 2004, death rates from cancer decreased by 18.4 percent among men and by 10.5 percent among women.

•Lung cancer incidence rates are declining in men and appear to be plateauing in women after increasing for many decades.

•Colorectal cancer incidence rates decreased from 1998 through 2004 in both males and in females.

•Female breast cancer incidence rates decreased by

3.5 percent per year from 2001 to 2004, after increasing since 1980. The decreases may reflect the saturation of mammography utilization and reduction in hormone replacement therapy use that followed the publication of study results from the Women's Health Initiative in 2002.

•Among males under age 40 years, leukemia is the most common fatal cancer, while lung cancer predominates in men aged 40 years and older.

•Among females, leukemia is the leading cause of cancer death before age 20 years, breast cancer ranks first at age 20 to 59 years, and lung cancer ranks first at ages 60 and older.

•African American men have a 19 percent higher incidence rate and 37 percent higher death rate from all cancers combined than white men. African American women have a 6 percent lower incidence rate, but a 17 percent higher death rate than white women for all cancers combined.

•Among other racial and ethnic groups, cancer incidence and death rates are lower than those in whites and African Americans for all cancer sites combined and for the four most common cancer sites.

•Cancer is the second leading cause of death among children between ages one to 14 years in the U.S., after accidents. The five-year relative survival rate among children for all cancer sites combined improved from 58 percent for patients diagnosed in 1975 to 1977 to 80 percent for those diagnosed in 1996 to 2003.

Estimates of the expected numbers of new cancer cases and cancer deaths should be interpreted with caution, ACS officials said. These estimates may vary considerably from year to year, particularly for less common cancers and in states with smaller populations. Despite these limitations, the ACS estimates of the number of new cancer cases and deaths in the current year provide reasonably accurate estimates of the burden of new cancer cases and deaths in the U.S.

Each year, Cancer Facts & Figures features a Special Section highlighting one aspect of cancer prevention, early detection, or treatment. This year, the section focuses on "Insurance and Cost-Related Barriers to Cancer Care." About 47 million people in the U.S. are uninsured; minority populations and/or those with low income are disproportionately represented in this category. Recognizing that reducing barriers to cancer care is critical in the fight to eliminate suffering and death due to cancer, ACS and its advocacy organization the American Cancer Society Cancer Action Network are working together to bring the need for meaningful healthcare reform to the forefront of public and political debate. A goal of this campaign is public education about the extent of the access to care problem. The Special Section provides an overview of systems of health insurance and describes the impact of being uninsured or underinsured on cancer prevention, diagnosis, treatment, and outcome.

"The progress that has been made in reducing cancer death rates is a direct result of investment in approaches that we know work, such as comprehensive tobacco control and screening for breast, cervical, and colorectal cancers, as well as research that has identified more successful treatments," said Otis Brawley, ACS chief medical officer. "However, we believe that lack of health insurance and inadequate health insurance is one of the most important barriers to continued progress. A growing body of data shows that compared to those with private insurance, those without health insurance are less likely to receive smoking cessation advice and treatment, about half as likely to receive cancer screening, more likely to be diagnosed at late stage, and less likely to survive after a cancer diagnosis. We are committed to addressing this critical issue."

The report is available at www.cancer.org/statistics.

In the Cancer Centers:

Shields Leads Public Policy Committee For Cancer Society

PETER SHIELDS was named chairman of the American Cancer Society Government Relations and Policy Committee for the District of Columbia. Shields is deputy director of Lombardi Comprehensive Cancer Center, interim academic chairman of medicine, and professor of oncology at Georgetown University. The DC GRPC develops public policy for the ACS government relation's staff on cancer health care control matters at the local and state level. The goals of the committee include tobacco use reduction, patient protection, funding for cancer research, detection services, prevention programs, and children's health. . . . **MACE ROTHENBERG**, co-director of the Gastrointestinal Specialized Programs of Research Excellence program at Vanderbilt-Ingram Cancer Center, will receive a 2008 American Cancer Society Lane W. Adams Quality of Life Award for cancer care. The award recognizes individuals who have made a difference through innovation, leadership and consistent excellence in providing compassionate, skilled care and counsel to persons living with cancer and their families. Rothenberg is known for work in FDA approved treatments for colorectal and pancreatic cancer.

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