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By Defending Potti, Duke Officials Become Target Of Charges Of Institutional Failure

By Paul Goldberg

A year ago, Duke University might have been able to dispense with researcher Anil Potti as an outlier who somehow infiltrated a world-class research institution.

Had they wanted to check Potti's credentials, five minutes on Google and a few phone calls would have inspired them to keep checking. They would have learned that Potti was not the Rhodes scholar he claimed to be. After all, deceptions about his credentials were in plain view—just like the problems with his science.

Instead, when questions about Potti's science emerged in scientific literature and in alarms sounded by internal critics, the Duke administration

(Continued to page 2)

FDA News:

ODAC Votes To Strip Breast Cancer Indication From Avastin In First Such Action By Committee

By Paul Goldberg

In an FDA "first," the Oncologic Drugs Advisory Committee voted to strip an indication from a cancer drug that was approved under the accelerated approval mechanism.

At a meeting July 20, the committee voted 12 to 1 to remove locally advanced or metastatic breast cancer from the label of Roche's widely used agent Avastin (bevacizumab).

The vote represents the first time the FDA staff consulted the oncology advisory committee on revocation of an accelerated approval. If the agency follows the committee's advice—which it's expected to do—Avastin would become the second drug to lose an indication received under the accelerated approval mechanism.

• In 2005, the drug Ethyol (amifostine), marketed by MedImmune, lost one of its indications, reducing the cumulative renal toxicity from cisplatin in non-small cell lung cancer. The drug is marketed for its other indications. The indication was withdrawn because of emergence of better treatment options for non-small cell lung cancer.

• Last month, Mylotarg (gemtuzumab ozogamicin) was withdrawn by the sponsor, Pfizer Inc., because three studies failed to demonstrate its efficacy in the approved indication, acute myeloid leukemia. Technically, this is not a revocation of an indication.

• Iressa (gefitinib), sponsored by AstraZeneca, was placed in a

(Continued to page 6)

Statisticians Write To Varmus; Lancet Registers Its Concern

(Continued from page 1)

formed a protective barrier around the man they considered their star, forming committees that operated in secret, and then incorrectly portraying the findings of one of these committees as validation of Potti's science (The Cancer Letter, May 14. 2010).

Prompted by revelations in this publication last week, the Duke administration suspended Potti and—for the second time—stopped enrolling patients into three single-institution trials that used his genomic technology to assign patients to chemotherapy.

"The recent allegations made last Friday regarding Dr. Potti's credentials are concerning and Duke immediately initiated a formal institutional investigation," said Douglas Stokke, a Duke spokesman. "In the interim Dr. Potti is on administrative leave pending the outcome of the investigation. Although we have had confidence in the peer review assessments of the science, in this new light the investigators of three clinical trials, based in part on Dr. Potti's published work, elected to suspend enrollment of new study subjects on Sunday, July 18, until a full review of the underlying data and a re-review of the science can be completed."

Duke officials didn't reveal who at the university is conducting the "formal institutional investigation" or how the scope of that investigation has been defined.

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Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

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University officials similarly didn't elaborate on the source of their "confidence" in the widely criticized peer review procedures they employed in last year's probe of Potti's work.

In a July 20 email to the faculty, Duke Chancellor for Health Affairs Victor Dzau was similarly vague in describing the probe. "As there is likely to be additional news related to this situation, I wanted to assure you that we have put in place a robust process to assess this situation," he wrote.

The names of the individuals conducting the investigation are important, because the same people who were responsible for Potti's spectacular rise at Duke and who protected the university's interests as this controversy became public could not be described as impartial. Their involvement could be expected to taint the probe.

Thirty-Three Top Biostatisticians Write to Varmus

Duke administrators accomplished something monumental: they triggered a public expression of outrage from biostatisticians. In a first such action in anyone's memory, 33 top-level biostatisticians wrote a letter urging a public inquiry into the Potti scandal.

The letter, which cites the potential for harm to patients, was addressed to NCI Director Harold Varmus, a molecular geneticist not known for tolerance of nonsense.

The message of the group's letter is simple: there is a world off-campus, and by the standards of that outer world, Duke's handling of the investigation of Potti's science was simply unacceptable.

Copies of the letter went to the American Cancer Society Chief Medical Officer Otis Brawley, who suspended payments on a $729,000 grant to Potti; the Department of Defense, which funds a Potti trial through the peer-reviewed breast cancer program; the HHS Office of Research Integrity; this publication; and Duke Comprehensive Cancer Center Director H. Kim Lyerly. (Lyerly is not known to have played a role in the scandal, which was handled on the level of associate deans.)

The text of the letter follows:

"We understand that NCI is aware of three cancer clinical trials funded by the Department of Defense and Duke University, based at least in part on results reported in papers by Duke oncologist and genomics researcher Anil Potti and Joseph Nevins. Drs. Potti, Nevins, and their colleagues have made claims about the ability of RNA expression patterns to predict responses to therapy in cancer patients, and these prediction models are currently being used in Duke's clinical trials to help

physicians choose the treatments that cancer patients receive.

"Recently, published and peer-reviewed re-analyses of the work done by Potti and Nevins revealed serious errors that questioned the validity of the prediction models upon which these ongoing clinical trials are based. This led to a temporary suspension of the trials and a Duke-led review involving independent statistical experts. However, despite written statements from the external experts, who uniformly stated they were not given sufficient information to confirm the validity of the models, the trials have been reinitiated.

"We, the undersigned, who have followed this debate closely have concluded that the inability of independent experts to substantiate the above researchers' claims using the researchers' own data means that it is absolutely premature to use these prediction models to influence the therapeutic options open to cancer patients.

"We strongly urge that the clinical trials in question (NCT00509366, NCT00545948, NCT00636441) be suspended until a fully independent review is conducted of both the clinical trials and of the evidence and predictive models being used to make cancer treatment decisions.

"For this to happen, sufficiently detailed data and annotation must be made available for review. The data should be sufficiently documented for provenance to be assessed (as both gene and sample mislabeling have been documented in these data), and the computer code used to predict which drugs are suitable for particular patients must be made available to allow an independent group of expert genomic data analysts to assess its validity and reproducibility using the data supplied.

"Should the data and analysis presented by Potti, Nevins, and colleagues be validated, it would then, of course, be appropriate to reinitiate the trials. Until that time, however, we believe that the steps outlined in this letter are necessary given the potential of patients being assigned to improper treatment arms in the clinical trials in question and of the associated potential risk posed to these patients.

"We are therefore requesting that NCI either intercede directly, or work with other entities with jurisdiction over these trials (e.g. ORI, DoD and Duke University) to ensure that the above requirements are met before these trials are allowed to continue enrolling patients."

The letter is signed by Who's Who of biostatistics. Perhaps most significant is the signature of Mauro Delorenzi, head of Bioinformatics Core Facility at the Swiss Institute of Bioinformatics, a Potti co-author on a paper published in Lancet Oncology in December 2007 (Bonnefoi *et al.*)

In an interview with The Cancer Letter early in the controversy, Nevins said that the Lancet Oncology paper represents a blinded validation of the Duke technology (The Cancer Letter, Oct. 2, 2009). This claim prompted Delorenzi to counter that the data were not blinded (The Cancer Letter, Oct. 23, 2009).

Lancet Issues Expression of Concern

The Lancet Oncology editor David Collingridge July 23 issued "An Expression of Concern" over the paper in question.

The text of the journal's statement follows:

"On July 21 and 22, 2010, The Lancet Oncology was contacted by Richard Iggo and Hervé Bonnefoi on behalf of the 15 European co-authors of an article we published in December, 2007. The authors expressed grave concerns about the validity of their report in light of evolving events. Their worries had arisen because statisticians from the MD Anderson Cancer Center, TX, USA, had questioned the methodology used to generate the response predictions. Repeated attempts by Iggo and colleagues to contact their co-authors at Duke University, NC, USA, who had been responsible for the statistical analyses in the report, had been ignored.

"In addition, a large group of scientists wrote on July 19, 2010, to Harold Varmus, director of the National Cancer Institute, MD, USA, also expressing concerns about the validity of the prediction models and calling for three ongoing clinical trials to be suspended until 'a fully independent review is conducted of both the clinical trials and of the evidence and predictive models being used to make cancer treatment decisions.'

"Furthermore, a news story in the New York Times of July 20, 2010, noted the suspension of Anil Potti (one of the article's co-authors) from Duke University School of Medicine on the grounds that he had falsely claimed to be a Rhodes scholar. The editors of The Lancet Oncology are now in the process of ascertaining the validity of these claims.

"However, pending investigation and clarification, we now issue an expression of concern about the article by Bonnefoi and colleagues. The 15 European co-authors have been informed and concur with this notice. The four co-authors from Duke University have been contacted separately. As and when further information becomes available to us we will pass this on to readers directly."

The effect of the Duke scandal on medical literature

could be substantial, as PubMed lists 128 papers with "Potti A" among authors.

The text of the letter from the biostatisticians, with the list of signatories and an appendix listing the most important of the potentially contaminated papers, appears at www.cancerletter.com/special-reports.

More Questions of Stewardship of Public Funds

By sending this letter, the statisticians are saying that they have no confidence in Duke's previous investigation of the scandal and are urging NCI to march in.

This lack of confidence in Duke administration's fitness to serve as stewards of public funds also resonates in a letter to Duke from the ACS chief physician Brawley:

"We have recently become aware that Dr. Anil Potti of your institution submitted a Mentored Research Scholar grant application in October 2006, to the American Cancer Society that may have incorrect biographical information about him. The application was judged worthy of funding and a grant was awarded to Duke University in the amount of $729,000 for the period July 1, 2007, through June 30, 2012.

"We are extremely concerned about these allegations as we take accuracy in the scientific process very seriously. We ask that you provide us with an official curriculum vitae for Dr. Potti and an explanation of any variance it may have from the one included in his grant application (copy attached). We are also interested in what action you are taking to assure that the funded work has been done to the highest standards of science, accuracy and integrity. Payments on the grant are being withheld until these issues are resolved."

As Potti's mentor on the grant, Nevins would have been expected to complete a portion of the application. A copy of Brawley's letter is posted at www.cancerletter.com/special-reports.

The bio released by ACS claims that Potti was a "1995 Rhodes Scholar (Australia)." There is no such thing as a "Rhodes Scholar (Australia)." Also, the bio submitted to ACS includes the claim that Potti had a "research fellowship" at "Queensland Research Institute" in Australia under mentorship of Gordon McLaren. Here, too, problems are transparent: no such institution exists. The place that comes closest to that name, Queensland Institute of Medical Research, says Potti had never worked there. A call to McLaren revealed that he had spent a brief sabbatical at QIMR, but didn't know Potti at the time (The Cancer Letter, June 16, 2010).

The bio also claims that Potti received the 2004 American Society of Hematology Clinical Research Scholar award, which he, in fact, did not.

Duke has regarded Potti as an academic star who brought in millions of dollars in grants, publications in top-tier journals, and patents for technologies that had the potential to bring about fundamental change in cancer care. Duke's Office of Licensing & Ventures still lists three inventions that list Potti and Nevins among inventors. The projects are posted at http://olv.duke.edu/search?SearchableText=Potti&go.x=11&go.y=11&go=go. A copy is posted at www.cancerletter.com/special-reports.

Recently, Potti was featured in Duke's television commercials, in which he spoke of "personalized medicine" available at the medical center.

Meanwhile, biostatisticians Keith Baggerly and Kevin Coombes at MD Anderson Cancer Center were unable to validate the results claimed by the Duke team, convincing journals to run multiple corrections from Duke investigators (and even one correction of a correction) of Duke's work. A publication by Baggerly and Coombes led Duke to briefly suspend clinical trials based on the technology (The Cancer Letter. Oct. 2, Oct. 9, and Oct. 23, 2009; and Jan. 29, 2010).

Baggerly and Coombes were able to examine only one of the Duke team's two principal technologies, because it was based on publicly available materials, a collection of cell lines maintained at NCI. They were in no position to verify the Lung Metagene Score assay, which was featured in a paper in a paper in the Aug. 10, 2006, issue of the New England Journal of Medicine.

However, a subsequent analysis by Kerby Shedden *et al.* in the August 2008, issue of Nature Medicine found that LMS had no predictive value. Also, earlier this year, NCI and Cancer and Leukemia Group B stopped use of LMS in clinical trials after biostatisticians were unable to confirm its usefulness (The Cancer Letter, May 14).

"LMS was independently analyzed by CALGB statisticians at Duke," the cooperative group chair Monica Bertagnolli said in an email to The Cancer Letter.

Until last month, Duke held the grant for the CALGB statistical center. "These statisticians were Duke faculty members who work with CALGB rather than with the Nevins group. The CALGB statisticians, just like Dr. [Lisa] McShane at the NCI, found by their review that it was not appropriate to use the LMS for further study. CALGB never used LMS to assign patient care, therefore this meant that CALGB decided not to study LMS at all, and therefore put into place

an amendment removing it entirely from the CALGB study (where it was previously a stratification factor only). This decision was made in collaboration with the NCI in May."

Reports of "Intimidation"

To be credible, the institutional investigation would need to address the role of the Duke administration in restarting the trials last January.

Last January, Duke officials said to The Cancer Letter that outside reviewers consulted by the university's Institutional Review Board concluded that "the approaches used by the Duke clinical predictors are viable and likely to succeed." While Duke officials cited a positive statement from the report, they didn't mention the negative findings or the fact that the committee didn't review all of the major errors that were known to exist.

Duke officials said that the conclusion was based on "an examination of the underlying scientific methodology that had been published by the Duke investigators, and used in these trials." The statement said that the conclusion was "confirmed by reviewers' own independent analysis using the respective datasets and prescribed methods of analysis."

The summary was signed by Michael Cuffe, vice dean, medical affairs and Sally Kornbluth, vice dean for research.

Since Duke chose to keep the report confidential, under ordinary circumstances, the review documents would not have become public. However, Duke officials sent a copy to NCI. There, the document became subject to the Freedom of Information Act, and—in a form heavily redacted by Duke—was obtained by The Cancer Letter (The Cancer Letter, May 14, 2010).

After reviewing the reports, Baggerly and Coombes said the documents do not amount to a validation of Potti's and Nevins's work. Negative findings from the report were not mentioned. These included a statement by the committee that it was unable to reconstruct how the studies were performed based on review of the literature.

Further, major errors made by the Duke investigators while the investigation was underway were not mentioned, despite the fact that the errors involve two of the drugs being used in clinical trials and that Duke deans, its IRB and NCI were informed of these errors before the report was finalized, Baggerly said.

The names of the biostatisticians Duke consulted before restarting the trials in January are not publicly known.

Now, 33 of their colleagues said publicly that they, too, have no confidence that the report's findings justify the decision to restart trials and, by inference, in Duke's ability to separate the science from institutional self-interest.

Meanwhile, sources at Duke describe a tense atmosphere, where administration officials are threatening staff with retribution, including legal action, should they speak with any outsiders, and those believed to be in charge of the investigation may themselves be implicated if the investigation has the appropriate scope.

"Rather than ask anyone who had knowledge or suspicions about Potti's work or background, including his Rhodes lies, to obtain his Duke fellowship, to come forward, they have warned people not to even Google the name 'Anil Potti,'" a source said. "They are walking around talking about how 'sorry' they feel for him—this is the guy who submitted false credentials to the NIH, the ACS, and who knows who else, to obtain millions of dollars in grants. They just don't get it.

"The biggest problem is that the fox may be guarding the henhouse. The same people who had been warned about the fact that Potti's data could not be replicated may be in charge of the investigation and response. The university president and board of trustees should take charge with outside investigators and scientists—not the medical deans.

"They should be interviewing—in a welcoming and encouraging atmosphere—anyone who had worked in the Nevins and Potti labs, the fellowship committee, and beyond, to figure out who suspected what about bad science and bad credentials and which deans they told. Because deans were explicitly warned at least two or three times that the data could not be replicated and that the scientific methods were a joke. Those who gave the warnings are now in hiding because of the toxic atmosphere," the source said.

"Right now, unless someone intervenes, those in charge may well be on track to covering up their own complicity."

Other accounts of problems at Duke are leaking out. "Have you explored the intimidation going on at Duke right now where researchers are being threatened if they talk to any outsiders about what they know?" an insider wrote on a blog beneath an article in the Raleigh News & Observer. The comment appears at http://blogs.newsobserver.com/campusnotes/duke-doc-definitely-not-a-rhodes-scholar#comments.

Another individual self-identified as a Duke scientist commented on The New York Times story

about the scandal: http://prescriptions.blogs.nytimes.com/2010/07/20/duke-suspends-researcher-halts-cancer-studies/.

"We'd opt to not comment on a single anonymous comment to a blog," Duke spokesman Stokke said.

"100 Percent Crap"

Donald Berry, chairman of the Department of Biostatistics and head of the Division of Quantitative Sciences at MD Anderson, said the Duke scandal puts the entire field of genomics at risk.

"About 10 years ago, I read in Newsweek that the high-paying, glamorous job of the new millenium was bioinformatics," Berry, one of the statisticians who signed the letter to Varmus, said in an email. "We were going to cure diseases in the near time frame. (Francis Collins was at the forefront of pushing this attitude.) My reaction was that we didn't know how to handle one gene (and we still don't), never mind 20,000 genes.

"It was clear then, and it is clear now, that false-positive leads pop up all over the place and we have to keep banging them back down, as in 'Whack-a-Mole.' I say 'we.' Unfortunately, few people understand this, although the plethora of unconfirmable observations gets people asking, 'Why?' I've been saying for years that 90 percent of biomarkers studies are crap. And this is so even if the logistical, study conduct issues are carried out flawlessly. Sloppiness a la Potti/Nevins leads to 100 percent crap."

This scandal's aftermath for genomics could be analogous to Werner Bezwoda's contribution to high-dose chemotherapy and bone marrow transplantation for breast cancer. Bezwoda, a South African physician, was found to have fabricated data supporting continued use of the procedure.

"Bezwoda's goal may have been to build a trial that he 'knew' would [produce the desired] result, if only he could afford to actually build a trial," Berry said. "He may have reflected an attitude that was present in the transplant community. In any case, his actions hastened the demise of the transplant movement. The funding dried up as soon as Bezwoda was exposed.

"The same sort of thing may happen in the Potti/Nevins aftermath. I hope it doesn't, and it is bound to be less severe. In the best of worlds, we would simply ignore their studies. But despite a few positive stories such as Oncotype DX, people start to think we have to fake it to make it, and they lose confidence," Berry said.

"A few years ago, I read in Newsweek that 'bioinformatics is a bust!' People are fickle. And even some of the people actually working in the area fail to understand just how daunting the problem is to solve."

Disclosure: ACS Chief Medical Officer Otis Brawley and Paul Goldberg are writing a book about evidence-based medicine under contract with St. Martin's Press.

FDA News:

Confirmatory Trials Showed Lower PFS Than Earlier Trial

(Continued from page 1)

restricted access program that barred physicians from prescribing it to new patients. This action was caused by failure of confirmatory trials to demonstrate a survival advantage. These restrictions do not amount to losing an indication.

Avastin is approved for use in combination with paclitaxel, for HER2-negative metastatic breast cancer who have not yet received chemotherapy for advanced disease. The agency deadline for taking action is Sept. 17.

Since the agent is approved for other indications, it will remain available for off-label use in breast cancer. Nonetheless, the loss of the indication could prompt some insurers and, possibly, the government to deny payment.

Getting an accelerated approval used to be equivalent to a full approval. FDA could do little but try to shame sponsors into conducting confirmatory trials to demonstrate that the agents provide tangible benefits.

Now, the agency has stronger authority under the FDA Amendments Act of 2007 to require confirmatory studies for drugs approved based on surrogate endpoints.

Last month, Richard Pazdur, director of the agency's Office of Oncology Drug Products, said that sponsors would be asked to present detailed plans for conducting confirmatory studies as part of the end of phase II meetings with the agency. Also, the agency is considering using ODAC to conduct annual reviews of outstanding confirmatory study commitments related to accelerated approval drugs (The Cancer Letter. June 25, 2010).

Avastin received an accelerated approval for the breast cancer indication in 2008, but two rigorously designed confirmatory studies conducted by the company failed to reproduce the dramatic improvement in delay of progression seen in the initial trial. The drug was approved based on the E2100 trial conducted by

Eastern Cooperative Oncology Group.

The accelerated approval was controversial. When ODAC considered the indication in December 2007, it voted 5 to 4 against approval. E2100 was never designed as a registration trial, there were problems with collection of data and interpretation of images.

However, the magnitude of effect—a 5.5 month increase in PFS—was sufficient to convince the agency to give the drug an accelerated approval for the indication. Two and a half years and two trials later, the agency found itself looking at two trials that presented very different picture:

• The Avado study (STN 125085\191), a 736-patient trial compared two different doses of Avastin and docetaxel with placebo in metastatic or locally recurring breast cancer. PFS was 7.8 months in the placebo arm and 8.9 months in the high dose Avastin arm. The finding was statistically significant. Overall median survival appeared to be lower on the Avastin arms. Survival was at 31.9 months for placebo, 30.8 months for lower dose Avastin and 30.2 months for higher dose. The findings were not statistically significant.

• The Ribbon 1 study (STN 125085\192) randomized 1,237 patients to chemotherapy with and without Avastin. The randomization was 2:1. In the taxane/anthracycline cohort, median PFS was 8 months for chemotherapy with placebo and 9.2 months for chemo and Avastin. In the capecitabine cohort, PFS was 5.7 months for placebo and 8.6 months for Avastin. The findings were statistically significant. Median survival was 22.8 months for capecitabine and placebo and 25.7 months for capecitabine and Avastin. The finding is not statistically significant. In the taxane and anthracycline cohort, the hazard ratio for median survival favored placebo.

ODAC's discussion of stripping Avastin's breast cancer indication is important because it constitutes the first ever public discussion of this sort.

An excerpted transcript follows:

WYNDHAM WILSON (ODAC chair and chief of Lymphoma Therapeutics Section at the NCI Center for Cancer Research): This is a very difficult question, because we are being asked to evaluate whether or not an indication for Avastin should be removed. These confirmatory trials are large, and they have across subset analyses not been able to show a survival advantage. They all show a very small benefit in PFS, and also they show toxicity from Avastin, which can be life-threatening and can lead to death in some patients. So I think the question we need to ask ourselves at this point is how comfortable do we feel allowing this indication to remain?

JEAN GREM (oncologist, University of Nebraska Medical Center): Previously, ODAC voted against approval, and in that case FDA did not follow our recommendation and approved it. I don't want to feel guilty, as if basically, FDA made a mistake, and they did it with good intentions.

PAZDUR: We do not think we made a mistake here. Obviously, accelerated approval is to take a look at the data, and if the data look promising, then to ask for confirmatory trials to clarify this. Believe me, we do not look at this as a mistake, and it's not a judgment on our past approval of the drug.

GREM: Because right now we are made to feel guilty.

PAZDUR: Let me absolve you of your guilt. We had data in 2008. We have more data here. And that's what we are looking at. There is a far more comprehensive picture here of the role of Avastin than we did in 2008. And many of you who were on the committee point out that you had different opinions then, based on one trial versus seeing the rest of the data. And that's why accelerated approval was given. We look at it as a split vote. Five-to-four is not some landslide vote. In internal discussions we felt that going the route of accelerated approval and looking at additional trials was warranted. We have those data now. What's the entire evaluation of Avastin in 2010, given the complete data package that we have. We are not talking about removing Avastin from the market. We are talking about removing indication. And, yes, they can study the drug further in breast cancer and submit any positive trial that demonstrates clinical benefit. But we don't look at it as a mistake. We look at this as part of the process of accelerated approval. And drugs will come off accelerated approval because there is a risk here in approving these drugs. And this is management of that risk.

JOANNE MORTIMER (vice chair, Medical Oncology & Therapeutics Research, City of Hope): I voted for [approval] last time we voted. My thought process as someone who takes care of these patients, the more than doubling of response rates and the doubling of PFS is incredibly meaningful. I looked hard at the fact that this was a cooperative group trial, which really does reflect community practice. Also, the primary endpoint for approval as first-line therapy was improvement in overall survival, which arguably is a justifiable endpoint. But having said all that—and the data from trials that are robust—but sponsored by

the pharmaceutical company—it's really hard to justify continuing this indication.

VIRGINIA MASON (executive director, Inflammatory Breast Cancer Research Foundation): What is the timetable, and is there a time limit for a compound to be moved out of accelerated approval status?

PAZDUR: The sponsors are supposed to do the trials with "due diligence." That does not have a regulatory definition. My personal definition of due diligence is that the sponsor should conduct these trials with the same enthusiasm and resources as they would with any registration trial. Obviously, we have discussed this at several ODAC meetings, and we plan on having an ODAC meeting in 2011 to look at accelerated approval commitments. We've made public statements regarding that with recent withdrawal of the Mylotarg application for accelerated approval. This is not the first time that we have done this. Most of the sponsors after having a discussion will usually voluntarily withdraw an indication. However, if this does not occur, there are other mechanisms outlined in the regulations for removing the indication.

MASON: Is there a way to tease out if there is a population of patients best responds to treatment?

WILSON: I think we have to be careful not to be distracted by trials in different groups that do not inform this indication, or subset analyses. We are at this point addressing whether or not based on the data we have seen so far in two large, well conducted studies in the same patient population in which the accelerated approval indication was made show clinical benefit. I think we should be careful not to get distracted by what-ifs.

BRENT LOGAN (associate professor of biostatistics, Medical College of Wisconsin): In the initial approval the magnitude of PFS was felt to be strong enough to overcome the number of concerns about trial design in terms of being blinded, missing assessments and data collection and those kind of things. Here we have two very well controlled studies. They are blinded, there is good follow-up, and we are seeing much smaller benefit.

WILSON: I think we just have to be very aware that the goal of medicine is first to do no harm. I think that the burden of proof is that a drug is helpful, not that it doesn't make people worse. And we have definitive evidence that Avastin causes serious and life-threatening side effects; small numbers, but if you are the one, that's not where you want to be. I think the Good Housekeeping seal of approval is important, and I think it needs to reflect what the data shows.

Mason, the only member of the committee to cast a vote for keeping the indication, said the drug's current label reflects its costs and benefits. "In the second paragraph of the indications for use it says, 'There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin," Mason said. "I can live with the fact that having that on the label would allow patients and physicians to make a decision."

Pazdur's Remarks

Pazdur's opening comments, which reflect the agency's thinking on Avastin and, by inference, accelerated approval, appear below:

In 2008, Avastin in combination with paclitaxel received accelerated approval for the first-line treatment of metastatic breast cancer based on the results of study E2100. Approval under these regulations required Genentech to conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients.

Genentech identified two trials—the AVADO trial and the RIBBON 1 trial-- to provide this evidence in the first-line treatment of metastatic breast cancer. The AVADO trial compared the combination of Avastin plus docetaxel to single agent docetaxel. The RIBBON 1 trial examined the benefit of adding Avastin to either anthracycline or taxane- based chemotherapy or capecitabine.

These trials could support additional new first-line breast cancer indications for Avastin combinations. In addition, these studies could convert the 2008 accelerated approval of Avastin to regular approval.

As previously noted, Avastin in combination with paclitaxel received accelerated approval for first-line treatment of patients with metastatic breast cancer based on the results of the E2100 study.

This trial was a randomized, multicenter, open-labeled trial of Avastin with paclitaxel or paclitaxel alone that enrolled patients with HER-2 neu negative breast cancer who received no previous chemotherapy for metastatic disease.

The addition of Avastin to paclitaxel resulted in a 52% increase in progression-free survival (HR 0.48, 95% CI0.39, 0.61; $p < 0.0001$) with an observed 5.5-month difference in median PFS. There was no significant difference in overall survival between the two treatment arms. The tumor response rate was higher with Avastin plus paclitaxel as compared to paclitaxel alone (48.9% versus 22.2%).

This application was discussed at an ODAC meeting in December 2007. A split vote (5 to 4) was recorded in response to the question of whether a favorable risk/benefit analysis for the use of Avastin plus paclitaxel was provided by E2100.

FDA subsequently granted accelerated approval to this indication with the provision that additional data be provided to further define the degree of clinical benefit. Progression-free survival has been used as a clinical benefit endpoint in a variety of diseases.

The magnitude of benefit attributed to the addition of Avastin to paclitaxel (median PFS difference of 5.5 months, HR 0.48) was considered to be clinically meaningful in light of Avastin's toxicity by several of the ODAC discussants. In addition, this supplemental BLA was supported by two prior approvals of Avastin in the first-line treatment of non-small cell lung cancer and colorectal cancer. Both the colorectal and non-small cell lung cancer indications that combined Avastin with chemotherapy regimens were supported by improvements in overall survival.

In the E2100 trial supporting the 2008 approval of Avastin the hazard ratio for overall survival was 0.87 (95% CI 0.72, 1.05) indicating that a detrimental effect on OS was unlikely with the addition of Avastin to paclitaxel.

As a condition of the accelerated approval, Genentech was required to submit data from two ongoing, placebo-controlled trials (AVADO and RIBBON1) to confirm the magnitude of the treatment effect on PFS and to provide additional information on the effects on overall survival. In a pre-BLA meeting on February 2009, Genentech was asked to provide mature survival data with evidence that the addition of Avastin did not have a detrimental effect on overall survival.

This ODAC meeting is called to re-evaluate the role of Avastin in breast cancer. At the present time we have the results of four trials allowing us to have a more comprehensive view of the role of Avastin in breast cancer. Three trials—E2100, AVADO, and RIBBON 1—were conducted in the first line setting have been submitted to FDA. An additional trial AVF 2119g, a trial comparing the Avastin plus capecitabine to single-agent capecitabine—was conducted in the second and third-line setting of breast cancer. This trial failed to demonstrate statistical significant effects on either PFS or OS. To date no trial examining the role of Avastin in breast cancer has demonstrated an improvement in overall survival.

Although an improvement in overall survival remains the gold standard for approval, progression-free survival and disease-free survival in the adjuvant setting, have been advocated as approval endpoints. Proponents of using PFS note that OS analysis may be confounded by cross-over and/or subsequent therapies and that PFS, measured prior to the introduction of other post-progression therapies, may more accurately depict a treatments therapeutic effect.

FDA believes that in accepting PFS as a regulatory endpoint a close examination of the magnitude of improvement in PFS must be closely evaluated in a risk-benefit analysis. Because treatment with Avastin is associated with considerable toxicity, the magnitude of PFS improvement—especially if not supported by an improvement in overall survival—should be substantial, clinically meaningful and be able to be replicated in additional trials. Also, the addition of Avastin to chemotherapy, should not result in a deleterious effect on survival. Hence, we ask you to evaluate the findings of the risk/benefit analysis of the E2100 trial in relation to the AVADO and RIBBON 1 trial.

AVADO was a double-blind, placebo-controlled, three-arm trial of docetaxel plus placebo, docetaxel plus Avastin 7.5mg/kg, and docetaxel plus Avastin 15 mg/kg. A total of 736 patients with HER-2 neu negative tumors who had not received prior chemotherapy for metastatic breast cancer were enrolled.

The addition of Avastin 7.5 mg/kg to docetaxel resulted in 30% increase in progression-free survival [HR 0.70 (95% CI 0.55, 0.90)] with less than a month difference in median PFS while the addition of Avastin 15 gm/kg to docetaxel resulted in 39% increase in progression-free survival [HR 0.62 (95% CI 0.48, 0.79)] again with less than a month difference in median PFS.

Objective responses were observed in 44% of patients in the placebo arm, 55% in the Avastin 7.5 mg/kg arm (p-value 0.0295) and 63% in the Avastin 15 mg/kg arm (p -value 0.0001).

Mature survival data showed a HR of 1.103 (95% CI 0.84, 1.45) favoring the placebo arm over the 7.5mg/kg Avastin arm. The HR for OS was 1.003 (95% CI 0.76, 1.32) for the 15mg/kg Avastin arm compared to the placebo arm.

Safety data showed an increase of grade 3-5 adverse events, serious adverse events and study drug interruption and dose reduction with the addition of Avastin to docetaxel. More patients in the Avastin -containing arms required interruption/dose reduction of docetaxel due to an adverse event.

The second trial that we will discuss today is the RIBBON 1 trial. RIBBON 1 was a double-blind,

randomized, parallel group study conducted in women with metastatic or locally recurrent HER 2- neu negative adenocarcinoma of the breast, who had not received prior chemotherapy for advanced or metastatic cancer.

A total of 1237 patients were randomized (2:1) to receive anthracycline- or taxane-based chemotherapy (n=622) or capecitabine (n=615) in combination with Avastin or placebo. The taxane/anthracycline cohort and capecitabine cohort were analyzed separately with the alpha split equally (1-sided α0.025) for comparisons of PFS within each subgroup.

The addition of Avastin to taxane/anthracycline-based chemotherapy resulted in 36% increase in PFS [HR 0.64 (95% CI 0.52, 0.80)], with an observed 1.2-month difference in median PFS. Objective response rate was higher in the Avastin-containing arm, with an absolute increase of 13.5 % (95% CI 4.6, 22.3%) with the addition of Avastin to anthracycline/taxane-based chemotherapy.

Mature survival analysis of the anthracycle/taxane arm yielded a HR of 1.11 (95% CI 0.86, 1.43) again favoring the placebo arm. Pre-specified subgroup analysis of patients treated in the taxane cohort showed a hazard ratio of 1.25 again favoring the placebo arm. This analysis was performed because of the relevance of the taxane-treated patients to the 2008 approved indication of Avastin plus paclitaxel in the first-line treatment of breast cancer.

The addition of Avastin to capecitabine resulted in 31% increase in PFS [HR 0.69 (95% CI 0.56, 0.84)], with an observed difference of 2.9 months in median PFS. Objective response rate was higher in the Avastin-containing arm, with an absolute increase of 11.8 % (95% CI 3.4, 20.2 %) observed with the addition of Avastin to capecitabine.

A comparison of the mature survival data for the capecitabine cohort showed a HR of 0.88 (95% CI 0.69, 1.13) favoring the Avastin-containing arm.

Overall, the incidence of grade 3-5 AEs and serious AEs were almost twice as high in the Avastin arms compared to placebo arms in both cohorts. In the taxane subgroup, there were more deaths in the Avastin-containing arm than placebo arm (49.8 % versus 43.1 %). The majority of the deaths were attributed to breast cancer.

Adverse events known to be attributed to Avastin were, as expected, increased in the Avastin-containing arms in both cohorts. The most common AEs associated with Avastin were hypertension, bleeding/hemorrhage and febrile neutropenia. The incidence of AEs is not significantly different than currently described in the package insert.

Both the AVADO and RIBBON 1 are well conducted, double-blinded trials. They demonstrated statistically significant improvements in PFS. However, as we have discussed at previous ODAC meetings, there is a difference in the demonstration of statistical significance and the determination of a clinically meaningful finding that must weigh the risks and benefits of the drug.

FDA questions whether the magnitude of the PFS improvement observed in the AVADO and RIBBON 1 confirms the magnitude of PFS improvement and the initial enthusiasm of the findings observed in the E2100 trial. This initial enthusiasm resulted from a 52% increase in progression-free survival (HR 0.48, 95% CI0.39, 0.61; $p< 0.0001$) with an observed 5.5-month difference in median PFS observed when Avastin was added to paclitaxel.

The magnitude of treatment effect is clinically important providing a measure of delaying symptoms from tumor progression and must be weighed against drug toxicity.

In 2010, we now have a more comprehensive understanding of the Avastin's role in the initial treatment of metastatic breast cancer compared to 2008 when accelerated approval was granted. We will be asking the committee to re-evaluate Avastin's risk and benefits in this clinical setting.

Genentech submitted two sBLAs requesting labeling expansion for Avastin for the initial treatment of MBC based on the results of the AVADO and RIBBON 1 trials. During your discussion and deliberations, we ask you to focus on the following:

First, consider the results of each trial individually, to determine if the requested new indications for Avastin in first-line metastatic breast cancer should be granted.

Second, based on the totality of findings, discuss if the results of the AVADO and RIBBON 1 trials support the conversion of Avastin in combination with paclitaxel r from accelerated approval to regular approval

Third, if you do not recommend that results of AVADO and RIBBON1 support the conversion of Avastin from accelerated approval to regular approval, should the indication of using Avastin with paclitaxel for the first-line treatment of metastatic breast cancer be removed from the Avastin label?