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House Committee Investigates FDA Head; False And Misleading Testimony Alleged

By Paul Goldberg

The House Committee on Energy and Commerce is investigating whether FDA Commissioner Andrew von Eschenbach provided misleading information in sworn testimony at a hearing March 22.

"At that hearing, questions were raised about the accuracy and candor of his testimony and prepared statement," Reps. John Dingell (D-Mich.) and Bart Stupak (D-Mich.) wrote in a letter addressed to HHS Secretary Michael Leavitt and dated March 28.

"Others who attended the hearing and had first-hand experience with some of the events described in [von Eschenbach's] testimony have also raised questions about whether the commissioner or those who helped prepare

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In the Cancer Centers:

M.D. Anderson Joins Middle East Partnership; Symposium On Metastasis Honors Fidler

M. D. ANDERSON Cancer Center has joined the U.S.-Middle East Partnership for Breast Cancer Awareness and Research, a collaboration to increase early breast cancer detection and reduce related deaths in the region through improved awareness, increased clinical resources and research. The partnership, which brings together medical professions and breast cancer advocates from Jordan and the U.S., was created by the U.S. Department of State Office of Public Diplomacy and Public Affairs and the Middle East Partnership Initiative and launched by First Lady **Laura Bush** in June. Other institutions involved in the initiative include Susan G. Komen for the Cure, and the King Hussein Cancer Center and the King Hussein Cancer Foundation, in Jordan. . . . **ISAIAH FIDLER**, professor and chairman of the Department of Cancer Biology at M. D. Anderson Cancer Center, was given a symposium in his honor on March 23-24 in Houston. The gathering, "Forty Years of Metastasis Research: A Symposium in Honor of Dr. Isaiah J. Fidler," reviewed the problem of metastasis in a microenvironment, said **John Mendelsohn**, president of M. D. Anderson Cancer Center. "Much of what we know about the fundamental biology and mechanisms of metastasis comes from the laboratory of Josh Fidler," Mendelsohn said. "His basic and translational research have profoundly altered the direction of cancer therapy." Fidler and colleagues demonstrated that 99.99 percent of cancer cells that depart a primary tumor die, with metastases originating from less than .01

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FDA Whistleblower Ross Says Von Eschenbach Misled House

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his testimony intentionally mislead the subcommittee," Dingell and Stupak wrote. "We take such allegations seriously."

Dingell is the chairman of the full committee and Stupak is the chairman of the Oversight & Investigations Subcommittee.

The Dingell and Stupak investigation is based on documentation provided by former FDA official David Ross, who was involved in handling the SanofiAventis antibiotic Ketek (telithromycin), which has been associated with fatal liver failure.

In his analysis, submitted to the subcommittee and first reported by FDAWebview (www.FDAweb.com), Ross wrote that von Eschenbach's testimony included 11 statements that were false and three that were misleading. His analysis includes extensive documentation.

Von Eschenbach isn't known as a hands-on manager. At NCI, he acknowledged that he ran the institute from the altitude of 60,000 feet. Now, he finds himself in a situation where details matter a great deal, and where he is being challenged by a whistleblower armed with detailed knowledge of events that occurred on the ground.

In his testimony before Oversight and Investigations, von Eschenbach said that even though a death from liver failure had occurred on the study, "it was not clear that this represented a signal beyond what had been seen in the data available at the time of approval."

"False," counters Ross. "This was exactly the signal that reviewers had been concerned about during the review."

In another instance, von Eschenbach testified that fraud had occurred at only one site conducting the Ketek study. False, says Ross. "There was evidence at this point of serious problems at least four high-enrolling sites, and the [FDA Office of Regulatory Affairs] field inspector had stated that 'it looks like the NDA should be put on hold.'"

The text of Ross's analysis of von Eschenbach's submitted testimony is posted at www.cancerletter.com, with permission from FDAWebview.

The stakes are high for FDA and for von Eschenbach personally. Deliberate misrepresentation of facts in sworn testimony is a felony punishable by imprisonment of up to five years. Efforts to mislead Congress are specifically cited in 18 USC 1505.

The Dingell and Stupak letter indicates that the committee is seriously exploring this matter, said Charles Tiefer, professor of law at the University of Baltimore law School and former solicitor and deputy general counsel of the House of Representatives.

"There is no more serious accusation than for Chairman Dingell's oversight subcommittee to lay out a pattern of false statements by a witness such as this FDA commissioner," Tiefer said to The Cancer Letter. "It's the trademark of the Dingell subcommittee to follow up its suspicions of false statements, as the subcommittee is now doing, by asking for documents and testimony about how the commissioner came to give his testimony, which is said to be at odds with the truth."

The options for defense in such cases are unattractive, Tiefer said. "The wise witness caught making false statements before this subcommittee either explains that he somehow made them in a state of extreme ignorance of what he is supposed to know about his job, or, frankly, checks himself into rehab," he said.

To establish who knew what when, the committee is asking for all materials that were used to prepare von Eschenbach to testify, and has requested interviews with all officials involved in coaching the commissioner for his Capitol Hill appearance.

"We request that you provide all documents prepared for or used in the preparation of Dr. von Eschenbach's testimony by any employee of the department including, but not limited to, any briefing books, background memoranda and all communications

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between and among the senior staff of the FDA, the Offices of Legislative Affairs of the FDA and the Department of Health and Human Services, the HHS Office of General Counsel, including the Office of Chief Counsel to FDA and Commissioner von Eschenbach and his senior staff," Dingell and Stupak wrote in the letter to Leavitt.

These records were expected to be delivered by the close of business April 4, but it could not be determined whether the deadline was met.

"Further, please have all senior staff and counsels who participated in the preparation of the testimony submitted on March 22, 2007, make arrangements to be interviewed by the committee staff in room 316 of the Ford House Office Building during the week beginning Monday, April 9, 2007," the letter states. "Please inform these individuals that they have a right to be accompanied by personal counsel. No employees of the Department will be allowed to participate in the interviews."

Tiefer said the von Eschenbach case reminds him of the troubles that befell Michael Deaver, a deputy chief of staff in Reagan's White House.

"The legal community on Capitol Hill can recall many times, going back to the felony conviction of president Reagan's former top aide Michael Deaver, that accusations of false statements before the Dingell oversight subcommittee have been followed with a catastrophic and irreversible drop in an official's standing," Tiefer said.

Deaver was indicted on charges of perjury before Dingell's subcommittee and of subsequent lying to a grand jury. He was convicted of perjury and false testimony and sentenced to three years' imprisonment and a $100,000 fine. His prison term was later replaced with probation and community service.

The Dingell and Stupak letter is part of a broader investigation of FDA. That investigation also involves erythropoiesis stimulating agents, which were approved without demonstration of impact on survival or disease progression in oncology. The agency allowed the sponsors to run direct to consumer ads and claim improvement in "quality of life" in oncology, despite inadequacy of data substantiating such claims.

Last month, the committee started an investigation of ESAs, but has refrained from contacting the agency, presumably pending the May 10 meeting of the FDA Oncologic Drugs Advisory Committee (The Cancer Letter, March 23).

The FDA handling of Ketek is also under investigation by Sen. Chuck Grassley (R-Iowa), a strong critic of von Eschenbach's management of FDA.

Grassley acknowledges that von Eschenbach didn't create the Ketek controversy, but alleges that the Texas urologist sided with those who did after arriving in the agency. According to Grassley, von Eschenbach personally intimidated FDA whistleblowers, who called attention to fraud and toxicities in Ketek clinical trials and irregularities in the agency's handling of approval of the antibiotic.

Also, Grassley alleges that von Eschenbach failed to cooperate with his investigation of the matter, resisting the subpoenas in the Ketek investigation (The Cancer Letter, Dec. 1, 2006).

Ketek remains on the market, albeit with a "black box" warning.

Von Eschenbach's predecessor at FDA, Lester Crawford, recently plead guilty to false writings and conflict of interest, and was sentenced to a $90,000 fine, three years of supervised probation and 50 hours of community service.

NIH News:

HHS Begins Probe Of Financial Conflicts Among NIH Grantees

By Paul Goldberg

The HHS Office of the Inspector General said it has begun a review of potential conflicts of interest on the part of NIH grantees.

"Because the majority of NIH appropriated funds are distributed to NIH grantees who undertake extramural research, and these extramural researchers are not covered by federal ethics rules that apply to NIH intramural researchers, OIG determined that this project was an important next step in examining NIH conflicts of interest," the HHS Inspector General Daniel Levinson wrote in a March 23 letter the House Committee on Energy and Commerce.

The committee's investigation of conflicts of interest at NIH previously focused on conflicts of interest on the part of intramural scientists.

The office, which started the investigation that led to the prosecution of former FDA Commissioner Lester Crawford, is also studying potential conflicts of interest on the part of clinical investigators involved in drug development.

"Our FY 2007 work plan includes a study designed to assess the nature of financial interests disclosed by clinical investigators to FDA," Levinsdson wrote. This would include reviewing "the extent to which drug, biologic, and device applicants monitor their clinical

investigators for conflicting financial interests, and the extent to which FDA monitors the financial interests disclosed by clinical investigators," Levinson wrote.

Levinson also wrote that his office is continuing an earlier investigation of 103 NIH intramural employees who had business and consulting relationships with pharmaceutical companies. "The review was generated by a written request from the Committee to several large pharmaceutical companies to provide the names of NIH employees with whom the company had consulting or business relationships," the letter states. The OIG Special Investigations Unit "are presently examining these cases to determine whether investigation is warranted."

Committee Chairman John Dingell (D-Mich.) praised the OIG for reviewing the conflict of interest cases involving intramural scientists.

"I am pleased that the inspector general is taking a much-needed closer look at these conflict of interest cases," Dingell said in a statement. "Even if only a few of these cases result in criminal prosecution, it is clear that the NIH bungled the investigation the first time around."

In 2003, committee staff identified a sample of 81 individual scientists hired by drug companies between 1999 and 2004 whose consulting agreements were not listed in information NIH provided to the committee. The agreements reported by Pfizer, Inc., ranged from $500 to $517,000 over the five-year period.

In July, 2005 NIH reported that of those 81 scientists, 37 were "cleared" and 44 were found to have violated one or more of NIH's rules.

A year later, Trey Sunderland, chief of the Geriatric Psychiatry Branch, and his former assistant Karen Putnam, appeared before the Oversight and Investigations Subcommittee and invoked the Fifth Amendment rights. Subsequently, Sunderland pleaded guilty to criminal conflict of interest.

Sunderland refused to answer questions about his decision to share thousands of priceless human tissue samples with Pfizer and the $600,000 he received from the drug company over much of the past decade.

The hearing focused on the collection, storage, tracking and use of human tissue samples in NIH's intramural research program. The committee investigation showed that Sunderland shipped to Pfizer 3,200 tubes of spinal fluid and 388 tubes of plasma collected at NIH for Alzheimer's research. The company subsequently paid him $285,000 for consulting work related to the samples.

"I am happy that the HHS inspector general has decided to re-open the 103 violations that the Oversight Investigations subcommittee referred to them three years ago," said Subcommittee Chairman Bart Stupak (D-Mich.) said in a statement. "The subcommittee discovered the violations through documents provided from pharmaceutical and biotech companies which detailed more than a million dollars in payments from the companies to NIH employees. Under NIH guidelines, the employees were required to disclose the payments, but failed to do so. Unfortunately, only Dr. Trey Sunderland's case was referred for criminal prosecution. I hope the inspector general takes a close look at these other violations."

Institute of Medicine:
Cancer Biomarkers Research Unorganized, Report Finds

Development of biomarkers in oncology is "hindered by piecemeal and unorganized efforts," said a report issued by the Institute of Medicine.

The report calls on federal agencies and other research funders, academic scientists, and private industry to coordinate their efforts in the area. The group, headed by Harold Moses, professor of cancer biology, medicine and pathology at Vanderbilt-Ingram Comprehensive Cancer Center, focused on in vitro diagnostic tests.

IOM is scheduled to analyze biomedical imaging biomarkers in another report.

The document is posted at http://national-academies.org.

At a time when reliance on biomarkers and the advent of "personalized medicine" are politicized by FDA and NCI officials, the report presents a balanced account of the state of the science and the obstacles to its advancement.

The report also includes a detailed, 93-page summary of an IOM workshop on developing biomarkers for cancer screening, diagnosis and treatment.

The report proposes that pharmaceutical and diagnostic companies should join with federal agencies to create international research consortia. "Past efforts, notably the Single Nucleotide Polymorphism (SNP) Consortium, demonstrate how such partnerships can decrease costs for each member and yield information that companies may transform into better diagnostics," IOM said in a statement.

"In addition, NIH, NCI and other agencies should sustain support for high-quality repositories to store patients' cell and tissue samples collected in prospective studies," the document states. "Such samples would

be very useful for discovering and validating new biomarkers."

The report states that "efforts to develop biomarkers for particular drugs are riskier investments of resources, because the indicators could become obsolete if the drugs failed or therapy guidelines changed.

"On the whole, government agencies and other stakeholders should cooperate to create guidelines for the development, validation, and use of biomarkers," the report says. "The number of false results generated by widely used biomarker-based tests for breast cancer underscores the need for uniform standards to validate tests and for greater regulatory oversight of tests once they reach the market. No federal agency now takes responsibility for ensuring the clinical validity or usefulness of biomarkers."

The study was sponsored by the Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Food and Drug Administration, Centers for Medicare and Medicaid Services, U.S. Health Resources and Services Administration, American Cancer Society, American Society of Clinical Oncology, C-Change, and UnitedHealth Group.

Cancer Screening:

"No Simple Recommendation" On Mammograms For Women In Their 40s, Group Says

The American College of Physicians earlier this week released a new clinical practice guideline for screening mammography for women between ages 40 and 49.

According to the guideline, the breast cancer risk is unevenly distributed among women in this age group, which is why the benefits of screening aren't the same for all women. Therefore, women need to take into account their level of risk and the possible benefits and harms of screening mammography.

"No simple recommendation applies to all women in their 40s," Joann Elmore and John Choe, both of the University of Washington, wrote in an editorial that accompanied the new guideline. "We must learn to become comfortable with using the art of medicine to translate the existing science. We must listen carefully to our patients and communicate honestly the benefits and limitations of our imperfect tests."

—Clinicians should periodically perform individualized assessment of risk for breast cancer to help guide decisions about screening mammography.

—Clinicians should inform women in this age group about the potential benefits and harms of screening mammography.

—Clinicians should base screening mammography decisions on benefits and harms of screening as well as a woman's preferences and breast cancer risk profile.

—ACP recommends further research on the net benefits and harms of breast cancer screening modalities for women in this age group.

If a woman between the ages of 40 and 49 decides not to have a mammogram, she and her doctor should re-address the issue every one to two years, the ACP said.

The guidelines, based on a systematic review of literature published between 1966 and 2005, are published in the Annals of Internal Medicine, www.annals.org. The guideline takes into account the false-positives and the potential of overtreatment.

"Current evidence indicates that women 40 to 49 years of age who undergo routine mammography screening will decrease their risk for death due to breast cancer but will increase their risks for undergoing unnecessary procedures, breast cancer-related anxiety, discomfort at the time of screening, and exposure to low-dose radiation," the guideline states. "Because the incidence of breast cancer and the effectiveness of mammography are lower among women in their 40s than among women 50 years of age or older, mammography screening results in less absolute benefit and greater absolute risk for women 40 to 49 years of age than for women 50 years of age or older. The proportion of women 50 years of age or older whose risks for mammography outweigh the benefits is widely accepted to be clinically insignificant. However, the evidence suggests that this proportion is higher and may be clinically significant for women 40 to 49 years of age. Given this difference, a woman 40 to 49 years of age who had a lower-than-average risk for breast cancer and higher-than-average concerns about false-positive results might reasonably delay screening. Measuring risks and benefits accurately enough to identify these women remains a challenge."

The new ACP guideline differs from those of NCI and the American Cancer Society. NCI recommends screening every one to two years for women in their 40s (http://www.cancer.gov/newscenter/mammstatement31jan02). ACS recommends annual screening for women in their 40s.

"The American Cancer Society and other organizations have endorsed mammography screening for women in their 40s because direct and inferential evidence supports its value in reducing morbidity and

mortality from breast cancer, the second leading cause of cancer death in women," said Robert Smith, director of cancer screening for ACS. "It would be a major public health setback if these new guidelines caused some women and their doctors to conclude that screening can safely be postponed."

ACS recently recommended that women at high risk of breast cancer undergo annual MRI scans. The update to the ACS guideline is posted at http://caonline.amcancersoc.org/cgi/content/full/57/2/75.

"Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease," ACS stated.

Other groups that recommend mammograms every one or two years for women in their 40s include the U.S. Preventive Services Task Force and the American College of Obstetricians and Gynecologists.

Computer-Aided Detection Reduces Accuracy

In another development in mammography earlier this week, researchers found that computer-aided detection that uses software designed to improve how radiologists interpret mammograms may instead make readings less accurate.

The research was conducted by investigators at the University of California Davis Health System, and the Breast Cancer Surveillance Consortium, which is sponsored by NCI.

The results of the study show that women who got screening mammograms at centers using CAD devices were more likely to be told their mammogram was abnormal and thus undergo a biopsy to rule out breast cancer.

The findings appear in the April 5 issue of the New England Journal of Medicine and were funded by NCI, the Agency for Healthcare Research and Quality, and the American Cancer Society.

CAD software analyzes the mammogram image and marks suspicious areas for radiologists to review, thus assisting them in determining which images could lead to in serious tumors. CAD was approved by FDA in 1998 and has been incorporated into many mammography imaging practices, but its effect on the accuracy of interpretation has been unclear.

Investigators looked at the use of screening mammography in 222,135 women who had 429,345 mammograms. The period of observation was from 1998 through 2002 and took place at 43 facilities in Colorado, New Hampshire, and Washington states. The study included 2,351 women who received a diagnosis of breast cancer within one year after screening and also received a mammogram that did or did not use CAD.

"Within three years of FDA approval, 10 percent of the mammography facilities in the country were using CAD," said lead researcher Joshua Fenton, of UC Davis Health System. "There had been no large-scale community-based review of CAD efficacy despite the rapid adoption of this technology, so we did this study to see if CAD was proving to be beneficial."

Seven facilities, representing 16 percent of the study sites, implemented computer-aided detection during the study period. With the use of CAD, 32 percent more women were recalled for more tests and 20 percent more women had a breast biopsy. Use of the software had no clear impact on the early detection of breast cancer.

The study suggests that, if anything, the software may promote the detection of the least dangerous breast cancers, such as localized, in situ breast cancers. The effect of in situ cancers on breast cancer mortality remains unknown and some evidence suggests that not all develop into serious cancers.

Every time the CAD software marks a real cancer, a radiologist has to consider about 2,000 additional false-positive marks, making it very difficult to distinguish between real cancers and those that are not cancer. The authors estimate that for every additional woman diagnosed with breast cancer on the basis of CAD, 156 women are falsely recalled for more tests and 14 had unnecessary biopsies to exclude cancer.

"It's unfortunate that the use of the software has proliferated so widely before we are certain of its benefits," said Fenton. "We need studies to determine if the benefits of the software outweigh its harms and costs. There is also the potential for new studies to improve the performance of CAD software."

The authors estimate that if all mammography facilities adopt CAD, the annual cost of mammograms in the U.S. could increase 18 percent, or an additional $550 million nationwide.

"This study points out the need for the use of other techniques to find cancer at its earliest stages," NCI Director John Niederhuber said. "NCI is incorporating techniques for imaging at the molecular level into many of its studies and is also conducting studies to improve the use of CAD and conventional mammography. In the end, technology facilitates screening. Ultimately, treatment requires radiologists working with the examining physician and the responsible surgeon to put everything together."

Professional Societies:

AACR Honors 14 Scientists For Research In Cancer

The American Association for Cancer Research announced the winners of its 2007 awards, to be presented at the association's annual meeting April 14-18 in Los Angeles.

The recipients are Richard Kolodner, Douglas Lowy, John Schiller, Donald Metcalf, Janet Butel, Harold Freeman, Alexander Varshavsky, Michael Kastan, Daniel Haber, Thomas Kensler, Kornelia Polyak, Kenneth Anderson, Samuel Danishefsky, and Webster Cavenee.

Kolodner, member of the Ludwig Institute for Cancer Research, and professor of medicine and member of the Moores Cancer Center at the University of California, San Diego School of Medicine, is the recipient of the Kirk A. Landon Prize for Basic Cancer Research. He will be recognized for his discoveries in DNA mismatch repair and its connection to human cancer.

The Dorothy P. Landon Prize for Translational Cancer Research will be awarded to NCI researchers Lowy and Schiller, for research leading to the development of the human papillomavirus vaccine. Lowy is chief of the Laboratory of Cellular Oncology and head of Signaling and Oncogenesis Section. Schiller is senior investigator in Laboratory of Cellular Oncology and head of the Neoplastic Disease Section.

Metcalf, recognized for his work on the control of blood cell formation, will receive the AACR Award for Lifetime Achievement in Cancer Research. He is the Carden Fellow in Cancer Research at the Walter and Eliza Hall Institute and Professor Emeritus, University of Melbourne.

Butel, the Joseph L. Melnick Professor of Virology and program leader, Dan L. Duncan Cancer Center; director, Baylor-UT Houston Center for AIDS Research, and Distinguished Service Professor and chairman, Department of Molecular Virology and Microbiology, Baylor College of Medicine, will receive the Women in Cancer Research-Charlotte Friend Memorial Lectureship, for contributions to the biology of tumor viruses, their oncogenic mechanisms, and their importance in the infectious etiology of cancer.

Freeman, professor of clinical surgery at Columbia University College of Physicians and Surgeons and president, founder, and medical director of the Ralph Lauren Center for Cancer Care and Prevention in New York, is the recipient of the Minorities in Cancer Research-Jane Cooke Wright Lectureship, for his work on the Patient Navigator Program, a community-based strategy to reduce cancer disparities; for his patient-focused programs in breast and cervical cancer screening in a public hospital; for translating hospital cancer care to the community; and for raising awareness of the economic, social, and racial injustices related to health disparities through his scholarship.

Varshavsky, Howard and Gwen Laurie Smits Professor of Cell Biology at the California Institute of Technology, will receive the Irving Weinstein Foundation Distinguished Lectureship, for his discovery of biological regulation by intracellular protein degradation and its central role in cell function and activity.

Kastan, cancer center director, St. Jude's Children's Research Hospital, will receive the G.H.A. Clowes Memorial Award for his studies of cellular responses to DNA damage.

Haber, director, Massachusetts General Hospital Cancer Center, and Laurel Schwartz Professor of Oncology, Harvard Medical School, will receive the Richard and Hinda Rosenthal Foundation Award for his work in the molecular basis of cancer and their applications in targeted therapies.

Kensler, professor, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, will be the recipient of American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention, for developing translational strategies using chemopreventative compounds for targeting reduction of liver cancer in the economically developing world.

Anderson, Kraft Family Professor of Medicine, Harvard Medical School; chief, Division of Hematologic Neoplasia, director, Jerome Lipper Multiple Myeloma Center and vice chairman of the program in transfusion medicine, Department of Medical Oncology at Dana Farber Cancer Institute, will be honored for translational and clinical advances in multiple myeloma. He will receive the Joseph H. Burchenal Memorial Award for Outstanding Achievements in Clinical Research.

Polyak, associate professor of medicine in the Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, will receive the Award for Outstanding Achievement in Cancer Research, in recognition of her work in the molecular alterations in breast cancer.

Danishefsky is the recipient of the first annual AACR-CICR Award for Outstanding Achievement in Chemistry in Cancer Research. Danishefsky, Kettering

Chair and director of the Laboratory for Bioorganic Chemistry at Memorial Sloan-Kettering Cancer Center, and professor of chemistry at Columbia University, will be honored for the synthesis of complex, biologically active organic molecules.

Cavenee, distinguished professor and director of the Ludwig Institute for Cancer Research at the University of California, San Diego, is the recipient of the Princess Takamatsu Memorial Lectureship for his discoveries of the genetic mechanisms of predisposition to human cancer and his commitment to the international cancer community.

In the Cancer Centers:

City Of Hope Receives Funds To Buy A 3T MRI Machine

(Continued from page 1)

percent of cells and even arising from a single cell. Metastatic cells are not the product of random chance, Fidler found, but rather exist in the genetic diversity of the original tumor and are uniquely suited to spread and grow. Fidler is stepping down as chairman of the department in September, but will remain at M. D. Anderson as a researcher working in brain metastases. . . . **CITY OF HOPE** received $500,000 award from the Henry L. Guenther Foundation for the purchase and installation of a 3 tesla magnetic resonance imaging machine. The 3T MRI, which has twice the power of most MRIs, allows for finer resolution images or faster scanning, which can improve the accuracy of cancer diagnoses and targeting of solid tumors. The technology will be installed in Helford Clinical Research Hospital. Also at City of Hope, **J. DOMINIC FEMINO** was named associate chairman of the musculoskeletal tumor program and director of the newly created Department of Orthopedic Surgery. An orthopedist and an oncologist, Femino will direct research and clinical care programs for sarcomas as well as benign bone and soft-tissue tumors. He was head of the orthopedic tumor program at Children's Hospital Los Angeles, where his orthopedic team separated conjoined twins fused at the pelvis. . . . **ALVIN SCHMAIER**, chief of the Division of Hematology/Oncology at the Ireland Cancer Center of University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, was appointed to the Robert W. Kellermeyer, MD, Chair in Oncology. Schmaier is known for his work in blood disorders and anticoagulant development. His research has led to the development of the blood-clotting inhibitor, Thrombostatin, and he is the founder of Thromgen Inc., of Ann Arbor. His recent work evaluates blood clot disorders in cancer patients. Schmaier and **Stan Gerson**, director of the Ireland Cancer Center and the Case Comprehensive Cancer Center, lead a team developing plans for a cancer hospital to be built on the UHCMC campus. The hospital will house the Ireland Cancer Center and the Division of Hematology/Oncology.

In Brief:

LESLIE FORD, associate director for clinical research and acting deputy director of the NCI Division of Cancer Prevention, will receive the European Institute of Oncology Breast Cancer Award 2007 at the 9th Milan Breast Cancer Conference. She will present a lecture at the June 20 meeting. Previous recipients of the award have been **Gianni Bonadonna, Sir Patrick Forrest, V. Craig Jordan, Richard Gelber, David Page, Kent Osborne, Marie Claire King** and **Dennis Slamon**. . . . **STEVEN ROSENBERG**, chief of surgery at NCI, will receive the 15th annual Herbert and Maxine Block Memorial Lectureship Award for Achievement in Cancer from the James Cancer Hospital and Solove Research Institute at Ohio State University. The award is given annually to a cancer researcher. . . . **PAUL LAUTERBUR**, a physicist who received the 2003 Nobel Prize in Physiology or Medicine for developing magnetic resonance imaging, died of kidney disease March 27 at his home in Urbana, Ill. He shared the prize with British physicist **Peter Mansfield** of the University of Nottingham, who expanded on Lauterbur's work. Lauterbur began his academic career at the University of New York at Stonybrook and moved to the University of Illinois Urbana-Champaign in 1984.

Funding Opportunities:

PAR-07-348: AIDS International Training and Research Program. D43. Letters of Intent Receipt Date: July 13; July 14, 2008; July 14, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-348.html. Inquiries: Jeanne McDermott, 301-496-1492; mcdermoj@mail.nih.gov.

PAR-07-344: Innovations in Biomedical Computational Science and Technolog. R01. Application Submission/Receipt Date: May 24, Sept. 24; Jan. 24, 2008; May 24; Sept. 24, Jan. 24, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-344.html. Inquiries: Peter Lyster, 301-451-6446; lysterp@mail.nih.gov.

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THE CANCER LETTER

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Business & Regulatory Report

Clinical Trials:

Amgen Discontinues Vectibix Treatment In Metastatic Colorectal Cancer Study

Amgen said it has discontinued Vectibix (panitumumab) treatment in a trial designed to advance the agent to front-line metastatic colorectal cancer.

The trial, PACCE, evaluated Vectibix in combination with standard chemotherapy and Avastin (bevacizumab). The PACCE trial investigated a treatment regimen that used dual biologics combined with oxaliplatin- or irinotecan-based chemotherapy.

The company said the decision to discontinue Vectibix was prompted

(Continued to page 2)

Product Approvals & Applications:

FDA Approves GSK's Tykerb For Use With Xeloda For Advanced Breast Cancer

GlaxoSmithKline plc (NYSE:GSK) of Philadelphia said FDA approved Tykerb (lapatinib), in combination with Xeloda (capecitabine), for advanced or metastatic breast cancer for tumors that overexpress HER2 and where prior therapy including an anthracycline, and trastuzumab has been received.

It is the first targeted, once-daily oral treatment option for this population, the company said.

The drug inhibits two validated targets, the kinase components of the EGFR (ErbB1) and HER2 (ErbB2) receptors, associated with cancer cell proliferation and tumor growth, the company said. As a targeted therapy, the agent interferes with discrete cellular processes or disease mechanisms in cancer.

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Baxter Healthcare Corp. of Deerfield, Ill., a subsidiary of Baxter International Inc. (NYSE:BAX), said it has received clearance from FDA on its Colleague infusion pump 510(k) pre-market notification.

The company said it is modifying pumps already in the market and will submit manufacturing and service documentation in advance of deploying upgrades to Colleague infusion pumps in the U.S.

Baxter said it would continue to communicate and work directly with customers to establish deployment schedules and begin remediation activities.

"Resolving issues with the infusion pump has been our top priority,"

(Continued to page 6)

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Adding Vectibix To Avastin Increases Toxicity, Study Finds

(Continued from page 1)

by review of data from a pre-planned interim efficacy analysis, which took place after the first 231 events, in this case death or disease progression.

The analysis showed statistically significant difference in progression-free survival in favor of the control arm, the company said. An unplanned analysis of overall survival also demonstrated a statistically significant difference favoring the control arm.

Amgen said it would present the results at a scientific conference.

"We had hoped that adding Vectibix to the current U.S. standard-of-care for patients newly-diagnosed with mCRC would improve outcomes without excessive added toxicity," Roger Perlmutter, executive vice president of research and development, said in a statement. "Unfortunately, it appears that adding Vectibix to Avastin, when used in combination with oxaliplatin- or irinotecan-based chemotherapy, increased toxicity, without improving efficacy."

In January, Amgen announced than an interim analysis in the trial showed an increased incidence of grade 3 severe events of diarrhea, dehydration and infections on the Vectibix arm. Also, an increased incidence of pulmonary embolism was observed in patients who received Vectibix compared with those who did not (4 percent and 2 percent, respectively). One (less than 1 percent) fatal event of pulmonary embolism occurred in a patient receiving Vectibix.

Amgen said it's continuing to study Vectibix as a single biologic combined with chemotherapy in phase III first- and second-line registration trials.

The PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) study is a phase IIIb randomized, open-label clinical trial evaluating oxaliplatin- and irinotecan-based chemotherapy and Avastin with and without Vectibix in the first-line treatment of patients with metastatic colorectal cancer.

The trial is powered to show a 30 percent improvement in progression-free survival, the primary endpoint. Secondary endpoints include response rate, overall survival, duration of response and safety. The PACCE trial enrolled 1,054 patients (824 patients were randomized to receive oxaliplatin-based chemotherapy, and 230 patients were randomized to receive irinotecan-based chemotherapy) at 240 trial sites in the U.S. between Q1 2005 and Q3 2006.

Vectibix is approved for the treatment of patients with epidermal growth factor receptor expressing metastatic colorectal cancer after disease progression on, or following fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens.

The FDA approval of the agent was based on progression-free survival. No data are available that demonstrate an improvement in disease-related symptoms or increased survival.

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AstraZeneca (NYSE: AZN) of Wilmington, Del., said it has begun a phase III study of its investigational once-daily orally administered drug, vandetanib (Zactima, ZD6474) for advanced lung cancer.

Study 36 will investigate the addition of vandetanib to pemetrexed (Alimta) as second line treatment for locally advanced or metastatic non-small cell lung cancer after failure of first line treatment. The 508-patient study will be conducted in 20 countries, including 20 sites in the U.S.

The study will evaluate progression-free survival with vandetanib 100mg plus pemetrexed 500mg/m compared with pemetrexed 500mg/m plus placebo, the company said. The trial also will assess overall survival, objective response rate, disease control rate, duration of response, effect on disease related symptoms, time to deterioration of disease-related symptoms, the safety and tolerability of vandetanib in combination with pemetrexed, and population pharmacokinetics of vandetanib.

The trial is the fourth phase III study in the NSCLC.

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Vandetanib has shown anti-tumor activity in NSCLC when used alone and in combination with docetaxel in phase II trials, the company said. It also has shown encouraging early data in hereditary medullary thyroid cancer and has been awarded FDA and EU orphan drug status, and FDA Fast-Track designation for medullary thyroid carcinoma, the company said.

* * *

Cell Therapeutics Inc. (Nasdaq and MTAX: CTIC) of Seattle said it has filed for a Special Protocol Assessment with FDA for the design of its phase III trial of pixantrone for indolent non-Hodgkin's lymphoma.

The 300-patient PIX303 trial will examine the complete remission rates and time to disease progression of the combination regimen of fludarabine, pixantrone and rituximab compared to the combination of fludarabine and rituximab in patients with up to five prior treatments failures for relapsed or refractory indolent NHL.

Pixantrone improves the activity and safety of the anthracycline family of anti-cancer agents, the company said. Anthracyclines, which are active clinically in tumors, are associated with cumulative heart damage that prevents them from being used in a large proportion of patients. Pixantrone reduces severe cardiotoxicities and has a simplified administration compared to the marketed anthracyclines.

A phase I/II study of the drug combined with fludarabine, dexamethasone, and rituximab for relapsed indolent NHL found that among 27 patients evaluable for response, the FPD-R regimen with pixantrone produced an 89 percent overall response rate by the Cheson criteria, including 70 percent experiencing a complete response/unconfirmed complete response (CR/uCR; 63 percent, CR and seven percent, u/CR). The estimated median duration of response was 25 months and the estimated progression-free survival rate at three years was 50.4 percent.

Also, a randomized clinical trial for indolent NHL compared pixantrone in combination with rituximab to rituximab alone, with time to progression as the primary efficacy endpoint. The study of 38 relapsed or refractory patients receiving the combination of rituximab and pixantrone had an 87 percent overall improvement in TTP compared to rituximab alone. The median TTP estimate for the pixantrone/rituximab recipients was 13.2 months compared to 8.1 months for rituximab alone (hazard ratio 0.13, log rank $p<0.001$). The one- and two-year progression-free survival estimates were 66 percent and 44 percent for the pixantrone/rituximab recipients compared to zero percent for the rituximab recipients for both measurement intervals ($p<0.001$ and 0.003, respectively).

A phase III single agent trial, known as EXTEND and a phase II combination study, known as RAPID, are evaluating the drug for aggressive NHL, the company said. The EXTEND trial explores the role of single agent treatment as a salvage regimen for relapsed aggressive NHL where at least two prior treatment regimens have failed. Randomization would occur for either pixantrone or another single-agent drug of physician's choice, the company said.

The RAPID trial is a first-line phase II study in aggressive NHL that will evaluate pixantrone as part of the CPOP-R combination regimen (cyclophosphpamide, pixantrone, vincristine, prednisone and rituximab) compared to the standard treatment regimen, CHOP-R (cyclophosphpamide, doxorubicin, vincristine, prednisone and rituximab), the company said. The study will explore the cardiac safety benefits of pixantrone in chemotherapy naïve patients when compared directly to doxorubicin.

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Chroma Therapeutics Ltd. , of Oxford, England, said its oral, once-daily experimental cancer therapy CHR-2797 has entered its first phase II trial for elderly patients with treatment refractory acute myeloid leukaemia.

Chroma said it had completed a dose- ascending phase I study haematological malignancies with a treatment for up to three months with CHR-2797. Encouraging signs of efficacy were noted.

The agent also is being evaluated for solid tumors in two phase I studies, as monotherapy and in combination with chemotherapy, the company said.

CHR- 2797 inhibits aminopeptidases, a family of intracellular enzymes that supply amino acids for cell growth.

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CuraGen Corp. (NASDAQ:CRGN) of Branford, Conn., and **TopoTarget A/S** (Copenhagen Stock Exchange: TOPO) said they have begun dosing in a phase II open-label, multi-center trial evaluating the efficacy and safety of intravenous belinostat (PXD101), a small molecule histone deacetylase inhibitor, in combination with Velcade (bortezomib) for Injection, in multiple myeloma refractory to or rapidly relapsed from at least one bortezomib-containing regimen.

James Berenson, medical and scientific director at the Institute for Myeloma & Bone Cancer Research, is principal investigator of the 35-patient trial, which will be conducted at multiple sites across the U.S.

'"Based on our preclinical studies that showed markedly increased anti- myeloma effects when belinostat was combined with bortezomib to treat a bortezomib-resistant myeloma in immunodeficient mice, we will determine whether the combination can provide clinical benefit to multiple myeloma patients that have failed, or who have relapsed on bortezomib therapy," said Berenson.

Data from in vitro studies indicate that HDAC inhibitors and bortezomib, when combined, act synergistically through independent mechanisms to kill cancer cells, the company said.

Belinostat is being investigated for solid and hematologic malignancies either as a single-agent, or in combination with other active anti-cancer agents, the company said.

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EntreMed Inc. (NASDAQ:ENMD) of Rockville, Md., said it has begun a phase II trial to evaluate the safety and efficacy of Panzem (2-methoxyestradiol or 2ME2), alone and in combination with Sutent (sunitinib) for metastatic renal cell carcinoma.

The study will be conducted by Glenn Liu, assistant professor of medicine at the Paul P. Carbone Comprehensive Cancer Center at University of Wisconsin, the company said.

The trial will evaluate Panzem NCD in patients who have failed treatment with sunitinib, as well as patients who are being treated with sunitinib, but are showing signs of disease progression, the company said. The combination portion will determine if the addition of Panzem NCD will restore tumor response by blocking tumor growth at both the level of the VEGF receptor and by inhibiting HIF-1alpha.

Panzem NCD inhibits HIF-1alpha and has been shown in preclinical experiments to be both an antiproliferative agent and an antiangiogeneic agent, the company said.

Panzem NCD is in phase II trials for brain, ovarian, carcinoid, and prostate cancers and a phase I study in metastatic breast cancer, the company said.

Sutent is a registered trademark of its owner and is not a registered trademark of EntreMed Inc.

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MAT Biopharma of Evry, France, said it has begun an escalating-dose phase I/II study of its antibody Ferritarg P for relapsed or refractory Hodgkin's disease.

The 20-patient study would evaluate the pharmacokinetic, the safety and the maximum tolerated dose of the drug, which was granted Orphan Drug designation in 2006. Mat Biopharma said it would be collaborating with Institut Curie.

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Northwest Biotherapeutics Inc. (Bulletin Board: NWBT.OB) of Bothell, Wash., said the University of California, Los Angeles, has been added as a clinical site in its ongoing phase II trial for DCVax-Brain for newly diagnosed glioblastoma multiforme.

Linda Liau, principal investigator and director of the Malignant Brain Tumor Program at the UCLA School of Medicine, performed the first UCLA surgery. The other surgery site is the Henry Ford Hospital. Nine other clinical trial sites are pending.

The DCVax-Brain treatment regimen consists of three initial immunizations at two-week intervals, followed by four booster injections at two- and four-month intervals for the remainder of year one, and then semi-annual maintenance injections in year two and year three, the company said.

The DCVax-Brain phase II trial is based on two phase I studies carried out at UCLA, the company said. Each of the trials included both newly diagnosed and recurrent GBM patients.

The treatment uses the tumor of the patient, surgically removed as part of the standard of care, to prepare a mix of their personal cancer biomarkers, the company said. The biomarkers are then loaded into the dendritic cells and injected back through a simple intra-dermal injection, similar to an insulin shot, at various intervals over a three-year period. The DCVax-Brain phase II trial will consist of 141 patients who all will receive full standard of care treatment, which includes surgery, radiation and chemotherapy. Of the group, 94 will also receive DCVax-Brain.

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Pain Therapeutics Inc. (NASDAQ:PTIE) of South San Francisco said it has received approval from the Ministry of Health in Israel to begin the Q2 2007 phase I trial of a proprietary radio-labeled monoclonal antibody for metastatic melanoma.

Enrollment would be limited and would take place at in academic medical centers in Israel, the company said.

Pain Therapeutics said it expect its net cash requirements for 2007 to be $10 million, inclusive of program expenses related to metastatic melanoma. At the end of last year, its requirements and marketable securities were $204.4 million.

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Roche of Basel, Switzerland and **Kosan Biosciences Inc.** (NASDAQ:KOSN) of Hayward, Calif.,

said they would begin a phase II development program with R1645 (KOS-1584), their second-generation epothilone, in multiple solid tumor types.

In phase I dose escalation trials, R1645 was well tolerated and demonstrated antitumor activity against ovarian and non-small cell lung cancers.

Kosan and Roche established a global development and commercialization agreement for epothilones to treat cancer in 2002. Under the agreement, Roche would fund development activities and have the worldwide exclusive rights to market and sell the epothilone. Kosan would co-develop and have the right to co-promote the product in the U.S. and receive royalties on sales.

In a phase I open-label trial of R1645 being administered as a single agent on a weekly dosing schedule, antitumor activity was observed in 17 percent of 37 patients with advanced solid tumors who had been heavily pre-treated (median of five prior chemotherapy regimens), the companies said. One confirmed partial response (44 percent tumor shrinkage by RECIST) was observed in non-small cell lung cancer. One patient with advanced refractory ovarian cancer had a 40 percent decrease in CA125 tumor marker, and four experienced stable disease over four or more cycles of treatment (greater than or equal to 16 weeks). Common toxicities were low-grade and typical of a cytotoxic agent and were most frequently gastrointestinal, the companies said.

In an open-label phase I 45-patient trial in which the agent was administered as a three-hour intravenous infusion every three weeks, for advanced solid tumors, antitumor activity was seen in 29.5 percent, the companies said. One patient with ovarian cancer (six prior therapies) had an unconfirmed partial response (31 percent tumor shrinkage by RECIST) with 62 percent decline in CA125 after the second cycle. Twelve experienced stable disease after four or more cycles, including one with ovarian cancer who had a 28 percent decrease in CA125 after six cycles of treatment. In this trial, R1645 was well tolerated. Common toxicities were primarily gastrointestinal (grade 1 and 2) and fatigue, the companies said.

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Semafore Pharmaceuticals Inc. of Indianapolis said it has begun a phase I trial of its lead PI3 kinase inhibitor, SF1126, in solid tumor cancers.

The trial is being conducted by Daniel Von Hoff, at TGen Clinical Research Services at the Scottsdale Healthcare Virginia G Piper Cancer Center, the company said. Indiana University Cancer Center is also a site for the study.

The open label, ascending dose trial is assessing safety, pharmacokinetic and pharmacodynamic parameters relapsed solid cancers that are driven by PI3 kinase activation or loss of the associated PTEN function. Cancer types include endometrial, renal cell, breast, hormone refractory prostate and ovarian cancers, the company said.

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Spectrum Pharmaceuticals Inc., (NASDAQ: SPPI) of Irvine, Calif., said it has additional data from the double-blind, randomized satraplatin phase III trial, the SPARC trial (Satraplatin and Prednisone Against Refractory Cancer), which is evaluating satraplatin plus prednisone versus placebo plus prednisone for hormone-refractory prostate cancer where chemotherapy failed.

"The additional data reconfirm that satraplatin provides both pain relief and improvement of progression-free survival, and if approved, will be the only drug for hormone refractory prostate cancer in the second-line setting," said Luigi Lenaz, chief scientific officer of Spectrum Pharmaceuticals. "The convenience of oral dosing and favorable tolerability will also offer an improvement in quality of life."

The additional trial data showed that pain response rates for treatment with satraplatin were statistically significantly superior compared to the pain response rates for the comparator arm, the company said. Pain response rates were 24.2 percent for the satraplatin plus prednisone arm compared with 13.8 percent for the prednisone arm ($p<0.005$).

Pain response was assessed by using a weekly present pain intensity and analgesic score, the company said. The PPI score was defined according to the McGill-Melzack questionnaire. The criteria for pain response are a greater than or equal to two-point reduction in the weekly PPI score from baseline and maintenance of the two-point reduction for at least five consecutive weeks in the setting of a stable or decreasing weekly analgesic score compared to baseline. Patients were evaluable for pain response if their baseline PPI score was greater than or equal to one and had completed four consecutive weekly assessments of PPI and analgesic scores during the study treatment, the company said.

Additional data also demonstrated the prostate specific antigen response rate for treatment with satraplatin was improved compared to the PSA response rate for the prednisone arm, the company said. PSA response rates were 25.4 percent for the satraplatin plus prednisone arm compared with 12.4 percent ($p<0.001$) for the prednisone arm.

PSA response was analyzed using the Bubley criteria of a decrease of PSA level by greater than or

equal to 50 percent from baseline, with confirmation at least four weeks later, the company said.

The pain and PSA response analyses, in addition to the previously presented PFS data, further define the clinical profile of the agent as a second-line treatment option in metastatic HRPC, the company said.

In accordance with the recommendation of the independent Data Monitoring Board, patients who have not progressed continue to be treated and all patients will be followed for overall survival. Overall survival data are expected to be available later this year.

Safety findings were consistent with previous clinical studies, the company said.

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Sunesis Pharmaceuticals Inc. (NASDAQ:SNSS) of South San Francisco said dosing has begun in a phase I trial of SNS-032 for advanced B-cell malignancies.

Clinical data on SNS-032, a selective small-molecule inhibitor of cyclin-dependent kinases 2, 7 and 9, has demonstrated the inhibitor depletes cells of myeloid cell leukemia sequence 1, or MCL-1, a protein associated with cell survival, particularly in lymphomas and other B-lymphoid malignancies, the company said.

The trial would examine the safety and tolerability, as well as the preliminary anti-tumor activity of the agent, the company said. The multi-center dose-escalation 30-40 patient study would establish a maximum-tolerated dose in this setting.

In another development, **Sunesis** said it has filed an Investigational New Drug with FDA for SNS-314, an internally-developed anticancer product candidate.

SNS-314 is a selective inhibitor of Aurora kinases A, B, and C, the company said. The inhibitor targets the uncontrolled cellular proliferation associated with cancer by halting cell division at the mitotic phase of the cell cycle.

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Threshold Pharmaceuticals Inc. (NASDAQ: THLD) of Redwood City, Calif., said its phase III trial of glufosfamide did not show a statistically significant improvement in overall survival compared to best supportive care in metastatic pancreatic cancer that had relapsed after gemcitabine chemotherapy.

While the overall survival in the glufosfamide arm was 18 percent higher compared to best supportive care alone, the result was not statistically significant, the company said.

In the multi-national, open-label 303-patient trial, randomization consisted of receiving glufosfamide every three weeks plus BSC (n=148) or BSC alone (n=155), the company said. An independent data monitoring committee performed an interim analysis in May 2006 and recommended continuing the study through completion.

The primary efficacy comparison of overall survival was based on 261 deaths and did not reach statistical significance (p=0.19); the hazard ratio of glufosfamide to BSC was 0.85 (95 percent confidence interval of 0.66 to 1.08), the company said. The median survival with glufosfamide was 105 days versus 84 days for BSC, the company said.

* * *

Wyeth Pharmaceuticals (NYSE:WYE) of Madison, N.J., and **Progenics Pharmaceuticals Inc.** (NASDAQ:PGNX) of Tarrytown, N.Y., said Wyeth would begin a clinical trial of new formulation of oral methylnaltrexone for opioid-induced constipation based on phase II findings.

Phase II trial results, conducted by Wyeth, showed the initial formulation of oral methylnaltrexone was generally well tolerated but did not exhibit sufficient clinical activity to advance into phase III testing, the company said. Should the new formulation be successful, the companies could file an NDA as early as late 2009 or early 2010.

Product Approvals & Applications:

Baxter Making Changes To Infusion Pumps In U.S.

(Continued from page 1)

said Peter Arduini, corporate vice president and president of the medication delivery business at Baxter

Baxter said it has completed deployment activities in markets outside the U.S., with 58,000 pumps in 55 countries upgraded, and then resumed sales.

In 2006, Baxter and FDA reached agreement in the form of a consent decree, which describes steps Baxter must take to resume sales of new Colleague infusion pumps in the U.S., the company said. More than 200,000 of the infusion pumps are in use in U.S. hospitals.

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Celgene Corp. (NASDAQ:CELG) of Summit, N.J., said its oral cancer drug Revlimid (lenalidomide) in combination with dexamethasone for multiple myeloma with at least one prior therapy, has received a positive opinion from the European Medicines Agency.

The EMEA Committee for Medicinal Products for Human Use, which reviews applications for the European Union as well as Norway and Iceland, has recommended

approval for Revlimid, the company said. The opinion will be forwarded to the European Commission, which should issue final marketing approval within two to three months, the company said.

The opinion from the CHMP was based upon the safety and efficacy results of two randomized phase III special protocol assessment trials, North American Trial MM-009 and International Trial MM-010, evaluating Revlimid plus dexamethasone in multiple myeloma that have received at least one prior therapy, the company said.

Revlimid has obtained Orphan Drug designation in the EU, U.S. and Australia for multiple myeloma and is already approved by FDA in combination with dexamethasone for previously treated multiple myeloma, the company said.

The drug also is approved for 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 by FDA, the company said.

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GlaxoSmithKline (NYSE:GSK) of Philadelphia said it has submitted a Biologics License Application for Cervarix (human papillomavirus vaccine, AS04 (adjuvant-adsorbed) to FDA for cervical cancer and precancerous lesions associated with cancer-causing human papillomavirus types.

For the candidate vaccine, GSK said it has selected a proprietary adjuvant system called AS04, to enhance immune response and increase duration of protection.

The BLA includes data from clinical trials in 30,000 females 10 to 55 years of age and reflects an ethnically diverse population, the company said. The submission also contains data from the largest phase III cervical cancer vaccine efficacy trial to date, which was conducted in 18,000 females 15 to 25 years of age.

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Nuvelo Inc. (NASDAQ:NUVO) of San Carlos, Calif., said it has been granted two separate Fast-Track designations by FDA for its product candidate, rNAPc2.

The first designation is for first-line treatment of metastatic colorectal cancer to improve progression-free survival and overall survival when added to Avastin-containing 5- flurourocil-based chemotherapy regimens. The other is for second-line treatment of mCRC to improve progression-free survival and overall survival when added to 5-FU-based chemotherapy regimens, the company said.

rNAPc2 is in a phase II trial for mCRC, the company said. The primary objectives are safety and efficacy of twice-weekly, subcutaneous rNAPc2 for the second-line treatment of mCRC in combination with select 5-FU-based chemotherapy regimens.

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Pharmion Corp. (NASDAQ:PHRM) of Boulder said the European Medicines Agency has accepted for review its Marketing Authorization Application for Thalidomide Pharmion (thalidomide) for untreated multiple myeloma.

The application is based upon a clinical data package comprised of four phase III studies in 1400 patients, including a study that showed a 21-month survival advantage when the agent was added to the standard of care, the company said.

Pharmion said it is seeking authorization for the following indications: Thalidomide Pharmion in combination with melphalan and prednisone for untreated multiple myeloma for those 65 years or older or ineligible for high dose chemotherapy and Thalidomide Pharmion in combination with dexamethasone for induction therapy prior to high dose chemotherapy and bone marrow transplant, for untreated multiple myeloma, the company said.

Deals & Collaborations:

Genta, IDIS Sign Agreement On Cancer Product Distribution

Genta Inc. (NASDAQ:GNTA) of Berkeley Heights, N.J., and **IDIS** of Weybridge, U.K., said they have signed a global agreement covering all territories except the U.S., whereby IDIS will distribute two of the Genta oncology products, Ganite (gallium nitrate injection) and Genasense (oblimersen sodium) Injection, on a named patient/compassionate use basis covering

IDIS, a privately owned company, will manage the named patient programs for Genta, the company said.

Ganite is approved and marketed by Genta in the U.S. for cancer-related hypercalcemia that is resistant to hydration, the company said. Early phase II studies using the agent as an investigational drug to reduce accelerated bone resorption, have been completed in bone metastases and in Paget's disease of bone.

The drug is being tested at higher doses as a direct anticancer agent for relapsed or refractory non-Hodgkin's lymphoma.

A Marketing Authorization Application for Genasense plus dacarbazine for advanced melanoma is pending review in Europe. Genta said it is testing

Genasense in ongoing clinical trials with other chemotherapy drugs for melanoma and other diseases.

A percentage of net proceeds from the IDIS program will be allocated to support compassionate use in indigent patients; the remainder will support further clinical research, the company said.

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HUYA Bioscience International LLC of San Diego and Shanghai said it has exclusively licensed worldwide rights outside China to the cancer compound chidamide from **Shenzhen Chipscreen Biosciences Ltd.** of Shenzhen, China.

Chidamide, an orally bioavailable histone deacetylase inhibitor derived from the benzamide class, is an investigational cancer compound approved for a phase I trial in China, the company said. Histone deacetylase inhibitors induce selective regulation of gene expression in cancer cells.

HUYA will co-develop chidamide with Chipscreen through phase I trials to be begun shortly in China, the company said. Thereafter, HUYA would file an Investigational New Drug application and begin trials of chidamide/HBI-8000 in the U.S. and Europe.

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IMPAC Medical Systems, Inc. of Mountain View, Calif., said the **Mannheim Medical Center Department of Radiation Oncology**, in Manheim, Germany, has begun clinical implementation of the Impac MOSAIQ Oncology PACS.

The medical center is using the MOSAIQ Oncology Picture Archiving and Communication System to manage and archive data and images from a range of treatment planning systems and imaging devices, the company said. The technology can electronically managing large data sets, department wide access to archived data, and achieve full integration with the MOSAIQ workflow.

"Our first goal is to establish an archiving solution for all three of our treatment planning systems and then to manage all of our IGRT planar and volumetric datasets, including cone-beam and conventional computed tomography," said Volker Steil, chief medical physicist and Frank Lohr, vice chairman of the Mannheim Department.

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Stemline Therapeutics Inc. of New York said it has in-licensed the exclusive worldwide rights to SL-401, a clinically active oncology compound as a cancer stem cell target.

SL-401 has demonstrated single agent anti-tumor activity in a multi-center phase I dose escalation study conducted at Duke University, the British Columbia Cancer Agency, and the Scott & White Cancer Research Institute/Texas A&M Health Science Center College of Medicine, the licensor. Thirty adults with relapsed, refractory, or poor risk acute myeloid leukemia were treated with escalating doses of SL-401 without dose limiting toxicity. Anti-tumor activity has been observed, including one durable complete response in a patient refractory to standard chemotherapy, two partial responses, and three minor responses, the company said.

The compound targets the interleukin-3 receptor and impairs cancer stem cells to form tumors, the company said. Importantly, in AML, IL-3R is over-expressed on both leukemia blasts as well as leukemia cancer stem cells. D

"SL-401 constitutes the first concerted clinical effort to target leukemia stem cells," said David Rizzieri of Duke University Medical Center, a hematological cancers scientist and investigator on the phase I trial.

* * *

Virax Holdings Ltd. (ASX: VHL) said it has entered into a license agreement with **Transgene S.A.** (Eurolist Paris: FR0005175080) granting Transgene exclusive access to the Virax Co-X-Gene technology patents for use in two of the Transgene immunotherapeutic products, TG4010 (MVA-MUC1-IL2) and TG4001(MVA-HPV-IL2) in the U.S. and Canada.

The products are in phase IIb trials for non-small cell lung cancer (TG 4010) and in preparation for phase III trials in Human Papilloma Virus-associated pathologies (TG 4001), the companies said.

Under the agreement, Virax said it will receive an upfront license fee and will share in fees and milestone payments received by Transgene for licensing out either of the products covered by the Co-X-Gene technology license and they achieve agreed development milestones. Virax also will receive a royalty on net sales of the licensed products in North America.

The patented Co-X-Gene technology was discovered at the Australian National University and licensed exclusively to Virax for human health applications, the companies said. Immunotherapeutic products that use Co-X-Gene technology are in development, including VIR201, an immunotherapeutic for HIV infection.

Virax said it has completed phase I/IIa trials with VIR201 and is seeking additional funding to take the product into larger international phase II trials in USA/Europe/Australia.