THE CANCER LETTER

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# Von Eschenbach Takes Leave Of Absence From NCI, Resigns From C-Change Board

*By Paul Goldberg*

Responding to scathing publicity and mounting scrutiny of his unprecedented powers, NCI Director and FDA Acting Commissioner Andrew von Eschenbach took a leave of absence from the Institute and relinquished his board seat on a nonprofit heavily funded by the pharmaceutical industry.

After learning about von Eschenbach's dual appointment two weeks ago, several lawmakers objected to his dual role, stating that no man is capable of running the two institutions properly (The Cancer Letter, Sept. 23).

Taking a leave of absence on Sept. 30, von Eschenbach named John Niederhuber—a long-time ally and fellow surgeon—to the position of "chief operating officer" at NCI.

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# FDA Commissioner's Drug Approval Strategy Rooted In Unproven Science, Technology

*By Paul Goldberg*

In an interview with The Wall Street Journal the day after he was named FDA acting commissioner, Andrew von Eschenbach said he planned to "streamline and accelerate" the process of approval of new therapies.

Did von Eschenbach believe that as an interim commissioner he had the political support needed to implement the far-reaching drug approval agenda he had developed during his four years at NCI?

In a message announcing his joint appointment to members of NCI advisory boards, von Eschenbach announced that the drug approval changes he had in mind wouldn't be limited to cancer.

He would alter all fields of medicine.

"The molecular metamorphosis in our understanding of disease has been led by the cancer community, but is not cancer-centric," he wrote in the email Sept. 26. "Although many of the fundamental principles in basic science, clinical care and technology development were initially developed in a cancer framework, they apply to many other diseases.

"My joint positions at the NCI and FDA allow the opportunity to closely integrate the discovery aspects of biomedical research that have been led by the NCI and NIH with the delivery aspects of the FDA… While the missions of the NCI and FDA are very different, the purpose is the same—to bring patients the full benefits of molecular medicine."

Conservative pundits applauded these plans. The Journal's editorial board described von Eschenbach's agenda as a long-overdue treatment for

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## Leavitt Says Permanent Post Unlikely For von Eschenbach

(Continued from page 1)

As the focus of adverse publicity shifted from von Eschenbach's conflicts of commitment to his conflicts of interest, on Oct. 4, the Texas urologist announced that he would also step down from his position as vice chairman of the board of C-Change, a coalition run by former President George H. W. Bush and Barbara Bush, where other board members included executives from Bristol-Myers Squibb and Johnson & Johnson.

These concessions demonstrated that, his power notwithstanding, the Texas urologist and Bush family friend is remarkably sensitive to sunlight, and that neither he nor the Administration appeared to have foreseen the uproar over his appointment or developed a strategy to contain it.

Von Eschenbach's stewardship of NCI and the controversial scientific and political beliefs that guide it have escaped notice in the national press. The FDA changed that. "You might think that after Michael Brown's FEMA fiasco, the White House would try to avoid any appearance of cronyism in job appointments requiring technical expertise," TIME reported earlier this week. "You might think that after the Plan B contraceptive flap and safety problems with drugs like Vioxx, it would seek to avoid controversy while picking someone to run the embattled FDA. Think again."

There is no need to guess what von Eschenbach would seek to accomplish at FDA. He has described his agenda in considerable detail, causing waves of applause from political supporters at conservative think tanks and sending chills through the spines of scientists who warn that von Eschenbach would abolish rational drug approval criteria and, ultimately, harm public health (See story on page 1).

It's unclear whether von Eschenbach's leave of absence from NCI in any way precludes him from running the Institute, lawyers say.

Though FDA regulates clinical trials conducted by NCI and approves drugs developed by the Institute, it's unclear whether this relationship constitutes a legal conflict of interest. There is, however, a political and policy conflict that could blow up in the Administration's face if a public health disaster like Vioxx occurs on von Eschenbach's watch, observers say.

Von Eschenbach's withdrawal from C-Change is, undoubtedly, a considerable sacrifice on his part. The non-profit, his primary constituency, had catapulted him to the top post at NCI and FDA.

While von Eschenbach likely sees his new dual role as an opportunity to implement his scientifically controversial plans, the Adminsitration's stance toward him is harder to gauge.

On the day von Eschenbach withdrew from C-Change, HHS Secretary Mike Leavitt said that it was unlikely that the urologist would become permanent FDA commissioner. "Andy is acting commissioner, and I suspect that will be his status until we fill it permanently," Leavitt said to The Washington Post.

This remark can be taken as a signal to Congress that von Eschenbach would be out of FDA before any investigation of his appointment and the mysterious circumstances surrounding the departure of his predecessor Lester Crawford could get up to speed. (Indeed, the Government Accountability Office has been asked to review the circumstances of Crawford's departure, and the Senate Health, Education, Labor and Pensions Committee is weighing launching a probe of the vetting procedures used by the White House, The Hill reported.)

By the same token, Leavitt's remark could mean that the Administration plans to keep von Eschenbach at the helm of FDA for some time without seeking to make him permanent commissioner. If Bush is willing to accept the consequences, von Eschenbach would be free to implement his agenda with few impediments. If the President is surprised by his FDA commissioner's political agenda, von Eschenbach could be asked to return to NCI—or blessed with the opportunity to spend more time with his family.

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Member, Newsletter and Electronic Publishers Association

**Editor & Publisher:** Kirsten Boyd Goldberg
**Editor:** Paul Goldberg
**Editorial Assistant:** Shelley Whitmore Wolfe

**Editorial: 202-362-1809 Fax: 202-318-4030**
**PO Box 9905, Washington DC 20016**
Letters to the Editor may be sent to the above address.

**Customer Service: 800-513-7042**
**PO Box 40724, Nashville TN 37204-0724**
Customer service FAQ: www.cancerletter.com

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To announce his agreement to take a leave of absence from NCI on Sept. 30, von Eschenbach held a conference call with the Institute's Executive Committee.

According to sources who were on the call, von Eschenbach said that the leave would be short-term, and reminded his top staff that he continues to live on the NIH campus and he might drop by. Also, von Eschenbach noted that he would maintain his office and attend some meetings, sources said.

The conversation left NCI officials confused. What would be his role at NCI? What would be Niederhuber's role? If von Eschenbach planned to drop in on meetings, how did his leave of absence address the issues of conflicts of interest?

"It's bizarre," an NCI official said. "He thinks he is going to do this for a little while and then come back."

Von Eschenbach's choice of titles for Niederhuber is a typical move for the NCI director who routinely borrows terminology from the business world. The title COO has never been used at NCI. In business, a COO usually reports to a CEO. Who could that be?

"Andy's still the director," said an NCI official.

Following the telephone conference with the Institute's Executive Committee, von Eschenbach broadcast an email to his other staff:

"I am grateful to you for your support as I assume the role of Acting Commissioner of Food and Drugs," he wrote in an email to FDA employees. "I know that change can be stressful for any organization, and I want to do everything possible to bring about a smooth and orderly transition.

"To ensure that the important work of the NCI moves forward, Secretary Leavitt has asked Dr. John Niederhuber to serve in the role of Chief Operating Officer to handle the day-to-day management at NCI. I am confident that John, and the rest of the superb senior leadership team at NCI, will continue the agenda and vision of a future free from the suffering and death due to cancer.

"As a prudential matter, I have also decided that, as Acting Commissioner, I will not participate in certain FDA matters in which NCI is a party, unless the Department requests that I participate on a case-by-case basis. This includes such matters as:

—Approval applications affecting drugs, devices, and biologics submitted by NCI or where an NCI employee was a Principal Investigator;

—FDA oversight/observation of adverse event reporting in NCI clinical protocols;

—Other matters involving NCI as a party in which FDA is exercising its regulatory authority.

"I am now devoting my energies to the work of FDA in protecting and advancing the health of the American people. I look forward to bringing my experience on the discovery side of medicine to the delivery side of medicine—making sure patients get the drugs and treatments they need as quickly and safely as possible."

This is not a solid and typical recusal, said Michael Clark, an attorney with the Houston firm of Hamel Bowers & Clark and an expert on bioethics.

"Dr. von Eschenbach doesn't remove himself from all potential decision-making in light of the 'case by case' basis language (if the Department requests he get involved)," Clark said.

"I'd characterize it more as a 'Recusal Lite.'"

Speaking to The Washington Post, Sen. Edward Kennedy (D-Mass.) said von Eschenbach's decision to take a temporary leave of absence as NCI director "does not go far enough."

"FDA deserves a commissioner who can commit completely to this important responsibility," and NCI "deserves a full-time director."

Von Eschenbach's subsequent actions raise further doubts about his leave of absence. On Oct. 4, von Eschenbach's quotes appeared in two different press releases issued by NCI and FDA.

Wearing the NCI hat, von Eschenbach expounded cancer statistics. Then, switching hats, he held forth on FDA's measures for prevention of bovine spongiform encephalopathy.

*Kirsten Boyd Goldberg contributed to this report.*

## Von Eschenbach's Activist Regulatory Vision No Secret

(Continued from page 1)

FDA's bureaucractic intransigence. And, writing for The Washington Times, Manhattan Institute's scholar Robert Goldberg warned that "bureaucrats within the FDA, and the external critics who believe he is the drug industry's hand puppet, are undermining efforts to move the FDA into the 21st century."

Indeed, it may be inaccurate to describe von Eschenbach as an industry puppet. The views he has expressed at NCI define him as an activist who is willing to ask for far greater incentives and looser drug approval criteria than the pharmaceutical industry would consider politically feasible or prudent.

Von Eschenbach has stated repeatedly that cancer is an engineering problem, which makes it similar to the space program. He argues that his goal to "eliminate suffering and death due to cancer" by the year 2015 would be achieved in part due to synergy between technologies that are either not yet proven or not yet invented.

There is no evidence that von Eschenbach has abandoned any of the fundamental positions he has taken as NCI director:

**—Drug approval can be based on measurements of biological activity—as opposed to survival or tumor shrinkage or other clinical outcomes.**

In an interview with The Cancer Letter two years ago, von Eschenbach said that both NCI and FDA "recognize… as we look down the road at the new paradigm, that we are looking at outcomes that are not going to be dependent upon survival, and may not even be dependent upon the demonstration of objective response to the tumor, but are going to be dependent upon our ability to demonstrate the module to the pathway, or [whether] we have affected a marker of gene expression, or a kinase expression, or whatever" (The Cancer Letter, May 16, 2003).

Skeptics agree that the measurement of biological activity on the molecular level is a valid area of research, and that at some point—not any time soon—it may be possible to evaluate cancer drugs based on their biological activity alone. However, von Eschenbach wasn't framing the question in terms of research. He was talking about research and regulatory policy.

Many of von Eschenbach's key allies believe that this switch should be made in the near future, especially in the area of prostate cancer. Advocates and some scientists believe that FDA should approve prostate cancer drugs based on their ability to lower the level of prostate-specific antigen. FDA hasn't accepted this view, and continues to insist on demonstration of clinical benefit.

Over the past two years, FDA conducted a series of workshops on "surrogate endpoints" in cancer, finding that such endpoints need to be validated before they can serve as a basis for approval. The workshops were sponsored by FDA, the American Society of Clinical Oncology, and the American Association for Cancer Research. Many NCI scientists took part in the proceedings.

The recommendations of these workshops were then presented to the FDA Oncologic Drugs Advisory Committee, translated into a guidance to industry, and posted on the web: http://www.fda.gov/cder/drug/cancer_endpoints/default.htm.

FDA observers say von Eschenbach would need formidable political clout to reopen this issue.

**—Scientists can rely on surrogate endpoints in treating precancerous conditions in people at risk of developing disease.**

Since chemoprevention implies giving potentially harmful drugs to people who haven't been diagnosed with disease, this strategy is even more controversial than reliance on surrogate endpoints as a basis for drug approval.

In the interview two years ago, von Eschenbach said the proof of principle for such interventions already exists.

"I don't have to prove to you that chemoprevention is, in fact, a viable strategy," he said. "That has already been done. What I need to do is get more of them. I don't have a full palette of those things, and so we need many, many more" (The Cancer Letter, May 16, 2003).

In a joint presentation with then-FDA Commissioner Mark McClellan at the 2003 ASCO annual meeting, von Eschenbach said the Institute and FDA need to "integrate chemopreventive strategies into our clinical arena."

"Work needs to be done in appropriately validating those interventions and having the science to underpin their approval, and then to be able to monitor them as chronic administration over a period of time," he said (The Cancer Letter, June 6, 2003).

While von Eschenbach spoke about the need for better science, his top political operatives were shopping around a plan that called for approval of treatments of pre-cancerous conditions based on surrogate endpoints and subsequent reliance on adverse events monitoring systems to keep track of toxicity.

Also, the NCI plan proposed a change in product liability laws as an inducement for drug companies to conduct such trials without fear of personal injury suits. ASCO's cancer prevention experts described the plan as "anti-science" and declined to endorse it.

"Andy von Eschenbach and [NCI Deputy Director] Anna Barker really want to get this done," James Mulshine, the Institute's point man on the pre-cancer project, said to The Cancer Letter at the time. "There is some tension at some levels with FDA, but the new Commissioner [McClellan] seems to have a more open mind about this than a lot of the other people there (The Cancer Letter, May 30, 2003)."

There are no indications that von Eschenbach has abandoned or modified that plan after NCI-sponsored trials of Celebrex and Vioxx for prevention of colon cancer found that patients who took these Cox-2

inhibitors were more likely to suffer strokes and heart attacks.

**—Though von Eschenbach hasn't stated flatly that randomized trials are a less than optimal way to develop cancer therapies, colleagues at the Institute said he has frequently characterized such trials as comparisons of "Coke vs. Pepsi."**

During his 2003 appearance with FDA's McClellan, von Eschenbach suggested mathematical modeling as an alternative to clinical research.

"We may need to design new biomathematics and biostatistical models," von Eschenbach said. "We may need to look at our ability to integrate multiple interventions that are based on mechanistic interruptions, recognizing that those interventions singly may appear to be ineffective, but in combination would, in fact, be quite effective at dealing with progression of disease" (The Cancer Letter, June 6, 2003).

In conservative think-tanks, the words "personalized medicine," which von Eschenbach uses frequently, have become shorthand for opposition to randomized trials. It suggests that tailoring of therapies to every patient would make randomization meaningless.

Earlier this year, at an event sponsored by the Manhattan Institute, von Eschenbach described his vision of personalized medicine:

"Genomics, proteomics, and emerging technologies are enabling us to profile not only diseases, but the persons who bear those diseases," von Eschenbach said at a meeting June 21. "We can thus understand the genetic and molecular differences so that we can begin to personalize intervention strategies.

"We have worked over the past 30 years in a statistical model. Clinicians such as myself have prescribed a therapy for a cancer based on a statistical probability of success. Today, we consider it a major breakthrough if we have a chemotherapy strategy for advanced pancreatic cancer that has a 60 percent complete response rate. Unfortunately, that means that 40 percent of patients are paying the full price of care and obtaining no benefit.

"We are just beginning to know which cases fall into which category. The technologies are now within our grasp that will enable us to make those kinds of decisions."

Von Eschebach's remarks—posted at http://www.manhattan-institute.org/html/mpb_01.htm—surprise cancer experts, in part because of his hypothetical example, a chemotherapy that produces complete disappearance of tumors in 60 percent of patients with advanced pancreatic cancer.

"Obviously, he is a urologist; he knows something about a tumor that starts with 'P,' but not this tumor," said a gastrointestinal oncologist who spoke on condition that his name would not be used. "If someone came up with a complete tumor remission in 60 percent of patients with advanced pancreatic cancer, there would be dancing in the streets. This isn't within our grasp. Maybe he is taller than the rest of us."

Last month, FDA advisors recommended approval of Tarceva for pancreatic cancer after that therapy produced minimal tumor shrinkage (partial response in fewer than 10 percent of patients and no complete responses) and extended survival by about two weeks. As of yet, there was no way to define patients who stood to benefit from the agent.

Unlike the Manhattan Institute and von Eschenbach's NCI, FDA exists in order to regulate therapies based on scientifically validated rules of evidence. Weeding out scientific hyperbole is one of its key functions.

Unless the new acting commissioner has the political support to move rapidly, decisively—and with total disregard for all consequences—skeptics at the agency, in Congress, and in academia will surely remind him that the technological revolution he glorifies is yet to occur, and until it does, FDA should base its regulatory decisions on tangible benefits.

## Niederhuber Named NCI "Chief Operating Officer"

*By Kirsten Boyd Goldberg*

HHS Secretary Michael Leavitt asked John Niederhuber to serve as "chief operating officer" handling NCI's "day-to-day management," NCI Director Andrew von Eschenbach said in a statement Oct. 4.

Niederhuber, until recently a professor of surgery and oncology at the University of Wisconsin, and former chairman of the National Cancer Advisory Board, joined NCI on Oct. 2 as deputy director for clinical and translational sciences.

"It has never been more important to ensure that NCI has stable leadership, and I'm confident that Dr. Niederhuber, in cooperation with the superb NCI senior leadership team, will ensure that our vital work continues unabated," von Eschenbach said.

After receiving a battlefield promotion due to extremely usual circumstances—von Eschenbach's apparently temporary deployment to head FDA—Niederhuber figures awkwardly on the NCI organization chart.

The COO title created for Niederhuber seems more

IBM than NIH, but with von Eschenbach continuing as NCI director, the Administration couldn't name an "acting director."

Niederhuber also couldn't be appointed as the NCI deputy director, the No. 2 spot, because Alan Rabson, the 50-year NIH veteran, continues in that position, although the scope of his activities has been limited primarily to cancer patient and advocacy issues.

Besides, Niederhuber already is deputy director for clinical and translational sciences, a rung officially just below Rabson's.

Sharing that rung with Niederhuber are three other deputy directors: Anna Barker, who has been von Eschenbach's de facto No. 2 as deputy director for advanced technologies and strategic partnerships; Mark Clanton, deputy director for cancer care delivery systems; and a vacant position of deputy director for management.

Scientists and clinicians contacted this week wondered what Niederhuber's authority would be as COO, and called the situation "baffling," "confusing," and even "bizarre." Niederhuber was unavailable for comment.

"You can't leave the largest NIH institute devoid of leadership," an oncologist said.

The choice of Niederhuber to fill in for von Eschenbach pleased some oncologists, but left others concerned. Niederhuber was asked to step down from his two previous managerial positions—as director of the University of Wisconsin Comprehensive Cancer Center and as chairman of surgery at Stanford University.

To many of his colleagues, he is known as one of the best surgical oncologists in the U.S., well-liked by patients and trainees, an academic who successfully combined clinical work with laboratory investigations.

A specialist in gastrointestinal, hepatobiliary, and breast cancer, he developed an implantable drug delivery system to provide continuous hepatic arterial infusion for patients with liver metastases from colorectal cancer. He was the first to implant venous access devices for patients on chemotherapy. His lab interests are in protein tyrosine kinases and signal transduction.

A search on PubMed lists Niederhuber as an author on more than 100 papers on surgery and oncology. He is co-author and editor of the textbook, "Clinical Oncology." He has served as president of the Society of Surgical Oncology (2001-02) and the Association of American Cancer Institutes (2001-03).

"John Niederhuber has had both basic science lab and clinical experience, as well as academic administrative experience, and he has an understanding of how NCI works through his service on the NCAB," said Samuel Wells Jr., professor of surgery at Duke University and president of the General Motors Cancer Research Foundation. "I think he will do well."

A biographical sketch of Niederhuber, prepared by John Daly, professor of surgery, Weill Medical College of Cornell University, and published in the Annals of Surgical Oncology in 2002, is posted at http://www.annalssurgicaloncology.org/cgi/content/full/9/8/705.

Born in Steubenville, Ohio, the son of a printer, Niederhuber graduated from Bethany College in West Virginia and received his M.D. from Ohio State University. He joined the Army and was stationed at the U.S. Biological Laboratory at Fort Detrick. After leaving the Army, he went to University of Michigan in 1969 for residency and then took a visiting research fellowship in immunology at the Karolinska Institute in Stockholm.

He returned to Michigan to complete training in surgery in 1973, and was appointed assistant professor of surgery and microbiology. Later, he became full professor and chief of the Division of Surgical Oncology and Transplantation. He was named associate dean for research from 1982 to 1985.

In Michigan, he married Tracey Williamson, who ultimately died of breast cancer in 2001.

In 1986, Niederhuber went to Johns Hopkins University, where he was a visiting professor of molecular biology and genetics. He stayed to become professor of surgery, oncology and molecular biology and genetics.

Niederhuber was well-regarded at Hopkins and could have been named director of the cancer center, according to Daly.

However, in 1991, David Korn, then the new dean of the Medical School at Stanford University, recruited Niederhuber to Stanford as chairman of the Department of Surgery.

Korn was brought in to "straighten out" the medical school, but eventually was asked to leave, sources said. That left Niederhuber in a precarious position. "Niederhuber came in with the clean-up dean, and he probably made some enemies," a scientist said.

"John set a new academic tone at Stanford," Daly wrote. "He did so through rigorous development of the clinical and scientific conferences, visiting professor programs, and faculty recruitment."

In 1995, Niederhuber was demoted from the position as department chairman, causing several of

his surgical residents to protest by going to the home of medical school dean Eugene Bauer to demand an explanation, according to the Palo Alto Weekly. The change was made for "administrative reasons," a medical school spokesman told the newspaper.

Niederhuber went to Wisconsin in 1997 to succeed Paul Carbone as the cancer center director. He merged the comprehensive cancer center with the McArdle Laboratories, and competed for renewal of the center's core grant from NCI.

"He was highly successful in both these endeavors," UW Hospital spokesman Linda Brei said to the Wisconsin State Journal in 2002, when Niederhuber was asked to step down as center director after medical school officials expressed disappointment in his fundraising efforts.

Niederhuber's resignation was "a mutual decision based on a change of focus for the center," Brei said. "The forward thrust of the cancer center is now focused around creating a new facility to house the bulk of the newly fused center and in developing highly translational research programs."

Fundraising "is not his forté," a source said. "It's not widely understood that fundraising is a big part of what center directors do."

In July 2002, Niederhuber was appointed by President Bush to serve as chairman of the NCAB.

Niederhuber is a member of C-Change, which began as the National Dialogue on Cancer. He serves as a member and vice chairman of the C-Change research committee, the fundraising committee, and the business planning and budget committee. He is a member of a C-Change initiative called the CEO Roundtable on Cancer, a group of pharmaceutical company executives putting together an industry collaboration.

## Cancer Death Rates Dropping 1.1% A Year, Report Finds

The nation's leading cancer organizations report that Americans' risk of dying from cancer continues to decline and that the rate of new cancers is holding steady.

The "Annual Report to the Nation on the Status of Cancer, 1975-2002," published in the Oct. 5, issue of JNCI, shows observed cancer death rates from all cancers combined dropped 1.1 percent per year from 1993 to 2002.

According to the report's authors, declines in death rates reflect progress in prevention, early detection, and treatment; however, not all segments of the U.S. population benefited equally from advances.

First issued in 1998, the report is a collaboration among NCI, the Centers for Disease Control and Prevention, the American Cancer Society, and the North American Association of Central Cancer Registries.

"These numbers reflect a trend in reduction of cancer mortality that has now persisted for nine years," NCI Director Andrew von Eschenbach said in a press release. "This can only be considered good news for the millions of cancer survivors who have benefited from recent research and treatment advances and emphasizes the expectation that we will achieve a time when no one will suffer or die from cancer."

Death rates from all cancers combined declined 1.5 percent per year from 1993 to 2002 in men, compared to a 0.8 percent decline in women from 1992 to 2002. Lung cancer is the leading cause of cancer deaths in both men and women. Death rates decreased for 12 of the top 15 cancers in men, and nine of the top 15 cancers in women.

"Declines in mortality rates from many tobacco-related cancers in men represent an important, but incomplete, triumph of public health in the 21st century," said John Seffrin, ACS chief executive officer. "These trends reinforce the importance of tobacco control programs in the U.S., as well as measures to combat the increase in tobacco use in other parts of the world, particularly in developing countries."

Overall cancer incidence rates for both sexes have been stable since 1992. Incidence rates were stable in men from 1995 to 2002 and increased 0.3 percent annually in women from 1987 to 2002. The persistent increase in overall cancer incidence rates for women can be attributed to increases in rates for breast and six other cancers: non-Hodgkin lymphoma, melanoma, leukemia, and thyroid, bladder and kidney cancer. However, according to more recent data from 1998 to 2002, female lung cancer incidence rates have begun to stabilize after increasing for many years, which is good news. Changes in overall incidence may result from changes in the prevalence of risk factors and from changes in detection practices due to introduction or increased use of screening and/or diagnostic techniques.

This year's report highlights patterns of care for cancer patients. The authors note that one strategy for reducing death and improving cancer survival is to ensure that evidence-based treatment services are available and accessible. In performing this analysis, the authors looked at data from NCI's Patterns of Care studies and SEER-Medicare databases, as well as other resources. Using these data, they examined whether

evidence-based care was delivered uniformly to diverse populations and how rapidly changes in evidence-based guidelines resulted in changes in cancer care.

"Day by day we are winning the war against cancer as more people than ever before are being screened and are receiving treatments necessary for them to lead healthy and productive lives," said CDC Director Julie Gerberding. "However, there are gaps and missed opportunities so we must continue to pull out all the stops to ensure proper screening and access to treatment regardless of one's age, race, or geographic location."

For breast cancer, data on trends in the treatment of early-stage disease show that the proportion of women diagnosed with stage I or II breast cancer who received breast-conserving surgery with radiation treatment increased substantially during the 1990s. This change followed evidence-based guidelines that breast-conserving surgery followed by radiation therapy may be preferable to mastectomy because it provides similar survival but preserves the breast.

The authors also report findings of a separate study on use of chemotherapy and radiation therapy for women with early-stage breast cancer. For women with lymph node positive disease, multi-agent chemotherapy, along with tamoxifen for those with estrogen-receptor positive tumors, has been recommended since 1985 by the NIH. This study found that, between 1987 and 2000, the proportion of women who received both chemotherapy and tamoxifen increased substantially. However, use of concurrent therapy remained relatively low among women age 65 and older, who were more likely to receive tamoxifen only.

For colorectal cancer, the authors found that use of adjuvant chemotherapy for stage III colon cancer patients increased rapidly between 1987 and 1995. However, delivery of this therapy was uneven across age groups, with much lower rates of treatment among patients age 65 and older. Also noted was the fact that the number of patients who received treatment decreased with the increasing number of pre-existing medical conditions, but the likelihood of receiving adjuvant therapy decreased with age even after taking other medical conditions into account.

For patients with advanced non-small cell lung cancer, evidence-based guidelines recommend that chemotherapy may be beneficial for patients who are well enough to withstand the treatment. One analysis found that, among patients age 65 and older diagnosed with this type of lung cancer between 1991 and 1993, only 22 percent received chemotherapy. A study of patients diagnosed in 1996 found similarly low levels of treatment among patients age 65 and older. However, more recent studies have found increasing trends in the late 1990s in the use of chemotherapy among late-stage non-small cell lung cancer patients.

Unlike breast and lung cancers, treatment for prostate cancer is more controversial. The most notable trend in prostate cancer treatment from 1986 to 1999 was the decreasing proportion of cases that received watchful waiting, surgical or chemical castration, or hormonal deprivation therapy as primary treatment. More aggressive treatments, including newer radiation techniques, were found to be on the rise. However, black men were found to receive substantially less aggressive treatment than white men.

The report concludes that substantial geographical variations in treatment patterns exist, but that much of contemporary cancer treatment is consistent with evidence-based NIH Consensus Development Statements.

The report is available at http://jncicancerspectrum.oupjournals.org/ and http://www.seer.cancer.gov.

## *Funding Opportunities:*

# Program Announcement

**PA 05-165: Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis**

NCI invites application for translational studies that would evaluate molecular or cellular characteristics of pre-malignant cells or tumors or the development of assays useful for cancer detection, diagnosis, and/or prognosis. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-05-165.html.

Inquiries: James Tricoli, Cancer Diagnosis Program, phone 301-496-1591; tricolij@mail.nih.gov. Karl Krueger, Cancer Biomarkers Research Group, phone 301-594-1044; kruegerk@mail.nih.gov. Heng Xie, Cancer Therapy Evaluation Program, phone 301-496-8866; xieh@ctep.nci.nih.gov.

# RFA Available

**RFA-DK-05-014: The Obese and Diabetic Intrauterine Environment: Long-term Metabolic or Cardiovascular Consequences in the Offspring**

Letters of Intent Receipt Date: Feb.16.

Application Receipt Date: March 16.

Participating institutes and NCI are soliciting applications on the effect of maternal obesity and diabetes on mechanisms that could contribute to obesity, cancer, cardiovascular or metabolic disease in the offspring. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-05-014.html.

Inquiries, for NCI: Cindy Davis, phone 301-594-9692; davisci@mail.nih.gov.

## A Notch-Signaling Pathway Inhibitor in Patients with T-cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

An investigational study for children, adolescents and adults with relapsed and refractory T-cell acute lymphoblastic leukemia/lymphoma is now accruing patients at various centers around the country.

This study's goal is to evaluate the safety and tolerability of a Notch inhibitor as a rational molecular therapeutic target in T-ALL, potentially uncovering a novel treatment for these cancer patients.

Eligibility criteria and treatment schema for the study include:

| Notch-Signaling Pathway Inhibitor in Patients with T-ALL | |
|---|---|
| Eligibility Criteria | Patient must be = 12 months with a diagnosis of T-cell acute lymphoblastic leukemia/lymphoma AND must also have:<br>• Relapsed T-ALL<br>• T-ALL refractory to standard therapy<br>• Not be a candidate for myelosuppressive chemotherapy due to age or comorbid disease<br>ECOG performance status =2 for patients >16 years of age OR Lanksy performance level >50 for patients 12 months to =16 years of age<br>Fully recovered from any chemotherapy and >2 weeks from radiotherapy, immunotherapy, or systemic steroid therapy with the exception of hydroxyurea or intrathecal therapy<br>Patient must be >2 months following bone marrow or peripheral blood stem cell transplantation<br>No treatment with any investigational therapy during the preceding 30 days<br>No active or uncontrolled infection |
| Treatment Plan | Open label and non-randomized, this study is conducted in two parts. Part I is an accelerated dose escalation to determine the maximum tolerated dose (MTD), and Part II is a cohort expansion at or below the MTD. MK-0752 will be administered orally. Plasma concentrations will be measured at defined time intervals. |

**For information regarding centers currently open for enrollment, please contact 1-888-577-8839.**

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THE CANCER LETTER

Vol. 20 No. 8
September 2005

# Business & Regulatory Report

*Product Approvals & Applications:*

## FDA Extends Review Date Of Revlimid By Three Months, Celgene Says

**Celgene Corp**. (Nasdaq: CELG) of Summit, NJ, said it has received notification from FDA that the action date for FDA's priority review of the New Drug Application for Revlimid (lenalidomide) has been extended to Jan. 7, 2006.

The company is seeking approval of Revlimid for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. The

(Continued to page 2)

*Clinical Trials:*

## CALGB, SWOG Begin Phase III Trial Of Cetuximab Vs. Bevacizumab

**The Cancer and Leukemia Group B** and **Southwest Oncology Group** has begun a randomized, multicenter phase III trial to determine whether the addition of cetuximab to chemotherapy or to chemotherapy and bevacizumab prolongs survival, compared to chemotherapy with bevacizumab in patients with untreated, advanced or metastatic colorectal cancer.

The enrollment of 2,289 patients is underway at the CALGB and SWOG networks of academic medical centers, community hospitals, and private practices.

"This study addresses a question that many physicians are eager to have answered: Of our new treatment options in this disease, what combination of cetuximab, bevacizumab and chemotherapy will most benefit patients as the initial treatment of their advanced disease?" said Richard Schilsky, CALGB chairman. "We look forward to enrolling this trial rapidly and to answering this question as soon as possible."

Patients will be randomized to one of three arms: 1) cetuximab with FOLFOX (a combination of oxaliplatin, leucovorin, and fluorouracil) or FOLFIRI (a combination of irinotecan, fluorouracil, leucovorin) chemotherapy; 2) cetuximab and bevacizumab with FOLFOX or FOLFIRI; and 3) bevacizumab with FOLFIRI or FOLFOX (the control arm). The study will also attempt to identify predictors of response to these therapies and will also look to confirm the reported 70% incidence of EGFR positivity in patients with advanced colorectal cancer.

* * *

**Breast Cancer International Research Group** of Edmonton, Alberta

(Continued to page 5)





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

## Agency Needs More Time To Review Revlimid

(Continued from page 1)

original action date under the Prescription Drug User Fee Act for the Revlimid NDA was Oct. 7, 2005.

The extension is a result of the FDA requiring more time to review additional information on Celgene's RevAssist risk-management program, the company said. FDA considers the additional material a major amendment to the Revlimid NDA, allowing the extension of the action date under PDUFA regulations.

"We are working closely with the FDA to enable completion of their review as quickly as possible for Revlimid approval," said Sol Barer, president and chief operating officer of Celgene. "We will be ready for immediate commercial launch upon FDA action, and expect a November submission of our Revlimid application for treatment of previously-treated patients with relapsed or refractory multiple myeloma."

Revlimid is being evaluated for a broad range of hematology and oncology conditions, including multiple myeloma, the malignant blood cell disorders known as myelodysplastic syndromes, chronic lymphocytic leukemia, and solid tumors.

* * *

**AmpliMed** of Tucson said Amplimexon (imexon) was granted orphan drug designation for ovarian cancer by FDA.

Amplimexon previously was granted orphan drug designation for metastatic malignant melanoma, multiple myeloma, and pancreatic cancer, the company said. The drug is completing a phase I dose-escalation study, phase I/II studies in combination with gemcitabine for pancreatic cancer, and with dacarbazine for metastatic melanoma.

Amplimexon, an injectable formulation of a cyanoaziridine compound, disrupts mitochondria, and ultimately cell death, the company said. The findings are translated into a series of phase I/II studies of combination therapy for a variety of cancers.

* * *

**AstraZeneca** (NYSE: AZN) of Wilmington, Del., said FDA granted full approval status to Arimidex (anastrozole) for adjuvant treatment of hormone receptor-positive early breast cancer in postmenopausal women.

Arimidex, an aromatase inhibitor, has study results representing five years of efficacy and safety data in the primary adjuvant setting. "The five-year profile of safety and efficacy is similar to that seen in the initial analysis with no new concerns arising from this mature data set," said Joseph Purvis, executive director medical science at AstraZeneca.

In September 2002, FDA approved a supplemental NDA for the drug under the provisions for accelerated approval, with further follow-up required for full approval, the company said. The supplemental approval was based on recurrence-free survival data from the Arimidex Tamoxifen Alone or in Combination trial with a median duration treatment of 31 months.

Arimidex significantly reduced the relative risk of breast cancer recurrence by 17 percent over tamoxifen in the clinically relevant hormone receptor-positive patients for whom Arimidex is indicated, the company said. The data was submitted to FDA to satisfy the accelerated approval requirement for five years of follow-up in early breast cancer.

The most common side effects with Arimidex versus tamoxifen in the early breast cancer clinical trial included hot flashes (36 percent vs 41 percent), joint disorders (36 percent vs 29 percent), weakness (19 percent vs 18 percent), mood changes (19 percent vs 18 percent), pain (17 percent vs 16 percent), nausea and vomiting (13 percent vs 12 percent), sore throat (14 percent vs 14 percent), depression (13 percent vs 12 percent), hypertension (13 percent vs 11 percent), osteoporosis (11 percent vs 7 percent) and headache (10 percent vs 8 percent). Fractures, including spine, hip and wrist fractures, occurred more often with Arimidex than tamoxifen (10 percent vs 7 percent).

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**Avalon Pharmaceuticals Inc.** of Germantown, Md., said it submitted an IND application to FDA for a phase I trial of AVN944 in hematologic malignancies.

AVN944 inhibits cell proliferation by denying dividing cells of the GTP necessary for synthesis of DNA and RNA, the company said. IMPDH is highly upregulated in hematologic cancers, but many other types of cancer cells are also sensitive to IMPDH inhibition.

Avalon acquired AVN944 from Vertex Pharmaceuticals Inc. in 2005.

* * *

**Bayer Pharmaceuticals Corp.** (NYSE: BAY) of West Haven, Conn., and **Onyx Pharmaceuticals Inc.** (Nasdaq:ONXX) of Emeryville, Calif., said FDA has granted Priority Review status to the NDA for Sorafenib (BAY 43-9006) for advanced renal cell carcinoma.

Sorafenib is available in the U.S. for advanced kidney cancer through a treatment protocol known as the Advanced Renal Cell Carcinoma Sorafenib study, the companies said.

The companies have begun a single-arm phase III trial in the European Union for advanced kidney cancer where treatment has occurred. The study, to be managed by Bayer and known as the European Advanced Renal Cell Carcinoma Sorafenib study, would take place at sites in 11 E.U. countries including Germany, France, U.K., Spain, Italy, the Netherlands, and Poland.

Sorafenib is the first oral multi-kinase inhibitor that targets serine/threonine and receptor tyrosine kinases in both the tumor cell and tumor vasculature, the companies said. In preclinical models, sorafenib targeted members of two classes of kinases known to be involved in both tumor cell proliferation and tumor angiogenesis. The kinases included RAF kinase, VEGFR-2, VEGFR-3, PDGFR-beta, KIT, FLT-3 and RET, the companies said.

Bayer has submitted a marketing authorization application to the European Medicines Agency approval for Sorafenib in the E.U. for advanced renal cell carcinoma.

* * *

**Cephalon Inc.** (Nasdaq: CEPH) of Frazer, Penn., said it has received an approval letter from FDA to market a sugar-free formulation of AIQ, oral transmucosal fentanyl citrate, for cancer pain.

The formulation, which is bioequivalent to the currently available product, would be marketed for the same indication as AIQ using the same name, the company said.

AIQ, which contains an opioid analgesic called fentanyl, is approved for the management of breakthrough cancer pain for those with malignancies who are already receiving and who are tolerant to opioid therapy for underlying persistent cancer pain, the company said.

* * *

**Dendreon Corp**. (Nasdaq: DNDN) of Seattle said it would submit a biologics license application to FDA to market Provenge, its investigational immunotherapy for advanced prostate cancer.

The data from the two completed phase III trials—the D9901 study in conjunction with the supportive data obtained from the D9902A study—demonstrated the absence of significant toxicity and served as the clinical basis of a BLA submission for Provenge, the company said.

The final three-year follow up of the D9901 phase III study of the investigational drug in 127 men with asymptomatic, metastatic, androgen- independent prostate cancer, showed a median survival benefit of 21 percent or 4.5 months and a three-fold improvement in survival at 36 months (p-value = 0.01; hazard ratio = 1.7) for those who were randomized to receive the drug compared to placebo, the company said. The hazard ratio implies that those receiving placebo have a 70 percent greater relative risk of dying than those who received Provenge.

The final three-year follow up of the D9902A phase III study in 98 men with asymptomatic, metastatic, androgen-independent prostate cancer showed a 20 percent improvement in median survival for those who were randomized to receive Provenge compared to placebo, the company said. At the three-year final follow up, the percentage in the Provenge-treated group was substantially greater than the percentage alive who received placebo.

In both studies, the treatment was well tolerated. The most common adverse events were fever and chills lasting for one to two days, the company said.

The drug is developed through the Dendreon' proprietary Antigen Delivery Cassette technology, which utilizes a recombinant form of an antigen found in 95 percent of prostate cancers, prostatic acid phosphatase.

The drug is being evaluated in a phase III study in asymptomatic, metastatic, androgen-independent prostate cancer. It is also being evaluated in a phase III trial, known as PROTE or P-11, for earlier stage prostate cancer.

* * *

**GTx Inc.** (Nasdaq: GTXI) of Memphis said it

would submit to the FDA Division of Oncology Drug Products a special protocol assessment on its design of the phase III trial for Acapodene, for prostate cancer in high risk men.

GTx said it expects the SPA would be sufficient to support the submission of the effectiveness portion of a NDA.

The trial is a randomized, double-blind, placebo-controlled study of 1,260 patients who receive either an oral 20 mg dose of Acapodene or placebo daily, the company said. Participants have high-grade prostatic intraepithelial neoplasia, a premalignant lesion of the prostate.

The primary endpoint of the trial is a reduction in prostate cancer incidence as determined by prostate biopsy, the company said. GTx would evaluate efficacy endpoints at 36 months, with an interim analysis at 24 months.

Enrollment began in early 2005 and is on schedule to be completed in the first quarter of 2006, the company said.

* * *

**Halozyme Therapeutics Inc**. of San Diego said it received clearance from FDA for its Chemophase Investigational NDA for superficial bladder cancer.

The clinical protocol has received Institutional Review Board approval, the company said. The objectives of the trial would determine safety, tolerability and pharmacokinetics of the drug administered intravesically with mitomycin.

* * *

**ImClone Systems** of New York, NY, and **Bristol-Myers Squibb Co.** (NYSE: BMY) said ImClone has submitted a supplemental biologics license application to FDA for approval of Erbitux (Cetuximab) for squamous cell carcinoma of the head and neck.

The application seeks U.S. marketing approval to use the treatment in combination with radiation for locally or regionally advanced SCCHN, and as monotherapy for recurrent and/or metastatic SCCHN where prior platinum-based chemotherapy has failed or where platinum-based therapy would not be appropriate. ImClone Systems has requested priority review of the application.

The submission is based on the following clinical trials: a randomized, international phase III trial, IMCL-9815, conducted by ImClone Systems and Merck KGaA, of Darmstadt, Germany, which examined the impact of combining Erbitux with radiation on locoregional control and overall survival in 424 for locally or regionally advanced SCCHN; and an open-label, multicenter phase II trial, EMR-016, conducted by Merck KGaA, which evaluated the response rate of Erbitux as a single agent in 103 patients with recurrent and/or metastatic SCCHN who have failed platinum-based chemotherapy.

In parallel, Merck KGaA, the ImClone Systems development and marketing partner for Erbitux outside of North America, today that it has filed a variation application to the European Medicines Agency and to the Swiss authority, Swissmedic, for approval of the drug for SCCHN in Europe using a similar filing package to that which was submitted by ImClone Systems and Bristol-Myers Squibb Company, the companies said.

* * *

**MGI Pharma Inc**., (Nasdaq: MOGN) of Minneapolis and **SuperGen Inc**. (Nasdaq: SUPG) of Dublin, Calif., said they have received an approvable letter from FDA for Dacogen (decitabine) injection for myelodysplastic syndromes.

The letter provides that Dacogen injection is approvable pending the FDA review of a requested analysis of the transfusion requirements of patients enrolled in the completed phase III trial, submission of certain other information, and completion of labeling discussions, the companies said.

Dacogen injection, a hypomethylating agent, is being tested in more than 40 trials, the company said.

* * *

**Neothermia Corp**. of Natick, Mass., said it has received FDA 510(k) clearance to expand indications of its en- bloc breast Biopsy System for complete or partial removal of an imaged abnormality for histological review.

The en-bloc, which received clearance in 2001, is a vacuum- assisted, image-guided system, the company said. The en-bloc slender probe is inserted through a small incision on the breast to remove tissue for histopathologic analysis. Unlike excisional surgical biopsy, en-bloc is minimally invasive and is conducted in an outpatient setting. To date, more than 15,000 en-bloc procedures have been performed in the U.S., the company said.

In addition to the indication for diagnostic sampling of breast abnormalities, the expanded FDA clearance for the system is now indicated to provide tissue samples, the company said.

The expanded indications are based on the results of an evaluation performed at the Oklahoma Breast Care Center, the company said. In an evaluation, the en-bloc breast Biopsy system showed equivalence to Mammotome core biopsy when totally or partially removing imaged lesions of the breast. During the trial,

15 breast biopsy captures were done under ultrasound guidance using both devices, and another 15 captures were done with each device under stereotactic guidance. Results showed that the en-bloc made complete captures of every imaged target with fewer attempts than required by the Mammotome, the company said.

* * *

**Tarceva** (erlotinib) was approved across the European Union for locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

An alliance among **OSI Pharmaceuticals**, **Genentech**, and **Roche** has developed Tarceva for the E.U. market. Chugai is pursuing its development and regulatory approval for the Japanese market. In the U.S., Tarceva is marketed by Genentech.

The E.U. approval was based on a pivotal Phase III study conducted by the National Cancer Institute of Canada Clinical Trials Group based at Queen's University, in collaboration with OSI Pharmaceuticals, with the participation of 86 sites from 17 countries around the world.

The trial enrolled 731 patients with advanced NSCLC whose cancers had progressed after first- or second-line chemotherapy. The study compared patients receiving Tarceva monotherapy with placebo.

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**Pfizer Inc** of New York said it has received European Mutual Recognition Procedure approval to market Aromasin (exemestane) for a new indication, adjuvant estrogen receptor positive invasive early breast cancer following two-to-three years of adjuvant tamoxifen therapy in postmenopausal women.

Aromasin is a hormonal therapy used to treat breast cancers that depend on estrogen, the company said.

The approval was based on the Intergroup Exemestane Study that showed that the switch to Aromasin after two to three years of tamoxifen had a 31 percent better probability of disease-free survival than remaining on tamoxifen, the company said.

The trial followed patients for an average of 35 months, the company said. Those who received the treatment, experienced a significant reduction in the risk for recurrence of the disease, as compared to those continuing on tamoxifen. The reduction includes fewer local and distant tumors as well as new cancer in the other breast.

Treatment was associated with fewer of the serious side effects associated with tamoxifen, including a significant reduction in thromboembolic events, the company said. Aromasin had no significant impact on bone fracture rate.

In 1999, Aromasin was approved in Europe through Mutual Recognition Procedure for advanced breast cancer after prior anti-estrogen therapy, the company said. U.S. FDA approved the drug for advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy in late 1999.

**In another development**, Pfizer said it is expanding of its treatment use program for Sutent (sunitinib malate) metastatic renal cell carcinoma, or kidney cancer, where there has been no response to standard therapies.

The program would allow eligible patients with metastatic renal cell carcinoma to receive Sutent from participating investigators at sites in the U.S., Canada, Europe, Latin and South America, and Asia.

Sutent, an oral, multi-targeted tyrosine kinase inhibitor, is being made available through a treatment use protocol that has been approved by health authorities globally, including FDA, the company said.

* * *

**Viventia Biotech Inc**. (TSX: VBI) of Toronto said it received FDA clearance to begin a phase II study evaluating Proxinium for chemotherapy-refractory recurrent head and neck cancer.

Proxinium combines a cytotoxic protein payload with the tumor-targeting characteristics of a monoclonal antibody, the company said. A single molecule of the cytotoxic protein payload, Pseudomonas exotoxin, is capable of killing a cancer cell. The antibody fragment of Proxinium targets EpCAM—an antigen that is expressed on many epithelial cancers including head & neck cancer, ensuring that the payload is delivered directly to the tumor, the company said.

The agent has been designated an Orphan Drug for head and neck cancer in the U.S. and E.U.

*Clinical Trials:*

## Phase III Trial Finds Herceptin Improved Breast Cancer DFS

(Continued from page 1)

and **Sanofi-Aventis** of Bridgewater, N.J., said an interim efficacy analysis of a phase III trial shows two Taxotere-based chemotherapy regimens in combination with Herceptin, monoclonal antibody therapy, improved disease-free survival for early-stage human epidermal growth factor receptor 2 positive breast cancer.

The BCIRG 006 trial compared a standard treatment arm of four cycles of doxorubicin and cyclophosphamide followed by Taxotere for six cycles, (AC-T) to two Herceptin-containing regimens following

initial surgery, the institutions said. One arm included the above regimen with one year of Herceptin and the other was a non-anthracycline regimen of Taxotere plus carboplatin plus one year of Herceptin. In the latter arm, the Herceptin was started concomitantly with chemotherapy.

The purpose of the trial was to determine if the introduction of Herceptin in early stage HER2-positive breast cancer significantly improves clinical outcomes and if the increased cardiotoxicity seen with Herceptin when used with anthracyclines could be avoided using a regimen of Taxotere without anthracyclines.

An Independent Data Monitoring Committee that looked at cardiac safety data reviewed findings from the 3,222-patient study and the first interim efficacy analysis based on 322 events. The relative reduction in the risk of relapse was 51 percent (95 percent CI: 35 percent-63 percent) and 39 percent [95 percent CI: 21 percent-53 percent] for the AC-TH and TCH arms, respectively, compared to the AC-T control arm.

The IDMC had reviewed and released the cardiac safety (cut-off Dec. 31, 2004) that showed the following proportion of protocol-defined cardiac events: 1.2 percent, 2.3 percent and 1.2 percent for the AC-T, AC-TH, and TCH arms respectively. Insufficient information is available at this time to evaluate the secondary endpoint of overall survival.

"In this poor prognosis population of women with HER2-positive breast cancer, the interim efficacy analysis of BCIRG 006 study conducted after 23 months of median follow up, demonstrates that the addition of Herceptin to two Taxotere-containing chemotherapy regimens, with or without anthracycline, significantly improved disease-free survival in the adjuvant setting," said Dennis Slamon, co-chairman of the BCIRG 006 study and director of clinical and translational research at the UCLA Jonsson Comprehensive Cancer Center. "In the first interim analysis, this novel regimen of Taxotere without anthracyclines appears to avoid the problem of increased cardiotoxicity that has been reported when Herceptin is used together with anthracyclines."

* * *

**CuraGen Corp**. (Nasdaq: CRGN) of New Haven, Conn., and **TopoTarget A/S** (Copenhagen Stock Exchange: TOPO) said they have begun patient dosing in a phase Ib open-label, multi-center, proof-of-concept trial evaluating PXD101, a small molecule histone deacetylase inhibitor, for advanced solid tumors, including ovarian cancer.

The trial would establish the maximum tolerated dose of PXD101 used in combination with carboplatin and/or paclitaxel, the company said. Following determination of the MTD, the study would be expanded to 15 additional ovarian cancer patients in need of relapse treatment, to further evaluate the safety and activity of PXD101 combined with carboplatin and/or paclitaxel. Enrollment would take place in Europe and the U.S., the company said.

PXD101 is a small molecule HDAC inhibitor for a range of solid and hematologic malignancies either as a single-agent, or in combination with other active anti-cancer agents, the company said.

* * *

**PharmaMar** (Spanish stock exchange, ZEL) of Madrid said it has begun a program of combination studies with Aplidin (plitidepsin) a marine-derived anti-tumor agent originally isolated from the tunicate Aplidium albicans.

The first, a phase I/II trial of Aplidin in combination with Dacarbazine, or DTIC, the standard agent for metastatic malignant melanoma, is a multicenter, randomized, open-label, clinical and pharmacokinetic trial to determine the recommended dose and assess efficacy of the drug when administered alone or in combination with DTIC as a first-line therapy, the company said.

The second phase I study would assess the safety and tolerability of Aplidin when administered in combination with carboplatin for advanced solid and hematological tumors.

The peptide is being evaluated in phase II trials for solid and haematological malignancies, including pediatrics, the company said. The trials are occurring in hospitals in Europe, Canada and the U.S.

PharmaMar is a subsidiary of the Zeltia Group.

* * *

**Pharmacyclics Inc**. (Nasdaq: PCYC) of Sunnyvalle, Calif., said it has begun enrollment in an open-label phase II trial of Xcytrin (motexafin gadolinium) in combination with whole brain radiation therapy and stereotactic radiosurgery for brain metastases from solid tumors.

The 45-patient trial would take place at 14 medical centers across the U.S. and Canada, the company said.

"For select patients with a limited number of brain metastases, stereotactic radiosurgery is becoming a widely-used treatment," said Minesh Mehta, professor and chairman of human oncology at the University of Wisconsin Medical School. "The trial would demonstrate that Xcytrin can improve treatment outcome in brain metastases treated with stereotactic radiosurgery and that magnetic resonance imaging with Xcytrin can be

used to better image tumors and define the radiosurgery treatment field."

The study endpoints are safety, tumor response, and time to neurologic progression, the company said. Treatment would be with WBRT in combination with 10 daily doses of 5 mg/kg of Xcytrin, followed by stereotactic radiosurgery boost to the tumors, the company said. MRI scans would be obtained at baseline and again after the Xcytrin treatment regimen. Because Xcytrin localizes in tumors and enhances the MRI signal, the post-Xcytrin MRI scan would be used to define the field for stereotactic radiosurgery. MRI scans also are obtained at three-month follow-up intervals to evaluate tumor response and safety of the radiosurgery procedure, the company said.

The company said it has been granted Fast-Track status by FDA for the drug for brain metastases in non-small cell lung cancer, the company said. Xcytrin is being evaluated in a randomized phase III trial, the SMART trial that compares the effects of WBRT alone to WBRT plus Xcytrin for brain metastases in NSCLC.

* * *

**Spectrum Pharmaceuticals Inc**. (Nasdaq: SPPI) of Irvine, Calif., said it has begun a phase II study of EOquin intravesical instillation for high-risk superficial bladder cancer.

The drug has shown encouraging activity and safety in superficial bladder cancer in phase I and phase II studies performed in 68 patients with multiple, recurrent disease, Eoquin said.

Fifty patients would be treated in the phase II study at teaching hospitals in the Netherlands.

* * *

**ViaCell Inc.** (Nasdaq: VIAC) of Cambridge, Mass, said it has suspended enrollment in its phase I trial of CB001, an investigational cord blood stem cell product for hematopoietic stem cell transplantation for a variety of cancers.

Of the eight patients who have completed treatment, two experienced grade IV acute graft-versus-host-disease, a known side effect in transplantation, the company said. Both patients have recovered, however, under the study protocol, the occurrence of two cases calls for a suspension of enrollment. The company said it would evaluate the cases and data with FDA and the institutional review boards for the clinical trial sites as part of obtaining the agreement to continue enrollment.

* * *

**Vion Pharmaceuticals Inc.** (Nasdaq: VION) of New Haven, Conn., said it has begun a phase II trial of Cloretazine for small cell lung cancer.

The 90-patient study would determine the response rate and toxicity of the agent for locally advanced or metastatic small cell lung cancer where non-response or relapse following treatment has occurred, the company said. Howard Burris of Sarah Cannon Cancer Center in Nashville, is an investigator for the trial.

Cloretazine also is being evaluated in a phase III trial in combination with cytarabine in relapsed acute myelogenous leukemia, the company said. Trials of Cloretazine as a single agent in adult and pediatric brain tumors, small cell lung cancer and chronic lymphocytic leukemia, and in combination with temozolomide in hematologic malignancies, are also underway.

*Deals & Collaborations:*

## Amgen, Abgenix Developing Treatment For Colon Cancer

**Amgen** (Nasdaq: AMGN) of Thousand Oaks, Calif., and **Abgenix Inc.** (Nasdaq: ABGX) of Fremont, Calif., said they are co-developing panitumumab, the first fully-human monoclonal antibody therapy targeted against the epidermal growth factor receptor for metastatic colorectal cancer where standard treatments have failed.

The companies said they are working toward the submission of the BLA for panitumumab in patients who have failed prior standard chemotherapy, including irinotecan and oxaliplatin.

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**DE-ID Data Corp.** of Philadelphia said NCI has licensed its DE-ID software as a de-identification component of software applications in the tissue banks and pathology workspace of the NCI-sponsored cancer Biomedical Informatics Grid.

NCI would use DE-ID internally and sublicense the software to sixteen NCI-designated cancer centers participating in caBIG in the U.S., as part of a program to advance the caBIG network, the company said.

The NCI license is for one year with the option to renew, the company said.

DE-ID was developed at the University of Pittsburgh Medical Center where it is used as the de-identification standard for all clinical research approved by the UPMC Institutional Review Board, the company said. DE-ID not only eliminates any or all of the 18 HIPAA safe harbor patient identifiers, but maintains the research integrity and usability of the data through name proxies and date offsets within the de-identified file, the company said.

* * *

**EntreMed Inc.** (Nasdaq: ENMD) of Rockville, Md, said it has entered into a cooperative research and development agreement with NCI to evaluate the role of HIF-1alpha inhibition in cancer treatment.

Under the three-year agreement, the NCI Developmental Therapeutics Program Screening Technologies Branch and EntreMed would investigate the mechanism of action by which the EntreMed lead compound, 2-methoxyestradiol and a second generation analog of 2ME2, ENMD-1198, inhibits tumor hypoxia factor-1 alpha in human cell lines, the company said. Also, animal tumor models would be used to establish the relationship between levels of 2ME2 in blood or tumor tissue and the inhibition of tumor growth.

The NCI Tumor Hypoxia Laboratory has developed expertise in defining the role of HIF-1alpha inhibition in the development of novel anticancer and antiangiogenic agents, the company said. The expertise would further clarify and define the antiangiogenic and antitumor properties of 2ME2 and its analog, ENMD-1198.

"The NCI collaboration would provide EntreMed with access to well-established in vitro and in vivo models of HIF-1alpha inhibition," said Carolyn Sidor, vice president and chief medical officer of EntreMed. "The company is evaluating several formulations of 2ME2 (Panzem Capsules and Panzem NCD) in phase I and II clinical oncology studies. We expect the results from these and other 2ME2 mechanism studies would help guide our ongoing Panzem clinical development program. We also are conducting IND-directed studies with ENMD-1198 and plans to submit an IND to FDA later this year."

* * *

**Invitrogen Corp**. (Nasdaq: IVGN) of Carlsbad, Calif., and the **Fred Hutchinson Cancer Research Center** have entered into a multi-year collaborative research program to develop diagnostics and screening tools for cancer.

Under the collaboration, Invitrogen said it would use its human proteome and proteomics-based approaches in combination with investigations by the lab of Sam Hanash, at the Hutchinson Center. Invitrogen also would use its proteomics technologies including its flagship ProtoArray protein microarrays and protein and antibody collections. Invitrogen said it would be able to license technologies produced as a result of the collaboration.

The Invitrogen proteomics capabilities include protein expression, separation, characterization and target screening, the company said. The Invitrogen ProtoArray, which contains more than 5,000 human proteins focused on drug target families, is a functional microarray used to measure protein interactions that could provide better therapeutic monitoring, and cures with fewer drug side effects.

* * *

**Lorus Therapeutics Inc.** of Toronto said it has entered into a research collaboration with Guido Marcucci, of Ohio State University Comprehensive Cancer Center, on a program of laboratory experiments on acute myeloid leukemia cell lines.

The experiments, which would be conducted in both tissue culture and animal models, would study the correlation between antitumor response and the cellular effects of GTI-2040 and cytarabine when given together, the company said.

The studies would provide additional scientific support for the ongoing clinical trial in recurrent or refractory AML led by Marcucci as principal investigator, and sponsored by the NCI Cancer Therapy Evaluation Program, the company said.

The NCI EP program would additionally sponsor a project by Kenneth Chan, also Ohio State University Comprehensive Cancer Center, and Marcucci to evaluate the optimal intracellular conditions for the activity of GTI-2040 and cytarabine in AML tissue culture models, the company said.

Marcucci and Chan would study intracellular drug distribution of GTI-2040 and examine how this correlates with target-related effects to explain and optimize the effects of GTI-2040 and cytarabine for AML and would take place in parallel with the ongoing clinical study, the company said.

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**MedImmune Inc.** (Nasdaq: MEDI) of Gaithersburg, Md., signed an agreement to acquire privately held **Cellective Therapeutics Inc.**

The transaction provides MedImmune with three preclinical stage programs developing monoclonal antibodies that target the B-cell antigens CD19, CD20 and CD22, the company said.

Under the agreement, MedImmune would acquire all outstanding equity interests of Cellective in a cash transaction. MedImmune also would provide Cellective shareholders with future payments for three preclinical antibody programs should certain product development and sales milestones be achieved.

**In another development**, MedImmune and **VasGene Therapeutics Inc**. of Los Angeles said they entered into a collaborative agreement to develop cancer-focused monoclonal antibodies targeting EphB4.