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Biostatistician Thomas Fleming Warns Against Approval Of Cancer Vaccine

By Paul Goldberg

Thomas Fleming, a prominent biostatistician who cautioned FDA against the ill-fated approval of the lung cancer drug Iressa, joined the unusual letter-writing campaign urging the agency to refrain from approving the cancer vaccine Provenge.

Fleming, a professor of biostatistics at the University of Washington, regularly takes part in meetings of FDA advisory committees, and frequently consults for pharmaceutical and biotech companies pursuing drug approval.

In the case of Iressa five years ago, Fleming warned that giving the drug an accelerated approval despite the absence of convincing evidence

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In the Cancer Centers:

Al Benson Elected Chairman Of NCCN; UT, MDA Break Ground For Joint Research Facility

AL BENSON III, associate director for clinical investigations at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and professor of medicine at Northwestern's Feinberg School of Medicine, was elected chairman of the board of the National Comprehensive Cancer Network. Benson succeeds David Hohn, of Roswell Park Cancer Institute, who served as chairman for three years. Hohn remains a member of the NCCN executive committee and board. . . . **M. D. ANDERSON CANCER CENTER** and **University of Texas Health Science Center at Houston** broke ground April 10 for a joint research facility dedicated to developing novel agents and imaging technologies that detect heart disease, cancer and other illnesses at their earliest stages. The six-story Center for Advanced Biomedical Imaging Research, scheduled for completion in late 2009, is the fourth building to be constructed and one of six centers that will comprise M. D. Anderson's Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer. The McCombs Institute is located at the UT Research Park. GE Healthcare and the Texas Enterprise Fund also are collaborating on the center. . . . **M. D. ANDERSON** Cancer Center has opened the $9.2 million BrainSUITE, a high-tech surgical facility that features a wide-bore 1.5 Tesla intraoperative magnetic resonance imaging system and data management technologies. Used in the most complicated and life-threatening brain tumors, BrainSUITE would decrease undesirable side effects after surgery and a need

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Premature Approval Would Endanger Trial, Fleming Says

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of efficacy would lead to an erosion of the agency's standards (The Cancer Letter, Sept. 27, 2002; Nov. 8, 2002; May 9, 2003). Two years later, as clinical trials failed to show increased survival for Iressa, FDA placed that drug into a restricted access program, advising doctors to steer patients to a similar drug, Tarceva, which demonstrated a survival advantage (The Cancer Letter, June 24, 2005).

In the case of Provenge, Fleming wrote that the agent's benefit-to-risk profile remains unknown. "The current data are inadequate to make a reliable assessment," he wrote in the letter dated April 20.

The trials presented by the company don't provide substantial evidence of efficacy, as required by FDA regulations, Fleming wrote. "Rather, at best, these trials provide plausibility of efficacy that would justify the conduct of a confirmatory survival trial," he wrote.

Fleming becomes the third prominent oncology expert to sound alarm about the March 29 recommendation of the FDA Cellular, Tissue and Gene Therapies Advisory Committee to approve Provenge. FDA is expected to make a decision by May 15.

Two participants in that meeting, Howard Scher of Memorial Sloan-Kettering Cancer Center, and Maha Hussain of the University of Michigan, wrote letters warning FDA about weaknesses in the Provenge case (The Cancer Letter, April 13, April 27).

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Fleming wrote that he was approached by FDA to serve on the advisory committee that met on March 29, but declined because he had "limited interactions with the sponsor in the capacity of critiquing available data," he wrote in the letter.

In the company's registration trials, Provenge failed to meet the primary endpoint of delaying progression of disease, and the recommendation to approve was based on an unplanned analysis of one of the two studies, which showed an increase in survival.

According to critics, the Provenge case went to an advisory committee that lacked expertise to evaluate a cancer therapy. Moreover, the committee was poorly managed and its members misunderstood the wording of the "approval question." Critics warn that a premature approval would harm the company's conduct of a clinical trial designed to answer whether Provenge prolongs survival.

Toxicity is a problem, too, Fleming wrote.

"In clinical trials, Sipuleucel-T has nearly three-fold higher rate of cerebrovascular events (17/345 on Sipuleucel-T versus only 3/172 on placebo patients)," he wrote. "Furthermore, sample sizes in the completed trials are too small to rule out that other important risks exist. In the absence of established benefit, Sipuluecel-T may readily provide more harm than benefit."

The warnings from Scher, Hussain, and Fleming come at a time when FDA faces Congressional scrutiny of its handling of the antibiotic Ketek, the painkiller Vioxx, as well as its conduct in recent scandals over safety of the food supply.

A copy of Fleming's letter was obtained by The Cancer Letter, and its text appears below:

In a letter to FDA published in the April 13, 2007, Cancer Letter, Howard Scher of Memorial Sloan-Kettering Cancer Center presented valid and compelling arguments that FDA await the completion of an ongoing 500 patient (9902B) Phase 3 trial before deciding whether to approve Sipuluecel-T in prostate cancer patients. Reportedly, Scher felt motivated to write the letter after being kept awake the night following the March 29, 2007, FDA Cellular, Tissue and Gene Therapies Advisory Committee by the thought that if Sipuluecel-T were approved, patients may well forego more effective treatment alternatives. He also struggled with what he might communicate to patients about Sipuluecel-T's safety and efficacy when discussing therapeutic options with them.

I also was kept awake the night following the panel. I had been invited by FDA to be screened to serve

on the March 29, 2007, FDA Advisory Committee, but declined because I had had limited interactions with the sponsor in the capacity of critiquing available data. Now that the FDA Clinical and Statistical Briefing Documents are in the public domain, I am at liberty to express my own serious concerns about some of the significant flaws and limitations in the 9901 and 9902A clinical trials evaluating Sipuluecel-T in prostate cancer patients.

As noted by Scher, the 9901 and 9902A trials provide evidence that the effect of Sipuluecel-T on the pre-specified primary endpoint, progression-free survival, was 1-2 weeks, far less than the 15 week improvement targeted in the 9901 protocol. Therefore, not only did the trials fail to achieve statistically persuasive evidence for benefit, the estimates of effect on that measure indicate that clinically meaningful effects were not achieved. The 9901 trial also failed to establish benefit on measures of pain or other pre-specified secondary endpoints.

Major concerns arise when interpreting the survival data from the 9901 and 9902A trials. Overall survival was not a primary or secondary endpoint in 9901 (specifically, only a "descriptive" analysis of overall survival was to be performed), and also was not the pre-specified primary endpoint in 9902A. The concerns regarding the unreliability of post-hoc analyses are far more profound than that they simply provide a violation of statistical "rules", as one might believe from comments by the sponsor's consulting biostatistician, Brent Blumenstein, (see O'Neill RT, "Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance." *Controlled Clinical Trials* 18: 550-556, 1997). Estimates of effect of Sipuluecel-T on overall survival are biased and p-values reported from such analyses convey a false sense of reliability of that evidence. An explanation for this bias was presented in a recent article discussing why proper adjustments must be made when multiple testing arises over the course of the trial, (Fleming et. al., "Maintaining Confidentiality of Interim Data to Enhance Trial Integrity and Credibility." *Annals of Internal Medicine,* under review). That article states:

"*This bias (a form of "regression to the mean" bias) occurs because there is true signal and random noise in every estimate of treatment effect and, when many analyses are conducted, there is a tendency for those results that appear to be most favorable to be, at least in part, due to random overestimates of true effect".*

The risk for "regression to the mean" bias is very substantial in the reported estimates of the survival effect in the Sipuluecel-T trials. A clear illustration of this bias is provided by the recent experiences from the GIPF-001 and the GIPF-007 trials conducted by InterMune to evaluate Actimmune in patients with idiopathic pulmonary fibrosis (IPF). Like Dendreon, InterMune conducted exploratory analyses after their primary analysis of GIPF-001 established Actimmune did not provide a beneficial effect on the primary endpoint (relating to pulmonary function). When a survival advantage (2-sided p=0.004) was found in patients with mild to moderate impairment in lung function, the sponsor provided a press release indicating "The mortality benefit is very compelling and represents a major breakthrough in this difficult disease." Fortunately, the sponsor eventually recognized that their post-hoc analyses of overall survival did not provide reliable evidence of benefit and conducted GIPF-007, a confirmatory trial in 826 IPF patients having mild to moderate impairment in lung function, precisely the same population in which benefit was suggested by the post-hoc survival analysis of the GIPF-001 trial. The GIPF-007 trial (called INSPIRE) was recently terminated since, according to the sponsor's March 5, 2007 press release, "the DMC found the overall survival result crossed a predefined stopping boundary for lack of benefit of Actimmune relative to placebo" and where overall mortality was "14.5% in the Actimmune group as compared to 12.7% in the placebo group." Many parallels between this setting and Dendreon's evaluation of Sipuluecel-T strongly illustrate the need to await the results of Dendreon's 9902B trial.

Important concerns with the sponsor's covariate adjusted survival analyses of the 9902A trial also should be highlighted. The covariate analysis in 9902A that changed the two-sided from $p = 0.33$ to $p<0.05$ was invalid in that the reported covariate analysis not only provided the intended adjustment for potential confounding, but also inappropriately excluded 10% of study patients, where the patients excluded from the Sipuluecel-T arm had less favorable survival and those excluded from the placebo arm had more favorable survival, as illustrated by the FDA Statistical Briefing Document.

FDA should bring consistent scientific and ethical standards to the oversight and evaluation of clinical research much like a court of law should bring consistent standards to legal justice. FDA approval of Sipuluecel-T would set an unfortunate precedent for accepting lack of rigor, including giving undue credence to post-hoc analyses that very likely reflect misleading estimates of

efficacy due to regression to the mean-type bias, and to invalid analyses, such as the covariate adjustment of the 9902A trial that inappropriately excluded many patients who did not have missing outcome data. Furthermore, in light of FDA's recent consideration of DN101 in prostate cancer that is discussed in Scher's letter to FDA, how would one defend internal consistency at FDA if Sipuluecel-T were to be approved before availability of the 9902B trial? Like Dendreon, Novacea had obtained a two-sided $p<0.05$ in supportive analyses of survival in their ASCENT1 trial evaluating DN101 in 250 prostate cancer patients. Extensive available data from ASCENT1 and other investigations of vitamin D also suggest a potential additional beneficial mechanism of DN101 through reduction in the risk of thromboembolic events, (Venner, ASCO, 2006). Nevertheless, ODAC and FDA have recognized the need for Novacea to conduct a 900 patient trial to confirm effects of DN101 on overall survival in prostate cancer patients.

Issues of safety and ethics also deserve further discussion. In clinical trials, Sipuleucel-T has nearly three-fold higher rate of cerebrovascular events (17/345 on Sipuleucel-T versus only 3/172 on placebo patients). Furthermore, sample sizes in the completed trials are too small to rule out that other important risks exist. In the absence of established benefit, Sipuluecel-T may readily provide more harm than benefit. Hence, one should re-examine the reasoning by FDA Advisory Committee member, Francesco Marincola. He supported approval of Sipuluecel-T by stating:

"*Even if we make a mistake, even if the [therapy] is not this effective, there is so much to learn by starting to see patients being treated with this and see what else can be added. We should not underestimate the importance of this decision. I don't think it's just about the drug and what the drug does, but it's about opening a field, and the investigation on that field."*

One does not need marketing approval in order to continue clinical research studies evaluating Sipuluecel-T. Marincola's position is tantamount to advocating that regulatory approval be provided for interventions that have not been established to provide a favorable benefit-to-risk profile, in order to enable a sponsor to market potentially ineffective and even harmful products to patients, without a requirement for obtaining informed consent, in order to further investigation in the field. Such use of patients for research purposes without obtaining full informed consent is illegal as well as unethical. Such practice would be in direct violation of federal law, (45 CFR 46.116 and 21 CFR 601.25(d)(2) and (3)).

I do not know whether Sipuluecel-T in truth has a favorable benefit-to-risk profile. The current data are inadequate to make a reliable assessment. The 9901 and 9902A trials do not provide "substantial evidence of efficacy." Rather, at best, these trials provide plausibility of efficacy that would justify the conduct of a confirmatory survival trial. That trial (9902B) is well underway. If there is a pre-mature approval of Sipuluecel-T by FDA, how would the Agency proceed in the likely scenario that the 9902B trial, when completed, would indicate that Sipuluecel-T does not provide survival benefit, as recently happened in the similar situation with Actimmune in the IPF setting? Or what if a pre-mature approval of Sipuluecel-T by FDA compromises the ability or commitment of the sponsor to successfully complete the 9902B trial? The patient advocate on the Advisory Committee, Robert Samuels, stated;

"*I look upon (Sipuluecel-T) as an opportunity for me to make a choice. That's all the patients want: an opportunity to make a choice*."

As a fellow person living with prostate cancer, I strongly disagree with his statement that all patients want is a "choice." Patients want an "informed choice." How then would pre-mature approval of Sipuluecel-T that could diminish the likelihood of obtaining reliable results from the 9902B trial be in the best interests of prostate cancer patients?

[The letter was addressed to Jesse Goodman, director of the Center for Biologics Evaluation and Research; Janet Woodcock, deputy commissioner and chief medical officer; Karen Midthun, director of the Office of Vaccine Research and Review, Center for Biologics Evaluation and Research; Celia M.Witten, director of the CBER Office of Cellular, Tissue and Gene Therapies; Mary Foulkes, director of the CBER Office of Biostatistics and Epidemiology].

Cancer Screening:
State Initiatives Would Offer CT Scans For Lung Cancer

By Kirsten Boyd Goldberg

Bills introduced in the New York State Assembly would provide $10 million to establish a research program that would mandate use of a controversial protocol for computed tomography screening for early lung cancer.

The legislation would establish a "lung cancer early detection research pilot program" to provide grants to "not less than" 10 institutions in the state. The programs

would have to use the CT scanning protocol developed for the International Early Lung Cancer Action program. Results from the I-ELCAP study were published in the New England Journal of Medicine last October.

The pilot programs funded by the state would be required to "continue and enhance the research initiated" by I-ELCAP. "An entity must agree to adopt the protocol" used by I-ELCAP, and "shall agree to collect, transmit and preserve imaging data as required under the I-ELCAP protocol."

I-ELCAP is led by Claudia Henschke, professor of radiology at the Weill Medical College and chief of the division of chest imaging at New York Hospital-Cornell Medical Center. Henschke has said she believes that her study showed that CT scanning "saves lives." Her remarks have been disputed by other experts, who say that positive results from randomized trials would be required to show a survival benefit (The Cancer Letter, Nov. 3 and Nov. 26, 2006).

An analysis of three single-arm studies of CT screening for lung cancer, published in the March 7 issue of the Journal of the American Medical Association, found a three-fold increase in the number of new lung cancer cases and a ten-fold increase in surgeries, but no change in advanced lung cancers or deaths from the disease (The Cancer Letter, March 9).

The Lung Cancer Alliance, a patient advocacy group that supports widespread CT scanning for early detection of lung cancer, applauded the bills. "Today is a special day for New York's lung cancer community," LCA President Laurie Fenton Ambrose said in a statement dated April 27, the day the bills were introduced. "It is the first time ever that the legislature is addressing the importance of detecting lung cancer early."

Senate Bill 5369 was introduced by state Sen. Betty Little and Assembly Bill 7803 by Assemblywoman Aileen Gunther.

"We've seen the benefit of programs that increase awareness and encourage more screening for other forms of cancer, but we've not had this type of emphasis on lung cancer," Little said in the LCA statement. "Early detection saves lives. This legislation is a great step in the right direction and it will have tremendous benefits for many New Yorkers."

Similar legislation, pending in Connecticut and California, would establish research programs for early detection of lung cancer. In those states, the legislation doesn't mandate the use of a specific protocol.

In Connecticut, Senate Bill 1033, introduced by state Sen. Mary Ann Handley, would require the Department of Public Health to establish a pilot hospital-based lung cancer screening program by Oct. 1, 2008. According to an analysis prepared by the state Office of Fiscal Analysis, the cost of the program would vary depending on the number of people screened, the screening method used, and the recovery of costs from patients or third-party payers. "For comparison purposes, providing a CT scan for 1,000 high-risk individuals, and a follow-up diagnostic PET scan for those having abnormal initial screens would cost an estimated $1.25 million," the analysis said.

In a footnote, the analysis said: "It should be noted that while clinical trials assessing the potential benefits of using computed tomography (CT scanning) for lung cancer screening are underway, a consensus regarding whether to recommend its use has not been reached within the medical community."

In California, Senate bill 458 would provide $30 million for the University of California to establish "a comprehensive grant program to support research efforts related to early detection and treatment of lung cancer, as well as a program for the collection, assessment, and periodic publication of data pertinent to the research."

Under the bill, the university would establish a research program with a director and staff, a scientific advisory committee, and peer review panels modeled on the NIH review system.

NCI News:

AACR, FDA, NCI Collaborate On Biomarkers Guidelines

The American Association for Cancer Research, FDA, and NCI announced the formation of the AACR-FDA-NCI Cancer Biomarkers Collaborative to facilitate the use of validated biomarkers in clinical trials, evidence-based oncology, and cancer medicine.

The collaborative brings together leaders from academia, government, industry, and patient advocacy groups to develop a set of guidelines for integrating predictive biomarkers into clinical trials.

The guidelines will inform policies that are a part of the Critical Path Initiative, the FDA's effort to modernize the scientific process through which potential drugs, biological agents, or medical devices are transformed from discoveries into medical products.

"Major advances in cancer biology over the last quarter century have provided us with a better fundamental understanding of cancer in all of its forms, yet the translation of this knowledge into medical practice remains painstakingly slow," said AACR President

William Hait. "Therefore, we are joining forces with our partners to find new ways of exploring the use of biomarkers in cancer detection and treatment, without sacrificing high standards for safety and efficacy."

The collaborative evolved from a "think tank" session of academic, industry and government researchers and patient advocacy groups held at AACR headquarters in Philadelphia in last November. The collaborative will meet again in Philadelphia this summer to begin to develop guidelines for integrating predictive biomarkers into clinical trials.

"We believe that the CBC will address the mission of the AACR, the goals of the NCI, and the FDA's Critical Path Initiative and will make a major contribution to the success of a new generation of clinical trials and to progress in cancer drug development, " said James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis.

* * *

Guiseppe Giaconne was named director of medical oncology in NCI's Center for Cancer Research.

He has been head of the Department of Medical Oncology at the Free University Hospital in Amsterdam.

Giaconne worked at NCI 20 years ago, spending two years conducting basic research on lung cancer at the U.S. National Naval Medical Center.

Working with CCR Director Robert Wiltrout and CCR Clinical Director Lee Helman, Giaconne will emphasize forging closer ties among CCR's clinical branches. He also will continue his research in lung cancer, in the area of apoptosis. His recent work has demonstrated that the proteasome inhibitor bortezomib (Velcade) modulates an important molecular mechanism of apoptosis in lung cancer and may have promise in treating non-small-cell lung cancer in combination with other molecules, such as rTRAIL, that engage apoptosis through a different pathway.

Giaconne also will lead NCI's Lung Cancer Program, begun last year to improve the early detection and treatment of lung cancer.

* * *

President George W. Bush signed the National Breast and Cervical Cancer Early Detection Program Reauthorization Act (HR 1132) into law on April 20.

Introduced by Sen. Barbara Mikulski and Rep. Tammy Baldwin, the legislation authorizes the National Breast and Cervical Cancer Early Detection Program to provide breast and cervical cancer screenings to uninsured and underinsured women living at or below 250 percent of the federal poverty level.

Since its inception in 1991, the program has served more than 2.9 million women and provided more than 6.9 million screening examinations. The program is funded at approximately $200 million annually, and is administered by the Centers for Disease Control and Prevention in all 50 states and U.S. territories.

The program is expected to provide more than 700,000 screenings for low-income and underinsured women.

ACS Begins CPS-3, Seeks To Enroll Half A Million Adults

The American Cancer Society has begun a study that seeks to enroll 500,000 people in the U.S. to discover the genetic and environmental factors that cause and prevent cancer.

The Cancer Prevention Study 3 (CPS-3) aims to enroll a geographically and ethnically diverse group of half a million adults to advance the understanding of the lifestyle, environmental, and genetic factors that cause or prevent cancer. It is the latest in a series of large-scale ACS studies that began in the 1950s.

"There are no U.S. studies on the horizon positioned to take advantage of rapidly developing new knowledge and technologies over the coming decades, except CPS-3," said Eugenia Calle, managing director of analytic epidemiology at ACS, who is leading the study. "This type of study involves hundreds of thousands of people, with diverse backgrounds, followed for many years, with collection of biological specimens and assessments of dietary, lifestyle and environmental exposures. It also requires active follow-up to discover if and when study participants develop cancer."

Enrollment will take place at 64 of the 4,800 Relay For Life events this year, and continue at select Relay events through 2011. Relay For Life raises money for ACS research and programs.

CPS-3 will enroll men and women between the ages of 30 and 65 who have never been diagnosed with cancer, and who are willing to make a long-term commitment to the study. Enrollees spend 20 to 30 minutes at a Relay For Life event, where after consenting to participate they complete a brief study questionnaire, get a waist measurement, and provide a small blood sample.

For the next 20 or more years, ACS researchers will track CPS-3 participants through questionnaires mailed every few years, identifying and studying factors associated with cancer occurrence or prevention in the study cohort.

In Brief:

Vanderbilt Joins NCCN

(Continued from page 1)

for second surgeries. A part of a brain tumor program at M. D. Anderson, BrainSUITE would be most effective for surgically treating primary, pituitary and skull-based tumors as well as meningiomas and metastases to the brain in patients as young as two years old to the very elderly, said **Jeffrey Weinberg**, assistant professor, Department of Neurosurgery and medical director of BrainSUITE. Also, BrainSUITE surgical procedures will be broadcast live via the Internet for training and educational purposes. Monitors both inside and outside the operating room are available for viewing by physicians, students and trainees, nurses and visitors. BrainSUITE is manufactured by BrainLAB Inc., of Munich, Germany. . . . **VANDERBILT-INGRAM CANCER CENTER** has been named a member of the National Comprehensive Cancer Network, becoming the organization's 21st member. "Promising discoveries in cancer research are being made every day, but our work is not finished until those findings are translated into advances in patient care," said **Jennifer Pietenpol**, interim director at Vanderbilt-Ingram. "We are excited to join this group of cancer centers to help make that happen." Also at VICC, **Jordan Berlin** was named medical director of the Clinical Trials Shared Resource. Berlin is an associate professor of medicine at the center and oversees the work of the Scientific Review, Resource Allocation, and Data Safety and Monitoring committees. Berlin has been a faculty member and clinical director of the gastrointestinal oncology program since 1999. . . . **VAN ANDEL** Institute broke ground on a $170 million, 240,000 square-foot expansion to its biomedical research and education facility in Grand Rapids. Once complete in 2009, the expansion is expected to generate 550 jobs and support a $125 million operation of 800 researchers and administrative staff that would triple the Van Andel Research Institute laboratory space. The expanded facility will house the new Van Andel Institute Graduate School in cellular and molecular biology, which will matriculate its first students in the fall of 2007, said **George Vande Woude**, director, Van Andel Institute. . . . **FAZLUL SARKAR** of the Barbara Ann Karmanos Cancer Institute and Wayne State University was honored for contributions to cancer research by the Society of American Asian Scientists in Cancer Research at the American Association of Cancer Research meeting in Los Angeles. In conjunction with **Omer Kucuk**, medical oncologist and professor of internal medicine, Sarkar found that soy isoflavones may increase sensitivity to chemotherapy or radiation therapy, thus requiring less treatment. Clinical trials are underway at Karmanos, and is being opened at M. D. Anderson Cancer Center in collaboration with **James Abbruzzese**. . . . **CORRECTION:** In an item in this column on April 27, on the appointment of Timothy Ratliff as director of the Purdue Cancer Center, the center was incorrectly referred to as part of University of Iowa. The center is located at Perdue University. Ratliff will move from University of Iowa to Purdue.

In Brief:

Fauci Wins Kober Medal For Academic Medicine

ANTHONY FAUCI, director of the National Institute of Allergy and Infectious Diseases, received the 2007 George M. Kober Medal of the Association of American Physicians for his contributions to academic medicine. The medal recognizes leadership in the field of internal medicine. Fauci, known for his work in human immunoregulation, has developed therapies for the formerly fatal rheumatological diseases polyarteritis nodosa and Wegener's granulomatosis. With the recognition of AIDS 26 years ago, he switched the focus of his laboratory, and made contributions to the understanding of AIDS pathogenesis. Fauci was honored April 15 at the joint meeting of the American Society for Clinical Investigation and the AAP in Chicago. . . . **NICHOLAS PETRELLI**, medical director of the Helen H. Graham Cancer Center, Christiana Care, Newark, and professor of surgery at Thomas Jefferson University, took office as president of the Society of Surgical Oncology at its annual business meeting in Washington, D.C. He succeeds **Raphael Pollock**. **William Cance**, chairman of the Department of Surgery at University of Florida, was elected president-elect. Others elected to serve on the SSO Executive Council are: vice president, **Fabrizio Michelassi**, the Lewis Atterbury Stimson Professor of Surgery and chairman, Department of Surgery at Weill Medical College of Cornell University, and surgeon-in-chief at the New York Presbyterian Hospital-Weill Cornell Medical Center; secretary, **Monica Morrow**, the G. Willing Pepper Chair in Cancer Research and the chairman, Department of Surgery at Fox Chase Cancer Center; executive council member, **Kenneth Tanabe**, chief, Division of Surgical Oncology, Massachusetts General Hospital, associate professor of surgery, Harvard Medical School, and deputy clinical director of the MGH Cancer Center;

executive council member, **Douglas Tyler**, professor of surgery, chief of the Section of Surgical Oncology, and vice chairman, Department of Surgery, Duke University Medical Center; and councilor-at-large, **Martin Heslin**, professor of surgery, University of Alabama School of Medicine in Birmingham. . . . **AMERICAN CANCER SOCIETY** and the LUNGevity Foundation are contributing $370,000 to fund three research grants for lung cancer research. The successful applicants were: **Timothy Starr**, University of Minnesota, Twin Cities; **Steven Zielske**, University of Michigan; and **Dwight Seferos**, Northwestern University. . . . **GRIFFIN RODGERS**, acting director of the National Institute of Diabetes and Digestive and Kidney Diseases, was named director, effective April 1. Rodgers is known for the development of the first effective therapy for sickle cell anemia. He also is chief of the NIDDK Clinical and Molecular Hematology Branch, which he has headed since 1998. . . . **BARBARA ALVING**, acting director of of the National Center for Research Resources at NIH, was named director. Previously, she was deputy director at National Heart, Lung, and Blood Institute. . . . **NATIONAL INSTITUTE** of Biomedical Imaging and Bioengineering will hold "Changing the World's Healthcare through Biomedical Technologies," a commemorative scientific symposium on technological innovation in medicine celebrating the first five years of the Institute June 1 in the Lister Hill Center Auditorium at NIH. The first NIBIB Landmark Achievement Award will be made to Nobel Laureate **Paul Lauterbur**. Due to his recent death, his wife, **M. Joan Dawson**, will accept the award in his honor. The symposium is free and open to the public. Symposium information and agenda are available at www.NIBIBmeetings.org/Symposium.

Obituary:

ALBERT W. HILBERG, a former NCI pathologist who worked with George Papanicolaou, inventor of the Pap smear, to develop diagnostic techniques for cervical cancer in the 1940s, died March 26 after a stroke. He was 84 and lived in Silver Spring, Md.

Hilberg was born in Michigan City, Ind., and was a graduate of Elmhurst College in Illinois. He graduated from the Indiana University School of Medicine in 1946 and did postgraduate work at Cornell University and the University of Iowa.

From 1949 to 1951, Hilberg taught at the University of Iowa's medical school, followed by a one-year fellowship at the Hospital for Joint Diseases in New York.

In 1952, he joined the U.S. Public Health Service and was assigned as a pathologist to NCI, where he worked on the effects of radiation on cancer. He also worked during the 1950s as a pathology consultant to the Atomic Energy Commission and helped edit the Journal of the National Cancer Institute.

From 1962 to 1965, he was chief of the radiopathology division of the Armed Forces Institute of Pathology. He later conducted research at the National Center for Radiological Health and served on several advisory committees and councils. In the late 1960s, he was a member of the National Academy of Sciences' Atomic Bomb Casualty Commission, studying survivors of atomic bombs in Japan.

In 1968, Hilberg was named senior staff physician at the National Academy of Sciences' Division of Medical Sciences, where he edited reports on the effects of radiation. He retired in 1979. His wife Rosemary died in 2003.

Funding Opportunities:

PA-07-362: Exploratory Cancer Prevention Studies Involving Molecular Targets for Bioactive Food Components. R21 Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-362.html. Inquiries: Young Kim, 301-496-0126; yk47s@nih.gov.

PAR-07-368: Preapplication for the Molecular Libraries Probe Production Centers Network. X02. Letters of Intent Receipt Date: May 29. Application Submission/Receipt Date: June 28. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-368.html. Inquiries: Carson Loomis, 301-594-5936; LoomisC@mail.nih.gov.

PAR-07-358: National Institutes of Health Rapid Access to Interventional Development. X01. NIH Roadmap Initiative. Letters of Intent Submission Date: May 28, Aug. 14, Dec. 15; April 15, 2008, Aug. 15. Application Submission Date: June 28, Sept. 14; Jan. 15, 2008, May 15, Sept. 15. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-358.html. Inquiries: Tony Jackson (301-594-4660; nih-raid@mail.nih.gov.

PA-07-354: Bioengineering and Obesity. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-354.html.

PA-07-356: Clinical Cancer Therapy and Prevention Research. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-356.html. Inquiries: Heng Xie, 301-496-8866; xiehe@mail.nih.gov.

RFI NOT-CA-07-014: Childhood Cancer Biospecimens for the Childhood Cancer TARGET Initiative. Full text: http://www.grants.nih.gov/grants/guide/notice-files/NOT-CA-07-014.html. Inquiries: Malcolm Smith, 301-496-2522; smithm@ctep.nci.nih.gov.

PAR-07-352: Bioengineering Research Partnerships. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-352.html. Inquiries: Albert Lee, 301-451-4781; alee@mail.nih.gov.

THE CANCER LETTER

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Business & Regulatory Report

Clinical Trials:

Consortium, Nereus Begin Phase I Trial Of New Proteasome Inhibitor For Myeloma

Multiple Myeloma Research Consortium and **Nereus Pharmaceuticals Inc**., of Norwalk, Conn., said they have begun a multi-center phase I trial of the Nereus second generation proteasome inhibitor, NPI-0052, for multiple myeloma.

The trial will evaluate the safety, tolerability, pharmacokinetic profile, pharmacodynamics and efficacy of the drug in a single-agent, dose escalation study for relapsed or relapsed/refractory multiple myeloma, the groups said.

Enrollment has begun at MMRC member institutions including Dana-Farber Cancer Institute under Paul Richardson, Ohio State University under Craig Hofmeister, Roswell Park Cancer Institute under Asher Chanan-Khan,

(Continued to page 2)

Deals & Collaborations:

Small-Molecule Developer Eisai Buys Morphotek To Expand Into Biologics

Eisai Corp. of North America, a wholly-owned subsidiary of Tokyo-based Eisai Co., Ltd., said it has completed its acquisition of **Morphotek Inc.**, of Exton, Penn., for $325 million.

Morphotek develops therapeutic monoclonal antibodies through its proprietary human antibody technologies, Human Morphodoma and Libradoma. Two of its programs are in early stage clinical trials for ovarian cancer and pancreatic cancer, with others in preclinical development, the company said.

Eisai, which has research laboratories in Japan, Europe and the U.S., has a global oncology research program for discovering small molecule anti-cancer agents and, with this acquisition, expands its capabilities into the biologic therapeutics field, the company said.

* * *

Rosetta Genomics Ltd. (NASDQ: ROSG) of Rehovot, Israel, said it has partnered with **NYU Medical Center** to develop early detection diagnostic products for lung cancers and mesothelioma.

The test will utilize the Rosetta Genomics proprietary protocol to extract microRNAs from a blood draw, the company said.

"A test that will be able to detect cancer at an early stage using a simple blood draw will have far reaching implications on the fight against cancer," said Harvey Pass, professor and chief, Division of Thoracic Surgery

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Myeloma Consortium, Nereus, Begin Trial Of New Agent

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and University of Chicago under Todd Zimmerman, the groups said.

The open label study treatment would consist of escalating, once-weekly intravenous doses of NPI-0052, to determine the safety profile. Secondary objectives will include response, pharmacokinetic and pharmacodynamic analyses, the groups said.

"The study will allow us to evaluate a new proteasome inhibitor, which preclinical studies suggest may have advantages compared to available therapies," said Paul Richardson, clinical director of the Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, who enrolled the first patient. Richardson and his colleagues Kenneth Anderson, director of the Jerome Lipper Multiple Myeloma Center and Dharminder Chauhan, have been investigating NPI-0052 in laboratory models of multiple myeloma and other cancers.

NPI-0052 was discovered from a marine actinomycete (Salinispora tropica), the groups said. The compound is an inhibitor of human proteasomes. Preclinical studies indicate the agent is active against models of common cancers, including solid tumors, lymphomas and myeloma, including myeloma cells from patients who are resistant to Velcade, steroid therapy, Thalomid (thalidomide, Celgene Corp.) and Revlimid(lenalidomide, Celgene Corp.). A clinical trial evaluating NPI-0052 in solid tumors and lymphomas (NPI-0052-100) has been ongoing since 2006, the groups said.

* * *

Bionovo Inc. of Emeryville, Calif., said it has initiated a multi-center phase I/II trial of BZL101 in advanced breast cancer.

The 80 volunteers would have measurable breast cancer and have had no more than two prior third-line cytotoxic treatments, the company said.

The trial will be open at 10 sites, including M. D. Anderson Cancer Center, University of Texas Southwestern Medical Center, University of Chicago, Duke University, Ohio State University Comprehensive Cancer Center, Memorial Cancer Institute, Montefiore Medical Center, Breastlink/Barbara K. Robinson Breast Cancer Research Program, comprehensive cancer centers in the Aptium Oncology Research Network, and Cancer Research Network Inc, the company said.

BZL101, an oral drug, induces cancer cell apoptosis while leaving normal cells unaffected, the company said.

* * *

Chroma Therapeutics Ltd. of Oxford, U.K., said its oral, once-daily experimental cancer therapy CHR-2797 has entered a phase II trial for refractory acute myeloid leukemia in the elderly.

Chroma said it completed a dose- ascending phase I study in hematological malignancies treated for up to three months with CHR-2797.

Also, the therapy is being evaluated for solid tumors in two phase I studies as a monotherapy and in combination with chemotherapy, the company said.

Inhibition of aminopeptidases has been shown to halt cell growth or cause apoptosis in cancer cell lines, the company said. Conversely, normal cells have been shown to be less sensitive to aminopeptidase inhibition. CHR- 2797, an inhibitor of aminopeptidases, has demonstrated preclinical efficacy as monotherapy and also has been shown to synergise with cancer therapies in cancer cells.

CHR- 2797 was originally licensed from Vernalis plc, the company said.

* * *

Coley Pharmaceutical Group Inc. (NASDAQ: COLY) of Wellesley, Mass., said **Pfizer Inc.** (NYSE: PFE) has completed target enrollment in two phase III trials of the Toll-like receptor 9 agonist drug candidate, PF-3512676, for advanced non-small cell lung cancer.

The combined study enrollment total 1,600 patients

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for stage IIIB/IV of the disease, the company said.

Coley and Pfizer said they entered into an exclusive global license agreement in 2005 to develop, manufacture and commercialize the Coley drug candidate for the treatment, control and prevention of cancer. In 2005, Pfizer began enrollment in the two phase III trials for advanced NSCLC. Both trials are being conducted under the Special Protocol Assessment procedure of FDA.

Each of the randomized, controlled trials is assessing the efficacy and safety of PF-3512676 administered in combination with standard-of-care chemotherapy as first-line treatment in locally advanced or metastatic NSCLC as compared to chemotherapy alone, the company said. The primary endpoint for each trial is overall survival. The first trial compares gemcitabine/cisplatin with and without PF-3512676, with target enrollment of 800 achieved in December 2006. The second trial compares carboplatin/paclitaxel chemotherapy with and without PF-3512676, with the target enrollment of 800 achieved in April 2007.

* * *

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 NCI-sponsored 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 previous bortezomib-containing regimen.

James Berenson, medical and scientific director at the Institute for Myeloma and Bone Cancer Research, is principal investigator of the 35-patient trial.

As the phase II study of belinostat and bortezomib begins, CuraGen said it will close enrollment in the ongoing phase Ib study of this combination in multiple myeloma.

* * *

Genta Inc. (NASDAQ: GNTA) of Berkeley Heights, N.J., said it would initiate a randomized controlled phase III trial of Genasense (oblimersen sodium) in advanced melanoma.

The company said the 300-patient study would target patients using a biomarker (serum lactate dehydrogenase) that identified who derived maximal benefit in a preceding trial of Genasense, including increases in overall and progression-free survival.

Genasense in melanoma has been designated an Orphan Drug in Australia and the U.S., and the drug has Fast-Track designation in the U.S, the company said.

"As the lead investigative site in the prior trial, we saw results that exceeded those from any other randomized study for advanced melanoma," commented Agop Bedikian, professor of medicine, M.D. Anderson Cancer Center.

Genasense blocks the production of Bcl-2, a protein that causes resistance to cancer treatment, the company said. By knocking down Bcl-2 in cancer cells, Genasense may enhance the effectiveness of chemotherapy in advanced melanoma. In its initial trial, Genta said it performed the largest randomized controlled trial ever been conducted for the disease.

In that trial, 771 patients from 139 sites in 9 countries were randomly assigned to receive chemotherapy with dacarbazine alone or in combination with Genasense, the company said. The paper includes data from a prospectively defined analysis that evaluated 24-months of minimum follow-up on all patients. Unless otherwise noted, the results were based on an intent-to- treat analysis: Endpoint Genasense/DTIC DTIC P; Overall response13.5 percent 7.5 percent 0.007; Complete response 2.8 percent 0.8 percent 0.03; Durable response 7.3 percent 3.6 percent 0.03; Pression-free survival, median 2.6 mos. 1.6 mos. 0.0007; Overall survival, median 9.0 mos. 7.8 mos. 0.077.

Prior to randomization, patients were prospectively stratified according to certain risk factors, including elevated blood levels of an enzyme known as LDH - a factor that previous clinical studies have shown is strongly associated with poor outcome. The final analysis has shown that LDH was the sole stratification factor significantly associated with a treatment interaction. When this treatment effect was evaluated, the efficacy of Genasense was significantly superior for all major efficacy outcomes in patients who had normal LDH at baseline, a group that comprised approximately two-thirds of patients in the trial (N=508). In this group, the following efficacy results were observed: Endpoint Genasense/DTIC DTIC P. Overall response 17.2 percent 9.3 percent .009; Complete response 3.4 percent 0.8 percent 0.04; Durable response 9.6 percent 4.0 percent 0.014; Progression-free survival, median 3.1 mos. 1.6 mos. 0.0007; Overall survival, median 1.4 mos. 9.7 mos. 0.018,

With regard to safety, the most frequent serious adverse events that occurred in greater than or equal to 5 percent were fever and disease progression (6.2 percent vs. 2.8 percent, and 5.1 percent vs. 4.7 percent, respectively, for Genasense/DTIC compared with DTIC alone). The most frequent Grade 3 or 4 adverse events

that occurred in greater than or equal to 5 percent were neutropenia (21.3 percent vs. 12.5 percent), thrombocytopenia (15.9 percent vs. 6.4 percent), leukopenia (7.5 percent vs. 3.9 percent), anemia (7.3 percent vs. 4.7 percent), and nausea (6.7 percent vs. 2.5 percent). Although there was an increase in discontinuations due to adverse events in the Genasense arm (19 percent vs. 11 percent), there was no difference in the number of fatal, treatment-emergent adverse events.

* * *

Oncolytics Biotech Inc. (TSX: ONC, NASDAQ: ONCY) of Calgary said it is proceeding with a phase II trial to evaluate the intravenous administration of Reolysin in sarcomas that have metastasized to the lung.

The principal investigators are Glenn Kroog of the Montefiore Medical Center/Albert Einstein College of Medicine; Laurence Baker of the University of Michigan Comprehensive Cancer Center; and Monica Mita of the Cancer Therapy and Research Center, Institute for Drug Development in San Antonio, the company said.

The REO 014 trial is a phase II, open-label, single agent 52-patient study that would measure tumor responses and duration of response, and describe evidence of antitumor activity of intravenous, multiple dose Reolysin in bone and soft tissue sarcomas metastatic to the lung.

Reolysin will be given intravenously at a dose of 3x1010 TCID50 for five consecutive days, the company said. Additional five-day cycles of therapy may be given every four weeks for a maximum of eight cycles.

Eligible conditions consist of a bone or soft tissue sarcoma metastatic to the lung deemed to be unresponsive to, or untreatable by standard therapies, including osteosarcoma, Ewing sarcoma family tumors, malignant fibrous histiocytoma, synovial sarcoma, fibrosarcoma and leiomyosarcoma, the company said.

* * *

Semafore Pharmaceuticals Inc. of Indianapolis said it has initiated a phase I trial of its lead PI3 kinase inhibitor, SF1126, for solid tumors.

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

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

Preclinical data on SF1126 demonstrates it to be an inhibitor of the biological processes in tumor growth and dissemination, the company said. The agent is a small molecule conjugate containing a pan-PI3K inhibitor that selectively inhibits all PI3K class IA isoforms and other members of the PI3K superfamily, including DNA-PK and mTOR. Preclinically, SF1126 has been shown to inhibit angiogenesis and cellular proliferation, induce apoptosis, block pro-survival signals and produce synergistic anti-tumor effects in combination with chemotherapy, the company said. The inhibitor has demonstrated in vivo activity in preclinical mouse cancer models, including prostate, breast, ovarian, lung, multiple myeloma, brain and other cancers.

* * *

SuperGen Inc. (NASDAQ: SUPG) of Dublin, Calif., said FDA has cleared MP470, an oral multi-targeted tyrosine kinase inhibitor, for a phase I trial.

The accelerated titration dose-escalation trial will assess the safety and tolerability of MP470 and determine the maximum tolerated dose, the company said. Pharmacokinetic and biomarkers data will also be collected and assessed to design follow-on clinical studies of MP470 as a single agent and in combination treatment modalities. Up to 30 patients with advanced stage solid tumor cancers will be enrolled.

The study protocol is undergoing final approval by Institutional Review Boards at two study centers in the U.S., the company said.

The receipt of FDA clearance for the drug triggers a milestone payment to the previous Montigen shareholders of $10 million dollars to be paid in SuperGen common stock, the company said.

* * *

Threshold Pharmaceuticals Inc. (NASDAQ: THLD) of Redwood City, Calif., said it has begun enrollment in a phase II trial evaluating the efficacy and safety of glufosfamide for previously treated, advanced, soft tissue sarcoma.

The twenty-two patient, open-label, study would consist of a treatment regimen of 5000 mg/m2 of glufosfamide every three weeks for up to six cycles, the company said.

The primary efficacy endpoint is objective response rate, the company said. The secondary endpoints include duration of response, progression- free survival, overall survival and various safety parameters.

Tumor response will be evaluated at baseline

and every six weeks. One exploratory objective is to evaluate the biological effects of glufosfamide on metabolic profile as determined by FDG-PET, or fluorodeoxyglucose-positron emission tomography. The role of the procedure is to detect metabolically active malignant lesions and to monitor their metabolic response to glufosfamide therapy. An additional exploratory objective is to correlate efficacy endpoints with expression of tumor-associated glucose transporter proteins, the company said.

* * *

VioQuest Pharmaceuticals of Basking Ridge, N.J., said it would proceed with phase II trials for the Akt inhibitor VQD-002.

Ongoing trials in refractory leukemia and solid tumors are expected to complete phase I enrollment in June, the company said.

VQD-002 is a direct inhibitor of activation of Akt, a serine-threonine kinase that is over expressed and or hyperactivated in resistant and refractory tumors as well as in aggressive hematologic malignancies, the company said.

Phase I/IIa trials are ongoing at the MD Anderson Cancer Center, and at H. Lee Moffitt Cancer Center.

Clinical trial objectives in hematologic malignancies conducted at MD Anderson and H. Lee Moffitt Cancer Center, include the evaluation of the VQD-002 safety profile, pharmacokinetic and pharmacodynamic parameters, and the effects the drug has on Akt modulation, the company said. In the leukemia trial, reductions in malignant cells have been seen following initial therapy and improvements have been observed in parameters of bone marrow function, the company said.

Objectives of the trial in solid tumors at H. Lee Moffitt Cancer Center, include the evaluation of the VQD-002 safety profile, pharmacokinetic and pharmacodynamic parameters, and the effects VQD-002 has on Akt modulation. Eleven have been enrolled in the phase I portion of the ongoing solid tumor trial. Thos who are refractory to prior standard therapy and who were screened and selected for study based on the high level of Akt expression in their tumors, have shown stable disease on study.

"It is important to note that our Akt activation inhibitor not only blocks the function of all three isoforms of Akt, but also does not result in feedback upregulation of P-Akt levels as observed in other Akt inhibitors, said Said Sebti, director of drug discovery program, Moffitt Cancer Center. "This is a selective, specific, and potent inhibitor of Akt activation."

Deals & Collaborations:

Rosetta, NYU To Develop Early Detection Products

(Continued from page 1)

and Thoracic Oncology at NYU Medical Center. "MicroRNAs have been shown to hold great potential as effective biomarkers for various cancers."

MicroRNAs (miRNAs) are a recently discovered, naturally occurring form of RNAi, the company said. The small RNAs act as protein regulators and could form the basis for a new class of diagnostics and therapeutics.

Product Approvals & Applications:

EU Committee Negative On Genasense For Melanoma

Genta Inc. (NASDAQ: GNTA) of Berkeley Heights, N.J., said it has received notice from the European Medicines Agency that the Committee for Medicinal Products for Human Use has adopted a negative opinion for the marketing authorization application for Genasense (oblimersen) for melanoma.

The MAA proposes using Genasense plus dacarbazine for advanced melanoma, the company said.

Genta said it has been accorded the option of requesting re-examination of the opinion, would promptly file the request, which will delay any formal action by the EU Commission pending its outcome. Pursuant to the request, Genta said it would submit the Detailed Grounds for Re-Examination document within 60 days, and request review of the outstanding issues by the Oncology Scientific Advisory Group.

During the re-examination, we would resolve and discuss outstanding issues with the OSAG, and expect a final opinion could be rendered within 4 to 6 months, the company said. Meanwhile, a randomized trial of the Genasense/dacarbazine combination will commence, and we have made provisions for the supply of Genasense via compassionate use and named-patient distribution programs for non protocol candidates.

In a separate action, Genta said it would file a formal complaint and request for correction of information with FDA under the Federal Data Quality Act. The complaint will challenge as erroneous a key statistical analysis of the Genta data on Genasense for melanoma used by FDA at the Oncology Drug Advisory Committee meeting on May 3, 2004. That analysis sought to discredit the finding that Genasense yielded

a statistically significant increase in progression-free survival. At that meeting, ODAC voted unanimously that PFS was an endpoint that would support full approval in the absence of a survival improvement in patients with advanced melanoma. The company said it will seek a formal public acknowledgement of the error, removal of the analysis from the FDA website (with a note that the previous analysis was in error), and revision of the transcript.

"We were unable to verify the integrity of this highly non-standard analysis in advance of the ODAC meeting," said Loretta Itri, president, pharmaceutical development at Genta. "Since then, we have been able to test the statistical model, and we show that the analysis was erroneous. We are concerned about the perpetuation of the error and its impact on public perception of our results, and we are formally requesting redress."

* * *

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

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

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

* * *

Exelixis Inc. (NASDAQ: EXEL) of South San Francisco said it has submitted an IND to FDA for XL765.

The compound is a selective orally available small molecule inhibitor of phosphoinositide-3 kinase activity, which is activated in tumors and promotes cell growth, survival and resistance to chemotherapy and radiotherapy. The agent also inhibits mammalian target of rapamycin, which also is activated in tumors and tumor cell growth, the company said.

In another development, Exelixis said its has received FDA permission to initiate a phase I trial for XL999 in non-small cell lung cancer.

The trial would evaluate the agent in NSCLC that has failed at least one therapy, the company said. The study would have a dose-escalation format starting at 0.4 mg/kg dosed weely, while monitoring for cardiovascular events.

"In the previous phase II trial of XL999 in NSCLC patients, nine patients participated, of whom two had partial responses and one had prolonged stable disease," said George Scangos, president and CEO of Exelixis. "We believe that the data warrant further evaluation of XL999 in this patient population, and we expect to begin enrolling patients in the new clinical trial this summer."

XL999, an inhibitor of receptor tyrosine kinases implicated in the development and maintenance of tumor vasculature and in the proliferation of tumor cells, inhibits the FGFR, VEGFR and PDGFR RTKs and also is a inhibitor of FLT3, a driver of leukemia cell proliferation in acute myelogenous leukemia, the company said.

* * *

Genzyme Corp. (NASDAQ: GENZ) of Cambridge, Mass., and **Bayer HealthCare** of Berlin said they have submitted to FDA a supplemental biologics license application for Campath (alemtuzumab) to expand the product label to include first-line treatment of B-cell chronic lymphocytic leukemia.

Campath is approved for B-CLL when prior alkylating agent treatment has occurred and where fludarabine therapy has failed, the companies said. Genzyme said it would make a similar filing in Europe within the next couple of weeks to support this label expansion.

The product is marketed outside the U.S. as MabCampath by Bayer Schering Pharma AG, Germany and in the U.S. by its affiliate, Bayer HealthCare Pharmaceuticals, as Campath.

The international, randomized, controlled phase III study was conducted to satisfy a post-approval commitment to FDA to demonstrate clinical benefit of Campath in B-CLL, and to complete the conversion to regular approval, the companies said. This confirmatory study was completed in accordance with timelines committed to FDA by Genzyme.

* * *

GlaxoSmithKline (NYSE: GSK) of Philadelphia said it has submitted a Biologics License Application to FDA for Cervarix (human papillomavirus vaccine,

AS04 adjuvant-adsorbed), its cervical cancer candidate vaccine.

The vaccine would be indicated for cervical cancer and precancerous lesions associated with human papillomavirus types, the company said. For the candidate vaccine, GSK said it selected a proprietary adjuvant system called AS04, to enhance immune response and increase duration of protection.

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

AS04 contains aluminum hydroxide and monophosphoryl lipid A. Published data have shown that the GSK cervical cancer candidate vaccine formulated with AS04 provides a stronger and longer lasting immune response compared to the same GSK vaccine composition formulated with a traditional aluminum hydroxide adjuvant, the company said.

* * *

GPC Biotech AG (Frankfurt Stock Exchange: GPC; TecDAX index; Nasdaq: GPCB) of Marinsried and Munch said FDA has accepted its NDA for satraplatin in combination with prednisone for hormone-refractory prostate cancer where chemotherapy has failed.

FDA also has granted the NDA priority review status, the company said.

Satraplatin, an investigational drug, is a member of the platinum family of compound used as part of chemotherapy treatments.

* * *

Indevus Pharmaceuticals Inc. (NASDAQ: IDEV) of Lexington, Mass., said it has submitted a Supplemental New Drug Application to FDA seeking approval to reintroduce Valstar for bladder cancer in the U.S.

The drug was originally approved by FDA in 1998 and is on the FDA Drug Shortages List, the company said.

The agent was removed from the market in 2002 due to manufacturing issues involving the stability of an excipient, the company said. The company said the stability issues have been resolved through the development of an improved manufacturing process.

Valstar is a sterile solution for intravesical instillation of valrubicin, a chemotherapeutic anthracycline derivative, and is the only product approved by FDA for therapy of Bacillus Calmette-Guerin- refractory carcinoma in situ of the urinary bladder, the company said. It is used in BCG-refractory bladder cancer when surgical bladder removal is not an option.

* * *

Novartis Oncology said Gleevec (imatinib mesylate) tablets have been approved as effective therapy for advanced metastatic or inoperable Kit-positive gastrointestinal stromal tumors.

A 600-patient study sponsored by NCI, was led by the American College of Surgeons Oncology Group, the company said. Novartis supplied Gleevec for the study, and also provided partial funding under a Cooperative Research and Development Agreement with NCI to support the clinical development of the drug.

Interim study analysis showed no recurrence of cancer in 97 percent given Gleevec for a year after surgery to remove tumors, compared to 83 percent of those who underwent surgery but received a placebo.

Investigators made the results public because the study had met its primary endpoint in terms of rate of recurrence-free survival, the company said.

Gleevec has already been confirmed as an effective therapy in its approved use for advanced metastatic or unresectable Kit- positive GIST. In the study, randomization was to one of two treatment arms. One group received Gleevec at a dose of 400 milligrams per day for one year, while the second group received placebo for one year. According to the study design, patients who developed a recurrence of their cancer while on a study therapy were unblinded to their treatment assignment. Those receiving placebo subsequently received Gleevec, while those already given Gleevec continued with the therapy but at a higher dose, the company said.

Investigators reported that Gleevec therapy was well tolerated, with side effects similar to those observed in other clinical trials with the drug. The side effects included nausea, diarrhea and swelling.

* * *

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 company said. The second designation is for second-line treatment of mCRC to improve progression-free survival and overall survival when added to 5-FU-based chemotherapy regimens.

The phase II trial of rNAPc2 for mCRC, would

determine the safety and efficacy of twice-weekly, subcutaneous rNAPc2 for the second-line treatment of mCRC in combination with select 5-FU-based chemotherapy regimens as its primary objectives, the company said.

Recombinant nematode anticoagulant protein c2 interferes with the tissue factor/factor VIIa/factor Xa protease complex, the company said. The complex activates the cellular signaling events leading to metastasis and angiogenesis in a variety of cancers.

In addition, rNAPc2 may have a anticoagulant effect resulting from its ability to prevent thrombin generation by blocking the factor VIIa/tissue factor protease complex, the company said.

* * *

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

The study, Q2 2007, would evaluate the pharmacokinetics of the antibody in academic medical centers in Israel, the company said.

Pain Therapeutics said its net cash requirements for 2007 would be $10 million, inclusive of program expenses related to metastatic melanoma. In December, its cash, cash requirements and marketable securities were $204.4 million.

* * *

Pharmacyclics Inc. (NASDAQ: PCYC) of Sunnyvale, Calif., said it has filed an NDA for Xcytrin (motexafin gadolinium) Injection with FDA.

The Prescription Drug User Fee Act date for completion of review by FDA is December 31, 2007, the company said. The company said it is seeking approval to market the drug for non-small cell lung cancer brain metastases.

In December 2006, the company said it submitted an NDA to the FDA Office of Oncology Drug Products requesting marketing clearance for Xcytrin in combination with radiation therapy for brain metastases from NSCLC. In February 2007, it received a refuse to file letter from the FDA citing failure to demonstrate statistically significant differences between treatment arms in the primary endpoint of the pivotal study to support approval. The company then filed the NDA over protest, a procedure permitted by regulation that allows sponsors to have their NDA filed and reviewed when there is disagreement over the acceptability of the NDA.

"After consultation with investigators, experts and patient groups, we decided to have our NDA filed over protest because clinical evaluation of Xcytrin for the brain metastases indication required use of a novel but clinically meaningful endpoint, which should be carefully reviewed by the agency, said Richard Miller, president and CEO of Pharmacyclics. Moreover, there are other examples of NDAs for oncology drugs that have been accepted for filing without meeting the primary endpoint with statistical significance. In some cases this has led to product approvals, particularly in cases where the unmet need is great, the drug is well tolerated and there are few if any other treatment options available."

The submission was based on the results of two randomized trials and an integrated analysis of both trials, the company said. The trials utilized a neurologic progression endpoint designed with FDA to assess the clinical benefit of treatment. The first trial, which included 251 NSCLC patients and 150 patients with brain metastases from other solid tumors, did not show a statistically significant benefit overall but did show a clinically and statistically significant improvement in time to neurologic progression in the subset with NSCLC, the company said.

The follow up 554-patient SMART trial showed a 5.4 month improvement in time to neurologic progression, the primary pre-specified endpoint, with a median time to neurologic progression of 15.4 months for Xcytrin compared to 10.0 months for the control (with a p-value equal to 0.12), the company said. While not statistically significant, this represented a very strong treatment effect in a disease for which nothing has worked beyond radiation therapy.

An integrated analysis of the 805 lung cancer patients in the two large phase III studies demonstrated a statistically significant 6.4 month improvement in time to neurologic progression for patients receiving Xcytrin plus whole brain radiation therapy compared to receiving radiation alone, the company said. The median time to neurologic progression was 15.4 months compared to 9.0 months, respectively, with a p-value equal to 0.016. Secondary endpoints also showed a benefit for Xcytrin plus whole brain radiation compared to radiation alone: time to neurologic progression as determined by investigators, $P = 0.015$ and time to neurocognitive progression, $P = 0.02$. In addition to the consistent treatment effect, Xcytrin plus radiation therapy was generally well tolerated across all studies, the company said.

Xcytrin is a redox-active drug that disrupts redox-dependent pathways in cells and inhibits oxidative stress

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