THE CANCER LETTER

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SPECIAL ISSUE

News Analysis:

Politics May Play Role In Avastin Decision

By Paul Goldberg

Wondering whether FDA will revoke the breast cancer indication of the Genentech drug Avastin?

For clues, let's look into regulatory filings tracked only by the most hardcore FDA-watchers.

Read carefully, because these obscure documents also confirm that the unprecedented hearing, scheduled June 28-29, will be the Greatest Oncology Show on Earth.

Here is why:

• The decision will set a precedent that will determine the value of an accelerated approval.

FDA grants such approvals when a company shows that a drug has an impact that is "reasonably likely to predict" clinical benefit. This is basically a guess, based on less-than-conclusive data.

In the case of Avastin, the benefit is defined as the drug's ability to delay progression of disease, as demonstrated in one randomized clinical trial.

However, this benefit to patients had to be confirmed in subsequent studies to earn a regular approval and stay on the market.

Two subsequent studies confirmed an improvement, which, alas, FDA's clinical advisors and the agency staff deemed to be insufficient to justify

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In the Cancer Centers:

NCI Scientists Lowy, Schiller Win Sabin Medal; MSKCC's Massagué Recieves Pasarow Award

DOUGLAS LOWY and **JOHN SCHILLER** were awarded the Albert B. Sabin Gold Medal Award for their discovery which provided the technology for commercially developed HPV vaccines. The annual award from the Sabin Vaccine Institute honors extraordinary contributions in the field of vaccinology.

Lowy and Schiller, of the NCI Laboratory of Cellular Oncology, Center for Cancer Research, are the first and second inventors on government-owned patents for HPV vaccines.

In 1992, they discovered that the single protein L1, of an animal model papillomavirus, could self-assemble into non-infection virus-like particles, and that antibodies raised against these particles were very effective at preventing viral infection of cultured cells. They subsequently determined that the L1's of the major cancer-associated HPVs behaved similarly, provided that the L1 genes were derived from virus producing lesions. They also

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Two Hours of Patient Testimony Will Open Avastin Hearing June 28

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continuation of the breast cancer indication.

A drug company got only one shot to demonstrate clinical benefit. Nothing in the law or regulations says you can't take multiple shots. It's just that no one had asked for a second chance, at least not publicly.

Until now.

Genentech wants another shot at confirmatory trials. If the agency rules in its favor in this dispute, sponsors could earn the opportunity to keep running multiple waves of confirmatory trials. Such trials can take years to complete, and while the trials are in progress, the drugs in question would stay on the market, and the cash registers would continue to emit pleasing sounds.

• It would be difficult—and more likely impossible—to conduct a trial involving an approved indication in the United States. Patients able to obtain Avastin (bevacizumab) would be more likely to do so rather than risking being randomized to, say, paclitaxel alone.

• If Genentech goes forward with conducting a confirmatory trial of Avastin, using the exact same regimen that served as the basis of an accelerated approval, this would likely be unprecedented.

The FDA Center for Drug Evaluation and Research encourages companies to conduct post-approval studies in combination with different agents, at different schedules, or in different stages of disease.

This approach helps to characterize the risks and benefits of the drug while allowing the applicant to obtain expanded indications.

• The Avastin decision is not likely to be based exclusively on science or interpretation of pertinent regulations.

There is ample room for politics to come into play.

In a "Notice of Hearing" made public May 11, the agency said that the June hearing would begin with two hours of testimony from patients. This is a change.

In an earlier document, a "Notice of Opportunity for Hearing," there was no mentioning of patient testimony. Chances are, nearly all the testimony will be positive. And, chances are, committee members will listen.

Is this change an effort by FDA to cross the t's and dot the i's as the indication is placed on skids? Or is this a way to create an opportunity to back away from a hardnosed stance? If anyone at FDA knows the answers, they aren't talking.

Two hours of testimony from patients is a lot—more than twice the time that is usually reserved. And it's clear that in the past, testimonials have swayed the committee.

One such episode occurred in 2003, when the committee voted in favor of approving the AstraZeneca drug Iressa (gefitinib) after hearing patients, most of whom received the drug on compassionate basis, state that the pill had extended their lives (The Cancer Letter, May 9, 2003).

Iressa received an accelerated approval, but was placed in a restricted access program after confirmatory trials showed that it didn't improve survival (The Cancer Letter, June 24, 2005).

Recently, AstraZeneca withdrew the drug from the U.S. market (The Cancer Letter, Feb. 11, 2011).

Even the current ODAC, at its most recent meeting, demonstrated willingness to consider special circumstances, voting for approval of two drugs for pancreatic neuroendocrine tumors (The Cancer Letter, April 15, 2011).

Avastin appears to be widely used in metastatic breast cancer. Though the drug is labeled for use in paclitaxel chemo-naïve patients, it's often used to treat refractory disease, and CMS and private insurers usually cover the $50,000 a year costs of treatment.

If the drug loses the indication, it would still be available off-label, since it's approved for metastatic colorectal cancer, non–small cell lung cancer, glioblastoma and metastatic kidney cancer. The U.S.

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breast cancer indication was worth $1 billion a year to the company.

If the drug loses its breast cancer indication, it's possible that CMS would institute a National Coverage Decision, which could lead to revocation of coverage. However, for now, CMS is refraining from restricting payment until resolution of this dispute.

How vulnerable is FDA to political pressure?

In the case of Avastin, the agency has been shown to be quite sensitive.

Last fall, the decision whether to start the accelerated approval proceedings was delayed past midterm elections, as conservatives portrayed any potential move to strip Avastin's breast cancer indication as something similar to convening "death panels."

When the agency said it would delay the decision, it said it would do so because of new data (The Cancer Letter, Sept. 24, 2010). However, no one in oncology was aware of any new phase III data that emerged since the meeting of ODAC, which recommended removing the indication (The Cancer Letter, July 23, Sept. 3, 2010).

Sources said the decision to hold off till after the election was made on the Commissioner's level or above, perhaps as high as White House.

Inventing the Process

To conduct the Avastin hearing, FDA will have to invent at least some bureaucratic procedures.

The 1992 law that created the accelerated approval process allows for involuntary removal of FDA approval for drugs that fail in confirmatory trials (57 FR 58942).

The provision is further described in 1997 amendments to the Food, Drug and Cosmetics Act (section 506b), which sets out criteria for expedited approval and withdrawal of approval of "fast-track products."

FDA argues that the section essentially codifies in the statute FDA's accelerated approval regulations. The Notice of Hearing describes the procedure scheduled for June 28-29 as "an informal hearing," and states that the decision is ultimately up to the HHS Secretary.

These provisions of the law have never been invoked because companies sponsoring drugs that fail in confirmatory trials simply pull them off the market when FDA suggests the idea.

Genentech didn't cave in.

According to documents made public by the agency, at the June 28-29 meeting, if ODAC will be acting as an equivalent of a jury, then CDER would be playing a role similar to that of an accuser—and the judge conducting the proceedings would be played by "Presiding Officer" Karen Midthun, director of the FDA Center for Biologics Evaluation and Research.

For the purpose of the hearing, the agency would be "observing separation of functions," which, in translation, means that Midthun will have to be as impartial as a judge, dismissing the fact that her CDER colleagues—the prosecuting team—are part of the same agency.

The Avastin Story In a Nutshell:

■ **May 2005.**

At the annual meeting of the American Society of Clinical Oncology, investigators present the results of a trial of a combination of Avastin (bevacizumab) and a weekly regimen of paclitaxel.

The trial, E2100, isn't designed to support registration, and Avastin's sponsor, Genentech, was initially reluctant to cooperate with the Eastern Cooperative Oncology Group to conduct it.

However, the trial finds that Avastin roughly doubles progression-free survival in metastatic breast cancer, but doesn't affect overall survival.

FDA's challenge would be to decide whether this study could support approval (The Cancer Letter, May 27, 2005).

■ **May 2007.**

FDA publishes a guidance to industry, titled "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," in which it describes a new approval standard:

"Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies."

■ **Dec. 5, 2007.**

In a 5-4 decision, the FDA Oncologic Drugs Advisory Committee votes against approval of the breast cancer indication for Avastin (The Cancer Letter, Dec. 14, 2007).

Approval would be unprecedented. It would mark the first approval of a non-hormonal agent in which evidence of a treatment effect on PFS alone was

This may be done because it's a fair guess that if Genentech loses, it will take the matter to court. At least an appearance of having bent over backwards in the "informal hearing" would be useful in that venue.

"Although no statute or regulation requires that separation of functions be applied to this proceeding, the agency is observing separation of functions as a matter of policy in this matter," the FDA notice of hearing states. "As the Center responsible for the proposed action, CDER, like Genentech, will be a party to the hearing and will be responsible for presenting its position at the hearing."

Of course Midthun wouldn't act exactly as the judge, since the ultimate decision is up to the HHS Secretary.

And ODAC members would not be a simple jury, since they will be allowed to question the presenters.

The presiding officer and three representatives from each party—CDER and Genentech—would be allowed to ask questions as well. In another matter involving politics and breast cancer, the administration demonstrated willingness to back away from scientifically purist stances in order to avoid setting off political landmines.

In November 2009, the U.S. Preventive Services Task Force recommended against routine screening of women between the ages of 40 and 49, and said that for older women, mammograms should be performed every two years (The Cancer Letter, Nov. 20, 2009)

This started a political firestorm, in which conservatives argued that the administration was preparing to ration health care services.

Facing a massive controversy, HHS Secretary Kathleen Sebelius quickly made distance between the administration and the recommendation of the panel of independent doctors and scientists.

To quell the outcry, she said that members of the panel "do not set federal policy, and they don't determine what services are covered by the federal government."

Later, the USPTF website was modified to include a "clarification" (The Cancer Letter, Dec. 4, 2009).

The Four Issues on the Table

Earlier in the controversy, Genentech argued that the decision to withdraw Avastin's breast cancer indication was inconsistent with precedents established in FDA's decisions on other drugs.

Now, it appears that the parties agree that arguing precedents is difficult in clinical medicine, and that discussion of this sort can consume all the time available for the hearing.

The Notice of Hearing, published by FDA May 11, reads:

"Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits.

"If the decision with respect to another product is in error, that would not justify continuing that error with respect to the MBC indication for Avastin. Moreover, as a practical matter, it would not be possible to evaluate the different circumstances associated with decisions with respect to other products in the context of this or any hearing.

viewed not as a surrogate endpoint, but rather as a clinical benefit because of the magnitude of the improvement in progression-free survival.

■ **Dec. 27, 2007.**

The New England Journal of Medicine publishes a paper stemming from the E2100 trial. The paper shows that Avastin significantly prolongs progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for disease progression, 0.60; P<0.001).

The paper is posted at http://www.nejm.org/doi/full/10.1056/NEJMoa072113

■ **Feb. 22, 2008.**

CDER approves the supplemental biological license application for Avastin for use in combination with the chemotherapy drug paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer (The Cancer Letter, Feb. 29, 2008)

The approval is subject to requirement that the product be studied further to verify and describe clinical benefit.

The two clinical trials identified to verify and describe clinical benefit are: Trial BO17708 (AVADO; NCT 00333775) and Trial AVF 3694g (RIBBON1; NCT 00262067). Both trials are in progress at the time ODAC makes the decision on accelerated approval.

These trials point to a risky strategy on the part of Roche, Genentech's parent company. The confirmatory trials evaluate Avastin in combinations other than weekly paclitaxel, the combination used in E2100.

AVADO tests Avastin in combination with docetaxel. RIBBON1 tests it with taxane-anthracycline combination and, in another arm, with capecitabine.

If the strategy produces a success, the company secures a broad label. If it fails, it fails completely.

"FDA has consistently rejected attempts to bring evidence with respect to decisions on other products into hearings on approval or withdrawal of approval of products and will not deviate from that position here."

Instead of sparring over precedents, the agency will focus on four issues directly related to the case in question.

The FDA Notice of Hearing is a remarkable document in part because it seems to be written from the middle ground, striving for at least an appearance of impartiality.

The document lays out the issues on the table. In this case, the parties agree that "During CDER's review of [the sBLA], Genentech proposed and CDER agreed that the AVADO and RIBBON1 trials could serve as the required trial(s) to verify and describe the clinical benefit."

Therefore, one ultimate issue in this hearing is:

Issue 1:) Do the AVADO and RIBBON1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?

If, after the hearing, the Commissioner concludes that these studies fail to verify the clinical benefit of Avastin for that indication, FDA may withdraw the approval.

CDER also seeks to base the withdrawal of approval on an alternative ground. This ground is set forth in the regulation and in the statute. Section 601.43(a)(6) states that FDA may withdraw approval if: "Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use."

Section 506(b)(3)(C) of the FD&C Act states that withdrawal is authorized if: "[O]ther evidence demonstrates that the fast track product is not safe or effective under the conditions of use."

In this case, the parties have agreed that the FDA-approved prescribing information for Avastin "is a fair and accurate description of the safety profile of Avastin," and that "[t]he safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information" (Joint Statement, paragraphs 22 and 23).

In light of this agreement, the dispute with respect to this issue centers on the effectiveness information for the breast cancer indication, and on the appropriate risk/benefit analysis to be made in light of that information as compared to the agreed risk of the product.

Thus, FDA does not anticipate that the hearing will involve any dispute about the safety information in the clinical studies. The safety profile of Avastin, described in its approved prescribing information, includes a black box warning concerning gastrointestinal perforation, surgery and wound healing complications, and severe or fatal hemorrhage. Genentech does not state that the use of this drug in the treatment of breast cancer is safe in the abstract. Instead, it states that the drug should be found to be safe because its use provides benefits to patients that outweigh its risks.

Applying the standard in the regulation and statute to the facts presented, therefore, the issue for resolution will be:

Issue 2.A:) Does the available evidence on Avastin demonstrate

Nov. 16, 2009.

Genentech submits the results of the AVADO and RIBBON1 trials to CDER.

AVADO and RIBBON1 meet their primary efficacy endpoints, but show a lower PFS benefit than E2100.

AVADO shows a 0.9-month median PFS increase and a 38 percent risk reduction (HR 0.62, 95% CI 0.48, 0.79) (p=0.0003).

In a later updated analysis of the AVADO trial performed at the time of the definitive analysis for overall survival, there is a 1.9-month median PFS increase and a 33 percent risk reduction (HR 0.67, 95% CI 0.54, 0.83)

In RIBBON1, the taxane/anthracycline comparison shows a 1.2-month increase in median PFS and a 36 percent risk reduction (HR 0.64, 95% CI 0.52, 0.80) (p<0.0001).

RIBBON1's capecitabine comparison shows a 2.9-month increase in median PFS with a 31 percent risk reduction (HR 0.69, 95% CI 0.56, 0.84) (p=0.0002).

July 20, 2010.

ODAC votes unanimously against converting the drug from accelerated approval to full approval (The Cancer Letter, July 23, Sept. 3, 2010).

Federal law precludes FDA from considering the cost of the therapies it regulates.

The agency has to act before Sept. 17, 2010.

The issue of Avastin's approval becomes political.

Some conservative groups describe ODAC's unanimous vote to recommend against approval as an act of rationing of health care. The words "death panels" and "Obamacare" are used (The Cancer Letter, Sept. 3).

that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

Issue 2.B:) Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication?

Both section 506(b)(3) of the FD&C Act and § 601.43(a) do not by their terms require the withdrawal of an accelerated approval even if the bases for withdrawal they describe are present. Instead, in each case, the statute and regulation state that FDA "may" withdraw approval in those circumstances. This standard reflects the fact that decisions on withdrawals of approval of products necessarily reflect judgment on FDA's part as to what actions are appropriate to protect the public with respect to approved products, and what uses of those products should be stated on the labels of those products.

Genentech has stated that the "core issue presented in this proceeding [is] whether FDA should maintain or withdraw the accelerated approval of Avastin for [the MBC indication], subject to Genentech's conduct of a new confirmatory study of Avastin with paclitaxel" (Letter from Michael Labson to the Presiding Officer, April 8, 2011, page 1). CDER has said on the issue: "Whether CDER has appropriately exercised its authority by proposing to withdraw approval of the MBC indication, rather than allowing the indication to remain on the label while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit."

Ultimately, while stated differently, the parties seem to agree that there is an issue of the propriety of CDER's proposed withdrawal of this indication now as opposed to the alternative of continuing the approval of the breast cancer indication while Genentech performs new clinical studies of Avastin with paclitaxel to verify the clinical benefit of the MBC indication.

This statement of the issue raises the question of why, to confirm an indication for combination use with paclitaxel, Genentech proposed, and CDER agreed, that Genentech could rely on studies of Avastin in combination with chemotherapeutic agents other than paclitaxel.

It appears that the explanation is that these studies were already ongoing at the time of the initial approval and both CDER and Genentech believed, at that time, that the results of these studies could provide evidence to verify the claim that Avastin, combined with paclitaxel, would have the effect indicated in the approved labeling.

FDA is addressing the issue of whether to maintain the accelerated approval while additional studies are conducted as the third issue for this hearing as follows:

Issue 3:) If the Commissioner agrees with the grounds for withdrawal set out in issue 1, issue 2.A, or issue 2.B, should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

While the parties would state the issues differently, the three

■ September 2010.

FDA delays the approval decision on Avastin, announcing that it needs another 90 days to review new data submitted by the company.

There are no new phase III data on the drug at that time, experts say. The decision date is pushed to Dec. 17, beyond the election (The Cancer Letter, Sept. 24, 2010).

■ Nov. 7, 2010.

Midterm elections.

■ Dec. 16, 2010.

CDER issues a notice of opportunity for hearing (NOOH) on a proposal to withdraw approval of the MBC indication for Avastin.

The NOOH states CDER's conclusions that AVADO and RIBBON1 failed to verify clinical benefit in the MBC indication, and that the risk/benefit assessment that supported the initial approval of the MBC indication had changed significantly and Avastin no longer met the safety and effectiveness requirements for continued marketing for that indication (The Cancer Letter, Dec. 17, Dec. 24, 2010; Jan. 20, 2011).

Centers for Medicare and Medicaid Services says it will continue to pay for therapy while the FDA proceedings run their course.

■ Jan. 16, 2011.

Genentech requests a hearing and submits the data and information on which it intends to rely at the hearing.

The case is precedent-setting. It marks the first time the agency would use—and, to some extent, invent—the withdrawal provision of its accelerated approval regulations.

Ultimately, the agency decides to appoint a presiding officer, who would conduct the hearing impartially. This is not specifically required in the regulation.

issues stated in this notice will be those upon which the Commissioner expects to decide this matter. If Genentech prevails on issues 1, 2.A, and 2.B, the approval will be continued.

If CDER prevails on issue 1, 2.A, or 2.B, the question of withdrawal will depend on issue 3.

In addition to the issues 1, 2.A, 2.B, and 3, Genentech has proposed to raise issues concerning the consistency of CDER's position here with CDER's decisions with respect to other products for the treatment of MBC or of other products approved under the accelerated approval program. Issues with respect to FDA action on other products are not relevant to this proceeding.

Dueling Summaries of Evidence

On May 13, Genentech and FDA submitted summaries of evidence they would present at the hearing six weeks later.

The filings present dueling answers to the same four questions.

One highlight of the FDA is the appendices—there are 35 documents, which include meeting summaries and "Complete Response" letters to Genentech.

FDA's central argument is that the hypothesis that Avastin would produce a different response in combination with weekly paclitaxel (a la E2100) than it did in combinations used in confirmatory trials is not based on convincing clinical or pre-clinical evidence.

Rather, the impact of the drug in E2100 could be explained by the flaws in that study, CDER argues.

The filing contains the following discussion of this justification for the trial:

Based on the data from the AVADO and RIBBON1 trials, Genetech hypothesizes that the specific chemotherapy partner with which Avastin is used will influence the magnitude of the drug's effect in treating MBC.

The company argues that the MBC approval for Avastin should be maintained while it conducts further studies with paclitaxel, the chemotherapy partner used in the E2100 trial.

Genentech argues that because the chemotherapy partner influences the magnitude of the treatment effect, only data generated with that chemotherapy partner are relevant to verifying the benefit of Avastin in combination with paclitaxel. Genentech claims that the lower magnitude of effect on median PFS in the AVADO and RIBBON1 trials is an observation consistent with clinical experience that some chemotherapy agents (and their dose and schedule) yield different levels of treatment effect.

Genentech thus contends that the lesser improvement in PFS in these confirmatory trials merely suggests that the choice of different chemotherapy partners in each of the trials may influence the magnitude of benefit observed in each trial, and not that the AVADO and RIBBON1 trials invalidate the findings of the E2100 trial.

To support its assertions, Genentech postulates that while "multiple hypotheses can be generated for why a differential effect would be observed with distinct chemotherapy partners, the current lead hypothesis is that chemotherapies that provide for prolonged

- **April 7, 2011.**
  In response to direction from the presiding officer to consult with each other and submit an agreed statement of the issues in dispute in this hearing. Counsel for Genentech and CDER report that they are unable to reach agreement on how to frame the issues to be resolved. The issues for decision will thus be stated in accordance with the statute and regulations.

- **May 11, 2011.**
  FDA publishes a Notice of Hearing.

- **May 13, 2011.**
  Genentech and FDA submit summaries of arguments they would make at the hearing.

- **May 27, 2011.**
  Genentech and the FDA's Center for Drug Evaluation and Research will separately submit their lists of witnesses who will present at the hearing. Also submitted will be summaries of the issues each witness would address.

- **June 3, 2011.**
  Genentech and CDER will submit their lists of hearing representatives (those who may question the presenters).

- **June 28-29, 2011.**
  The hearing will be conducted.
  Additional information will be published in the FDA docket.

combined exposure with Avastin may yield the strongest treatment effects."

This hypothesis, as Genentech itself concedes, remains unproven…

As CDER has explained, "assertions that there is a unique interaction between Avastin and paclitaxel providing a rationale for the magnitude of PFS change observed only in E2100 has not been substantiated by either clinical or non-clinical evidence."

Genentech does not disagree. Genentech argues, however, that because the magnitude of the treatment effects observed with different chemotherapy partners is different, those differences must be due to the use of different chemotherapy partners.

To support this argument, CDER expects that there should be some proven scientific basis for substantial differences, such as evidence of drug interactions or synergistic/overlapping toxicity between Avastin and other chemotherapy drugs. There is none. To the contrary, all evidence submitted to date (e.g., population pharmacokinetic analyses) indicates that there are no unique interactions between Avastin and any of the chemotherapy partners administered in the trials. In the absence of a scientifically supported basis for chemotherapy-specific interactions, the more likely explanation for the failure of the clinical trials to verify the results of the E2100 trial is that the magnitude of the PFS treatment effect observed in E2100 is an outlier.

Genentech: Approval Standard Inconsistent

In its filing, Genetech argues that FDA has been inconsistent in setting approval standards.

An excerpt follows:

CDER has not been clear in articulating a consistent standard for the showing of clinical benefit necessary to support approval for treatments in first-line MBC.

This is seen in the regulatory history for Avastin in MBC. The uncertainty resulting from the lack of a clear, predictable, and consistent regulatory standard risks discouraging oncologic drug development in MBC.

When CDER granted accelerated approval to Avastin for first-line MBC, the agency accepted AVADO and RIBBON1 as confirmatory studies, with PFS as the primary endpoint. CDER did not establish a specific magnitude of PFS improvement necessary for continued approval and, in fact, accepted AVADO as a confirmatory study aware that the final protocol-defined PFS data showed an improvement in median PFS at the time of 0.8 months with an HR of 0.64.

Similarly, the agency knew that neither confirmatory study was powered to show an OS benefit.

CDER accordingly premised conversion from accelerated to full approval on a "demonstrated improvement in progression-free survival and evidence that survival is not impaired."

Although it was clear that AVADO and RIBBON1 were not powered to show an OS benefit, the agency now cites the studies for failing to show a statistically significant OS effect. Then, CDER stated only after its decision to withdraw Avastin's MBC indication that any PFS effect "must confirm the magnitude of treatment effect of E2100."

Significantly, CDER has not provided general guidance to the broader industry on these issues, limiting its actions to Avastin.

CDER also has not articulated a clear rationale for its view that a 5.5-month improvement in median PFS is clinically meaningful but lesser improvements are not.

It is important to maintain clear and consistent approval criteria to establish a predictable regulatory environment that minimizes uncertainty and facilitates development efforts by sponsors.

Patient advocates and members of the oncology development community have expressed this concern. The Melanoma Research Foundation, for example, noted the increased "regulatory burden on drug development" caused by poorly-defined approval standards: "criteria that are unclear or are changed mid-process adds to cost of development and, more significantly, results in delays in ensuring patients have access to drugs that may be life-saving."

Other groups have also urged FDA to provide "standards and consistent processes" for approval.

CDER should not take adverse regulatory action that would deprive thousands of MBC patients of a valuable treatment, having failed to set out clear standards for drug development ex ante.

The summary documents by Genentech and FDA are posted at www.cancerletter.com/categories/documents.

All documents, which include the appendices to the FDA filing, are posted at http://1.usa.gov/lnikAy.

In the Cancer Centers:

The Ohio State University Receives Over $140,000 from Komen Columbus

(Continued from page 1)

developed widely employed tests for measuring HPV infection-inhibiting antibodies and conducted the first controlled clinical trial of an HPV VLP vaccine

Today, Lowy and Schiller are working with the World Health Organization and other organizations to find ways to distribute HPV vaccines to those in need. They have also partnered with pharmaceutical manufacturers in emerging countries to produce second generation HPV vaccines that may be cheaper to manufacture or easier to deliver to underserved populations.

JOAN MASSAGUÉ has received the Pasarow Award in Cancer Research, which recognizes accomplishments in cancer, cardiovascular disease, and neuropsychiatry research.

Massagué holds an Alfred P. Sloan Chair at Memorial Sloan-Kettering Cancer Center, and is chair of the Cancer Biology and Genetics Program in the Sloan-Kettering Institute. He is also a Howard Hughes Medical Institute investigator and a member of the National Academy of Sciences.

MELISSA PESSIN has been appointed chair of the Department of Laboratory Medicine at Memorial-Sloan Kettering.

Previously, she served as the vice chair for operations in the Department of Pathology at Mount Sinai Hospital, where she led the updating and replacement of the laboratory automation system. Pessin is board certified in clinical pathology/laboratory medicine and transfusion medicine/blood banking.

She is a fellow of both the College of American Pathologists and the American Society of Clinical Pathologists.

THE OHIO STATE UNIVERSITY will receive over $140,000 in grants from Komen Columbus, to fund breast cancer programs at the Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

The four programs receiving grants are:

• ACE that Mammogram: Reducing Issues Related to Access, Cost & Expertise. A $60,000 grant will expand efforts to educate and screen eligible women in the Columbus area with mobile mammography visits to underserved communities and those with access issues.

• The Black Bonnet Project. A $13,275 grant focuses on Amish women living in Gallia and Jackson Counties to help improve their breast cancer knowledge and increase breast cancer screening.

• Sister Screen Saver. A $26,340 grant will provide mobile mammography screening services at community churches and educate African-American women about breast cancer prevention and early detection, including a screen saver and video. The program will provide information on local resources for free or low-cost mammograms and support services.

• Think Pink. A $41,620 grant to the Meigs County Cancer Initiative will help provide education about breast health as well as increase mammography screening rates among women ages 40 and older.

EU News:

The WHO Accepts Turkey Into Its Cancer Research Agency

The WHO International Agency for Research on Cancer accepted Turkey as its 22nd Participating State. Turkish cancer researchers will have opportunities to participate in international collaborations aimed at reducing the cancer burden worldwide. Turkey will also have a role in the governance of IARC as a participating state.

Cancer has become Turkey's leading public health problem, with 170,000 new cases a year. Cancer incidence in Turkey is substantially higher in men than in women (275 and 165 per 100,000, respectively).

Lung and prostate cancers are the most common cancers in men, and breast cancer is the most common in women. It is estimated that if effective measures are not implemented by 2030, cancer-related expenditures in Turkey will double, and 1.3 million people will be afflicted with cancer.

Correction: In a previous version of this issue, *In the Cancer Centers* was published with the incorrect headline. It has been changed.

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