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SPECIAL ISSUE

With Flashing Lights, Heckling & Folk Song Avastin Sets New Tone for FDA Debates

By Paul Goldberg

Under ordinary circumstances, a police cruiser doesn't figure on anyone's list of equipment required for approval of a cancer drug.

Yet, shortly after 6 a.m. on June 28, seven cruisers bearing the insignia of the Department of Homeland Security Federal Protective Service and the Montgomery County Police Department partially blocked the turnoff to the FDA White Oak campus.

Just before 7 a.m., a crowd started to form across New Hampshire Avenue: a couple dozen women, men, and children; predominantly wearing pink T-shirts, holding cardboard signs that made claims the agency would never allow on a drug's label.

"Avastin Saves Lives," declared one sign, extolling the virtues of a drug that increases progression-free survival in metastatic breast cancer, albeit by a margin that's not large enough to satisfy FDA.

Slowly, demonstrators began to move across New Hampshire Avenue to the gates of the FDA complex, where police officers stood ready to turn them away. As the group halted, a folk singer named Andrew Katz hit the guitar and the harmonica, and, in a drawl vaguely reminiscent of Bob Dylan's, started to sing something called The Avastin Fight Song:

I guess if you have a hundred grand to burn,
You call your doctor and you take your turn.
But if you don't, you're out of luck,
Just gotta sit there and wait
To get run over
by the ol' gov'rnment truck.

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Protesters outside the FDA White Oak campus, June 28, before the Avastin hearing.

Meeting Showcases Old Data, New Bureaucratic Procedure

(Continued from page 1)

Frank Burroughs, the founder of Abigail Alliance for Better Access to Developmental Drugs, was in the crowd, holding up a sign that read "The Greatest Risk to Health is No Avastin." The protest wasn't an Abigail Alliance production, though. It was staged by a group called Freedom of Access to Medicines, based in suburban Detroit. Folks came from all over the country, without as much as a dime in pharma company funds, said founder Terry Kalley, whose wife is receiving Avastin.

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That's the beginning. Now, fast-forward to the conclusion.

Mid-afternoon, June 29.

Day Two of the hearing has almost run its course. The audience had observed the functioning of the odd bureaucratic procedure designed specifically for the occasion.

Standard process employed by the agency's advisory committees is quirky enough: it turns debate of technical issues into a spectator sport. But this was not your standard committee meeting.

This was the first-ever deliberation over removal of an accelerated approval—an accelerated withdrawal.

The drug in question, Avastin, received an accelerated approval for metastatic breast cancer in 2008, but is now losing that approval because confirmatory trials failed to demonstrate a risk-benefit ratio that would satisfy FDA and its advisors (The Cancer Letter, May 27; the issue is available at no charge here: http://www.cancerletter.com/articles/20110526).

The procedural add-ons the agency made up were at once reminiscent of a courtroom and a church wedding.

There were two hours of testimony by patients. There was heckling from Burroughs, who shouted, "How would you like Rick Pazdur [director of the FDA Office of Oncology Drug Products] to be your doctor and his hand-picked crew here?"

And there were hundreds of slides that displayed data that the FDA Oncologic Drugs Advisory Committee had seen before. But the hearing was not about new data. It was about used data and new procedure.

ODAC started to vote, unanimously upholding FDA's position on three of the four questions posed by the agency.

Then the committee turned to the fourth and final question—whether Avastin should be allowed to keep its accelerated approval. There was no reason to expect surprises. Avastin would sink.

Yet, a surprise was coming.

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Seven women stood up.

They were in the witness section, just behind the reporters. They stood side by side, their hands locked.

These were the same women who had protested outside. All of them had testified before the committee on the previous day, giving Avastin credit for keeping them alive. And now they stood silently, staring, glaring, tearing up.

There was something electric about their presence. They stood like a chorus in a Greek tragedy, observing action unfolding before them, filling with emotion, preparing to scream out.

Slowly, everyone in the massive room grew aware of their presence, yet the process went on, with ODAC members, Genentech executives, reporters, lawyers and tieless Wall Street analysts stealing glances, looking away to get an emotional breather, then coming back for another look.

Decorum was about to be smashed in a way it had never been smashed before, after which there would be no way back.

Uniformed security guards showed up, executing

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perfect law enforcement stares, yet doing nothing. Somebody at the agency was wise enough to know that handcuffing stage IV breast cancer patients before rolling cameras is not good for anyone.

ODAC members saw them, too, but the committee had a job to do, and so it did, voting unanimously, 6-0, to recommend taking away the indication.

Abigail Alliance founder Frank Burroughs outside FDA. He later heckled Pazdur and ODAC members at the meeting.

Explaining his vote, committee member Wyndham Wilson, chief of the Lymphoma Therapeutics Section of the NCI Center for Cancer Research, addressed the women, who kept a demonstrative, silent watch over the committee:

"I voted no. I feel the confirmatory trials were extremely well done. They used the same class agents and did not show any clinically meaningful improvement in progression-free survival or in overall survival.

"I would encourage the company—if they are, in fact, convinced that there is a clinical benefit here—to do this follow-up trial as complete as plausible.

"I would say also to patients out there with breast cancer that I think that these have been extremely important trials, and that I hope that they look at of the evidence and look to see that in very large randomized studies using other very important taxanes there is no evidence that this drug was upheld to them and not come away feeling as though an important drug that was going to make them feel better or make them live longer is being taken from them."

Far from convincing the seven women to sit down, Wilson's comments triggered an outburst.

"What would you like us to take, for those of us who are triple-negative and have nothing but Avastin?" shouted Christi Turnage, one of the seven.

"I've been on it for eight years," joined in Heraleen Brown, holding up an album with snapshots from her travels. "Here is my quality of life: Europe, Asia."

"You allowed me four years ago in a clinical trial that I was thrilled to be in," shouted Patricia Howard.

Spectators who had been stealing glances were now looking away.

Even reporters stared silently at the screens of their laptops. But the women had more to say, and they went on:

Turnage: "Do we look terminal? We have nothing. Trial or no trial, we have nothing. I have children. I have four children. We have nothing else. Triple-negatives have nothing. Nothing. I don't even qualify for a single trial in the U.S. or Canada."

At this point, Steven Walker, co-founder of the Abigail Alliance and author of multiple Pazdur-bashing opinion pieces that appeared on The Wall Street Journal's editorial pages, joined the women:

"We've just requested an immediate meeting with the Commissioner. This is a sham. They [ODAC members] were all selected by Dr. Pazdur, except for the patient representative. We are going to ask that this vote be overturned and that this panel be unseated.

"You should be ashamed of yourselves. This isn't even a close call. You didn't have a single dissenting thought, let alone a dissenting vote.

"This is a joke."

Abigail Alliance had challenged FDA authority before, pursuing a legal case that sought to make experimental drugs available to patients once they clear phase I testing. Walker once described his group and its allies as "an insurgency." Many members of this loose

confederation were opposed to the 1962 requirement that drugs demonstrate efficacy (The Cancer Letter, Aug. 5, 2005; the issue is re-posted at http://www.cancerletter.com/categories/documents). Walker says he and Abigail Alliance support the efficacy standard.

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While the ODAC vote was predictable, the next act of this drama is not.

A very different process has been set into motion, and there is no reason to expect that it would run its course anytime soon.

The docket in the case will remain open through July 28.

After that, FDA Commissioner Margaret Hamburg will decide whether the indication stays or goes. There is no deadline for her to make the decision, and since the situation is political, there is no way to predict what she will do.

"I will then sit down with Commissioner Hamburg to discuss the record that has been created in the hearing process, and she will make a decision based on all of this information," said Karen Midthun, director of the Center for Biologics Evaluation and Research, who presided over the meeting. "I will work with Commissioner Hamburg in drafting this documents, explaining the reasons for whatever decision is ultimately reached."

The two-day meeting was adjourned, and ODAC members and FDA staff quickly left through the door at the front of the room.

But the seven women remained standing, and after a brief pause, they returned to haranguing the agency and its advisors:

Howard: "Seventeen thousand women you have just killed."

Brown: "Where is my next medicine? Can you tell me which one to take? Do I go to Walgreens?"

Turnage: "And the patient representative, you better hope your breast cancer never comes back. You are an embarrassment to all of us."

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While the hearing was focused on Avastin, the implications were much broader than one agent used for one indication.

It was about the FDA's criteria for converting accelerated approvals to regular approvals. It was about politicization of the drug approval process—about transforming it through introduction of legal procedure.

No drug that got on the market under the accelerated approval mechanism has ever lost its indication involuntarily.

The parties involved have very different views of standards for withdrawal of accelerated approval.

Genentech argues that even though its confirmatory trials failed to demonstrate the level of efficacy that would satisfy the agency and its advisors, now they should be allowed to conduct another study.

"Genentech was aware of the accelerated withdrawal standards when CDER approved the breast cancer indication for Avastin in 2008," said John Jenkins, director of CDER Office of New Drugs, said in closing remarks during the first day of the hearing. "Now, three years later, they propose that withdrawal of accelerated approval is appropriate only when "there is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit.

"This unprecedented interpretation of the accelerated withdrawal standards would turn the accelerated approval program on its head, allowing protracted marketing of drugs that have not been shown to be safe and effective, while sponsors take numerous 'bites at the apple' in an effort to confirm clinical benefit. Such a standard could seriously undermine the integrity of the accelerated approval program."

Explaining the company's position on the second day of the hearing, Michael Labson, an attorney with the law firm of Convington & Burling said the agency should exercise greater flexibility in situations where there is an unmet medical need and evidence of some benefit to patients.

"Our point here is simply that, where the data that you have—from the original trials and the post-approval trials—show a benefit, but there's uncertainty, the purpose of the accelerated approval law is met by keeping the medicine as a treatment option," Labson said. "That's sort of the fundamental purpose of the statute.

"And that still exists when you are looking at the data after the post-approval trials are confirmed. It is how we think the withdrawal—what the withdrawal standard means and how it's interpreted. It provides that—we agree that the withdrawal provision is an important part of scheme, and it provides that FDA may withdraw approval if post-approval trials don't confirm benefit.

"But it has to be judged based on the facts that you have. And in light of the purposes of the law, to make treatments available in areas of unmet medical need."

The texts of the closing remarks by Jenkins and

Labson begin on p. 6 of this issue.

Genentech was the first company to challenge the agency on its determination to get the drug off the market.

To conduct the first hearing of its sort, FDA had to invent courtroom-like procedure for the two-day hearing.

At the meeting, ODAC members sat in a role analogous to a jury.

CBER's Midthun sat in a role partially reminiscent to that of a judge, and the disputants sat in sections of seats separated by an aisle.

In addition to usual presenters, both sides were represented by lawyers, and cross-examination and legal summation of arguments were required.

Midthun's job was to keep the meeting on schedule, and she could ask questions. However, that was where her authority ended. At least on paper, the final decision would be Hamburg's, a political appointee. Some observers believe that HHS and the White House would also play a role.

Announcing the June 28-29 meeting in the Federal Register, FDA offered the following description of the procedure:

"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. 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 in accordance with Sec. 601.43 and part 15.

"In accordance with Sec. 601.43(e)(2), no person other than the Presiding Officer, the three designated representatives for each party, and the members of the advisory committee may question witnesses present at the hearing."

The announcement is posted at: http://www.regulations.gov/#!documentDetail;D=FDA-2010-N-0621-0143

At least at this stage, FDA officials appeared to protect Hamburg from involvement in the dispute. Walker said he was told that the commissioner wouldn't meet with him.

It's unclear whether this decision would end the controversy. It's possible that the company could take the matter to court.

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One of the new details was produced by the company, as it described its plans for another confirmatory trial that would run through 2016 or 2017.

The trial would be conducted regardless of whether Avastin would be allowed to retain the breast cancer indication, said Hal Barron, Genentech chief medical officer and executive vice president of global product development.

The study would randomize 480 patients to receive weekly paclitaxel with or without Avastin. Co-primary endpoints will be PFS in all patients and PFS in the high VEGF-A subset.

Oncologists say that Avastin appears to benefits some patients, but there is no way to know prospectively who they are.

Joyce O'Shaughnessy, a breast oncologist at Baylor University Medical Center, co-chair of the U.S. Oncology Breast Cancer Research Program, and Genentech's expert witness at the hearing, said she uses the Avastin-paclitaxel combination to treat triple-negative metastatic breast cancer and aggressive ER-positive disease.

"In my practice, the Avastin/paclitaxel combination plays an important role in alleviating the symptoms that occur with aggressive metastatic breast cancer," O'Shaughnessy said. "Just last week alone, having carefully considered all of the available options, I recommended to three patients who have metastatic triple-negative breast cancer and who are in need of rapid relief from severe bone pain, chest wall and arm pain and liver pain that they begin treatment with Avastin/paclitaxel."

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Progression-free survival is a statistical construct that's difficult to explain to patients.

ODAC member Mikkael Sekeres, associate professor of medicine at the Cleveland Clinic Taussig Cancer Institute, asked O'Shaughnessy to tell the committee how she explains Avastin's benefits to her patients: "I understand hazard ratios from a statistical perspective, and I understand how progression-free survival can vary slightly, depending on what exactly is happening to the curves and whether they're pinching in at exactly the median or not. It won't vary significantly.

"But I'd actually like to ask Dr. O'Shaughnessy a question, if that would be okay.

"No one in this room would doubt that you're a fantastic breast cancer doctor. How would you explain to a patient a hazard ratio of 0.6 for progression-free survival when you're consenting her for chemotherapy?"

O'SHAUGHNESSY: "The way I understand progression-free survival is I really have grown up always looking at the entire curve. And what that means to me and to my patient is that at any time along that curve the average reduction in her risk of progressing will be 40 percent, for example.

"And I don't discuss medians with patients. I really don't. I just say the data show—obviously, I'm making a recommendation to her based on her individual disease, of course—but my opinion is that you have got the kind of disease that would likely benefit, but for every step along that curve—no matter where you end up being, because I don't know where she's going to end up being—that she's going to have whatever that relative reduction in risk of progression is. I'm a total curve person."

SEKERES: "I am trying to think this through practically, because I see patients just like you do, and have these sort of conversations about the relative benefit of a therapy. So if I were a patient hearing that, and I heard a 40 percent reduction at any point in that curve, I would think, gee, well, that sounds like it's 40 percent less likely that my breast cancer would come back."

O'SHAUGHNESSY: "No, no. In terms of the likelihood of progression, length of progression-free survival, it's keeping the disease under control. It's a disease control issue. How long will it be before I have to face a bad scan?"

SEKERES: "So how long would it be? That sounds like a time of progression-free survival, which gets to a median."

O'SHAUGHNESSY: "No, no. At every point along the curve, though. You know, because we don't know whether she's going to be a median or a quick progressor or a late progressor.

"The average reduction in her risk of progression is going to be 40 percent at any time along that curve. So I don't know where she's going to fall, but it's so meaningful to patients to have a scan that's okay so she doesn't have to go on to something else—and that's important. And that's something that isn't in our classic clinical benefit list. But that's important.

"But the main reason I recommend it to a patient is I think that for her particular disease, that that progression-free survival is going to be meaningful to her in the context of her risk for symptoms or other end organ failure.

SEKERES: "So, again, I would have explained progression-free survival the same way. I think my patients, at least in my experience, need something else to hang onto. Hearing they have a 40 percent less chance at each time they get a scan isn't going to satisfy somebody. They're not going to walk away from that interaction thinking, 'Okay, so I have how long before my breast cancer comes back?' In terms of being meaningful to patients, at face value, that seems like that would be true.

"Yet, the quality of life studies that have been conducted in adjunct to the therapeutic aspects of the trials haven't validated that at all."

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The text of closing remarks by John Jenkins, director of the CDER Office of New Drug follows:

As you have heard, CDER's decision in 2008 to grant accelerated approval for Avastin for the first-line treatment of metastatic breast cancer was an extremely challenging one. At that time, the only data supporting approval came from a single positive trial, E2100, which showed a promising effect on progression free survival, or PFS, but not on overall survival or quality of life. In contrast, a second trial available at that time failed on all three endpoints.

These data were reviewed by ODAC in December 2007, and following a vigorous debate the members narrowly voted against approval, 5 to 4.

After carefully considering ODAC's advice and the available data, CDER concluded that accelerated approval should be granted on the basis of the PFS finding from E2100, which, if confirmed by subsequent trials, was felt to result in a positive benefit/risk assessment for Avastin in patients with breast cancer. The approval was conditioned on the requirement

that Genentech conduct additional post-marketing trials to confirm clinical benefit of Avastin. CDER's decision allowed Genentech to market this promising new treatment while additional trials were completed, which is consistent with the principles that underlie the accelerated approval program.

Assuming no change in the risk profile of Avastin, confirmation of clinical benefit could have been shown by demonstration of an effect on PFS similar in magnitude to that seen in E2100, demonstration of an improvement in overall survival, which is the gold standard for cancer drug approval, or demonstration of an improvement in quality of life, such as symptoms, which patients value even in the face of no improvement in overall survival.

Unfortunately, none of the post-marketing trials have confirmed any of these clinical benefits. Genentech has now submitted the results of five completed clinical trials of Avastin in patients with breast cancer, and the facts are the following:

First, no trial on its own, or the combined results of the five trials, has shown an improvement in overall survival. In other words, no trial has shown that patients treated with Avastin lived longer than patients not treated with Avastin.

Second, no post-approval trial has shown an improvement in PFS of the magnitude seen in E2100.

And finally, no trial has shown an improvement in health-related quality of life. In other words, no trial has shown that patients treated with Avastin feel better than patients not treated with Avastin.

The totality of the data available today strongly suggest that the PFS results seen in E2100 were an over-estimate of the true effect of Avastin on PFS, and the true effect appears to be much smaller than that predicted at the time of accelerated approval.

This small effect of Avastin on PFS must be considered in light of the serious, often poorly tolerated, and potentially lethal, toxicity of the drug. The most serious adverse events of Avastin include gastrointestinal perforation, hemorrhage, fistula formation, hypertension, proteinuria, wound healing complications, congestive heart failure, stroke, and death.

After carefully considering the totality of the available data, CDER now concludes that the modest effects of Avastin on PFS do not outweigh its risks in the treatment of metastatic breast cancer, and the indication should be withdrawn.

Our decision is supported by ODAC's recommendation from the July 2010 meeting in which the Committee voted 12 to 1 in favor of withdrawing the indication.

Genentech now argues that the Agency should maintain the breast cancer indication for Avastin while the company designs and conducts an additional trial, or trials, in another attempt to confirm clinical benefit in this disease. The study that Genentech has proposed is essentially a repeat of the E2100 trial–a comparison of Avastin plus paclitaxel to paclitaxel alone.

A sponsor independent of Genentech recently completed such a trial, which Dr. Keegan referred to as "Study 10." Study 10 was a phase II trial that enrolled approximately 300 patients with HER2-negative metastatic breast cancer. The magnitude of improvement in PFS in Study 10, was less than half of that seen in E2100. The results of Study 10 provide support to CDER's conclusion that the PFS results from E2100 were an outlier, and are more in line with the results of the other trials completed to date.

When we approved Avastin for breast cancer we understood that the indication would be subject to the accelerated withdrawal procedures if clinical benefit was not confirmed. Accelerated withdrawal is a fundamental

part of the accelerated approval pathway and serves as a backstop to protect the public from continued marketing of a drug if clinical benefit is not confirmed. Under the accelerated withdrawal regulations, FDA can withdraw an indication if the postmarketing clinical trials fail to confirm clinical benefit or if the evidence demonstrates that the product has not been shown to be safe or effective for the indication.

In the case of Avastin for metastatic breast cancer we concluded that both of these conditions have been met.

Genentech was aware of the accelerated withdrawal standards when CDER approved the breast cancer indication for Avastin in 2008. Now, three years later, they propose that withdrawal of accelerated approval is appropriate only when "there is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit."

This unprecedented interpretation of the accelerated withdrawal standards would turn the accelerated approval program on its head, allowing protracted marketing of drugs that have not been shown to be safe and effective, while sponsors take numerous "bites at the apple" in an effort to confirm clinical benefit. Such a standard could seriously undermine the integrity of the accelerated approval program.

And, it is very important that we preserve the integrity of the accelerated approval program, which has been used very successfully in oncology and other disease areas to provide early access to promising new therapies. Forty-nine indications for cancer drugs have been approved under this program since 1995, and clinical benefit has been confirmed for a majority of those drugs. In other cases, when post-approval trials failed to confirm clinical benefit or could not be completed in a timely manner, sponsors have voluntarily withdrawn their oncology drugs or indications.

Failure to confirm clinical benefit for a drug approved under accelerated approval, as occurred in the case of Avastin, is not an indication of a failure of the approval pathway. Rather it is evidence that CDER is striking the right balance in making promising drugs available to patients, while ensuring confirmation of clinical benefit following approval. To maintain the integrity of this approval pathway, CDER must be able to use the accelerated withdrawal process when confirmatory trials fail to confirm clinical benefit. We cannot permit sponsors to "evergreen" approval of a drug that has not been shown to be safe and effective.

As I described earlier, the decision to grant accelerated approval for Avastin in the treatment of breast cancer in 2008 was a "close call" based on the results of a single positive trial in the face of a second negative trial. CDER's current recommendation to withdraw this indication is based on the totality of the data from 5 controlled trials that enrolled more than 3500 patients with breast cancer. The totality of the data show that Avastin has only a modest effect of Avastin on PFS and this small effect, in the absence of an effect on overall survival or patient quality of life, does not outweigh its substantial and life-threatening risks. The lesser magnitude of benefit on PFS alters the benefit/risk assessment of Avastin and does not support continued approval.

Let me restate several important points to remind the committee that: No clinical trial on its own, or the combined results of the five trials, has shown an improvement in overall survival; No post-approval clinical trial has shown an improvement in PFS of the magnitude seen in E2100; No clinical trial has shown an improvement in health-related quality of life; And all clinical trials show an increase in serious adverse events with the addition of Avastin to a chemotherapy regimen.

Withdrawal of the indication for Avastin in breast cancer is clearly supported by the data from five adequate and well-controlled trials, and is the right public health decision.

At CDER, we value the views and perspectives of those who do not agree with our decision, and we have carefully considered these views as we have reviewed the available data. In the end, CDER's decision must be based on the available scientific data from adequate and well-controlled trials. These data inform our assessment of the benefit/risk of the drug for the population of patients with breast cancer. That is our obligation under the law, and we take that obligation and our public health mission very seriously.

We stand ready to work with Genentech and others to design trials to define what, if any, subpopulation of patients with breast cancer might derive benefit from this drug that outweigh its risks. If such data are generated, a new science-based indication could be approved.

Until that time, it is not appropriate for the drug to continue to be approved for treatment of breast cancer when the totality of the available data does not support such an approval.

I will now review the questions posed to the panel for this hearing and restate CDER's answers:

Question No. 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?

The answer to this question is "yes." The AVADO

and RIBBON1 trials, which Genentech designated as the confirmatory trials, failed to verify the magnitude of PFS that was seen in the E2100 trial, and did not show an improvement in overall survival or quality of life. Absent an effect on overall survival or improved quality of life, which we consider measures of direct clinical benefit, the modest effect on PFS is not enough to confirm clinical benefit in light of the serious risks associated with the use of Avastin.

Question No. 2: (a) Does the available evidence demonstrate that Avastin has not been shown to be effective for the breast cancer indication for which it was approved? (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?

The answer to these questions is also "yes." The totality of the data demonstrates that Avastin has not been shown to be safe and effective for the treatment of breast cancer. Four of the five trials that Genentech submitted in support of this indication showed no effect, or only a small effect on PFS, and none of the trials showed that Avastin improved overall survival or quality of life. All trials showed an increased risk of serious side effects. Therefore, the benefits of Avastin do not outweigh its risks for the treatment of breast cancer.

Question No. 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?

The answer to this question is "no." The accelerated approval program is built on the foundation that approval may be withdrawn when post-approval trials fail to confirm clinical benefit, or when the evidence establishes that the drug is not safe and effective for its approved indication.

In the case of Avastin, both of the conditions have been met. Permitting continued approval of Avastin for the breast cancer indication while Genentech designs and conducts additional trials would be counter to the totality of the data, which support our conclusion that the benefits of the drug do not outweigh its risks in this disease, would not be in the interest of the public health, and could jeopardize the integrity of the accelerated approval program.

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The text of closing remarks by Michael Labson, an attorney with the firm of Covington & Burling, representing Genentech, appears below:

My focus today, as an attorney specializing in food and drug regulation will be on why the legal provisions governing accelerated approval call for retaining Avastin as an approved treatment option.

I will review the statute, regulations, prior guidance from CDER and the Department of Health and Human Services.

I will also do a fuller walkthrough of the regulatory history of Avastin because it explains why we are here and why we disagree with the statement yesterday that we are seeking multiple bites at the apple.

The overarching purpose, as set out in the statute, the reason we have accelerated approval, is to facilitate the availability of treatments in areas of unmet medical need.

Metastatic breast cancer is an area of high unmet medical need.

The approval provision states that FDA may approve a medicine based upon an effect on a clinical endpoint or on a surrogate endpoint reasonably likely to predict clinical benefit. FDA's regulations specify further that the clinical endpoint may be an effect other than survival or irreversible morbidity where there remain unanswered questions about a medicine's effect on ultimate outcomes.

Avastin's approval for breast cancer is based on progression-free survival.

As you heard yesterday, an endpoint CDER agrees is meaningful in this setting without a showing of overall survival or improvement in quality of life.

For withdrawal, the law states that FDA may withdraw approval if a post-approval study fails to verify clinical benefit or other evidence demonstrates

that a treatment is not safe or effective.

CDER's view on withdrawal is that Avastin had its chance; we had chance to submit post-approval studies to confirm benefit and did not make that showing.

That rigid approach is not required under the law and it is not consistent with the law's purposes to provide access to a medicine that addresses serious unmet medical need where there is a meaningful showing of benefit but questions remain regarding the magnitude of that benefit.

The data and the regulatory history for Avastin call for the exercise of the flexibility that the law provides to maintain accelerated approval.

Let's look first at the regulatory option CDER had for Avastin in 2008.

At that time, CDER had data from E2100, top-line AVADO data, mature PFS results and immature OS data.

CDER also had later-line capecitabine data from the 2119g study.

After heavily vetting the E2100 study, CDER concluded the data were reliable and supported approval.

In particular, CDER accepted PFS as a meaningful endpoint, accepted Avastin's safety profile and determined that Avastin provided clinical benefit with favorable benefit-risk.

CDER had three regulatory options: Full approval, accelerated approval or no approval. And as CDER has explained, and the review documents show, CDER utilized accelerated approval to address CDER's uncertainty about the scopes of Avastin's effects.

The accelerated approval provisions worked in a flexible manner, as the law intends, to provide a treatment option to patients with significant unmet medical need and with post-approval studies to address the open questions that existed at that time.

Today we see the additional data, the mature OS data for AVADO and data from RIBBON1.

There are also the data from RIBBON2, showing a PFS effect outside the first-line setting.

AVADO and RIBBON1 met their PFS endpoints, but with a lesser magnitude of effect for Avastin with non-paclitaxel chemotherapy.

Safety is unchanged, as you heard from CDER yesterday.

The question is, do these data on Avastin, with other chemotherapy agents, refute the substantial effect on PFS for Avastin with paclitaxel from E2100? One view is that the data on Avastin with paclitaxel stand distinct and benefit is confirmed.

That is the view of the European Medicines Agency, numerous other health authorities and the National Comprehensive Cancer Network.

Until 2010, Genentech also thought that benefit was confirmed under the standards set by CDER based on the positive showing in AVADO and RIBBON1.

I will come back to this point further in a few minutes.

CDER's view is at the other extreme, that although the study showed a robust effect and involved different chemotherapy agents than E2100, the results negate the showing of benefit from E2100.

That view leads to withdrawal.

Indeed, we heard yesterday that CDER has not even considered any other options.

But there is a middle ground drawing on the discretion CDER acknowledged yesterday.

Based on the showing of benefit, if there are open questions about the nature of Avastin's effect in metastatic breast cancer, and particularly its effect with paclitaxel, the appropriate course is to retain accelerated approval, subject to a new study designed directly to confirm the magnitude of benefit for Avastin with paclitaxel.

This is the course Genentech has proposed.

The law provides this flexibility, and this middle course best meets the purposes of accelerated approval, to facilitate needed treatment options for a severe disease, pending further study to confirm the level of benefit already shown in E2100.

CDER and HHS have both previously emphasized this precise point.

At the 2003 ODAC on the accelerated approval program, Dr. Robert Temple explained, "When a drug has proved active, you don't lightly remove it because a trial failed.

You try to do other studies.

You think about why the studies failed.

At the same ODAC, Dr. Pazdur emphasized that the regulations provide flexibility on withdrawal decisions and that "withdrawal may not be appropriate where a confirmatory study does not confirm clinical benefit."

As Dr. Pazdur explained, the withdrawal provision in the regulation "gives us judgment so we don't need to have a reflex situation: You fail; therefore, you must come off." Here, CDER agrees that the post-approval studies met their endpoints and show that Avastin is active in metastatic breast cancer with no new safety signals.

On these facts, Dr. Temple's and Dr. Pazdur's cautions to exercise regulatory judgment and not to move automatically to withdrawal are particularly on

point.

CDER's comments from the 2003 ODAC have been echoed by the Department of Health and Human Services, HHS, FDA's parent agency, also emphasizing that FDA should proceed with caution in considering withdrawals of accelerated approval.

In 2009, in official comments to the Government Accountability Office, HHS explained, "When trials do not appear to confirm clinical benefit, FDA must carefully assess each case and the consequences of all regulatory options, including their potential impact on patients." HHS further stated, "Failure to confirm clinical benefit in a completed trial may reflect unforeseen limitations in trial design rather than clear evidence of lack of effectiveness." Here, the post-approval trial showed effectiveness.

In a disease with extremely limited treatment options, the impact on patients from withdrawal would be great.

The unforeseen limitation was the difference in magnitude by chemotherapy partner, particularly when focusing heavily on the medians and, relatedly, CDER's evolving emphasis on replicating the magnitude of improvement in median PFS from E2100.

Because accelerated approval is intended to keep a medicine available where there is a meaningful showing of benefit but some remaining uncertainty, we strongly disagree with CDER's assertion that allowing a new confirmatory study here undermines the accelerated approval program.

As the comments from HHS, Dr. Temple and Dr. Pazdur caution, a rigid approach to withdrawal does not best serve patients.

Here, the regulatory history of Avastin shows that one of the unforeseen limitations of AVADO and RIBBON1 is that the trials would be expected not just to show a PFS benefit, but to replicate the 5.5-month change in median PFS from E2100.

That is not the guidance Genentech received when identifying AVADO and RIBBON1 as appropriate confirmatory trials.

In 2008, when CDER granted accelerated approval, it understood that AVADO and RIBBON1 would not replicate the PFS results from E2100.

The slide shows the office director's review memo supporting approval in 2008.

As indicated, CDER specifically requested the preliminary results of AVADO before taking regulatory actions.

The definitive PFS data were available, and the office director noted that there was an improvement in PFS based on data for the standard Avastin dose showing a hazard ratio for PFS of 0.64, a 36 percent reduction in the risk of disease progression or death, an improvement in median PFS of 0.8 months and an 18.6 percent improvement in objective response rate.

There is no mention of overall survival or an overall survival trend.

CDER, thus, knew, in approving Avastin for metastatic breast cancer and accepting AVADO as a post-approval trial, that AVADO would show benefit but would not replicate the magnitude of benefit—excuse me—the magnitude of median PFS effect from E2100.

And we heard yesterday that CDER never communicated to Genentech that AVADO was not adequate to confirm benefit.

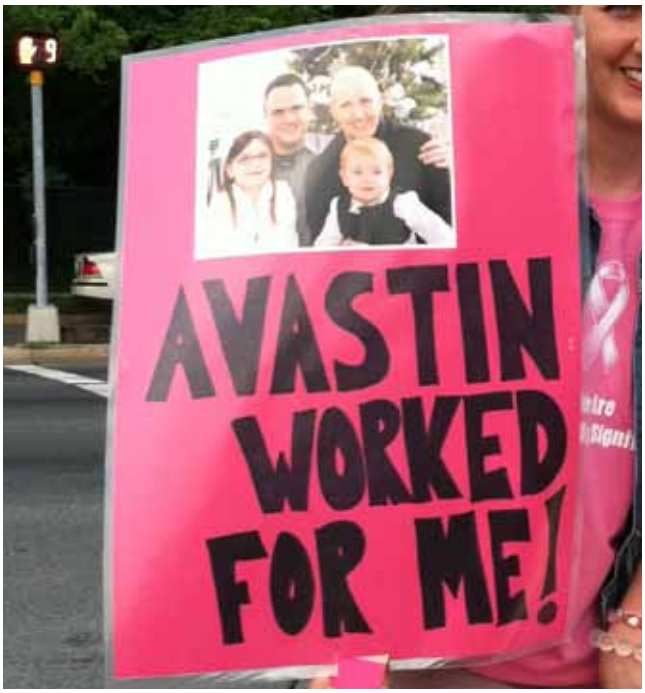
For RIBBON1, in a January 10, 2006 meeting, CDER acknowledged that, "The treatment effect will vary according to the chemotherapy regimen used. The test will be whether there is a treatment effect for each chemotherapy pairing."

CDER recognized that the different chemotherapy regimens will yield different effects.

CDER accepted the study design with target hazard ratios of 0.7 and 0.75 for the two study arms, and did not say that RIBBON1 would only be considered to show clinical benefit with a level of effect on median PFS near 5.5 months.

Here is the key Type B meeting from February 2009 before the AVADO and RIBBON1 supplements are submitted.

In advance of that meeting, Genentech provided



CDER the top-line AVADO and RIBBON1 results.

With this information in hand, CDER stated in official meeting minutes, "FDA confirmed that the basis for conversion to full approval will be demonstrated improvement in progression-free survival and evidence that survival is not impaired.

There is no statement that AVADO and RIBBON1 failed to confirm benefit, even though CDER had received the median PFS results from the studies.

There is also no reference to the need for Genentech to replicate a change in median PFS near 5.5 months, as in E2100, to confirm benefit.

It is not until the July 2010 ODAC and the NOH that CDER states that the magnitude of median PFS change from E2100 must be replicated or there must be an effect on overall survival.

But Genentech did not have this guidance when identifying AVADO and RIBBON1 as confirmatory trials.

In fact, we heard yesterday that CDER felt it was unable at that time to give specific guidance on the required magnitude of benefit.

This explains where we now are.

CDER's thinking changed over time, and we thus have post-approval studies that, in hindsight, are limited in their designs to meet CDER's expectation of reproducing the magnitude of median PFS benefit from E2100.

This regulatory history shows that Genentech is not trying to undermine the accelerated approval program by gaining inappropriate multiple bites at the apple.

Rather, Genentech is trying to respond to its understanding of CDER's evolving thinking on how to establish clinical benefit for Avastin in this setting.

Maintaining approval subject to a new study is an opportunity to conduct a confirmatory trial squarely addressed at confirming the magnitude of benefit for Avastin with paclitaxel, with the required showing for full approval now clearly established.

The need to consider the option of a new study rather than withdrawal is especially great under our facts.

All of the first line studies met their agreed-upon PFS endpoints.

The data from the secondary endpoints also showed consistent effects.

The greatest effect we have is for with Avastin with paclitaxel, and CDER accepts it is robust and clinically meaningful.

CDER's open questions are the magnitude of benefit and the role of the chemotherapy partner.

These questions can be addressed through further study.

Safety is well-characterized and presented in the approved prescribing information.

CDER agrees there are no new safety signals.

And as you have heard from Dr. Horning and Dr. O'Shaughnessy, the overall safety profile is in line with other treatment options.

Genentech completed the post-approval studies with rigor and diligence.

An unmet medical need persists.

In over three decades, looking at non-hormonal HER2 status unspecified medicines, FDA has approved only one other treatment for first-line metastatic breast cancer, Gemzar, with a 2.3-month improvement in disease progression, no proven survival benefit and toxicity.

As you heard yesterday, there are no MBC treatments approved with labeling for quality of life, and no survival benefit has been approved for first-line treatments outside hormone-positive, HER2-positive disease.

We are not aware of any other instance where FDA has sought to withdraw accelerated approval on such facts, and it is not the right outcome here.

Withdrawal would remove a therapeutic option with demonstrated efficacy, and it would narrow the viability of the accelerated approval pathway for sponsors by establishing an inflexible approach to the consideration of post-approval studies.

The issues the presiding officer has stated will be presented in this proceeding:

Issue 1 asks whether AVADO and RIBBON1 failed to verify clinical benefit for Avastin with paclitaxel.

The answer is no because they showed a statistically significant benefit and a robust effect seen especially in the hazard ratios.

Issue 2(a) asks whether the totality of the data show that Avastin with paclitaxel does not provide benefit. No.

The data show clear effectiveness in the first-line setting, particularly with paclitaxel.

Issue 2(b) asks whether the data failed to establish safety and favorable benefit-risk. No.

The safety profile is well-characterized and has not changed.

It is a profile that CDER accepts across a range of other approved indications for Avastin.

The most common adverse events are generally manageable; other serious adverse events are rare.

Issue 3 asks if the data have not confirm the

safety and effectiveness for Avastin with paclitaxel, should accelerated approval be maintained subject to the conduct of an additional study? The answer is yes.

Maintaining Avastin as an approved option is called for by law, supported by the data, and in the best interest of patients.

This final issue is in large measure the fundamental question for these proceedings.

The EMA, other health authorities, the NCCN and many oncologists, patients and cancer organizations on the same studies have concluded that the data validate that Avastin is a valuable treatment option.

Others are not convinced, but the issue here is whether there should be a sweeping regulatory action that withdraws Avastin as an approved option for all in an area where the options are already too few, or whether physicians and patients should be left to make informed individual decisions with appropriate prescription information while further work is done.

The law provides a path forward between the two poles of full approval, as in Europe, or full withdrawal, as CDER has proposed.

Retain accelerated approval and require a true confirmatory trial designed to meet the expectations

Guest Editorial:

After NLST: Trial Results Justify Uniform Guideline for Screening

By Gerard A. Silvestri

Screening for cancer is something of an obsession with the American public.

In one study, 87 percent felt that screening is almost always a good idea, and three quarters believed that screening saved lives, most or all of the time. A substantial portion believed that if an 80-year-old chose not to be screened, they were being irresponsible, and nearly 75 percent would prefer a total body CT scan to $1,000 cash.

Celebrities tout the benefits of screening on television while national organizations issue screening guidelines. There are currently active screening programs for prostate, colorectal, and breast cancer—and based on the cues that the public garners from the media, one might wonder why the medical community even bothers to study the subject in the first place.

But unlike the general public, physicians continue to debate the benefits of screening. Screening is advocated by most physicians (lets face it, doctors are subjected to the same TV programming, and influenced by the same anecdotes of family members being saved by screening, or lost due to a lack thereof).

But there is a growing body of literature that calls into question the benefits of screening for diseases such as prostate and breast cancer, and reports the harms—both physical and psychological—from participating in screening programs.

In short, the benefits must be weighed against the risks—and the idea that there is always an overwhelming benefit from screening is probably an overstatement.

Where does that leave lung cancer? It is the only one of the aforementioned solid tumors that doesn't have a recommended screening program. And yet, lung cancer is the leading cause of cancer death in the United States, with more than 150,000 deaths expected this year. More patients die from lung cancer than breast, colon and prostate cancer combined.

Variations of the last two sentences have been on the front pages of more manuscripts on this subject than I care to remember, and with good reason.

This largely preventable, devastating disease often presents late in its course, when the treatment options are usually palliative rather than curative. Overall five-year survivorship is about 16 percent. Improvements in survival from lung cancer have been painstakingly slow over the past 40 years. Meanwhile, better outcomes are being seen with other cancers leaving the lung cancer community frustrated and demoralized.

While the overall survivorship from lung cancer is poor, survival for early-stage disease is quite good. Unfortunately, fewer than 20 percent of patients currently present with early-stage disease. This has led to intense efforts to examine strategies for early detection.

In the 1970's and 80's, several international randomized trials focused on the utility of screening using chest X-ray for the early detection of lung cancer. Unfortunately, none showed a reduction in lung cancer mortality from screening.

Fast-forward a few decades, and reports began to surface regarding the usefulness of low-radiation-dose chest CT scans in detecting lung cancer. While these reports were promising, they were single-arm trials without a comparator group. But the studies provided valuable information about practical matters related to the performance of the test and the follow-up of abnormal scans.

However, the key question of whether lung cancer mortality would be reduced by screening could not be answered using this study design. Still, these studies were the proof of principle that screening using low-dose CT detected more cancers at an early stage than would be expected. This laid the groundwork for the National

Lung Screening Trial.

Published this week in the New England Journal of Medicine, the NLST represents the largest and most expensive randomized trial for a single-cancer screening test—with 53,454 participants and weighing in at over $200 million—in the whole history of U.S. medicine.

The inclusion criteria were "healthy" persons, age 55-74, who were heavy current or former smokers. Each participant was randomly assigned to chest X-ray or low-dose CT of the chest. Groups were scanned annually for three years and followed without further screening for three-and-a-half more years. This was a well-planned and well-executed study.

The results showed a remarkable 20-percent reduction in lung-cancer-specific mortality, and a 6.7 percent reduction in overall mortality in the group screened using chest CT. In the CT group, 247 patients died of lung cancer, alongside 309 in the chest X-ray group.

Several other important findings are worth mentioning. An abnormal scan was noted in nearly a quarter of the CT screened group, and 96.4 percent of those findings were false positives. Fortunately, very few required invasive testing, suggesting that radiographic follow-up would be sufficient. However, a tiny minority will need to undergo invasive testing to sort out a screen-detected abnormality. This will have consequences, particularly for those ultimately found not to have cancer.

Of those who underwent CT, 16 people died within 60 days of invasive testing. Six of those did not have cancer. This information will have to be contemplated by any individual debating getting screened for lung cancer. Given the 20-percent mortality reduction from lung cancer, perhaps most will be willing to take the risk—but others may not.

One important aspect of any study is the ability to generalize the findings to the population and healthcare setting in which it will be utilized. The answer, as it relates to this study, is not so clear.

Screening was performed in urban tertiary care and teaching hospitals with expertise in all aspects of cancer care. Scans were interpreted by dedicated chest radiologists—experts in characterizing nodules and providing appropriate recommendations for follow-up of abnormal scans.

The study design allowed for patients with abnormal scans to be managed in the community. However, at least in our institution—we were a site for NLST—patients were given the option (and many took it) of having follow-up care for an abnormal screen delivered in our cancer center, which has a multidisciplinary lung cancer clinic with dedicated expertise in lung cancer.

This may be one reason the mortality rate for lung cancer surgery in this study is so low (1 percent), when national data suggest that the rate is between 3 and 5 percent. A small change in the death rate from surgery could diminish the beneficial effect of screening.

There are several other unanswered questions. If three years of screening is good, should we continue to provide an annual screen? If so, when should screening stop? Who will pay for this program? Remember, in the U.S. the average age at diagnosis for lung cancer is 70 years. Will this become a benefit covered by Medicare?

Modeling the length of screening and cost-efficacy analysis is underway to better inform these questions. Policymakers will struggle with whether or not payment for screening services should supersede funding for programs which prevent initiation of smoking, fund cessation programs, and nicotine replacement products.

Buried beneath these questions about lung cancer screening is the fact that if a mass screening program for lung cancer is advocated by the United States Preventive Services Task Force, it will be the first screening program that targets persons with a poor health habit—namely cigarette smokers, whose attitudes and beliefs about screening may be different than the general public.

Statistically, smokers are poorer, less educated and less likely to have an identifiable medical home—all attributes which have been shown to be significant barriers to screening.

In one study that assessed beliefs about lung cancer screening, smokers reported they screen less for other cancers than their non-smoking counterparts, have less comprehension of what effective screening means, and were less likely to want to participate in screening for lung cancer when compared to non-smokers.

To implement an effective screening program healthcare providers will need new and innovative approaches to reach the target population—which may be no easy task when it comes to smokers.

So where are we now? The reduction in lung cancer mortality reported in the NLST should be welcomed news. The possibility of saving lives from this deadly disease cannot be ignored and it is likely that those at risk and fitting the criteria for screening will be offered chest CT in the future. However, health care providers should wait for the cost-efficacy analysis and further recommendations from the USPSTF before beginning a comprehensive screening program in their practice.

Guidelines for appropriate screening and management of screen-detected abnormalities are being assembled by representatives of societies such as the American Cancer Society, the American College of Chest Physicians, the National Cancer Care Network and other stakeholders within the cancer community.

Having a uniformed accepted approach to screening should improve the chances of saving lives from lung cancer without introducing harm to our patients.

Silvestri is a professor of medicine at Medical University of South Carolina in Charleston.

The Cost of CT Screening:
Year Gained via Lung Cancer Screening Could Cost $38,000

By Ridge Phelan Montes

Preliminary cost-effectiveness analysis of the National Lung Screening Trial estimates that three annual screenings with low-dose computed tomography would cost $38,000 per life-year gained.

The number is not adjusted for quality of life.

This appears to be in line with costs accepted for screening in the United States, said William Black, a member of the NLST executive committee and director of chest radiology at the Dartmouth Hitchcock Medical Center, professor of Community & Family Medicine at Dartmouth Medical School, and professor in the Dartmouth Institute for Health Policy and Clinical Practice.

"There is no formal, fixed, rigid threshold for cost effectiveness, but most people who are familiar with this area will say [that a patient is willing to pay] $100,000 per quality-adjusted life-year in duress, and most people consider under $50,000 well worth it," Black said, presenting preliminary cost-benefit projections for the trial at the June 28 meeting of the National Cancer Advisory Board.

The NLST results were published online by The New England Journal of Medicine June 29. The death rate in the CT arm (247 deaths per 100,000 person-years) was 20 percent lower than the chest X-ray arm (309 deaths per 100,000 person-years). Sixteen participants in the low-dose CT group (10 of whom had lung cancer) and 10 in the chest X-ray group (all of whom had lung cancer) died within 60 days after an invasive diagnostic procedure.

In an accompanying editorial, Harold Sox, former medical editor of Annals Internal Medicine, noted that "the rate of death associated with diagnostic procedures is low."

Cost-effectiveness analysis is not included in the NEJM paper. NLST compared CT with standard chest X-ray rather than the current standard of care, which is no screening. A comparison with no screening would likely have to be derived through modeling.

Black's preliminary analysis assumed conditions similar to the conditions of the trial. The trial, which required three annual screenings in the CT arm, was conservative in its screening intensity and follow-up testing. NLST was also conducted at centers where the surgical mortality rate would be lower than the national average, said Black, one of the authors of the NEJM paper.

"The cost effectiveness analysis that we'll be doing with NLST will answer a lot of questions, but will not answer all the questions about how screening can be implemented," Black said in his presentation to the advisory board.

Black said the selection criteria for screening will strongly affect costs. "In the NLST, we had fairly rigorous criteria: age 55–74, 30-plus pack-years," Black said. "There are eight million such people in the United States, [and] in the first year, we would spend about $4 billion in their screening."

In his editorial, Sox proposed that "it may be possible to define subgroups of smokers who are at higher or lower risk for lung cancer and tailor the screening strategy accordingly."

Sox wrote that overdiagnosis may have occurred in the CT arm of the trial, citing disparity between the numbers of lung cancer diagnoses in the CT arm (1,060) versus the chest x-ray arm (941). "Ten to 15 additional years of follow-up will be necessary to test the hypothesis that low-dose CT in the NLST led to overdiagnosis," Sox wrote. "If the difference in the

number of cancers in the two groups of the NLST persists, overdiagnosis in the low-dose CT group is the likely explanation."

Both Black, in his presentation, and Sox, in his editorial, concluded that further cost-effectiveness analysis and additional models are needed before screening can be implemented effectively.

"I think low-dose CT screening is potentially cost-effective," Black told the advisory board. "However, it depends on several critical variables which have to be controlled."

Black's estimate is much lower than the estimates by Scott Gazelle, director of the Massachusetts General Hospital Institute for Technology Assessment, and Pamela McMahon, a scientist at ITA and the principal investigator for the NCI Cancer Intervention and Surveillance Modeling Network (The Cancer Letter, Nov. 26, 2010).

According to a projection Gazelle and McMahon's group presented at the Radiological Society of North America's 2009 annual meeting, the cost of screening would range between $135,000 and $180,000 per quality-adjusted life year.

."We are well above what most people would consider a typical dollar amount for a screening intervention, based on our modeling study," McMahon said.

Most cancers are screened for around $50,000 per quality-adjusted life year. For example, the cost of screening for breast cancer in women over the age of 50 falls under $50,000—but exceeds $100,000 in populations aged 40 to 50.

After the NLST preliminary results were announced in November, Peter Bach, a pulmonologist and director of the Memorial Sloan-Kettering Cancer Center's Center for Health Policy and Outcomes, decided to test the belief that, in the U.S., a screening can cost in the neighborhood of $300.

Bach surveyed 50 screening centers and found that the going price was closer to $1,800. Bach's story is posted at http://www.slate.com/id/2274942/.

An excerpt from Black's presentation to NCAB follows:

We know that about 17 out of 1,000 people in the chest x-ray arm of the NLST died from lung cancer over our observation period. We also know that there was a relative risk reduction of about 20% in the CT arm compared to chest x-ray arm. So if you multiply these two numbers, you get an absolute risk reduction of about 3 per 1,000. We also know what the years of lost life are for lung cancer; this is based on published data (US mortality data). With adjustments for discount rate, it's about 12 years. So if you multiply the absolute risk reduction times the years of lost life due to lung cancer (12), you come up with life years gained per screenee of about 4 per 100 or 40 per 1,000. That's the benifit per screenee. That looks small: this is a screening trial and we will always have small absolute benefits.

Now if you look at the cost, I'm going to estimate that the cost of the CT is about $300 (that's close to what Medicare reimburses today), we're going [estimate that] the non-medical costs associated with travel and time to get the screen [are] about $100 (and that's based on a recent estimate on screening in Canada for CT colonography). So I'm assuming that the average cost per screen is now prospected to about $400; and for three screens, we say that the average cost per screenee is $1,200. For the follow-up CT, I'm going to assume that 40% have a positive test, and on average each has two CTs. That's 80% of a screening CT, or 80% of $400 is $320. So if you add up three screens and the cost of the follow-up, you come up with $1,520.

So we have a cost difference of $1520, and we have life years gained from screening of 40 per 1,000; so if you divide this cost by this life years gained, you come up with an incremental cost effectiveness ratio of about $38,000.

Now let me just put that in perspective: I said earlier that there is no formal, fixed, rigid for cost effectiveness, but most people who are familiar with this area will say somewhere around $100,000 per quality adjusted life year in duress, and most people consider things under $50,000 well worth it. So in this preliminary analysis, I'm showing you that it is certainly plausible that this could be done in a cost-effective way.

I want to make a couple other caveats here. First of all, while we should ideally be making decisions based on the societal perspective, what actually happens in the real world is going to depend on other perspectives, such as the perspective of the screenee. What is the screenee going to have to pay for this CT screening? Well, if we don't have insurance coverage, the screenee may

be paying well over $2,500 on average, just based on the out of pocket expenses for a screening test and the deductable associated with the insurance for the work-up. On the other hand, if the screenee is completely covered by insurance, the screenee may end up paying nothing.

We also don't know what the true cost is to the provider. The estimate of $300, [which] I said before [was] based on Medicare reimbursement, is pretty close to the cost—probably a little higher than the true cost—to most institutions to perform a CT and to read it in a standardized fashion. However, if we are going to be implementing screening in an effective way, we are probably going to have to be doing it a little differently than the way we just do an ordinary CT scan, and we will probably have to assume some of the burden of following up these screenees. So I don't know what the true cost will be; it will depend on exactly how we implement [screening], and there are lots of different options as far as how we implement CT screening in the future.

The other thing I want to point out is that there are a lot of variables in this cost-effectiveness as we extrapolate the results from the NLST to the community. I want to just go over a few of these. One of the most important factors is what is the risk for lung cancer. In the NLST, we selected a fairly high-risk population. If we disseminate this screening to the rest of the country and we loosen the criteria for screening, we are going to decrease the lung cancer risk (the risk of dying from lung cancer) and we are going to increase the incremental cost.

Same thing with the screening intensity. We were pretty conservative in the NLST: we only had three rounds of screening. Again, if this goes out into the public and we do more than three rounds of screening and we follow up the lesions more aggressively, we are going to increase the screening intensity and increase the cost.

Surgical effectiveness: the NLST was done at centers that had a lot of surgical expertise. If this is disseminated widely, we may be doing it in places where we don't have that surgical expertise. The surgery will be less effective, and again that will increase the relative cost. Also surgical mortality: the study was done at centers where there was a very low surgical mortality, probably much lower than in the US overall.

Now here is one area that I didn't talk about yet, and that is smoking cessation. If it turns out that screening does in fact help with smoking cessation, there could be an additional benefit. But I haven't yet taken it into account when I gave you that estimate of $38,000 per quality adjusted life year. So we'll certainly have to be looking at that. That's a very important factor.

[But] one of the most important factors is who do we select for screening. And I just want to drive this point home. In the NLST, we had fairly rigorous criteria: age 55–74, greater than 30 pack years. There are about 8 million such people in the United States. If we were to embark on screening right now, in the first year, we would spend about $4 billion in their screening. However, notice that as we loosen the criteria, we get more and more people who are eligible for screening. If you look at all adults that have ever smoked, we have almost 100 million people in the United States, and the first year of screening alone would cost $53 billion. So this is a huge factor: who do we end up screening?

I want to say a word about going beyond our cost-effectiveness analysis. In our planned cost-effectiveness analysis, we are going to be focusing on what happened in NLST. We will be able to make some projections about what might happen if we [examined] slightly different populations, but we'll be somewhat limited in our projections. If we want to investigate the possibility of changing the threshold for interpreting a nodule or changing the frequency of screening, we will need what's known as a "deep model" of natural history in our cost effectiveness. Now, we don't have the resources in NLST to build such a model, but there is another organization called CISNET, [the] Cancer Intervention and Surveillance Modeling Network, which has already built a lot of these natural history models of lung cancer; and so teaming with them, we will be able to do much more robust analyses of what are the possibilities for lung cancer screening and what are the consequences.

In summary, I think low-dose CT screening is potentially cost effective. However, it depends on several critical variables, which will have to be controlled. I also want to point out that though it appears to be cost effective from the societal perspective, other perspectives have to be considered, particularly that of the potential screenee and the providers of the service. The cost effectiveness analysis that we will be doing with NLST will answer a lot of questions, but will not answer all the questions about how screening can be implemented. Our collaboration with CISNET should help inform the development of future guidelines on CT screening.