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ODAC Votes 10-0 In Favor Of Avastin For Recurrent Glioblastoma Multiforme

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee voted 10-0 in favor of approving Avastin (bevacizumab) as a single agent for recurrent glioblastoma muliforme.

The committee accepted objective response as a basis for granting an accelerated approval, as the sponsor prepares to conduct a trial that would measure survival and delay in progression in an earlier setting.

The unanimous vote at the meeting March 31 was also notable because the committee was unable to interpret the biological rationale for the objective

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Capitol Hill:

Kennedy, Hutchison Introduce Long-Awaited Bill To Reauthorize The National Cancer Program

By Kirsten Boyd Goldberg

For the past year, oncopoliticians have been anticipating a big cancer bill known informally as Kennedy-Hutchison.

Intended to renew the National Cancer Act of 1971, the bill was expected to be comprehensive and hard-hitting. It was expected to bring resources, agencies, regulation, and science into alignment to "reinvigorate" cancer research for the 21st century.

"This bill will renew our efforts to make progress in the battle against cancer, and to give patients and their families a renewed sense of hope," Sen. Edward Kennedy (D-Mass.) said at a hearing last year.

Kennedy and Sen. Kay Bailey Hutchison (R-Tex.) first proposed the idea for comprehensive cancer legislation last May, when the Health, Education, Labor and Pensions Committee held a hearing on the need for a renewed focus on the disease (The Cancer Letter, May 9, 2008).

Lending urgency to the bill-writing effort was Kennedy's diagnosis of a brain tumor 10 days after announcing his plan to develop the legislation to supercede the original Cancer Act, for which he was the author in the Senate (The Cancer Letter, May 23, 2008).

When Richard Nixon signed the National Cancer Act in December 1971, he called it "a Christmas gift" to the American people. The gift was easily quantifiable—it authorized $400 million for cancer research, doubling the NCI budget.

When Kennedy and Hutchison introduced the big cancer bill on May 26, the 82-page legislation indeed had the appearance of a gift—or at least

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Durable Responses Accepted For Accelerated Approval

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response rate, which was measured at 19.6% in one phase II study and 25.9% in another. The duration of responses was 3.9 months in one study and 4.2 months in another.

The committee accepted these results despite concerns raised by FDA reviewers that radiographic evidence is unreliable in attributing the objective response to tumor shrinkage or control of cerebral edema caused by either the disease or radiation treatment.

The sponsor's data showed that Avastin decreased the use of steroids. The drug neutralizes vascular permeability induced by vascular endothelial growth factor and stabilizes the blood-brain barrier.

Three years ago, the agency held a workshop on surrogate endpoints for brain tumors, but the meeting didn't produce any specific results. "With each drug, it depends on the risk-benefit and toxicity," said Richard Pazdur, director of the FDA Office of Oncology Drug Products.

In this case, FDA took the unusual step of hiring a radiologist to review the scans. "I think it's important for people to realize that this was one of the first applications where we reviewed all of the x-rays independently," Pazdur said at the meeting. "Even though the numbers didn't match up exactly in one study, they did match with the other one. I think there is a high degree of confidence in what we are reading here."

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Founded Dec. 21, 1973, by Jerry D. Boyd.

Three brain tumor experts who served on the committee as temporary voting members supported the application.

"I view this as a bet on the success of the randomized trial that the sponsor has planned," said Frederick Barker, associate visiting neurosurgeon at Massachusetts General Hospital, explaining his rationale for voting in favor of approval.

The data represent "something different" from the historical controls, Barker said. "On the face value, based on what I have seen with other agents in this disease, the response rate of 20 to 25 percent is a robust number. And so to me, what we are struggling with more, is whether they reflect clinical benefit. But I personally think that if they do. This is a very good number."

Jay Loeffler, chairman of the Department of Radiation Oncology at MGH, said Avastin "represents a new generation of modalities to treat our patients with brain tumors."

The response rates are a reasonable surrogate for clinical benefit, he said. "I am actually confident that the phase III trial is going to be positive," Loeffler said. "I think it's going to increase the effectiveness of radiation and chemotherapy as part of the initial therapy."

The third brain tumor expert, Mark Kieran, director of Pediatric Neuro-Oncology at Dana-Farber Cancer Institute, said the data were consistently encouraging.

"The comparison data over multiple studies tells us that we may be onto something, and it would be a shame to ignore it," Kieran said. "The safety data, though not completely negative—there is no such thing as a drug without toxicity—certainly seems appropriate for this patient population."

The company-sponsored trial presented to ODAC randomized 167 patients with relapsed glioblastoma to receive either Avastin alone or Avastin plus irinotecan. Also presented was an NCI-sponsored 60-patient single-arm trial of Avastin as a single agent, conducted by Howard Fine, chief of the institute's Neuro-Oncology Branch.

"Certainly, the independent results from Howard Fine's study can't be ignored, given that they were completely independent and arrived at the same conclusion," Kieran said. In the planned phase III trial, "I think that the answer is going to be positive, not just with respect to symptom management, but I think also to disease outcome," he said.

Several committee members said they were voting for approval even though it was unclear whether the drug produced tumor shrinkage or eased cerebral edema.

"I felt that the totality of the data raised a

reasonable likelihood of clinical benefit," said Wyndham Wilson, chief of the Lymphoma Therapueutics Section at the NCI Center for Cancer Research, who served as temporary chairman of the committee. "I also felt that edema in a close space such as the brain does have side effects and those effects are alleviated through steroids. Even if there is not a survival advantage, I feel there is a reasonable likelihood that these radiographic changes will be reflected in improved quality of life."

Committee member Michael Link, a pediatric oncologist and chief of the Division of Hematology/ Oncology at Stanford University School of Medicine, agreed. "I voted yes, because I believe in this response rate, whatever is responding, and however ambiguous the interpretations of the MRIs, is significant and certainly everything else we have seen in this tumor over the last 30 years," Link said.

Biostatistician David Harrington, of the Dana-Farber Cancer Institute Department of Biostatistics and Computational Biology, said the drug's risk-benefit profile of the agent was acceptable. "I agree that we are seeing some activity here, and that the risk-benefit profile is very much in favor of the drug," Harrington said at the meeting.

The vote followed the FDA presentation that pointed out that "by modern standards, response rate has not been accepted as surrogate endpoint for accelerated approval of glioblastoma multiforme" and cited the 2006 workshop that concluded that survival was the only clearly accepted trial endpoint.

Also, FDA invited Victor Levin, chairman of cancer Research at the M.D. Anderson Cancer Center's Department of Neuro-Oncology, to present data on the use of Avastin as a treatment for radiation necrosis in brain cancer. In a small, randomized phase II study conducted by Levin, all radiation necrosis patients receiving Avastin improved on therapy and none of the patients receiving placebo reported improvement.

The FDA is expected to make a decision on the application by May 5.

Patient's Husband Had An Idea: Use Avastin For Glioblastoma

The history of medicine should credit Lester Bergeron's contribution to development of Avastin as a treatment for recurrent glioblastoma.

Bergeron is neither a physician nor a basic scientist. He worked at the garden department at a Home Depot store in Fort Worth, Tex., and his wife, Dorothy, had recurrent glioblastoma multiforme.

In February 2004, a scan showed that Dorothy's tumor was neither advancing nor receding despite several months of irinotecan.

"I said, 'We really ought to think about doing something different,'" recalled Virginia Stark-Vance, Dorothy's neuro-oncologist. "When I brought up the possibility of changing treatment to something else, Lester said, 'What about this new drug Avastin?'"

Dorothy's disease justified grasping at straws. She had been living with GBM for over three-and-a-half years and had undergone several forms of chemotherapy, radiation, and three surgeries.

Lester's scientific rationale impressed Stark-Vance: Dorothy's tumor expressed VEGF, and Avastin blocked it.

Avastin was just approved for colorectal cancer, but the leap from colon to brain wasn't completely wild. A few days earlier, the new biologic agent was approved for use in combination with irinotecan and 5-fluorouracil to treat metastatic colon cancer, and Dorothy was already receiving irinotecan for her brain tumor.

Stark-Vance called Genentech and asked whether they had a clinical trial underway. "They said no, we don't even have any plans, because this drug can cause intracranial hemorrhage," Stark-Vance said. "It made sense."

Stark-Vance went back to the Bergerons and told them about these concerns. "And Dorothy says, 'What have I got to lose? This tumor sooner or later is going to kill me.'" The oncologist finally agreed to give the drug off-label, but this would have to be done at a hospital

She had no idea what to expect. "If there were a hemorrhage, would this happen while we are infusing the drug?" Stark-Vance said. "Is it going to happen overnight? Will she be walking down the street some day and her tumor hemorrhages at that point? I couldn't find out anything about it, because no one had ever used it in brain tumors before."

Dorothy received the drug as an inpatient at Harris Methodist Hospital in Fort Worth. (Soon after that, the hospital instituted a rule that bars doctors from giving drugs off-label unless hospital officials review a protocol showing that the drug had been used before and is safe.)

Dorothy had two infusions two weeks apart. She reported improvement almost immediately, and after a month, a scan demonstrated tumor shrinkage. "Her tumor shrank immediately," Stark-Vance said. "She actually had a clinical response before she had a radiographic response."

In a matter of days, Dorothy and Lester told a

number of Stark-Vance's patients about her response. "I am sure they probably went on the Internet and told everybody in the chat rooms about this," Stark-Vance said.

Soon, Stark-Vance's other patients who had been receiving irinotecan wanted to get Avastin as well, and in a matter of weeks, she had accumulated a series of scans that showed improvement, and one scan where an especially aggressive tumor practically disappeared. "It was almost as though you erased it with a pencil eraser," Stark-Vance said.

She ordered some PET scans, which confirmed that the tumors had, in fact, disappeared. "I went through several months before I saw even one patient who didn't have improvement in their scan after Avastin," Stark-Vance said. "In the first year, I only had three patients whose tumors didn't get better on MRI after Avastin."

While some of the patients she treated at that time are still alive, Dorothy died several months later. She had suffered a fracture and was taken off Avastin because it interferes with the healing process. Lester later left the area, and The Cancer Letter's efforts to reach him were unsuccessful.

In the spring of 2004, about three months after first using the drug, Stark-Vance ran into Henry Friedman, deputy director of the Preston Robert Tisch Brain Tumor Center at Duke University. Friedman was giving a CME talk on Gliadel, a treatment for GBM. The meeting was held at a Dallas restaurant.

Stark-Vance brought along a series of scans from seven patients.

Unbeknownst to Stark-Vance, earlier that year, an associate of Friedman's at Duke, James Vredenburgh, had asked Genentech and FDA to sign off on a trial of the agent. Both the company and the regulatory agency had said no.

Now Friedman saw that Stark-Vance had moved rapidly by simply giving the drug off-label and taking pictures.

"I was blown away, because I knew irinotecan would never do that," said Friedman. "It would never get those many responses in a row like that."

This had to be Avastin. Friedman brought the scans back to Durham.

Eager to move forward, Friedman called Arthur Levinson, chairman and CEO of Genentech. He knew Levinson because of Genentech's collaboration with a non-profit called Accelerate Brain Cancer Cure, which was founded by the families of Dan and Steve Case.

Dan Case, the brother of AOL founder Steve Case, had died of a brain tumor, and Friedman was involved in his care.

"I called Art Levinson and said, 'Art, I know that Genentech is worried about intracranial bleeds, but there are eight patients, seven of whom have responded with recurrent GBM," Friedman said. "And Art Levinson basically then said that we are going to do this. Once the CEO said we'll do it, Genentech was on board."

Genentech's initial reluctance was understandable. A case of cerebral hemorrhage was observed in an early trial. The prospect of giving the drug to brain tumor patients in pursuit of a small indication could have uncovered serious toxicities, potentially jeopardizing the more valuable lung and breast cancer indications.

Grade 3-5 hemorrhagic events reported in the Avastin label range from 2.2% to 5.2% in patients receiving the drug, compared with 0.7% to 1.1% in the control groups.

"Testing the drug in that context was incredibly risky," said Philippe Bishop, Genentech's vice president for clinical development of Avastin. "Any time you take a new molecular entity forward, there are a lot of considerations that come into play, and one thing that can kill a drug early is safety, and we know that there are ample examples of drugs that ended up having rough bumps early on and their development was delayed."

Another year was required to convince FDA to allow Duke to proceed with its single-arm trial, which began in April 2005. The trial enrolled 68 patients with recurrent malignant gliomas (35 patients with GBM and 33 patients with WHO grade 3 gliomas). The results were roughly consistent with Stark-Vance's.

After the Duke data started to come in, ABC2 attempted to come up with a strategy for development of the agent.

The advocacy group brokered a meeting between Genentech and a group of neuro-oncologists. "Basically, we decided that we wanted to go to FDA and NCI and do a study to look at Avastin and see what was going on," Friedman said.

The principal question was to determine the contribution of irinotecan.

"The Stark-Vance data was Avastin plus irinotecan, and we didn't want to back away from what was clearly working," Friedman said.

Of course, Stark-Vance was using irinotecan because it was part of the colorectal cancer regimen and because of Friedman's work that led to acceptance of that drug in neuro-oncology.

Initially, NCI suggested a three-arm randomized phase II study design that would compare Avastin plus irinotecan, Avastin alone, and irinotecan alone. "We said

we couldn't accrue to irinotecan alone," Friedman said. Ultimately, this became a two-arm 12-intitution trial.

"We needed to see whether irinotecan was doing anything," said Friedman, the principal investigator of the study. "It wasn't powered to do a direct comparison. It was powered to see whether there was activity in each arm."

The study showed higher response rates for Avastin plus irinotecan, but slightly lower overall survival. "It was quite possible that the additional toxicity produced by irinotecan caused patients to come off therapy and die more rapidly," Friedman said.

Though initially Friedman thought that the study would support registration under an accelerated approval, in July 2006, FDA told the sponsor that this would not be the case.

According to the FDA presentation at ODAC, the agency determined that the study couldn't support registration, because it lacked internal comparison for the primary efficacy endpoint of six-month progression-free survival and because the effect of Avastin is not isolated in the Avastin-irinotecan arm.

Genentech's Bishop said the company initially viewed the trial as exploratory.

"Once we saw the readout of the trial, we felt compelled to bring it forward for accelerated approval, because the data was speaking to an effect that was attributable to Avastin that was well in excess of what would be expected by historical control," Bishop said. "When we became aware of these results, we engaged with the FDA."

The company is conducting a global 920-patient randomized, placebo-controlled trial of Avastin in combination with radiotherapy and temozolomide for first-line GBM.

In January 2008, FDA suggested that Genentech submit the data in conjunction with a separate study, conducted by NCI neuro-oncology expert Howard Fine. For consistency, radiographic evidence from that trial was submitted to the same independent reviewers who reviewed Genentech's data.

Also, FDA hired a radiologist to review the responding patients' scans from both studies.

Looking back, Bishop sees an unusual story. "It's a wonderful story line, something we don't usually tend to think of," Bishop said. "Here, you have a single-patient experience leading to an academic question, and an academic institution getting interested, an advocacy group in the background providing the right environment, and industry in the background dealing with very difficult decisions."

Capitol Hill:

On Clinical Trials Coverage, Brown Bill Stronger Than K-H

(Continued from page 1)

it had the gift-wrapping. It carried a title that would denote a big cancer bill: "The 21st Century Cancer Access to Life-Saving Early Detection, Research and Treatment (ALERT) Act." However, the bill authorized no new funds.

"Last year, my colleague Senator Hutchison and I agreed that to build on what the nation has accomplished, we must launch a new and more urgent war on cancer," Kennedy said in a statement March 26. "The 21st Century Cancer ALERT Act we are introducing today will accelerate our progress by using a better approach to fighting this relentless disease. Our goal is to break down the many barriers that impede cancer research and prevent patients from obtaining the treatment that can save their lives."

"Our nation declared the War on Cancer in 1971, yet, nearly 38 years later, cancer is expected to become the leading killer of Americans," Hutchison said in a statement. "We must bring renewed focus and vigor to this fight. The prescription isn't simple, but there are steps we must take if we are going to see the cancer diagnosis rate decline, while raising the prognosis for survival among those who do have the disease. Our legislation will enact those necessary steps so we may see more progress and coordination in cancer research and treatment."

The Kennedy-Hutchison bill, S.717, is silent on the problem of access to care and health disparities.

On the issue of Medicare coverage for clinical trials, the bill is significantly weaker than other legislation recently introduced. In late February, Sen. Sherrod Brown (D-Ohio) introduced the Cancer Clinical Trials Act, and companion legislation was introduced in the House by Rep. Steve Israel (D-N.Y.).

The Brown and Israel bills aren't identical, but cancer patient advocates say the bills are superior to Kennedy-Hutchison, because they would require coverage of routine patient costs in clinical trials across the spectrum of private insurance. Kennedy-Hutchison would require such coverage only in ERISA plans, the self-funded plans that are federally regulated. In effect, the Brown and Israel bills would reach into other private plans that are traditionally regulated by the states.

Also, the Brown and Israel bills set clear standards for a "routine patient care cost," generally following the standards of Medicare coverage. The lack of clarity

in Kennedy-Hutchison will lead to less expansive and much less certain coverage for clinical trials, advocates say.

In the House earlier this week, Reps. Lois Capps (D-Calif.) and Charles Boustany (R-La.) re-introduced the Comprehensive Cancer Care Improvement Act. The bill would reform Medicare reimbursement to encourage care planning and coordination, giving patients written information necessary to make informed decisions and to coordinate care with other providers.

The Kennedy-Hutchison bill doesn't address this issue. The Capps-Boustany bill includes a number of provisions that would promote a system integrating primary treatment with symptom management and encouraging more communication between cancer survivors and their physicians.

"Cancer survivors in this country have long needed a better system of comprehensive, coordinated care that addresses their distinct needs," said Ellen Stovall, acting president and CEO of the National Coalition for Cancer Survivorship. "We applaud the leadership of Reps. Capps and Boustany in bringing these issues to the forefront, and we are hopeful that other members of Congress will soon follow in supporting the Comprehensive Cancer Care Improvement Act."

No Dollars Included

The Kennedy-Hutchison bill doesn't include any authorization of funding for NCI, the agency it designates to lead the National Cancer Program, or any of the other agencies named in the legislation, including CDC, FDA, CMS, and AHRQ. Meanwhile, the bill requires the agencies to carry out a host of projects.

The National Cancer Act of 1971 authorized an appropriation for the National Cancer Program of $400 million for 1972, $500 million for 1973, and $600 million for 1974. Also, the bill authorized additional amounts for cancer control: $20 million, $30 million, and $40 million for those years.

At the time, when NCI's appropriation was $190 million, the authorization to more than double the budget for cancer research in one year was a clear statement of the importance of the National Cancer Program to Congress.

Why was this authorization important? The appropriations committees felt the political heat generated by the successful lobbying effort led by Mary Lasker. NCI appropriations rose to $379 million in 1972, $492 million in 1973, and $527 million in 1974. Appropriations to NCI "have almost quadrupled from 1971 to 1977, indicating how conspicuously successful Mary Lasker and her associates have been," Richard Rettig wrote in his 1977 book, "Cancer Crusade: The Story of the National Cancer Act of 1971."

The ALERT Act's lack of authorization couldn't have been accidental. Authorization amounts were likely omitted for ease of passage, although it would seem that a bipartisan cancer bill, introduced by a legendary Democratic senator in treatment for a brain tumor, wouldn't have much difficulty, with Democrats controlling both houses of Congress and the White House.

Kennedy and Hutchison might have considered an authorization unnecessary with a science-friendly president in the White House who has proposed doubling the cancer research budget over five years. Also, it's still possible that authorization amounts could be included in markup of the bill.

The question is, without an authorization does Kennedy-Hutchison squander an opportunity to make a forceful point about federal funding for cancer research? What if cancer research advocates don't get an opportunity like this for another nearly 40 years?

Many biomedical and physical scientists have spoken out in recent years against the roller-coaster funding of U.S. science agencies. Budgets for NIH, FDA, NSF and others rise and fall each year, while grant funding usually is committed for four or five years in advance. Some thought that Kennedy-Hutchison would include a strong recommendation, if not an outright authorization, for steady increases related in some way to inflation.

ALERT Act Summary

A summary of what the ALERT Act does:

—Reauthorizes the National Cancer Program, led by the National Cancer Institute. This gives NCI the coveted Congressional mandate to continue to do the many things it has been doing for the past 37 years, including develop a budget estimate for the "entire Program." The budget estimate must be submitted to the National Cancer Advisory Board "for review" before submitting it to the President and Congress.

—Adds to the NCAB membership representatives from Centers for Medicare & Medicaid Services, the Health Resources and Services Administration; the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.

—Directs NCI to develop a standard process through which federal agencies may engage in early detection research.

—Directs NCI to identify promising translational

research opportunities and fund research at public or nonprofit entities, emphasizing the role of young researchers, and rewarding team science. Any non-federal funds made available by these entities would be eligible for matching funds from HHS through a peer review process.

—Establishes an entity within NCI to support a network of biorepositories with consistent systems for collection, storage, annotation, and information sharing.

—Orders guidance from the Office for Human Research Protections use of the NCI Central Institutional Review Board for all NCI-supported translational and clinical research.

—Permits privacy disclosure of de-identified patient information in research if an IRB has granted a waiver or if patients have been informed on first contact that the research institution "may conduct research using their de-identified medical records."

—Calls for HHS to study the advantages and disadvantages of the synchronization of the standards for research under the Common Rule and the Privacy Rule.

—Clarifies the application of the Privacy Rule to external researchers.

—Calls for NCI to report annually on research on cancers with low incidence and low survival rates and establishes a grant program for research on these cancers.

—Establishes a grant program through CDC to states for colorectal cancer screening and referrals for medical treatment (similar to the national breast and cervical cancer early detection program). States are given the option to cover screened persons found to have cancer under Medicaid.

—Authorizes grants for a medical mobile van program to conduct cancer screening in underserved communities. Only screening services that receive an "A" or "B" recommendation by the U.S. Preventative Services Task Force would be provided.

—Calls for the HHS Secretary to include cancers with especially low survival rates in the Cancer Genome Atlas Consortium.

—Calls for the Secretary to establish formal working groups for cancers with especially low survival rates in the Early Detection Research Network.

—Calls for the National Institute of Biomedical Imaging and Bioengineering to ensure that the Quantum Grant program and the Image Guided Interventions program expedite the development of interventions for cancers with low survival rates.

—Establishes a contract program to support the development of biomarker discovery technologies.

—Calls for FDA and CMS to create guidelines for clinical study designs that will enable sponsors to generate clinical data adequate for review by both agencies.

—Calls for a demonstration project by FDA and AHRQ to provide "a limited regional assessment of biomarker tests to facilitate the controlled and limited use of a risk assessment measure with an intervention that may consist of a biomarker test."

—Requires post-market surveillance by FDA and CMS of biomarker tests.

—Requires ERISA-governed health plans to continue to provide coverage of routine care regardless of whether a patient enrolls in a clinical trial.

—Supports retired nurse military officers to work as nurse faculty.

—Directs HHS to identify oncology workforce gaps.

— Reauthorizes the Patient Navigator program through 2015 and requires that patient navigators meet minimum core proficiencies.

—Codifies current Medicare policy to reimburse for routine care while patients are enrolled in clinical trials.

—Conducts a demonstration project to evaluate the cost, effectiveness, and potential savings to Medicare of reimbursing providers for comprehensive cancer care planning services to the Medicare population.

—Directs states to offer tobacco cessation medications and counseling to pregnant women enrolled in Medicaid.

—Establishes priority areas for NIH activities related to childhood cancer survivorship.

—Authorizes grants for research on the causes of health disparities in childhood cancer survivorship and to evaluate follow up care for survivors.

—Defines "complete recovery care" which includes care to address secondary effects of cancer and its treatment, including late and psychosocial effects.

—Coordinates complete recovery care activities across federal agencies.

—Establishes a collaborative to develop a plan for workforce development for complete recovery care.

—States that it is "the sense of the Senate" that FDA should harmonize policies to facilitate the development of drugs, explore clinical trial endpoints, and modernize the Office of Oncology Drug Products.

The text of S.717 is available at http://www.govtrack.us/congress/bill.xpd?bill=s111-717.

Looking Forward To Refining The Bill

Representatives of cancer professional societies and some patient advocacy groups issued statements of support for the bill. Three major organizations—the American Society of Clinical Oncology, the American Association for Cancer Research, and the Association of American Cancer Institutes—said they look forward to working with Kennedy and Hutchison to "refine" the bill.

Richard Schilsky, ASCO president and professor of medicine at University of Chicago: "The American Society of Clinical Oncology commends the significant work that Senators Edward Kennedy and Kay Bailey Hutchison have devoted to promoting the interests of individuals with cancer through prevention, research and treatment. This legislation lays important groundwork to strengthen America's cancer research enterprise.

"ASCO applauds the senators' efforts to improve access to cancer clinical trials, including efforts to expand coverage to patients participating in clinical trials, as well as efforts to develop a national biorepository network for collecting tissue samples that will advance cancer research efforts. Access to biospecimens will help ensure the successful transition to personalized medicine.

"Now is the time to renew our fight against cancer. Cancer deaths are decreasing, and the survival rates for many cancers are rising. But only renewed national commitment and investment will enable this country to deliver on President Obama's challenge to cure cancer."

"While defeating cancer will require research to develop better treatments, it also will require making effective therapies accessible and affordable to those in need. ASCO appreciates the leadership and dedication of Senators Kennedy and Hutchison in providing this unprecedented opportunity for the cancer community to collaborate on this legislative effort.

"ASCO looks forward to continuing to work with Senators Kennedy and Hutchison, other members of Congress, and the Administration to refine and advance this legislation that will benefit millions of Americans fighting cancer today and many more in the future."

Ray DuBois, AACR president and provost and executive vice president of M. D. Anderson Cancer Center: "The AACR has been grateful for the opportunity to contribute its expertise in cancer research to this undertaking. We look forward to working closely with Senators Kennedy and Hutchison to refine this legislation and advance it quickly through Congress for the benefit of cancer patients and their families."

Edward Benz Jr., president of Dana-Farber Cancer Institute, co-chairman of the Research Working Group for the 21st Century Cancer Act, and president of the Association of American Cancer Institutes: "We are extremely grateful for the leadership of Senators Kennedy and Hutchison in bringing this important legislation forward. Despite the great progress that has been made against cancer in the past quarter century, the burden of the disease on patients and their families around the world remains unacceptably high.

"This legislation holds significant promise. It stands to improve access to latest advances in cancer care. It places much needed focus on national initiatives in cancer prevention. It outlines a strong set of priorities to improve patient participation in clinical trials. It acknowledges that more people are surviving cancer and addresses the need for greater cancer survivorship care and services. It calls for reducing disparities in cancer mortality. It provides the resources for workforce development to help ensure that we have the highly skilled caregivers needed to expertly and compassionately care for patients.

"It also recognizes that current research has immense potential to lessen that burden for future generations and provides a powerful impetus for continued progress. We will be working closely with Senators Kennedy and Hutchison and their staffs to refine the bill and work for its passage."

John Mendelsohn, president of M.D. Anderson Cancer Center: "I applaud Senators Kennedy and Hutchison for their strong leadership and vision in renewing the nation's war against cancer. This measure comes at a critical time as we are making significant strides against cancer. Just as the National Cancer Act of 1971benefited the last generation, it is our hope that this legislation will set the stage for a new generation's progress over this disease.

"This is a thoughtful piece of legislation that addresses many of the most critical needs in cancer today. I'm especially impressed with the balance that is achieved between support for clinical research to fuel long-term success and provisions that will address the needs of cancer patients right now. The Kennedy-Hutchison bill will bring research findings even more quickly from the laboratory to the bedside for to the benefit of cancer patients everywhere.

"We look forward to working with the Congress and the Administration to make this bill a critical, major step in our shared goal of reducing the burden of cancer through prevention, early detection and better treatment."

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Business & Regulatory Report

Approvals & Applications:

FDA Approves Novartis Agent Afinitor For Advanced Renal Cell Carcinoma

FDA has granted approval to Afinitor (everolimus tablets) for the treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

The agent is sponsored by Novartis Pharmaceuticals Corp.

The agent was approved on the basis of an international, multicenter, randomized, double-blind trial comparing everolimus to placebo. All patients received best supportive care. The trial was conducted in metastatic renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Prior therapy with bevacizumab, interleukin-2, or interferon was also permitted.

Randomization was stratified according to prognostic score and prior

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Deals & Collaborations:

Roche Completes Purchase Of Genentech For $46.8 Billion; R&D Stays In California

Roche (SWX: ROG.VX; RO.S, OTCQX: RHHBY) Roche has completed its acquisition of **Genentech** (NYSE: DNA). The company sold $95, pursuant to tender offer which expired March 25. Total acquisition price as $46.8 billion.

The special committee of Genentech's Board of Directors has approved the agreement and recommends that Genentech shareholders tender their shares in Roche's tender offer.

Roche has owned a major stake in Genentech for over 18 years.

The combined company will be the seventh largest U.S. pharmaceuticals company in terms of market share. It will generate approximately $17 billion in annual revenues and will employ around 17,500 employees in the U.S. pharmaceuticals business alone, including a combined sales force of approximately 3,000 people.

Research and early development will operate as an independent center within Roche from its existing campus in South San Francisco, retaining its talent and approach to discovering and progressing new molecules. Roche's Pharma commercial operations in the U.S. will be moved from Nutley, New Jersey to Genentech's site in South San Francisco.

The combined company's U.S. commercial operations in pharmaceuticals will operate under the Genentech name, leveraging the strong brand value of Genentech in the U.S. market. The existing U.S. sales organizations of

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FDA Approves Afinitor For Renal Cell Carninoma

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anticancer therapy.

Altogether, 416 patients were randomized (2:1) to receive everolimus (n=277) or placebo (n=139). Progression-free survival (PFS) was the primary endpoint. The median PFS was 4.9 and 1.9 months in the everolimus and placebo arms, respectively (HR = 0.33, p value < 0.0001).

The treatment effect was similar across prognostic scores and prior treatment status. The overall survival results were not mature; 32% of patients had died by the time of data cut-off. The objective response rates were 2% and 0% for everolimus and placebo, respectively. After documented radiological progression, patients receiving placebo could receive everolimus.

The most common adverse reactions were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. Anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine were the most common laboratory abnormalities.

The most common grade 3/4 laboratory abnormalities were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) occurred on the everolimus arm but not on the placebo arm.

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FDA has announced a collaboration with the Houston-based **Alliance for NanoHealth** and its eight member institutions to help speed development of safe and effective medical products in the emerging field of nanotechnology.

Under a Memorandum of Understanding, the FDA/ANH Nanotechnology Initiative will work to expand knowledge of how nanoparticles behave and affect biologic systems, and to facilitate the development of tests and processes that might mitigate the risks associated with nanoengineered products. All outcomes from this public-private partnership will be placed in the public domain for the benefit of all stakeholders.

The academic institutions include Baylor College of Medicine, M. D. Anderson Cancer Center, Rice University, the University of Houston, the University of Texas Health Science Center at Houston, Texas A & M Health Science Center, the University of Texas Medical Branch at Galveston, and the Methodist Hospital Research Institute.

"We are delighted with this partnership between the FDA and the eight institutions that constitute the Alliance for NanoHealth," Larry Kaiser, president, the University of Texas Health Science Center, said in a statement. "We see this agreement as an important step on the path to taking advantage of the enormous power of nanotechnology to improve the diagnosis and treatment of disease."

FDA's collaboration with the ANH is administered through the agency's Critical Path Initiative.

Arno Therapeutics Inc. (BULLETIN BOARD: ARNI) of Parsippany, N.J., said FDA accepted the company's Investigational New Drug application for the use of AR-42.

AR-42 is an orally available, novel, potent, small molecule that modifies the acetylation of histones and other molecules, and is a targeted inhibitor of the Pan-DAC and Akt pathways.

HDAC inhibitors disrupt HDAC-PP1 complexes and cause signaling kinase dephosphorylation. In preclinical studies, AR-42 has demonstrated greater potency and a competitive profile in tumors when compared with vorinostat (also known as SAHA and marketed as Zolina by Merck), the leading marketed histone deacetylase inhibitor. Arno in-licensed the exclusive worldwide rights to AR-42 from The Ohio State University.

GlaxoSmithKline (NYSE:GSK) said it has submitted two simultaneous regulatory applications to expand the use of Tyverb/Tykerb (lapatinib).

If approved, Tyverb/Tykerb could be used as a first-line therapy regimen combined with anti-hormonal therapy for patients with hormone-sensitive, metastatic breast cancer in Europe and the U.S.

The variation to the EU marketing authorization and the supplemental New Drug Application) were submitted respectively to the European Medicines Agency and to FDA for the combination of Tyverb/Tykerb plus an aromatase inhibitor based on the recent study, EGF30008. This study evaluated Tyverb/Tykerb in combination with letrozole in women whose breast cancer expressed was hormone receptor positive and may or may not also over-expressed the HER2+/ErbB2+ receptor.

These data were presented at the San Antonio Breast Cancer Symposium last December.

Therakos Inc. of Exton, Penn., said FDA has approved its CELLEX Photopheresis System for the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma that are unresponsive to other forms of treatment.

The CELLEX Photopheresis System uses extracorporeal photopheresis, an innovative cellular therapy, to relieve the symptoms of CTCL. The system also has been cleared recently in Canada and Europe.

The new system features several improvements designed to enhance the patient treatment experience, such as shorter treatment times and reduced extracorporeal blood volume.

Specific features of the new system include an automated, closed system design that provides users the ability to switch between double and single needle treatment, if necessary. The system also utilizes a new, patented separation technology to separate white blood cells from whole blood.

Sopherion Therapeutics LLC, of Princeton, N.J., said it completed enrollment in its Phase III study of nonpegylated liposomal doxorubicin (Myocet) in metastatic HER-2-overexpressing breast cancer.

The study is a global, randomized, multicenter pivotal Phase III study in 363 patients who have metastatic HER-2-overexpressing breast cancer.

It will compare Sopherion's lead product in combination with the current standard of care, paclitaxel (Taxol) and trastuzumab (Herceptin(R)), vs. paclitaxel and trastuzumab alone. Progression-free survival (PFS) is the primary efficacy endpoint, with monitoring for cardiac safety.

Eligibility criteria included no prior chemotherapy for metastatic disease, nor any trastuzumab, anthracyclines or taxanes within the previous 12 months. Eligible patients were randomized to receive either Myocet, paclitaxel and trastuzumab, or paclitaxel and trastuzumab alone in a 1:1 randomization ratio.

Myocet is a liposome-encapsulated doxorubicin-citrate complex. By encapsulating doxorubicin in a liposome—a manufactured, microscopic, vesicle consisting of discreet aqueous compartments surrounded by membranes composed of naturally occurring fats—its distribution in the body is altered in such a way as to reduce doxorubicin's toxicity, the company said.

OSI Pharmaceuticals Inc. (Nasdaq: OSIP) and Genentech Inc., (NYSE: DNA) said OSI submitted a supplemental New Drug Application to FDA for the use of Tarceva (erlotinib) as a first-line maintenance therapy for advanced non-small cell lung cancer patienst who have not progressed following first-line treatment with platinum-based chemotherapy.

The companies announced that Roche, their international collaborator for Tarceva and owner of Genentech, filed an application in Europe with the European Medicines Agency.

"If approved, Tarceva will be the first EGFR targeted and oral therapy available as a first-line maintenance treatment for people with NSCLC, which we believe is an important advancement in the treatment of lung cancer," Colin Goddard, OSI CEO said in a statement.

The submissions are based on a Phase III placebo-controlled, randomized, double-blind trial known as SATURN. In November 2008, OSI, Genentech and Roche announced that SATURN met its primary endpoint and showed that Tarceva significantly extended progression-free survival when given immediately following initial treatment with platinum-based chemotherapy, compared to placebo.

The SATURN study, conducted by Roche, enrolled 889 patients with advanced NSCLC at approximately 160 sites worldwide. Patients were treated with at least four cycles of standard first-line platinum-based chemotherapy and were then randomized to Tarceva or placebo if their cancer did not progress. The primary endpoint of the study was progression-free survival. Secondary endpoints included overall survival, safety and an evaluation of exploratory biomarkers.

Deals & Collaborations:

Roche Becomes 7th Largest U.S. Pharmaceuticals Firm

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both companies will be maintained, resulting in a very strong presence in several specialty areas.

The transaction will provide the opportunity to simplify the structure of the combined organization and maximize the benefits of enhanced scale. Roche has already begun to wind down operations at its Palo Alto facility and will relocate the site's Virology research and development activities to South San Francisco.

Roche's Palo Alto Inflammation group is in the process of becoming part of Roche's Nutley research and development organization. Genentech's Late Stage Development and Manufacturing operations will be combined with the global operations of Roche, achieving substantial scale benefits, operational synergies and cost avoidance. Roche's manufacturing operations in Nutley will be closed and support functions, such as informatics and finance, will be consolidated with those of Genentech.

AMDL Inc. (NYSE Alternext US: ADL), of Tustin, Calif., said it has entered into a collaborative agreement with **Mayo Clinic** to conduct a clinical study for the validation of AMDL's next generation version of its US FDA-approved DR-70 (FDP) cancer test.

Through this validation study, AMDL and Mayo Clinic will perform clinical diagnostic testing to compare AMDL's DR-70 (FDP) cancer test with a newly developed, next generation test. The primary goal of the study is to determine whether AMDL's next generation DR-70 (FDP) test serves as a higher-performing test to its existing predicate test and can lead to improved accuracy in the detection of early-stage cancers.

For FDA regulatory approval on the new test, AMDL intends to perform an additional study to demonstrate the safety and effectiveness of the next generation test for monitoring colorectal cancer. The validation study will run for three months and final results are expected in the second or third quarter of 2009.

Micromet Inc. (NASDAQ: MITI), of Bethesda, Md., said that it is regaining from its partner **MedImmune** the rights in North America to its most advanced BiTE antibody candidate, blinatumomab, also known as MT103.

In Europe, Micromet is conducting a phase 2 clinical trial with blinatumomab for the treatment of patients with acute lymphoblastic leukemia and a Phase I clinical trial for the treatment of patients with non-Hodgkin's lymphoma.

The two companies plan to initiate a research program for the development of a new BiTE antibody for the treatment of hematological cancers. Micromet also announced its financial results for the fourth quarter and full year ended Dec. 31, 2008.

Samtheo Biopharma LLC of New York has entered into a license agreement, through its subsidiary, Lyndor Biosciences LLC, with **Moffitt Cancer Center**, gaining exclusive worldwide rights to a small molecule that selectively inhibits the activation of all three isoforms of Akt.

Persistent activation of the Akt pathway has been found to play an important role in oncogenesis and chemo- and radiation-resistance and to be responsible for cancer cell proliferation, survival and invasiveness

Co-inventors are Jin Cheng, and Said Sebti, from Moffitt. "This small molecule is a highly selective and potent inhibitor of Akt activation, leading to tumor growth arrest and induction of cancer cell death, and results in overcoming chemoresistance," said Cheng, professor, Molecular Oncology Department at Moffitt.

"Patients whose tumors contain persistently activated Akt are predicted to be more likely to respond to this inhibitor either as a single agent or in combination therapy," said Sebti, professor and chair, Drug Discovery Department at Moffitt. "Akt is abnormally hyperactivated in many advanced malignancies and late stage tumors, such as breast, prostate, lung, pancreatic, liver, ovarian and colorectal cancers. Increased activation is also linked with drug and radiation resistance," said Cheng.

Through this license, Lyndor plans to develop and commercialize the new anti-cancer agent, which it refers to as LD-101, for refractory and resistant tumors as well as metastatic malignancies.

Clinical Trials:

Infinity Begins Phase II Trial Of Heat Shock Protein Inhibitor

Infinity Pharmaceuticals Inc. (NASDAQ: INFI), announced the initiation of a Phase II trial of IPI-504 (retaspimycin hydrochloride), a heat shock protein 90 (Hsp90) inhibitor, in combination with Herceptin (trastuzumab) in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

"This trial will explore the combination of two

targeted agents, IPI-504 and trastuzumab (Herceptin), which should complement each other by disrupting HER2 signaling in different ways," Clifford Hudis, chief of the Breast Cancer Medicine Service and Attending Physician at Memorial Sloan-Kettering Cancer Center and an investigator in the trial, said in a statement. "In earlier trials with a related agent we documented clear evidence of activity when Hsp90 inhibition is added to trastuzumab in patients with HER2-positive breast cancer."

The goal of the open-label, international, multi-center Phase II trial is to evaluate the safety and anti-tumor activity of IPI-504 in combination with Herceptin in patients with pretreated, locally advanced or metastatic HER2-positive breast cancer, the company said. IPI-504 will be administered intravenously at 300 mg/m2 on a three-week cycle, consisting of twice-weekly treatment for two weeks followed by one week off treatment. Herceptin will be administered intravenously once every three weeks. Evidence of anti-tumor activity will be evaluated using RECIST criteria (Response Evaluation Criteria in Solid Tumors).

The study will enroll 46 patients, and Infinity said it anticipates presenting preliminary data in mid-2010.

"By blocking HER2 signaling through a novel mechanism, IPI-504 may provide a new option for patients with HER2-positive breast cancer—one that may overcome resistance to HER2 targeted agents," said Jose Baselga, chairman of the Medical Oncology Service and director of the Division of Medical Oncology, Hematology, and Radiation Oncology at the Vall d'Hebron University Hospital in Barcelona, Spain, professor of Medicine at the Universidad Autonoma de Barcelona and an investigator in the trial.

Preclinical data suggest that the HER2 oncoprotein is degraded rapidly when Hsp90 is inhibited by IPI-504, which eliminates HER2 signaling and ultimately causes the tumor cell to die. Infinity researchers have demonstrated that IPI-504 potently inhibits the growth of tumor cells when administered as a single agent in both Herceptin-sensitive as well as Herceptin-resistant breast cancer xenograft models, the company said. Moreover, in these models, the combination of IPI-504 and Herceptin results in more robust anti-tumor activity than when either agent was administered alone, the company said.

Infinity is evaluating Hsp90 inhibition in a range of cancers. These include The RING trial, an international Phase III registration trial in refractory gastrointestinal stromal tumors that positions IPI-504 as the potential first-in-class Hsp90 inhibitor. IPI-504 is also being evaluated in a Phase II study in advanced non-small cell lung cancer and in a Phase Ib combination study with Taxotere (docetaxel) in patients with advanced solid tumors. Infinity is also evaluating its oral hsp90 inhibitor, IPI-493, in a Phase I study in patients with advanced solid tumors.

Celator Pharmaceuticals of Princeton, N.J., said that the first patient has been treated in its Phase II multicenter, randomized, open-label clinical trial of CPX-351 (Cytarabine:Daunorubicin) Liposome Injection versus intensive salvage therapy in adult patients (up to 60 years old) with acute myeloid leukemia in first relapse.

The study is supported through a partnership with The Leukemia & Lymphoma Society.

"CPX-351 represents a unique approach to enhancing the clinical benefit of the two most active drugs used in the treatment of patients with AML," Jonathan Kolitz, director of the Leukemia Service at North Shore University Hospital and lead investigator for the study, said in a statement. "There is no standard of care established for patients in first relapse. We expect that this study will build on the promising results initially obtained in this patient population in the Phase 1 study and provide additional confirmation of the clinical benefit of CPX-351."

The study (protocol CLTR0308-205) will enroll up to 120 patients between the ages of 18 and 60 who have pathological confirmation of relapsed AML after an initial complete response to prior therapy lasting at least one month. Patients will be randomized (2:1) to receive either CPX-351 (100u/m2; Days 1, 3, 5) or one of several control arm regimens, including high dose cytarabine with or without daunorubicin; conventional "7+3" (cytarabine/daunorubicin regimen); "MEC," the mitoxantrone/etoposide/cytarabine regimen; and other published salvage regimens.

Patients will be monitored for all clinical adverse events as well as laboratory evaluations. The primary efficacy endpoint of the study is the comparison of overall survival at one year between the two arms. Secondary endpoints include complete remission rate and duration, event-free survival, aplasia rate, and rate of transfer for stem cell transplant. The study will be open for enrollment at leading institutions in the U. S. and Canada.

CPX-351 has been granted orphan drug status by FDA for the treatment of AML and is also currently being studied in a Phase II randomized trial comparing CPX-351 versus conventional cytarabine and daunorubicin

therapy ("7+3") in patients 60-75 years of age with untreated AML, the company said.

Helix BioPharma Corp. (TSX, FSE: HBP) of Aurora, Ontario, said it has received the necessary regulatory approvals in Germany to initiate its planned Phase II pharmacokinetic study of Topical Interferon Alpha-2b in patients with low-grade cervical lesions.

The clinical study was designed, as mandated by regulatory authorities, to gather data on the absorption and elimination profile of Topical Interferon Alpha-2b in patients with low-grade cervical lesions, in addition to further data on its safety and efficacy. Depending on the data generated in the study, it is expected that interim results, which Helix anticipates will be received during its fiscal fourth quarter 2009, will allow the company to proceed with its planned regulatory filings in the U.S. and Europe respectively for its future Phase IIb and Phase III pivotal efficacy trials for this indication.

The primary objective of the clinical study is to determine the multiple-dose pharmacokinetic profile of Topical Interferon Alpha-2b following intravaginal application every other day of a total of 14 doses of the cream, the company said.

Following the pharmacokinetic portion of the trial, assessment of efficacy and safety parameters will continue until 35 doses of the cream have been applied. As such, the clinical study is designed to also provide support for the dosing regimen intended to be applied in the future to U.S. Phase IIb and European Phase III pivotal efficacy trials for this indication.

The study will be an open-label, single-arm trial in 28 female patients. Eligible women will be between 18 and 45 years of age and will present with a cytological diagnosis of Pap IIID, a colposcopic diagnosis of mild to moderate cervical dysplasia and confirmed human papilloma virus positive status.

The clinical study will be conducted under the direction of Achim Schneider, director of the Department of Gynecology at the Charite University Hospital in Berlin, The clinical portion of the study is expected to be completed during the first half of the 2010 calendar year.

Interferon alpha-2b is an immune system modulator that is active against a variety of HPV-induced lesions. Interferon alpha-2b is thought to function by triggering an antiviral response within infected cells, by activating certain intracellular enzymes which cause degradation of viral RNA, and by mobilizing the body's natural immune system to destroy the infected cells. Interferon alpha-2b, which has been commercially available for over 20 years, has been widely used by physicians as a treatment for certain HPV induced lesions, but is not generally favored due to the fact that conventional administration requires painful intradermal injection by a medical professional.

Nereus Pharmaceuticals Inc. of San Diego said it is conducting a randomized Phase II trial evaluating the vascular disrupting agent NPI-2358 in combination with Taxotere (docetaxel) in non-small cell lung cancer.

Preclinical and clinical data suggest that VDAs may be complementary or synergistic with chemotherapeutics and anti-angiogenesis agents due to the different targets and mechanisms of action, the company said. In addition, the non-overlapping side effect profile of VDAs compared to most other anti-cancer treatments makes them ideal candidates to employ in new combination therapies. Models combining NPI-2358 with docetaxel have produced particularly positive results in both efficacy and tolerability.

The ADVANCE (Assessment of Docetaxel and Vascular Disruption in Non-Small Cell Lung Cancer) trial will assess NPI-2358 in combination with docetaxel compared to docetaxel alone in patients with NSCLC who previously failed at least one chemotherapy regimen. Overall survival will be the primary endpoint of the trial, and progression free survival and tumor response rates will be compared as secondary endpoints. Approximately 150 patients will participate in the trial at sites in the U.S., Australia, India, and South America.

NPI-2358 is one of over 200 synthetic analogues that were prepared following the discovery of the compound Halimide isolated from a marine fungus, the company said. According to the company, the compound selectively attacks existing tumor blood vessels leading to hemorrhagic tumor necrosis without affecting normal vasculature, and it has a direct apoptotic effect on tumor cells.

Medivation Inc. (NASDAQ: MDVN) of San Francisco said it has received written permission from FDA to begin a pivotal phase III trial of MDV3100, its novel androgen receptor antagonist, in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy.

The placebo-controlled, double-blind, multinational trial will enroll approximately 1,200 patients who will be randomized (2:1) to receive either MDV3100 or placebo. The primary endpoint of the trial will be overall survival.

The FDA informed the company that it could

test a dose of MDV3100 up to 240mg/day. There are no driving or other restrictions placed on the activities of participants in the trial. Final trial specifics will be announced when the first patient is enrolled.

MDV3100 is being evaluated in an ongoing open-label, U.S., Phase I-II study of a total of 140 men with CRPC. Patients in this trial were heavily pretreated, with all having failed standard hormonal therapies and many having also failed docetaxel-based chemotherapy.

Micromet Inc. (NASDAQ: MITI) of Bethesda, Md., announced the commencement of a randomized, controlled Phase II trial of its human anti-EpCAM IgG1 antibody adecatumumab (MT201) for colorectal cancer after complete resection of liver metastases.

The trial has three arms comparing single agent adecatumumab to combination chemotherapy (FOLFOX: 5-FU/Leucovorin plus Oxaliplatin), and to FOLFOX followed by adecatumumab. The primary endpoint will be the disease-free survival rate at one year.

Apart from being the most highly and frequently expressed target antigen on colorectal cancer cells, EpCAM has recently been shown to drive tumor growth and to be expressed on colorectal cancer stem cells.

The ability of adecatumumab to potentially control and eliminate newly developing metastases has been suggested in a recently reported Phase II trial of adecatumumab as monotherapy in metastatic breast cancer, the company said. In that trial, patients with high levels of EpCAM expression, in a dose-dependent fashion, developed significantly less new lesions as compared to patients with low levels of EpCAM.

Rigel Pharmaceuticals Inc. (NASDAQ: RIGL) announced the enrollment of the first patient in a Phase II, multi-center clinical trial of R788 (fostamatinib disodium) in refractory or relapsed peripheral T-cell lymphoma.

The trial's primary objective is to assess the efficacy of R788, an orally bio-available Syk kinase inhibitor, in patients suffering from this subset of non-Hodgkin's lymphoma that originates in the patient's T-cells, the company said.

Prior studies have suggested increased expression of Syk at the cellular level in many of these patients with PTCL, the company said.

"Since we have seen that R788 shows clinical therapeutic benefit in certain types of B-cell lymphomas and that Syk kinase appears to play an important role in certain PTCLs, we believe that R788 may offer new hope to the 12-15% of non-Hodgkin's lymphoma patients with the T-cell variety," Elliott Grossbard, executive vice president and chief medical officer of Rigel, said in a statement.

In general, patients with PTCL have a poorer prognosis and fewer treatment options than B-cell lymphoma patients.

The standard treatment regimen for PTCL—cyclophosphamide, hydroxydoxorubicin, vincristine (oncovin) and prednisone—fails provide adequate or durable responses in many patients.

The Phase II trial will be conducted in two stages at several centers in North America with each patient receiving 200mg of R788 twice a day for a minimum of 8 weeks, or until disease progression or withdrawal from the trial.

During stage one, 19 men and women with PTCL who have previously failed to respond to standard of care treatment for their disease are expected to be evaluated. Stage two is expected to include the enrollment of approximately 36 patients.

Efficacy will be assessed by CT/PET scans at baseline and CT scans of the disease-involved areas at 8 weeks. Safety will be assessed by periodic physical exams, blood tests and clinical laboratory work, among others. Results of the clinical trial are expected in the second half of 2010.

In June 2008, Rigel first reported results of a Phase II trial of R788 in the treatment of patients with relapsed or refractory B-cell non-Hodgkin's lymphomas.

R788 was well-tolerated in this patient population and showed therapeutic benefit in patients suffering from certain subcategories of the disease, especially small lymphocytic lymphoma/chronic lymphocytic leukemia and diffuse large B-cell lymphoma.

Tekmira Pharmaceuticals Corp. (TSX:TKM) announced that one of the company's collaborators, **Alnylam Pharmaceuticals, Inc**. (NASDAQ:ALNY), has initiated a Phase 1 human clinical trial of ALN-VSP in the United States. ALN-VSP, a product that utilizes Tekmira's SNALP technology, is being developed as a treatment for advanced liver cancers, including hepatocellular carcinoma and other solid tumors with liver involvement.

A milestone payment is payable to Tekmira upon the initiation of the Phase 1 trial and additional milestone payments become due as ALN-VSP is advanced through development.

Mark Murray, Tekmira's president and CEO, said, "We are pleased that Alnylam has initiated their

Phase 1 clinical trial of ALN-VSP as this represents an important milestone in the advancement of our SNALP technology. We will continue to support Alnylam and the ALN-VSP product as we manufacture the ALN-VSP clinical supplies on behalf of Alnylam."

ALN-VSP contains small interfering RNA (siRNA) molecules formulated for systemic delivery with Tekmira's SNALP technology. Tekmira has supported Alnylam in their advancement of ALN-VSP by generating preclinical data, providing analytical services and in the manufacture of ALN-VSP for clinical trials.

Pre-clinical data in mouse tumor model studies have demonstrated robust efficacy of ALN-VSP, including suppression of targeted genes, demonstration of an RNAi mechanism of action, tumor reduction, and extension of survival.

Alnylam's ALN-VSP Phase I trial, being conducted in the U.S., is a multi-center, open label, dose escalation study designed to enroll approximately 55 patients with advanced solid tumors with liver involvement, who have failed to respond to or have progressed after standard treatment.

The primary objective is to evaluate the safety, tolerability, and pharmacokinetics of intravenous ALN-VSP, including demonstration of the maximum tolerated dose. Other exploratory objectives include the assessment of tumor response through Response Evaluation Criteria for Solid Tumors, a set of published guidelines that define when cancer patients' disease improves, stabilizes or progresses during treatment; change in tumor blood flow or vascular permeability measured by DCE-MRI; and, change in plasma biomarkers of angiogenesis.

In addition, the analysis of pharmacodynamic effects of ALN-VSP on tumors will be measured in patients electing to proceed with voluntary pre- and post-treatment biopsies.

Oncology Management:

Pharma Invested $65 Billion In Research & Development

U.S. pharmaceutical research and biotechnology companies invested $65.2 billion last year, an increase of roughly $2 billion from 2007, the Pharmaceutical Research and Manufacturers of America and Burrill & Co. said.

This sets a new record, the association said.

Oncology accounts for the largest share of development activities. Altogether, there were 750 compounds in development for cancer, more than a quarter of the 2,900 agents in development in the U.S. Heart disease and stroke—with 312 compounds—is a distant No. 2, followed by 150 compounds for diabetes, 109 for HIV/AIDS and 91 for Alzheimer's and dementia.

Poniard Pharmaceuticals Inc. (NASDAQ: PARD), of South San Francisco announced that it will concentrate its cash resources on the clinical and commercial development of its late-stage oncology candidate, picoplatin.

As a result, the company said it has discontinued its in-house preclinical research operations and reduced its workforce by approximately 12 percent, or eight employees, effective March 31. The company said it continues to evaluate strategic alternatives for its preclinical research programs.

"Concentrating our resources on advancing our lead product candidate, picoplatin, currently in Phase II and III clinical trials for the treatment of lung, colorectal and prostate cancers, supports our goal of commercializing picoplatin in 2010, initially for the treatment of small cell lung cancer," Jerry McMahon, chairman and CEO, said in a statement.

US Oncology, Inc. has established US Oncology Clinical Development (USOCD), a full service contract research organization.

USOCD formalizes many of the services that US Oncology Research has provided since its inception in 1999. For more than a decade US Oncology Research has offered pharmaceutical and biotechnology companies elements of the clinical trial management process.

The formation of USOCD focuses the company's extensive resources in order to provide full service CRO capabilities.

USOCD understands the complexities of oncology clinical trials and assists pharmaceutical and biotechnology companies in navigating the trial process to better manage their portfolio of products and expedite marketing approval. USOCD can identify key government and industry dynamics to intelligently plan and manage the enrollment strategy for clients.

"We have built an experienced team that enhances our ability to serve our clients for all of their oncology clinical trial needs," said Steve Smith, vice president and general manager of Research and Personalized Science. "We will leverage all of the strengths of the US Oncology network and its proven history of accrual performance and commitment to quality."