THE CANCER LETTER

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ACS Creates $1 Billon Nationwide Organization, Taking Fiduciary Control From 12 Divisions

By Paul Goldberg

A board of the American Cancer Society last week voted to fundamentally change its governance structure, centralizing fiduciary powers within its National Board, and executive powers within a single nationwide organization.

The National Volunteer Assembly of the Atlanta-based society Nov. 10 voted 102-19 to take fiduciary responsibilities from its 12 divisions and cede its own fiduciary powers to the society's 43-member National Board.

The resolution, adopted by a resounding margin, scraps the governance structure that the 98-year-old non-profit adopted in 1944.

The move gives the ACS National Board and the CEO control over the society's $900 million purse, as well as substantial real estate holdings nationwide. Supporters of the changeover say that it will transform the society

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Appropriations

No Budget in Sight, NCI Takes Careful Steps; Success Rate Last Year Was At 14 Percent

By Paul Goldberg

In fiscal 2011, NCI funded 1,106 competing research project grants at an average cost of $384,000.

Using a review procedure instituted by the NCI Director Harold Varmus, all R01 grants scored up to the seventh percentile received funding. This added up to 379 R01s.

On top of that, the institute relied on special panels of NCI officials to sift through grants that were scored above the seventh percentile, in what Varmus calls "the zone of uncertainty."

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The Avastin Controversy

FDA Revokes Avastin's Accelerated Approval In Metastatic Breast Cancer Indication

By Paul Goldberg

FDA Commissioner Margaret Hamburg Nov. 18 announced her decision to revoke the breast cancer indication of the Genentech drug Avastin, making it the first agent to lose an accelerated approval.

Avastin (bevacizumab) has not been shown to be safe and effective in that indication, Hamburg said in a statement, backing an earlier decision of the agency's Center for Drug Evaluation and Research and the Oncologic Drugs Advisory Committee.

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The Cancer Letter will not be publishing Nov. 25, in observance of Thanksgiving Day. The next issue will appear Dec. 3.

Once Powerful National Assembly Votes Itself Out of Power

(Continued from page 1)

from an arcane political structure to a relevant force in 21st century America.

Critics, who spoke at the Nov. 10 meeting, lamented the demise of a political structure that reached deep into America's neighborhoods at a time when society volunteers canvassed door-to-door.

The society's former federated structure included the national headquarters, a National Assembly that met annually, a separate National Board, and 12 divisions that were chartered by the assembly.

The structure needed to be transformed because the world has changed, said W. Phil Evans, the just-installed society president and director of the UT Southwestern Center for Breast Care.

"One of the big issues in today's nonprofit world is: what is community?" Evans said to The Cancer Letter. "There are so many communities out there. There is a virtual community. Many people have friends online, and there are many ways in which people relate and call each other a part of their community."

Evans was a co-chair of the volunteer group which focused on "leadership, governance and accountability," and put together the governance structure approved by the assembly.

"We decided on an organization that would provide a line-of-sight accountability between the national CEO and the division executives, which is something we haven't had," Evans said.

Before voting on Nov. 10, assembly members received an email from Jerome Yates, a former ACS national vice president for research and a society volunteer. The move away from geographic representation is a fatal mistake, Yates wrote.

"It is with some concern that I watch the ACS centralize its efforts while leaving the communities to function primarily as a source of funding," Yates wrote. "As a long term volunteer and a loyal staff member at the NHO for a number of years, the leadership appears to be leading the organization down a path toward irrelevance.

"Clearly there are efficiencies to be gained through shared infrastructure activities across the divisions, but diminished regional representation comes at the price of diminished broad based regional dedication to the ACS and the loss of protective checks and balances for that core of volunteers who are without accessible representation," Yates wrote.

The text of Yates's letter is posted at http://www.cancerletter.com/categories/documents

Change is occurring at a time when the society's fundraising has dropped from a high of $1,039 million in 2007 to the current level of $903 million. The people who give money to the American Cancer Society likely have no idea of these divisions of power, which determine how the money is distributed and spent.

The 12 ACS divisions turn 40 percent of their proceeds over to the national organization. Each division was, in effect, a separate nonprofit, but in situations where their charters were revoked, their assets reverted to the national organization.

What the divisions did with their 60 percent has been their business.

The divisions had separate boards of directors, hired their own CEOs, and filed separate tax forms. In one recent case, a division made plans to issue its own cancer screening guidelines.

Altogether, prior to the Nov. 10 vote, 513 volunteers throughout the ACS system had fiduciary responsibilities.

Proponents of the change said it would be charitable to characterize the existing system as duplicative. Some tasks are repeated 13 times.

Last year, the society ordered over 900 variations of t-shirts for its Relay for Life fundraising event, said Greg Donaldson, national vice president for corporate communications. This variation is astonishing, because the design is standardized.

Purchasing and contracting were disparate, too. The society had 46 health insurance plans for employees

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nationwide. "We have already taken steps to negotiate them collectively and reduce the number of options to a more consistent offering," Donaldson said to The Cancer Letter.

The old governance structure was so intricate—so dependent on horse-trading and old alliances—that it could only be run by a consummate insider. This is particularly important at a time when the society's CEO, John Seffrin, is entering his 20th year at the helm.

Seeking Ratification from Division Boards

The division boards will still exist. "They will just not have the governance responsibility," Evans said.

The society hopes that sometime before Sept. 1, 2012, all the division boards would vote to accept the merger plan, effectively consenting to join the single legal entity.

Evans said that ACS recently conducted a study to see how the division boards spent their time, finding that about 30 percent of the time was spent on governance activities. Now, the boards will be focused on "mission delivery, cancer control and implementation and actually determine what will work in their specific areas," Evans said.

The decision by the National Assembly to transfer its powers to the board is at least as important as the decision to eliminate the fiduciary powers of the division boards.

The assembly was composed of division volunteers—six delegates per division—who came to Atlanta once a year to vote on the manner funds were to be split up, to elect the nominating committee and the National Board, and to change the bylaws.

Members of the National Board also sat on the National Assembly. Some former members could also attend the meetings, but had no authority to vote.

"We now have one fiduciary board," Evans said, reflecting on the resolution.

The assembly has become an advisory group, which will be called the National Leadership Summit. The summit will be held annually, as a meeting of volunteers. "That's where we will exchange ideas, inspire and engage," Evans said.

"The [old governance] model served us well for many years, but this is not the model for most not-for-profits in this day and age," Evans said. "You need to be able to respond more quickly to what goes on and be able to make decisions in a much more effective manner, and you need to have one group that makes the decisions."

Gary Streit, an attorney in Cedar Rapids, Iowa, said he doesn't foresee opposition to the plan in his division.

"I am excited, I am anxious, but it's clearly the right direction to be heading," said Streit, who is also a past chair of the ACS National Board and a non-voting member of the National Assembly. "Many of the divisions now are multi-state divisions, which means they have gone through that process.

"This is the beginning of the beginning," Streit said. "There was so much work. Think about it, you have to run the organization. If you are going to work on what's your organization going to look like after the vote, (a) that would have aggravated some people, who would say, 'You are assuming the outcome of the vote. That's not right,' and (b) there just aren't the resources. You take things in the right sequence."

Streit said he doesn't expect political wrangling.

"In their heart of hearts, everybody wants the organization to be better, to be more effective, and to save more lives," he said. "I think people embrace a lot of the change that's going on in the organization. The governance part is hard, but many of the divisions are multistate divisions, where they have gone through this process and they see how much more effective they are as a combined organization."

Seffrin has been trying to streamline the society since taking office in 1992.

At the time, the society had 57 divisions, mostly broken up by state, though some states had more than one division.

First, the society stripped power from two grassroots levels of the divisions—"units" and "areas"—making them purely advisory. Then, over the years, the society divisions were merged, shrinking to 12.

An earlier effort by Seffrin to create "one organization" was shot down by the assembly in mid-1990s.

Some long-time activists don't see virtue in Seffrin's pursuit of efficiency.

"If you have royalty and a castle in Atlanta, it can be totally efficient, but that is not the way we do things," said Helene Brown, a nonvoting honorary life member of the National Assembly, who says she is the society's longest-serving volunteer. "I don't think that you can continue to raise funds that you if you have volunteers who cannot vote."

Brown, 82, spoke against the changes at the assembly meeting Nov. 10.

"I don't believe there was anybody truly listening for new information," she said to The Cancer Letter. "There is no longer check or balance on that board. It would be a self-perpetuating board."

An overview of the society's finances is posted at: http://bit.ly/l8WMS7.

The text of the Nov. 10 resolution follows:

WHEREAS, at its August 2011 meeting, the Board of Directors of the American Cancer Society, Inc. adopted resolutions approving a Transformed Governance Structure comprised of the following:

• A single 501(c)(3) nonprofit corporation.

• A single strategic, fiduciary governing board that sets policy, develops and approves an enterprise-wide strategic plan and is responsible for the performance of the organization as a whole.

• Defined geographic Divisions, each with a board that serves an advisory and execution/implementation role.

• An executive in each Division who reports to the national CEO or designee, with a dotted line reporting relationship to the Division board.

• Enterprise functional volunteer groups (councils, committees, etc.) - continuation of existing groups and new groups formed based on need and appropriateness.

• Established, substantive links between the Division volunteer boards and the National Board to facilitate two-way dialogue to/from National Board and maintain critical connection to the grassroots constituency.

• Continued opportunities for enterprise-wide discussion and collaboration via leadership forums and an annual summit of volunteers, representative of the Divisions.

• Transfer of the National Assembly's current governance responsibilities to the National Board.

WHEREAS, the Board of Directors instructed that the Transformed Governance Structure be submitted to the National Assembly for its consideration; and

WHEREAS, the Reference Committee has recommended that the National Assembly approve the Transformed Governance Structure and corresponding amended bylaws;

WHEREAS, the National Assembly has determined that the Transformed Governance Structure is in the best interest of the American Cancer Society.

NOW, THEREFORE, BE IT RESOLVED, that the National Assembly hereby approves the Transformed Governance Structure, including the transfer of its governance responsibilities, by approving and adopting the amended bylaws.

DISCLOSURE: Paul Goldberg and the ACS Chief Medical and Scientific Officer Otis Brawley are co-authors of a book, HOW WE DO HARM: A Doctor Breaks Ranks on Being Sick in America, which will be published by St. Martin's Press Jan. 31, 2012.

Appropriations

NIH Funded 379 R01 Grants Scored Above 7th Percentile

(Continued from page 1)

This resulted in funding another 279 grants. As they decide whether to fund such grants, the panels consider the science, the applicants' work in the past, and the proposals' contribution to the institute's overall objectives.

The remaining competing grants—454 of them—included P01s, R21s, and R33s. The seventh percentile pay line for guaranteed funding doesn't apply to these grants.

Overall, this adds up to a success rate of 14 percent, which is similar to the overall success rate across the NIH.

Going forward at a time of fiscal uncertainty will require cautious moves, Varmus said to the Board of Scientific Advisors Nov. 7.

Congress passed a continuing resolution the day before its Nov. 18 deadline. The government will be funded through Dec. 16.

Under the best-case scenario, a full-year Labor-HHS spending bill that funds NIH would get through Congress by the end of the calendar year.

Capitol Hill sources said the spending bills will likely be grouped into "minibus" packages, and the Labor-HHS bill would likely be paired with the Department of Defense.

"It wouldn't surprise me if we didn't have a final bill until sometime in mid-winter or early spring," Varmus said to the board.

The level of funding NCI would receive is uncertain.

At best, it would be at three percent above the 2011 level. At worst, the funding would be one percent below. That would be the second one-percent decline in two years—the institute's funding dropped by a percentage point in 2011.

The Senate appropriations bill for fiscal 2012 proposes a 0.6 percent drop for NIH. However, a bill introduced by House Republicans calls for a three-percent boost, but contains provisions NIH officials don't like.

The Obama administration's proposal last year included a two-percent increase.

"2012 is a year still in flux," Varmus said to the BSA. "The budget for NIH can be anywhere from minus one from 2011 to plus three.

"We are taking a very conservative position with

respect to making awards," he said. "This not very different from previous years, with Type 5 awards and non-competitive renewals at roughly 90 percent, which is traditional under these circumstances," Varmus said. "And we are going to pay about 80 percent across approved Type 1 and 2s until we get a full budget.

"We are just trying to get some money out the door so people can get to work. The institute will rely on the same strategy with R01s that it used in fiscal 2011.

"We will be funding at the moment roughly from the 7th percentile on down," Varmus said. "We will be looking at grants below that, playing cautiously, because we don't know where we are going to end up this year.

"There are so many things in motion, because the final funding decisions will have to depend upon getting a final budget and we will not have a final budget probably until sometime next calendar year."

Last year, the institute applied relatively small cuts, which Varmus calls "haircuts" to all of its programs. Now, NCI and NIH officials are plotting strategy for continuing to fund good science during long-term decreases in appropriations and buying power.

"We have been discussing how we might deal with the budgets that we might have this year," Varmus said. "We had a retreat in July, which mostly consisted of senior leadership at NCI, but we talked in great detail how we are going to adapt to a negative budget if we had one.

"We came to a consensus that we are not going to shrink things forever by taking haircuts. We have to make decisions on how to deal with budget reductions, and my own view is that if we have programs that we think have not been that productive, then we should at least decrease them if not stop them."

Preparing for 2013, the NIH institutes have been asked to submit three new initiatives each, and a group of institute directors are judging those.

"[NIH Director] Francis Collins sent a proposal to [HHS] that all institutes will not be equal, that is they would be funded based on these initiatives," Varmus said.

Also, NCI is drafting its 2013 bypass budget. Last year, this document focused on progress against six cancers. The next iteration will focus on another six.

Appropriations Legislation

In September, the Senate appropriations subcommittee that covers NIH marked up the 2012 appropriations bill, giving NIH a .06 percent cut. However, the bill is free of mandates, Varmus said.

For example, it funds the National Center for Advancing Translational Sciences, an NIH initiative that appears to be central to the Collins agenda.

During the markup, Sen. Jerry Moran (R-Kan.) attempted to add some money into the bill for NIH.

However, the effort was rebuffed by the Democratic leadership, on grounds that other important programs were losing funds.

Despite the funding cut, "the bill is a clean bill," Varmus said. "It's free of any stipulations that would harm us."

The House bill, H.R. 3070, sponsored by Rep. Denny Rehberg (R-Mont.) and referred to the appropriations committee, contains an increase, but also mandates.

For one thing, the bill doesn't acknowledge the creation of NCATS, and instead provides funding to the NIH entity it intends to replace: the National Center for Research Resources.

The bill's NIH-related highlights include:

• A mandate for the NIH Clinical Center to collect third-party payments for the cost of clinical services that are incurred in NIH research facilities, and that such payment be credited to the NIH Management Fund.

• The NIH director is obligated to ensure that at least 9,150 new and competing research project grants are awarded.

• The director must maintain an allocation of 90 percent to extramural activities and 10 percent for intramural activities.

• The director must ensure that at least $487,767,000 is provided to the Clinical & Translational Sciences Awards program.

• Up to $10 million would be available for the Director's Discretionary Fund, of which up to $2 million may be used to establish the Cures Acceleration Board within the Office of the Director's Division of Program Coordination, Planning, and Strategic Initiatives to develop a plan with prioritized recommendations related to the Cures Acceleration Network for consideration in future appropriations.

The bill was introduced by Rehberg, the committee chair.

"That proposal is saddled with a number of other stipulations about the actual number of new and competing grants that the NIH should be sustaining and supporting in 2012, a formula for distribution of money between intramural and extramural programs, and some other statements that are anathema to us," Varmus told the BSA.

"We don't want to be inappropriately smothered by the Congress, by conditions for our awards that are not in their purview."

Drug Shortages

Generic Drugs in Short Supply Available From One or Two Sources

By Lucas Thomas and Paul Goldberg

The shortage of generic drugs is highly concentrated, and most drugs that are in short supply are available from one or two suppliers, according to a research group that tracks the pharmaceutical industry.

If the findings published by the IMS Institute for Healthcare Informatics are correct—that the problem is isolated and the number of players is small—eradication of the problem should be a manageable task.

Like rolling blackouts, the shortages have been part of day-to-day oncology practice for about six years. Earlier this month, President Obama issued an executive order expanding FDA authority to prevent these shortages (The Cancer Letter, Nov. 3).

There is no shortage of bulk materials and no shortages have been reported outside the country. Branded drugs are unaffected by the problem.

The report, titled: "Drug Shortages: A Closer Look at Products, Suppliers and Volume Volatility," was published Nov. 14. It is available on the IMS website, at: www.imshealth.com.

Among the report's findings:

• The drug shortage problem is highly concentrated. More than 80 percent of products impacted are generics, and more than 80 percent are injectables. While representing a small part of the overall medicines market, affected products include a number of critical drugs used to treat cancer, infection, cardiovascular disease, central nervous system conditions and pain. Oncology drugs make up 16 percent of the products in short supply.

• The shortages involve a large number of suppliers, yet most drugs in short supply have only one or two manufacturers. More than 100 companies supply 168 products included on the shortages lists compiled by FDA and the American Society of Health-System Pharmacists. However, 51 percent of those products have only one or two suppliers. Thirteen companies have stopped supplying products on the shortages lists within the past two years. This leaves a growing number of products open to possible production disruptions that cannot be offset rapidly by other manufacturers.

• Total supply volume for many impacted products has been stable or growing—yet significant volatility exists among suppliers. The total monthly supply volume for all products on the shortages lists has increased 4 percent over the past five years. And, for more than half of the listed drugs, total supply is relatively stable or has increased. However, there are recent signs of increased volatility in the month-to-month supply of impacted products by specific suppliers, resulting in disruption to providers.

• For a group of 75 drugs, supply volume has fallen substantially. A subset of products has experienced supply declines of more than 20 percent in recent months, compared with a three-year base period ending in 2009. The per-capita supply of injectables has fallen more than 30 percent in 13 states, suggesting significant treatment protocol disruption for patients.

The IMS Institute recommends that the FDA or healthcare industry establish an early warning system to improve drug supply monitoring. This system should include a volatility index, risk identification, demand forecasting and predictive modeling.

The IMS study was produced independently as a public service, without industry or government funding.

Industry Groups Lobby For Lower FDA Approval Standards

By Paul Goldberg

A model bill circulated by Sen. Kay Hagan (D-N.C.) proposes to lower the standards for FDA's approvals of drugs, including cancer drugs.

The measure appears to be consistent with an earlier report issued by the Biotechnology Industry Organization. Similar lowering of the standards has been proposed by the National Venture Capital Association.

Capitol Hill observers say the language similar to the draft could be attached next year to the reauthorized version of the Prescription Drug User Fee Act.

PDUFA, which brings over $600 million into the agency through industry-paid fees, is set to expire at the end of this fiscal year.

The model legislation, called the Transforming the Regulatory Environment to Accelerate Access to Treatments, or TREAT, creates two provisional approval categories—progressive approval and exceptional approval:

• **Progressive approval** "may be granted if the secretary determines, based on relevant science, the strength and quality of the available data, and consideration of the benefits and risks of progressive approval with respect to the product under review for the intended population (or subpopulation) and use, that the evidence submitted in the application is reasonably likely to predict clinical benefit for such population and use."

• **Exceptional Approval** could be granted by the secretary "on the basis of an alternative showing" of data, at times when, after meeting previous criteria, "the data necessary to satisfy the standard for approval… cannot ethically, feasibly, or practicably be generated with respect to such drug."

The Cancer Letter obtained a copy of the TREAT document, which is posted at http://www.cancerletter.com/categories/documents.

The two approval categories would be applied to drugs intended to provide a meaningful advancement in the treatment of diseases or conditions that are "serious or life threatening or that present a significant risk to the public health."

Both categories are proposed in a BIO report titled "Unleashing the Promise of Biotechnology," published June 28.

That report is posted at http://www.bio.org/sites/default/files/PromiseofBiotech.pdf.

Also, in following the BIO report's example, the Hagan bill would establish a six-year term of office for the FDA commissioner, without a limit to the number of reappointments.

The bill would establish a Management Review Board, which would represent the regulated industries, venture capital and patients. The 21-member board would include at least one representative from each of the pharmaceutical, biotechnology, medical device and food industries.

The conflict-of-interest rules would narrow, replacing the current standard—"financial interest that could be affected by the advice given to the secretary"—with "direct and predictable financial interest in the outcome."

Hagan sits on the Senate Health, Education, Labor and Pensions Committee.

The Avastin Controversy

Genentech Vows To Conduct Avastin-Paclitaxel Phase III Trial

(Continued from page 1)

Hamburg described her decision in detail in a 69-page opinion. It can be downloaded at: http://1.usa.gov/v3KYnY.

An in-depth analysis of the controversy appears in the May 27 issue of The Cancer Letter, and is available for free at: http://www.cancerletter.com/articles/20110526.

Genentech sought to keep the indication while conducting another confirmatory trial of Avastin in combination with paclitaxel.

The agency will now remove the breast cancer indication, which allowed the anti-angiogenesis drug to be used in combination with paclitaxel in patients who have not been treated with chemotherapy for HER2 negative metastatic breast cancer.

Avastin will remain on the market for its other indications—colon, lung, and kidney cancers, as well as glioblastoma multiforme—and will be available for being prescribed off-label.

The Centers for Medicare and Medicaid Services said they would not take any moves to stop paying for the drug, pending FDA determination. CMS uses a separate process, called the National Coverage Analysis, to determine payment policy.

"This was a difficult decision," Hamburg said in a statement. "FDA recognizes how hard it is for patients and their families to cope with metastatic breast cancer and how great a need there is for more effective treatments. But patients must have confidence that the drugs they take are both safe and effective for their intended use.

"After reviewing the available studies, it is clear that women who take Avastin for metastatic breast cancer risk potentially life-threatening side effects without proof that the use of Avastin will provide a benefit—in terms of delay in tumor growth—that would justify those risks.

"Nor is there evidence that use of Avastin will either help them live longer or improve their quality of life," Hamburg said.

The agency said Hamburg's decision was based on an extensive record, which includes thousands of pages submitted to a public docket, data from several clinical trials and the record from a two-day hearing held in June (The Cancer Letter, July 1, 2011; available for free at: http://www.cancerletter.com/articles/20110701).

Genentech said the company was disappointed

with the outcome and pledged to continue to study the drug in the breast cancer indication.

"We remain committed to the many women with this incurable disease and will continue to provide help through our patient support programs to those who may be facing obstacles to receiving their treatment," the company said.

"Despite today's action, we will start a new phase III study of Avastin in combination with paclitaxel in previously untreated metastatic breast cancer and will evaluate a potential biomarker that may help identify which people might derive a more substantial benefit from Avastin."

Avastin was approved for metastatic breast cancer in February 2008 under the FDA's accelerated approval program. The drug was approved based on data that demonstrated its ability to delay progression. There was no impact on survival.

Genentech's confirmatory trials showed a smaller impact on time to progression than the initial trial, and ODAC recommended against granting it a full approval. In fact, the committee determined that an accelerated approval was no longer justified.

CDER, the FDA center responsible for the approval of this drug, ultimately concluded that the results of these additional studies did not justify continued approval and notified Genentech it was proposing to withdraw approval of the indication.

Genentech did not agree with the center's evaluation of the data and, following the procedures set out in FDA regulations, requested a hearing on the center's withdrawal proposal, with a decision to be made by the commissioner.

That two-day hearing, on June 28-29, included recommendations from ODAC, voting 6-0 in favor of withdrawing approval of Avastin's breast cancer indication.

During a telephone press conference, Hamburg acknowledged that there may be some women who benefit from Avastin, but said that it would be impossible to leave the indication in place for that subpopulation.

"I considered that question," she said. "However, because there isn't an identified subset of women for which that benefit can be demonstrated, it is very difficult to provide an indication for appropriate use.

"When you look at the overall body of evidence and data, the early findings upon which the accelerated approval was based were not confirmed in terms of the delay in tumor progression.

"None of these studies demonstrate an increase in overall survival or improvement in quality of life, but all of the studies confirm the very serious adverse events associated with the use of Avastin—ranging from high blood pressure, to heart attack and heart failure, to bleeding and hemorrhage and perforation of tissues and body parts, and, in some instances, death.

"In light of the fact that we couldn't confirm the initial benefits demonstrated when the accelerate approval was granted and the serious, even life-threatening adverse events associated with its use, I didn't feel that I could really advocate for maintaining the indication for Avastin for metastatic breast cancer.

"However, we do very much hope that Genentech will continue to pursue studies that might shed further light on whether we can identify a subset of responders to Avastin, and we hope that the science will advance."

Hamburg said women receiving Avastin should discuss their treatment options with their physicians.

Now that the administrative remedies have been exhausted, Genentech has the option to pursue the matter in court or in Congress.

Responding to Hamburg's decision, Genentech offered the following information for doctors and patients:

- Genentech will issue a letter to healthcare providers and will also provide them with a letter to distribute to their patients. Both letters will be made available on Genentech's website.
- Patients with questions or concerns about insurance coverage or doctors with questions about reimbursement can call Genentech's Access Solutions Group at (866) 4-ACCESS.
- Doctors with questions about Avastin can call Genentech's Medical Communications group at (800) 821-8590.
- The FDA's action does not impact ongoing trials with Avastin in breast cancer. For more information, call Genentech's Trial Information Support Line at (888) 662-6728 or visit clinicaltrials.gov.

Timeline

The Avastin Story In A Nutshell

May 2005

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

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

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

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

May 2007

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

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

Dec. 5, 2007

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

Approval would be unprecedented. It would mark the first approval of a non-hormonal agent in which evidence of a treatment effect on PFS alone was viewed not as a surrogate endpoint, but rather as a clinical benefit because of the magnitude of the improvement in progression-free survival.

Dec. 27, 2007

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

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

Feb. 22, 2008

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

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

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

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

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

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

Nov. 16, 2009

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

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

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

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

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

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

July 20, 2010

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

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

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

The issue of Avastin's approval becomes political.

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

September 2010

FDA delays the approval decision on Avastin,

announcing that it needs another 90 days to review new data submitted by the company.

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

Nov. 7, 2010

Midterm elections.

Dec. 16, 2010

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

The NOOH states CDER's conclusions that AVADO and RIBBON1 failed to verify clinical benefit in the MBC indication, and that the risk/benefit assessment that supported the initial approval of the MBC indication had changed significantly and Avastin no longer met the safety and effectiveness requirements for continued marketing for that indication (The Cancer Letter, Dec. 17, Dec. 24, 2010; Jan. 20, 2011). Centers for Medicare and Medicaid Services says it will continue to pay for therapy while the FDA proceedings run their course.

Jan. 16, 2011

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

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

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

April 7, 2011

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

May 11, 2011

FDA publishes a Notice of Hearing.

May 13, 2011

Genentech and FDA submit summaries of arguments they would make at the hearing.

May 27, 2011

Genentech and the FDA's Center for Drug Evaluation and Research separately submit their lists of witnesses who will present at the hearing. They also submit will be summaries of the issues each witness would address.

June 3, 2011

Genentech and CDER submit their lists of hearing representatives (those who may question the presenters).

June 28-29, 2011

ODAC votes 6-0 to recommend removing Avastin's accelerated approval.

Protestors line up in the early morning outside FDA's White Oak campus before breast cancer patients testify before the committee for two hours about their quality of life while taking Avastin.

Two hours of public testimony represents a significant bureaucratic change from the committee's past procedures.

Following the vote, several breast cancer patients begin to shout at the committee members as they explain their decisions.

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

Committee member Wyndham Wilson said, "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," he said.

Members of the Abigail Alliance for Better Access to Developmental Drugs say they've requested a meeting with FDA Commissioner Margaret Hamburg and will work to overturn ODAC's recommendation.

The full story appeared in the July 1, 2011 issue of The Cancer Letter. It is available for free here:

http://www.cancerletter.com/articles/20110701

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In Brief

Ohio State Receives 23.8% Boost As NCI Renews Core Grant

THE OHIO STATE UNIVERSITY Comprehensive Cancer Center received a five-year, $23 million core grant renewal from **NCI**.

This is a 23.8 percent increase over the amount awarded in 2005, the last time NCI reviewed the university's cancer program. OSUCCC was rated "exceptional," the highest possible rating, following a site visit by a group of 28 scientists from other universities.

"This core grant is truly transformative and validates the commitment for resources dedicated to cancer research across the spectrum at Ohio State," said Michael Caligiuri, director of the cancer center and CEO of the James Cancer Hospital and Solove Research Institute. "The money provided to us by the NCI is critical for our infrastructure and facilitation of groundbreaking research to prevent, detect, treat and cure cancer."

CITY OF HOPE and **Children's Hospital Los Angeles** received a $2.5 million grant from **NCI's Tumor Microenvironment Network** to investigate drug resistance in neuroblastoma. The grant will establish an Environment-Mediated Drug Resistance center at Children's Hospital.

"Our research demonstrated that the interactions between cancer cells and normal cells in the tumor microenvironment are essential for the growth and spread of neuroblastoma cancers," said Yves De Clerck, principal investigator on the grant and professor of Pediatrics and Biochemistry/Molecular Biology at the Keck School of Medicine of the University of Southern California.

"We found that one such pathway of interaction called STAT3 is persistently activated in both tumor cells and in the tumor microenvironment, and we believe that targeting STAT3 signaling in bone marrow stromal cells will inhibit EMDR for neuroblastoma," said Hua Yu, co-leader of the Cancer Immunotherapeutics Program at City of Hope.

Yu is principal investigator for one of the two projects of the new NCI Program Project Grant. The co- principal investigator of the project is Richard Jove, director of the Beckman Research Institute, and holder of the Morgan and Helen Chu Director's Chair.

The researchers are collaborating with De Clerck, the program project's principal investigator, and his colleagues Robert Seeger and Shahab Asgharzadeh, from The Saban Research Institute at Children's Hospital.

"By inhibiting environment-mediated drug resistance, we will provide a new paradigm that will result in improved survival not only for children with neuroblastoma but also for children and adults with other types of cancer," said Seeger, director of the Cancer Research program at Children's Hospital.

The investigators at both institutions credit a 2009 seed grant from ThinkCure, the official charity of the Los Angeles Dodgers, in helping researchers collaborate for the initial stages of their research, which led to securing the NIH grant.

MARK ROH was named incoming president of **MD Anderson Cancer Center Orlando**, and will take over as president next year. Roh will maintain his clinical practice as a liver cancer surgeon.

Roh also serves as the cancer center's medical and scientific director, overseeing all clinical activities within the cancer center and clinical, basic and translational research programs. Roh will take over for Clarence Brown, who will be retiring from his current post after 36 years.

Roh joined Orlando Health in August 2009 as the chairman of the Department of Surgery of MD Anderson Orlando and academic chairman of the Department of Surgery of Orlando Health.

Roh was recently named among the top one percent of physicians in the nation by US News & World Report and is on the American Cancer Society's Florida Board of Directors. Since 1994, he has served as the executive editor of the Annals of Surgical Oncology.

NORTH COAST CANCER CARE was acquired by the **Cleveland Clinic** health system.

NCCC, a full-service cancer treatment center with 70 employees at three locations, will join the clinic's Taussig Cancer Institute.

North Coast Cancer is now a department within the Taussig Cancer Institute--and NCCC's former president, Steven Roshon, will serve as the department chair.

NCCC's three centers are located in Sandusky, Clyde, and at the Fisher-Titus Medical Center in Norwalk, Ohio.

Each location will continue to provide outpatient cancer services including consultations in hematology and oncology, chemotherapy, radiation therapy, diagnostic services and patient support. The main building in Sandusky will be called the North Coast Cancer Campus.

NCCC supports cancer education programs and community outreach through the North Coast Cancer Foundation. Cleveland Clinic will provide the foundation with yearly donations over the next five years.