THE CANCER LETTER

Vol. 36 No. 31
Sept. 3, 2010

© Copyright 2010 The Cancer Letter Inc.
All rights reserved. Price $375 Per Year.
To subscribe, call 800-513-7042
or visit www.cancerletter.com.

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Avastin May Trigger Two FDA Decisions: One On Approval, Another On Withdrawal

By Paul Goldberg

FDA officials will likely have to make two separate decisions about the future of the Roche drug Avastin as a first-line treatment for metastatic breast cancer.

First, by Sept. 17, the agency is expected to decide whether to grant additional marketing claims and full approval for the indication. Approval is unlikely, considering that on July 20, the FDA Oncologic Drugs Advisory Committee voted unanimously against converting the drug from accelerated approval to full approval.

Second, the agency will have to decide whether to start formal proceedings aimed at revocation of the accelerated approval it had granted the drug in 2008. At its most recent meeting, which considered two confirmatory

(Continued to page 2)

In the Cancer Centers:

Craig Thompson Of Abramson Center Named President, CEO, Of Memorial Sloan-Kettering

CRAIG THOMPSON was named the president and CEO of Memorial Sloan-Kettering Cancer Center effective Nov. 2. His appointment concludes a search that began last January. He succeeds **Harold Varmus**, who left Memorial Sloan-Kettering in July 2010 and is the NCI director.

Thompson has served since 2006 as director of the Abramson Cancer Center at the University of Pennsylvania and associate vice president for cancer services of the University of Pennsylvania Health System.

"Craig Thompson is an exemplary physician-scientist, educator, and academic leader. This breadth of expertise will serve MSKCC well as he helps to guide our institution into the next decade," said Douglas Warner III, chairman of the Boards of Overseers and Managers of Memorial Sloan-Kettering. "He brings to his new role significant contributions to the understanding of the biology of cancer, a strong and committed appreciation for the needs of patients with cancer, and superb executive skills. We are very fortunate to have him as we seek to maintain and enhance the accomplishments of Memorial Sloan-Kettering and move ambitiously into the future."

Thompson oversaw the work of several hundred cancer researchers as well as more than 300 full-time physicians and faculty across the University of Pennsylvania Health System involved in cancer prevention, diagnosis, and treatment. During his tenure, his accomplishments included the opening

(Continued to page 8)

Roche Trials Aimed To Broaden Indication Beyond E2100 Study

(Continued from page 1)

studies conducted by the sponsor, ODAC voted and 12 to 1 in favor of revocation (The Cancer Letter, July 23).

The authority to withdraw accelerated approvals is included in the original 1992 legislation that creates this regulatory mechanism, but the agency has said—until now—that as a practical matter such drugs would not be removed if there is even an inkling of evidence that some patients might be benefiting from treatments.

This stance appears to be changing as the agency has demanded speedy conduct of confirmatory trials to convert accelerated approval to full approvals. In June, the FDA oncology unit said sponsors would be asked to present detailed plans for conducting confirmatory studies during end of phase II meetings. Also, the agency is considering using ODAC to conduct annual reviews of outstanding confirmatory study commitments (The Cancer Letter, June 25).

In a related development, last month, the agency began the process that could lead to withdrawal of the indication of a hypotension drug. On Aug. 16, FDA notified Shire Development Inc. that it has begun such proceedings for Proamatine (midodrine hydrochloride), sponsored by, as a treatment for symptomatic orthostatic hypotension.

Accelerated approval drugs have lost indications before, but by less bureaucratically cumbersome means than formal withdrawal procedures. In the past, the sponsors have either caved under pressure or simply accepting the harsh reality demonstrated in studies.

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

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

• Iressa (gefitinib), sponsored by AstraZeneca, was placed in a restricted access program that barred physicians from prescribing it to new patients. This action, in 2005, was caused by failure of confirmatory trials to demonstrate a survival advantage.

Untested Procedures for Withdrawal

With the prospects of approval of the breast cancer indication appearing dim, Roche would likely have to decide whether to cave and voluntarily give up the indication or to take a chance on the untested withdrawal process.

The process requires a separate public hearing before an expert panel. It's likely that in the case of an oncology drug, this panel would be comprised of ODAC members, sources said.

Considering complexity of bureaucratic procedures that will come into play, this means that Avastin (bevacizumab) could retain its accelerated approval for months to come, as oncologists, patient groups and politicians continue to wrangle over the future of the billion-dollar indication.

Withdrawal procedures are spelled out in 21 CFR Subpart H 314.530. Here is how the process works:

• The director of the FDA Center for Drug Evaluation and Research writes a letter containing a "notice of an opportunity for a hearing" on the center's proposal to withdraw the approval of an application. The letter contains the reasons for the action. This is what has happened with the Proamatine application last month.

• The sponsor then has 15 days of receipt of the notice, the applicant waives the opportunity for a hearing. If the sponsor requests a hearing, the agency announces the hearing in the Federal Register. The sponsor then has 30 days of receipt of the notice of opportunity for a

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $375 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Other than "fair use" as specified by U.S. copyright law, none of the content of this publication may be reproduced, stored in a retrieval system, or transmitted in any form (electronic, photocopying, or facsimile) without prior written permission of the publisher. Violators risk criminal penalties and damages. Founded Dec. 21, 1973, by Jerry D. Boyd.

hearing to submit the data and information which would form the basis of the hearing.

• "An advisory committee" would be present at the hearing, the regulations state. However, it's not clear whether this would be the same committee that would have been consulted on approval. The committee will be asked to review the issues involved and to provide advice and recommendations to the FDA commissioner.

• The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the center may question any person during presentations. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

• The commissioner's decision would constitute final agency action from which the applicant may petition for judicial review.

Roche officials declined to speak with The Cancer Letter.

Scientific Questions

Avastin's approval in 2008 was based on a 5.5-month advantage in progression-free survival demonstrated in Eastern Cooperative Oncology Group trial E2100. At the time, the committee voted 5 to 4 against granting an accelerated approval, but the agency disregarded the recommendation and approved the drug.

Confirmatory studies conducted by Roche and presented to the committee in July showed a far less dramatic improvement in PFS, producing an overwhelmingly negative recommendation from the committee and casting substantial doubt on the drug's future in breast cancer.

Scientific discussion of the drug in the breast cancer indication gets nebulous fast. Though anecdotally there seem to be women who benefit, there is no biomarker to predict who they may be.

Also, the dose at which the drug should be given is uncertain. One of the confirmatory trials showed that the 15 mg/kg dose produced a similar PFS result as half of that dose. In the US, the drug is labeled at 10 mg/kg for the breast cancer indication.

Some breast cancer experts wonder whether Roche made a miscalculation when it launched confirmatory trials that sought to broaden the breast cancer indication beyond the regimen used in the E2100 trial. In E2100, Avastin was administered with weekly paclitaxel.

However, in one of the Roche confirmatory trials—AVADO—the drug was used with Taxotere (docetaxel) every three weeks. In another trial—RIBBON 1—Avastin was used with a taxane/anthracycline combination in one cohort and with capecitabine in another. RIBBON 1 had no weekly taxane arm.

This difference between regimens used with Avastin could, at least theoretically, affect the outcome of studies. Breast cancer experts point to one of the more puzzling phenomena in their field: data show that weekly paclitaxel appears to produce greater efficacy than once-every-three-week docetaxel.

By launching these confirmatory trials, Roche could have ended up with a broad indication. However, victory was elusive. Though PFS ended up being positive in both trials, ODAC determined that the magnitude of improvement didn't justify the side effects.

"I wish we had more data regarding how to individualize this drug, and I wish we knew more about the biology of it, and I wish it didn't cost so much," said Daniel Hayes, clinical director of the breast cancer program at the University of Michigan.

Since there is no reliable biomarker that would predict which patients respond to Avastin, Hayes has worked out an algorithm for prescribing the drug.

"I have not been using it in every patient who walks in the door," Hayes said. "I take into consideration how much I need a response. If they have relatively indolent disease, I haven't been adding it. If I am going to start an oral medication for chemotherapy and I am not going to do anything IV anyway, then I don't use Avastin, because I hate to lead them to IV therapy if they are not going to get it otherwise. So I start it in people who have relatively rapidly progressive, especially with visceral, disease. I've given Taxol with Avastin. I will continue to do it. But every time I do it, I think, 'This is so expensive. I don't know if we can afford this.'"

A year's worth of Avastin costs around $100,000.

Julie Gralow, director of breast medical oncology at Fred Hutchinson Cancer Research Center, said the absence of predictive tests is making it difficult to decide how to use the drug.

"I don't know who is benefiting, although I am certain that there is a population of breast cancer patients who are getting real benefit," Gralow said. "Which tumors, which patients has not been well sorted out, and it's not easy. I don't know whom to treat and I don't truly know which is the best combination, although the data increasingly support that there is a difference between the weekly paclitaxel vs. every three-week

docetaxel."

Gralow, who is a co-chair of the Southwest Oncology Group Breast Cancer Committee, said she still believes the results of E2100 were credible. "I think what we've seen that the best combination for reasons we don't understand is weekly paclitaxel, and I don't think PFS of 12 months is a fluke in E2100," Gralow said. "I think they were being greedy, maybe, and going for every-chemo-works kind of approval. It's hard to know ahead of time, but it looks like it may be important in how you combine it."

This is, of course, a belief. The Roche trials, which were conducted separately from then-independently run Genentech Inc., were well underway at the time Avastin received an accelerated approval. What if the company had chosen a different approach, mimicking the regimen used in the E2100 trial? This what-if is no less intriguing than another oncology mystery: what if AstraZeneca had chosen a higher dose for its lung cancer drug Iressa? And here, too, there is no way to know.

Both Hayes and Gralow said they oppose taking away Avastin's indication. "My patients who are already on the drug, I am continuing it," Hayes said. "My patients who are starting new metastatic therapy, if I believe they fall into category where I would have treated them last week or two weeks ago, I still recommend it. It's not off the market yet. I haven't changed much. I am letting the smoke clear."

Hayes said that if the drug loses the indication, he will likely continue to give it off-label, assuming that there is payment for it. "But if I had Hayes insurance company, I would probably say we are not going to pay for it at this price," he said. "Either drop the price to something reasonable or we are not going to do it."

Gralow said that patients are caught in the middle of this fight. "It's not the right thing to use anecdotes, but there are a lot of patients out there who have done amazingly well on this drug," she said. "I don't want to have to pull it from them. But I don't want to give it to patients who don't benefit."

Aman Buzdar, a breast cancer expert and interim vice president, clinical research, at MD Anderson Cancer Center, said he doesn't give Avastin outside clinical trials. Buzdar sat on ODAC at both meetings where Avastin was considered and voted against approval both times.

"I don't think it is helping many patients," he said. "You have to look at the risk-benefit ratio, and the risk-benefit ratio is close to one or maybe even slightly in the other direction."

For one thing, Buzdar has no confidence in the findings of E2100 and believes that the confirmatory trials provided more realistic results. "The question is how robust was the data of E2100," he said. "On 10 percent of the patients, there were initial missing scans. If you don't have baseline information, it's difficult to assess progression-free survival. In 34 percent of the patients there was not adequate information about when the event occurred. And then the FDA requested that two independent reviewers look at these data, in 50 percent of the data endpoints there was discordance between two independent reviewers."

The differences in methods of administration of Avastin aren't the problem, Buzdar said. "The best way to give docetaxel is Q3 weeks, the best way to give paclitaxel is to give it weekly," Buzdar said. "AVADO trial included Taxotere in optimal schedule."

It's unclear how FDA's actions would affect ongoing NCI-sponsored clinical trials. In some cases in the past, the institute has responded to new trial data and regulatory actions by altering or stopping trials. This was, for example, the case with Iressa. However, in the case of Avastin, the institute's actions are difficult to predict. The trials, after all, are positive, just not positive enough to warrant approval.

Buzdar is not interested in this form of speculation. "You have to look at the data at its face value," he said. "If they think that this was a wrong approach and the wrong combination, they need to do appropriate studies and bring it back to FDA."

After FDA's action, Kathy Miller, chair of an Study E5103 in adjuvant breast cancer said the rationale for that study is still intact."

"The purpose of this correspondence is to confirm and clarify the status of the E5103 trial," wrote Miller, a breast cancer expert and associate director, clinical research, at the Indiana University Cancer Center. "As you know, E5103 is a randomized Phase III trial to evaluate the potential benefit of adding bevacizumab to standard chemotherapy for breast cancer patients with high risk of relapse.

"It is not known at this time whether there is any benefit that would result from adding bevacizumab to the standard therapy or from increasing the number of bevacizumab treatments beyond the initial twenty-four month period. These are the questions that we hope will be answered by this trial. In short, E5103 is proceeding as planned. The scientific rationale for E5103 has not changed and the data that supported its design remain. Additionally, the safety profile for bevacizumab remains identical to that seen in prior studies—no new safety signals have emerged."

The full text of Miller's letter is posted here.

Buzdar said the future of ongoing trials should become more clear after FDA's decision. "First, we have to see what is the decision of the FDA after hearing from ODAC and looking at all the evidence they have," he said. "Then, whatever the FDA decision is, it will be up to the investigators and the cooperative groups to see how they should adjust their research portfolio in light of whatever the decision is."

Death Panels

A week after the ODAC vote, Sen. David Vitter (R-La.) fired off an error-riddled letter to Richard Pazdur, director of the FDA Office of Oncology Drug Products.

"Avastin has been shown to extend the life of metastatic breast cancer patients for an average of five months," Vitter wrote incorrectly in a letter dated July 27. (A five-month advantage in overall survival would have been very nice, but the drug has not demonstrated it.)

"For those battling terminal cancer, every additional day that they can beat the disease and extend their time with their loved ones is valuable and treasured," Vitter wrote. "My family has been directly affected by the horrible disease of breast cancer, and I have strong reservations about any recommendation that would take life-extending options off the table for these patients."

Vitter asserted—with no proof—that ODAC's decision was "based on cost-effectiveness."

"The decision on whether a patient should use a possible life-extending drug is a decision that should be made solely between a doctor and patient, not a government panel. I find it outrageous that a government panel would put a price on those precious months for the families that are living through the trauma of a losing a mother, wife, sister, daughter, or aunt," Vitter wrote "Taking Avastin off-label for breast cancer treatment is essentially government rationing….

"I am not suggesting that Avastin is a perfect drug, but it has a proven record of effective treatment for some patients when used along with chemotherapy. Lacking any safety concerns, we should not deny patients access to a treatment that might extend their lives and their time with their loved ones."

In a joint statement Aug. 17, Susan G. Komen for the Cure and the Ovarian Cancer National Alliance urged keeping Avastin on the market for patients receiving it now and out of concern over "the message that this decision sends about drug development in women with advanced breast cancer."

The two groups noted anecdotal accounts of Avastin's efficacy. "We recognize the benefits of Avastin overall are modest for women with metastatic breast cancer. However, we do know that for some women, Avastin offers a greater benefit—but we do not yet know how to determine which patients will experience greater benefits.

"We hope that drug manufacturers will continue to develop medications for the treatment of metastatic breast cancer, and would not want this decision to mean that drug development for breast cancer comes to a crashing halt."

The text of the letter is posted here.

Gabriel Hortobagyi, chairman of the Department of Breast Medical Oncology at MD Anderson Cancer Center, has similarly emerged as a vocal advocate for the drug. Hortobagyi appeared as a consultant for Roche at the ODAC presentation and subsequently advocated for the drug in the press.

At the ODAC presentation, Horetobagyi's slides bore the MD Anderson name. This struck his MD Anderson colleague Buzdar as inappropriate. "He was speaking not as an MD Anderson spokesperson," Buzdar said. "He was speaking as a private person. Since I work with him, I would say this was inappropriate."

In a written statement drafted for a reporter but circulated to a large list of colleagues, Hortobagyi said that some ODAC members failed to understand the Avastin presentation.

"During the discussion, I got the strong impression that several ODAC members had a poor understanding of clinical trials and statistics (based on some of the questions that were somewhat bizarre!), and that very few had any experience using bevacizumab in the clinic," he said in a statement for the press. The text of the statement is posted here.

Buzdar disagrees. "I was in that same meeting," he said. "People who were on the committee are highly respected members of society, and they understood statistics and every aspect of the disease far better than some of the people who are criticizing it.

"People who were sitting on the panel are very knowledgeable people. People looked at the data. You have a difference of three weeks. It is not a major step forward. This could be just a three-week visit. There was a trend, but in the wrong direction when you look at survival, which was a slightly higher risk of death from all causes, and some of the deaths might have been related to the therapy."

In a separate interview, which appeared in St.

Petersburg Times, Hortobagyi asserted that the agency was guided by financial considerations. "I wonder if the outcome would have been the same if the drug cost $100 a month instead of $100,000 a year," Hortobagyi said.

FDA is precluded by law from considering cost in making approval decisions.

Buzdar said the committee was not influenced by financial considerations. "There is no net gain from Avastin," he said. "Money is not the issue. We don't take that issue for a second. It's never discussed."

Post-ODAC discussions of Avastin are evidence of politicization of the field, Buzdar said. "The decisions about drug safety and efficacy have to be made by rigorous studies, not by campaigning by email," he said. "These are not political decisions. We are making decisions about people's lives."

Patients Campaign Against Avastin

A large number of breast cancer groups petitioned the agency to maintain rigorous approval standards and follow the ODAC recommendations. Several of these groups urged FDA to demand demonstration of a survival advantage.

"It is now clear that Avastin is not providing a meaningful improvement to patients, and is exposing them to a greater risk of serious toxicities," said one letter signed by 26 breast cancer groups and 25 individuals.

"We urge the FDA to reverse course on Avastin approval and restore the highest standards for drug approval. No meaningful benefit has been established for Avastin in breast cancer, but we have seen evidence of significant harm. We must put patients needs and their trust above all else--patients must trust that the drugs they are given can be expected to give them benefit and not expose them to greater."

In another letter AdvancedBC.org and 32 other groups and individuals said CMS and private insurers should continue to cover the costs associated with the drug for metastatic breast cancer patients responding to Avastin-containing regimens.

"However, based on the results of the confirmatory trials, we strongly support withdrawal of the indication for Avastin in metastatic breast cancer," the letter said. "We ask that you show us that the accelerated approval process can and does work as it was intended to--to offer early access to promising new agents, but withdraw approval should that promise not be realized."

The letters are posted here.

The most rigorously argued patient letter to FDA was submitted by the National Breast Cancer Coalition.

The text of the NBCC letter follows:

In 2008, The National Breast Cancer Coalition strongly urged the FDA not to weaken the standard for approval of drugs in the first-line treatment of metastatic breast cancer by granting approval of bevacizumab in combination with paclitaxel without any evidence that the addition of bevacizumab improves overall survival. We were extremely disappointed that the FDA granted accelerated approval, choosing to ignore the recommendations of the Oncologic Drug Advisory Committee and others who expressed concerns about the use of progression free survival as an endpoint for drug approval.

If the FDA was granting accelerated approval with the understanding that PFS was a potential surrogate for a more meaningful outcome, we can now be certain, after two additional years of data, that this is not the case. In a meta-analysis presented at the 2010 annual meeting of the American Society of Clinical Oncology, with data from over 2200 patients in E2100, AVADO, and RIBBON-1 trials, the addition of bevacizumab to chemotherapy failed to demonstrate a significant improvement in overall survival. Median overall survival in the chemotherapy plus bevacizumab arms was 26.7 months compared to 26.4 months in the chemotherapy alone arms.

It is clear that bevacizumab in combination with chemotherapy is not improving overall survival compared with chemotherapy alone. We urge ODAC to stand by its original recommendation on bevacizumab in combination with the chemotherapy drug paclitaxel for patients who have not received chemotherapy for their locally recurrent or metastatic HER2 negative breast cancer. Particularly in light of the updated data, ODAC should urge the FDA to rescind approval rather than convert accelerated to regular approval.

In addition, we strongly urge ODAC to recommend against further approval for bevacizumab as first-line treatment of HER2-negative metastatic breast cancer in combination with either docetaxel, capecitabine, taxanes or anthracyclines. Though an improvement in PFS may occur with the addition of bevacizumab to these chemotherapy drugs, the data has clearly shown that an improvement in PFS with bevacizumab has not proven to be a surrogate measure for overall survival.

Not only has bevacizumab failed to demonstrate an increase in overall survival, but its use is associated with greater toxicities than chemotherapy alone. According to the data from E2100, the addition of bevacizumab to paclitaxel was associated with a 20.2% increase in

serious side effects classified as Grades 3-5 adverse events. In addition, death occurred in 1.7% of patients (6/363) in the bevacizumab arm compared to 0% (0/348) for those who received paclitaxel alone.

Futhermore, since 2008, pre-clinical research has introduced a disturbing possibility with anti-angiogenesis agents that requires careful consideration before furthering the use of bevacizumab for any indication. In March 2009, results from a study with mouse models confirmed that treatment with an anti-angiogenic agent initially stabilized or shrank tumors, but later caused an adaptive response, with increased invasion into adjacent tissue. These results are consistent with a small number of clinical trials suggesting that anti-angiogenic therapy may alter the natural history of tumors in a detrimental way.

The possibility that anti-angiogenesis agents may promote more invasive tumor growth over time could explain the failure to see an improvement in PFS ultimately translate into an improvement in overall survival. The FDA must carefully consider the broad and meaningful impact of bevacizumab use on patients and not just focus narrowly on PFS. The FDA must consider not only bevacizumab's failure to improve overall survival, but the increase in toxicities and lowering of quality of life for patients, and the disturbing possibility of the agent promoting invasive tumor growth.

The ultimate goal in drug approval must be to make meaningful progress towards finding cures and saving patients' lives while minimizing toxicities and protecting the quality of their lives. Since its inception in 1991, NBCC has fought for federal funding for research aimed at eradicating breast cancer. From the start we insisted on the involvement of trained consumer advocates at all levels of the research process to ensure impact, accountability and scientific rigor.

We have always insisted on high standards for research in order to generate high levels of evidence for health care. The FDA plays a critical role in protecting the public health by setting high evidentiary standards for clinical utility. In the first-line metastatic setting, it is the hope of consumer advocates that the research effort aims to improve survival and eventually lead to cures.

We believe that lowering the standard for drug approval has undermined the quest for advancement in treatment and for cures, as we lose the ability to determine whether new treatments truly save lives. We urge the FDA to reverse course on bevacizumab approval and restore the highest standards for drug approval.

Industry News:

FDA Rejects Genentech's Bid For Accelerated Approval For T-DM1 In Breast Cancer

Genentech said FDA issued a Refuse to File letter for accelerated approval for the company's trastuzumab-DM1 Biologics License Application.

Genentech, a member of the Roche Group, made the announcement on Aug. 26.

The company said it will continue with its phase III registration trial, EMILIA, and expects to submit a new BLA in mid-2012.

The BLA submitted in July 2010 requested accelerated approval for T-DM1 based on the results of a single-arm phase II study, which showed T-DM1 shrank tumors in one-third of women with advanced HER2-positive breast cancer, who had received on average seven prior medicines, including two HER2-targeted medicines.

The company said that following the pre-submission meeting with the FDA in March 2010, Genentech concluded it was appropriate to submit a BLA for accelerated approval.

The EMILIA study compares T-DM1 to lapatinib in combination with capecitabine in people with advanced HER2-positive breast cancer whose disease has worsened after receiving initial treatment.

T-DM1 is an antibody-drug conjugate, also known as an armed antibody, studied for advanced HER2-positive breast cancer. T-DM1 attaches trastuzumab and the chemotherapy DM1 together using a stable linker, which is designed to keep T-DM1 in one piece until it reaches specific cancer cells.

The antibody (trastuzumab) binds to the HER2-positive cancer cells, and is thought to block out-of-control signals that make the cancer grow while also calling on the body's immune system to attack the cells. Then, once T-DM1 is absorbed into those cancer cells, it is designed to destroy them by releasing the DM1. Genentech licenses technology for T-DM1 under an agreement with ImmunoGen Inc.

The company said the submission was based on a Phase II study known as TDM4374g, a single-arm, multi-center trial designed to assess single-agent T-DM1 in 110 women with advanced HER2-positive breast cancer whose disease had worsened after receiving at least two prior HER2-targeted treatments (Herceptin [trastuzumab] and lapatinib) in the metastatic setting, as well as an anthracycline, a taxane and capecitabine.

The primary endpoint of the study was objective

response rate (a complete or partial tumor shrinkage of at least 30 percent, determined by two tumor assessments at least 28 days apart), as measured by an independent review facility.

Allergan Pleads Guilty To Promoting Off-Label Botox

Allergan Inc. pled guilty to promoting off-label uses of the neurotoxin Botox and agreed to pay $600 million to settle charges in a federal investigation.

Under the settlement agreement, the company dropped a lawsuit challenging the FDA authority to regulate what companies can say about off-label uses of drugs (The Cancer Letter, Jan. 15).

In the Cancer Centers:

Craig Thompson To Lead Memorial Sloan-Kettering

(Continued from page 1)

of a new multidisciplinary cancer outpatient facility; the development of the first proton therapy center in the Mid-Atlantic region; and the expansion of Abramson's translational research effort.

Thompson's current research focuses on the role that metabolic changes play in the origin and progression of cancer. He has also done pioneering research on the genes that control programmed cell death and how the misregulation of such genes can contribute to cancer. In earlier work he contributed to the development of innovative treatments for autoimmune diseases and leukemia.

"We are at a time when transformative developments in biomedical research are greatly expanding opportunities to understand disease and to improve human health," said Thompson. "With Sloan-Kettering's extraordinary strength in patient care, research, and education, I could not be more enthusiastic about this new role and new challenge. I look forward to building on MSKCC's achievements and tradition of excellence and to working with my colleagues here in making progress in controlling and ultimately curing cancer."

In 1999, Thompson joined the University of Pennsylvania as the founding scientific director of the Abramson Family Cancer Research Institute (the basic science arm of the Abramson Cancer Center), the university's first chair of the Department of Cancer Biology, and a professor of medicine.

Thompson attended Dartmouth College and completed his studies at Dartmouth Medical School. He received his MD degree from the University of Pennsylvania in 1977 and completed his residency at Harvard's Peter Bent Brigham Hospital in 1979. Following his residency, he spent two years as a senior resident at Boston University while serving as a medical officer in the US Navy assigned to the Naval Blood Research Laboratory. He spent a total of eight years as a Navy medical officer, including two years at the Naval Blood Research Institute, three years at the National Naval Center/Naval Medical Research Institute, and three years as a clinical research associate at the Fred Hutchinson Cancer Institute.

In 1987, Thompson joined the University of Michigan's Department of Medicine. In 1993, he was recruited by University of Chicago as the first director of the Gwen Knapp Center for Lupus and Immunology Research and professor in the departments of medicine and molecular genetics and cell biology.

From 1989 through 1993, Thompson was a Howard Hughes Medical Institute associate investigator, and an HHMI investigator from 1993 to 1999.

Thompson is a board-certified internist and medical oncologist, and has extensive research experience in cancer, immunology, and translational medicine. In 2003, he was elected to the Institute of Medicine and in 2005 was elected to the National Academy of Sciences. He currently serves as chair of the HHMI Medical Advisory Board. He is also a member of the Board of Directors of the Association of American Cancer Institutes and the American Association for Cancer Research, and is a member of the Lasker Prize Jury. Thompson has been a member of the advisory boards of several cancer centers including St. Jude Children's Research Hospital and the University of Texas MD Anderson Cancer Center.

IAN THOMPSON JR., professor and chair of urology at The University of Texas Health Science Center at San Antonio and executive director of its Cancer Therapy & Research Center, was elected chairman of the NCI Early Detection Research Network.

The EDRN is a collaborative effort overseen by the NCI Division of Cancer Prevention. It involves dozens of institutions working to improve early detection of cancers using the body's own biomarkers, and it coordinates validation studies to determine whether a biomarker delivers on its early promise.

Thompson previously held the position of vice chairman of the EDRN, running its executive committee. His leadership has been key in the committee's reviews of validation studies, said EDRN program director

Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Group.

Thompson serves as chairman of the Genitourinary Committee of the Southwest Oncology Group. He is principal investigator on two large prostate cancer studies.

DAVID GERSHENSON has been elected co-chair of the NCI Gynecologic Cancer Steering Committee. Gershenson is professor and chair of the Department of Gynecologic Oncology and J. Taylor Wharton, MD Distinguished Chair in Gynecologic Oncology at The University of Texas MD Anderson Cancer Center in Houston.

The GCSC works to implement an efficient, cost-effective, science-driven, and transparent process that will identify and promote the "best science" in gynecologic cancer clinical research by addressing the design and prioritization of phase III trials and evaluating randomized phase II studies. As part of its mission, this GCSC is intent on fostering collaboration with international groups and institutions engaged in conducting trials in gynecologic cancers.

MAURIE MARKMAN was named vice president of patient oncology services and national director for medical oncology at Cancer Treatment Centers of America.

Markman will also serve patients as a medical oncologist at the hospital network's Philadelphia location, where he will treat patients within the recently launched Patient Empowered Care model, which gives patients more time and greater access to their dedicated care team for more responsive, personalized care.

Markman served as the vice president for clinical research and chairman of the department of gynecological medical oncology at MD Anderson, and chairman of the department of hematology/oncology at The Cleveland Clinic Foundation.

GYNECOLOGIC ONCOLOGY GROUP principal investigators elected **Philip DiSaia** to a third term as group chair.

DiSaia, who has held the group chair position since 2003, is the Dorothy J. Marsh Chair in Reproductive Biology; director, Division of Gynecologic Oncology Professor, Department of Obstetrics and Gynecology, at the University of California, Irvine College of Medicine.

As group chair, DiSaia is the principal investigator of the six-year GOG cooperative group grant from NCI and chair of the GOG Board of Directors and Principal Investigators committee.

MING YOU was appointed director of the Medical College of Wisconsin Cancer Center, effective Sept. 1.

An internationally recognized lung cancer researcher, You also has been appointed senior associate dean for cancer research, education and clinical care, professor of pharmacology and toxicology, and the Joseph F. Heil Professor in Molecular Oncogenesis.

You comes to the Medical College from Washington University, St. Louis, where he was the Mary Culver Distinguished Professor; director of the chemoprevention program at the Alvin J. Siteman Cancer Center and professor of surgery.

You is currently the principal investigator or the co-principal investigator for eight NIH research project grants on genetics and chemoprevention of lung cancer and is a member of the NCI Board of Scientific Counselors.

NCI News:

NCI Breaks Ground For New Campus At Shady Grove

NCI Director Harold Varmus, Maryland Gov. Martin O'Malley, Sen. Benjamin Cardin, and Reps. Chris Van Hollen and Donna Edwards, and other officials marked the start of construction Sept. 1 on a $200 million satellite campus at the Shady Grove Life Sciences Center for 2,100 NCI employees.

"This new facility represents a collective investment in the talents, skills, creativity, and education of our people," O'Malley said. "In these tough times, it will create much needed jobs for our families during construction, and its sustainable design will help our environment. When it is complete, the vital research and innovation that will happen here will improve our health and biosciences sectors and help us to secure a better, stronger and healthier future for generations to come."

NCI's new satellite site will be located on Johns Hopkins' Montgomery County Campus, which is home to more than 4,000 students, 450 full and part-time faculty members and 16 biotech companies and research centers.

"We continue to champion improved healthcare and biosciences here and everywhere Johns Hopkins University has a presence," said Ronald Daniels, president of Johns Hopkins University. "Our vision is to provide the right environments for scientists, educators,

students, caregivers and entrepreneurs to work and live. We welcome NCI to our campus and look forward to a long and productive relationship with its leaders and staff."

Most of the NCI staff members who will work at the Life Sciences Center are located in other commercial buildings that do not afford space for future expansion. JBG signed a long-term ground lease with Johns Hopkins, which owns the land, to build the 575,000 square foot facility, scheduled to be delivered in early 2013.

NIH News:

New Breast Cancer Committee To Develop Research Agenda

A new advisory committee will develop and coordinate a strategic federal research agenda on environmental and genetic factors related to breast cancer.

The 19-member Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) was established by the National Institute of Environmental Health Sciences, in collaboration with the National Cancer Institute, to review all breast cancer research efforts conducted or supported by federal agencies.

The committee will develop recommendations for the secretary of the U.S. Department of Health and Human Services, NIH, and other federal agencies, to improve existing research programs related to breast cancer research. The committee will create a comprehensive plan to expand opportunities for collaborative, multi-disciplinary research, and develop a summary of advances in federal breast cancer research.

"The broad range of expertise and insight of these individuals will ensure the federal research portfolio continues to advance our understanding of the critical links between our environment, our genes, and our health," said Linda Birnbaum, director of NIEHS and the National Toxicology Program.

"The committee's focus on breast cancer and the environment research across federal agencies will be valuable in identifying scientific opportunities to better understand the impact of the environment on this disease," said Robert Croyle, director of the NCI Division of Cancer Control and Population Sciences.

The IBCERCC includes 19 voting members, including representatives of federal agencies; non-federal scientists, physicians, and other health professionals from clinical, basic, and public health sciences; and advocates for individuals with breast cancer. The business of the committee will be facilitated by federal officials including NIEHS Director Birnbaum, NCI Director Harold Varmus, and other NIEHS and NCI officials.

The first meeting is scheduled for Sept. 30-Oct. 1, in the Washington, D.C., area. The committee roster follows:

Federal Representatives:

Christine Ambrosone, member, NCI Board of Scientific Advisors, professor of oncology, Roswell Park Cancer Institute.

Sally Darney, acting national program director, Human Health Research Program, Environmental Protection Agency.

Suzanne Fenton, reproductive endocrinologist, NIEHS.

Vivian Pinn, director, Office of Research on Women's Health, NIH.

Marcus Plescia, director, CDC Division of Cancer Prevention and Control.

Gayle Vaday, program manager, Breast Cancer Research Program, Congressionally Directed Medical Research Programs, U.S. Department of Defense.

Shelia Hoar Zahm, deputy director, NCI Division of Cancer Epidemiology and Genetics.

Non-Federal Representatives:

Michele Forman, professor of epidemiology, University of Texas M.D. Anderson Cancer Center.

Michael Gould, professor of oncology, University of Wisconsin-Madison.

Sandra Haslam, professor of physiology, Michigan State University.

Ronda Henry-Tillman, medical director, Women's Oncology Clinic and Director, Cancer Control Arkansas Cancer Research Center, University of Arkansas for Medical Sciences.

Kenneth Portier, statistician, American Cancer Society.

Cheryl Walker, professor of carcinogenesis, University of Texas M.D. Anderson Cancer Center.

Advocates:

Janice Barlow, executive director, Zero Breast Cancer.

Beverly Canin, president, Breast Cancer Options.

Alice Chang, president, Academy for Cancer Wellness.

Karen Joy Miller, president, Huntington Breast Cancer Action Coalition.

Laura Nikolaides, director, Research & Quality Care Program, National Breast Cancer Coalition.

Jeanne Rizzo, president, Breast Cancer Fund.

Lawrence Tabak Named NIH Deputy Director

NIH Director Francis Collins appointed **Lawrence Tabak** as principal deputy director of the institutes.

"I am delighted to have Dr. Tabak as deputy director during this critical time for biomedical research," Collins said. "His outstanding service in numerous activities across the NIH and combination of skills and experience will help the NIH move forward in these revolutionary times for the biomedical sciences."

Tabak assumes the position held by **Raynard Kington**, who served as NIH deputy director since 2003, as well as acting NIH Director from October 2008 to August 2009. Kington is leaving to become president of Grinnell College.

Tabak has served as director of the National Institute of Dental and Craniofacial Research from September 2000. He served as acting NIH deputy director in 2009 and most recently as the acting director of the Division of Program Coordination, Planning, and Strategic Initiative.

He came to NIH from the School of Medicine and Dentistry at the University of Rochester, where he had most recently been the senior associate dean for research, director of the Center for Oral Biology, professor of dentistry, and professor of biochemistry and biophysics. While maintaining an active research lab within the National Institute of Diabetes and Digestive and Kidney Diseases, Tabak's major research focus has been on the biosynthesis and function of mucin-glycoproteins, molecules that are heavily decorated with sugars and help form the coating that protects the delicate inner soft (mucosal) tissues of the body.

A native of Brooklyn, NY, Tabak received his undergraduate degree from City College of the City University of New York, his D.D.S. from Columbia University, and both a Ph.D. and certificate of proficiency in endodontics from the University of Buffalo.

SALLY ROCKEY has been named NIH deputy director for extramural research. She has been serving in the position in an acting capacity since the fall of 2008. She joined NIH as deputy director of the Office of Extramural Research in 2005.

Before joining NIH, she led the US Department of Agriculture Extramural Competitive Research Program at the Cooperative State Research, Education and Extension Service.

ROBERT KAPLAN was appointed director, Office of Behavioral and Social Sciences Research and NIH Associate Director for Behavioral and Social Sciences Research. Kaplan is expected to join the NIH in early 2011.

Kaplan is a distinguished professor in the Department of Health Services at the School of Public Health and the Department of Medicine at the David Geffen School of Medicine at University of California, Los Angeles. He has also served as the principal investigator of the UCLA/RAND CDC Prevention Research Center and director of the UCLA/RAND Health Services Research training program. He was also professor and chair of the Department of Family and Preventive Medicine at the University of California, San Diego School of Medicine.

JAMES ANDERSON was named director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives. Anderson has served as professor and chair of the Department of Cell and Molecular Physiology in the School of Medicine at the University of North Carolina at Chapel Hill since 2002. Previously, he was professor of medicine and cell biology and chief, Section of Digestive Diseases, at the Yale School of Medicine.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES has renewed a research effort to develop medical products to diagnose, prevent and treat the short- and long-term consequences of radiation exposure after a radiological or nuclear terrorist attack.

NIAID's Centers for Countermeasures Against Radiation program, first established in 2005, will support research at seven institutions. NIAID will provide five years of additional funding to the program beginning in fiscal year 2010, for an estimated total of $105 million.

"Medical countermeasures are vital to protecting the public and caring for patients in the event of a deliberate or accidental exposure to radiation," said NIAID Director Anthony Fauci. "Such treatments also might help diminish the organ and tissue damage that occurs after radiation exposure in other settings, such as in cancer therapy."

The CMCR program, part of NIAID's larger medical countermeasures program, supports research in radiation biology as well as projects to develop diagnostic tools to measure radiation exposure and

therapeutics to treat the resultant tissue injury. Each center conducts its own research projects and also supports pilot projects proposed by investigators outside the CMCR core program.

In the initial CMCR program, NIAID supported eight centers and funded 130 pilot studies. The next phase of the program will continue to investigate many of the most promising treatments for radiation injury. A new center at Dartmouth College will be dedicated to developing techniques and devices that examine the radiation-induced physical and chemical changes in teeth, hair and fingernails.

The following seven academic institutions and principal investigators will participate in the program:

Albert Einstein College of Medicine, Chandan Guha.

Columbia University, David Brenner.

Dartmouth College, Harold Swartz.

Duke University, Nelson Chao.

University of California, Los Angeles, William McBride.

University of Pittsburgh Medical Center, Joel Greenberger.

University of Rochester, N.Y. Medical Center, Jacqueline Williams.

In the Courts:

Justice Department Appeals Judge's Stem Cell Injunction

The Justice Department earlier this week challenged a court ruling handed down last week by U.S. District Judge Royce Lamberth that froze federal funding for embryonic stem cell research.

The temporary injunction has put many experiments on hold and has been criticized by scientists and research advocacy organizations. Lamberth's ruling was based on a 1996 amendment that prohibits federal funds from being used for research that destroys human embryos. It would suspend $54 million in funding for more than 20 research projects.

The Justice department is seeking a stay of the court's injunction and has filed a notice of its intention to take the decision to the U.S. Court of Appeals. The notice is available at http://www.nih.gov/about/director/stemcell/appeal_08312010.pdf. The appeal is posted at http://www.nih.gov/about/director/stemcell/stay_08312010.pdf.

Blocking stem cell research could cause "irrevocable harm to the millions of extremely sick or injured people who stand to benefit," the department's filing says.

In a statement Aug. 26, NIH Director Francis Collins said the research "holds great promise" for new treatments. "The recent court ruling that halted the federal funding of human embryonic stem cell research could cause irreparable damage and delay potential breakthroughs to improve care for people living with serious diseases and conditions such as spinal cord injury, diabetes, or Parkinson's disease," Collins said. "The injunction threatens to stop progress in one of the most encouraging areas of biomedical research, just as scientists are gaining momentum—and squander the investment we have already made. The possibility of using these cells to replace those that have been damaged by disease or injury is one of the most breathtaking advances we can envision. Human embryonic stem cells also represent a powerful new approach to the early stages of screening for new drugs, and may hold the secrets to creating entirely new, targeted clinical therapies. We must move forward—without delay—to sustain this field of research that provides so much hope for thousands of patients and their families."

The American Association for Cancer Research called the injunction a "setback for scientific discovery."

"We believe the NIH's human embryonic stem cell research policies are sound, ethical, and responsible," said AACR President Elizabeth Blackburn. "Stem cell research is part of a multifaceted approach to understand the biology of cancer and develop new ways to combat the 200 diseases collectively called 'cancer.' It is disconcerting that the scientists who were given the opportunity to pursue important research questions through the investigation of stem cells, not their creation, have now been stopped in their tracks."

In response to the court injunction, the Endocrine Society re-issued its 2009 position statement (http://www.endo-society.org/advocacy/policy/upload/Stem-Cell-Position-Statement-October-2009-Final.pdf) calling for an increase in NIH funding for stem cell research as well as expanding the scope of funding to include promising yet neglected areas of stem cell research.

In 2001, President Bush imposed federal funding restrictions limiting the use of human embryonic stem cells. On March 9, 2009, President Obama signed Executive Order 13505 overturning the restriction in the previous policy. This allowed for a greater number of cell lines derived from IVF embryos to be qualified for use in federally funded research.