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FDA Advisors Discuss Establishment Of Standards For Showing Equivalence

In addition to recommending approval of three drugs, the FDA Oncologic Drugs Advisory Committee last week held a discussion of standards for demonstrating equivalence of cancer therapies.

Such discussions appear to be part of an effort by FDA to use ODAC as a forum for discussion of drug approval standards.

Last summer, the committee was asked to consider the use of time to progression—as opposed to survival—as a basis for approval of breast cancer therapies (**The Cancer Letter**, June 18). Next February, ODAC is expected to convene a subcommittee to examine the question of

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In Brief:

Hood To Form Institute For Systems Biology, To Unite Biologists, High-Tech Industry

LEROY HOOD, the William Gates III Professor of Biomedical Sciences at University of Washington, will leave the university to form the Institute for Systems Biology, an independent, non-profit organization to be based in Seattle. The Institute will provide a means of collaboration between academic and private-sector interests, particularly high-tech industries, to advance the understanding of complex biological systems, Hood said earlier this week. "Our goal is to establish a unique and powerful Institute to achieve pioneering discoveries within the field of systems biology that can greatly advance preventive medicine," Hood said. "The Institute will unite biologists with specialists from other fields to unravel complex biological codes. By doing so, we can create the tools needed to analyze an individual's genes, identify disease predisposition and use preventive medicines to block the onset of diseases such as cancer, heart disease and auto-immune diseases." The Institute's Board of Trustees includes **George Rathman**, former CEO of Amgen and ICOS, and **Roger Perlmutter**, executive vice president of Merck Research Laboratories. The first to join the Institute's Scientific Advisory Board are **Lee Hartwell**, director of the Fred Hutchinson Cancer Research Center, and **Sydney Brenner**, a pioneer in molecular biology and genetics. **Louis Coffman** will serve as the Institute's acting chief operating officer. The Institute will commence operations next month. An anonymous donor provided $5 million to fund the Institute's initial efforts. Collaborative agreements are in place or being negotiated with eight companies. . . . **JONATHAN SIMONS** was named director of Winship Cancer Institute of Emory University effective Feb. 1. Known for his work in translational research,

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ODAC Recommends Approval Of Celebrex For FAP Patients

(Continued from page 1)

measuring the quality of life.

At least in principle, such theoretical discussions can offer guidance to sponsors and make the agency more transparent without issuing industry guidelines or setting policy.

At its meeting, ODAC also:

—Recommended approval of Celebrex (celecocib), a Cox-2 inhibitor, for the reduction and regression of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients. The sponsor, G.D. Searle & Co., a unit of Monsanto Co., sought accelerated approval, which is usually contingent on the sponsor's conduct of studies.

The committee offered no definitive advice on the trials that should be done. The application is unusual because it does not directly mention caner, but rather a "reduction and regression" of pre-cancerous polyps in a population highly susceptible to colorectal cancer.

—Recommended full approval for Taxotere (docetaxel) for locally advanced or metastatic non-small-cell lung cancer after failure of prior chemotherapy. The drug is sponsored by Rhone-Poulenc Rorer.

—Recommended full approval for Targretin (bexarotene) for cutaneous manifestations in early stage cutaneous T-cell lymphoma patients who have not tolerated other therapies and patients with refractory or persistent late-stage CTCL. The committee did not recommend approval for early stage disease. The drug is sponsored by Ligand Pharmaceuticals Inc.

"Ayesian Tatistics" or Humor for Statisticians

The issue of equivalence is likely to come into play occasionally, usually when sponsors design trials to demonstrate superiority, and failing to do so, claim the "non-inferiority" of an active control as the next best thing.

Though such claims don't always sail through ODAC, the standards for demonstration of equivalence to an active control are likely to become increasingly important as ODAC considers cancer risk reduction claims as well as equivalence claims from companies seeking approval for less toxic therapies than current standards.

The presentation last week is likely to send drug company executives and their biostatistical consultants to the June 1999 issue of the journal Biometrics, where ODAC member Richard Simon described the perils inherent in demonstrating equivalence of therapies.

Simon, chief of the NCI Biometric Research Branch, was not speaking for FDA. The paper reflects 30 years of research, which began with his involvement in NCI sponsored comparisons of mastectomy and lumpectomy and evaluation of other conservative treatments, he said to **The Cancer Letter**.

Still, FDA-watchers would do well to notice that Simon's presentation was preceded by similar remarks by Robert Temple, Director of the FDA Office of Drug Evaluation I.

In the paper, Simon attempted to evaluate Bayesian methods through application to clinical trials data, rather than through theoretical arguments. Hence, the joke on Simon's slides: "aysian tatistics," which is what you get when you take the B.S. out of Bayesian statistics.

The message of Simon's presentation was far from amusing. To demonstrate that a new therapy is equivalent to the control treatment, it is essential to consider all the data pertaining to the control treatment. In other words, by approving drugs on the basis of equivalence, regulators run the risk of flooding the market with a series of drugs of uncertain efficacy.

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"I think what's important is to look at the body of evidence for your active control," Simon said at the meeting Dec. 14. "If that body of evidence doesn't exist, or if the degree of effectiveness is very small, or if it has occurred inconsistently, then, I think there is a question of whether you are doing your patients any favors by giving them a toxic treatment whose effectiveness is highly questionable."

The example Simon used in his paper involved a drug for the treatment of unstable angina. Temple's slides used the example of antidepressants. Nonetheless, ODAC discussion pointed to the need for establishing standards for demonstrating equivalence, as well as the need for methodology of measuring equivalence while considering quality of life measurements.

At the meeting, ODAC member David Johnson asked whether Simon's approach applies to trials that are designed to demonstrate superiority of the new therapy, but fail to do so.

"When a study is designed to show superiority and none is identified, can one use these approaches that you've outlined in the posterior analysis to come up with the probability that these data demonstrate equivalence?" asked Johnson, director of the division of medical oncology at Vanderbilt University Medical School.

"I would say yes, but I would say that the work part of it is putting together the evidence for the effectiveness of the control regimen," said Simon.

JOHNSON: "It's very important that we look at that type of an approach, because when one looks to define equivalence, typically the sample size is larger than what one would be to show superiority. And, given the option, every time, whether it's a cooperative group or a pharmaceutical company, always we go with a smaller size, just for the practicality of getting the study done."

SIMON: "Our approaches to randomized clinical trials are pretty effective. But I think with the equivalence trials, we are still at a level where we have not established good criteria, or good practice."

The use of quality of life criteria is likely to make it extremely difficult for ODAC to resolve the questions of equivalence, said committee member Derek Raghavan.

"Richard, life is going to become much tougher for you, or maybe the person who follows you as the resident captive statistician," said Raghavan, head of medical oncology at the University of Southern California Norris Comprehensive Cancer Center. "There will be a tension between survival and alleged measurements of quality of life.

"There are a lot of new drugs that presumably will come to this committee at some point that, whether they are effective or not, are less toxic," Raghavan said. "So, there is certainly starting to be a proven efficacy predicated on survival, and new drugs that are less toxic, that will be acceptable to patients, but which may or may not give equivalent survival. How are you going to model that mathematically? What are going to be the parameters that would allow you to weigh quality of life versus duration?"

SIMON: "I think we do need to have some assessment in the imperfect world we live in, of what the effect on survival is of what we are holding up as a standard."

Standards are essential, because approval based on equivalence can lead to ongoing erosion in the standard of care, Simon and Temple said in their remarks. Since trials in oncology tend to be relatively small, a new therapy could be 80 percent as effective as the control and still be considered equivalent.

Follow-up Studies in FAP Uncertain

Recommending accelerated approval, ODAC recognized the regression and reduction of adenomatous polyps as a reasonable surrogate for patient benefit in FAP.

Physicians who presented for the company said the therapy would most likely be used in young patients who choose to delay the removal of the colon, a standard therapy for those afflicted with the disorder.

Several committee members cautioned that following the accelerated approval, large numbers of FAP patients may be unwilling to be randomized, which would make further trials for this rare disease not feasible.

Earlier copies of the ODAC agenda indicate that originally Searle sought approval for the "regression and prevention of adenomatous polyps which may lead to the development of colorectal cancer" in FAP patients.

The change in the wording of the application is not surprising. Last year, the committee declined to give Zeneca the breast cancer "prevention" indication for tamoxifen, making the company use the words "risk reduction" instead.

In the case of tamoxifen, the application, based on the landmark Breast Cancer Prevention Trial,

didn't have a long enough follow-up to warrant the prevention claim or demonstrate the mechanism of action for the drug, the committee said.

Celebrex, a drug approved in the U.S. for the treatment of osteoarthritis and adult rheumatoid arthritis, was tested in 83 FAP patients over six-months. The three-arm study randomized 17 patients to placebo, 34 to the 100 mg bid dose of the drug, and 32 to the 400 mg bid dose.

The trial was conducted by the NCI Division of Cancer Prevention in collaboration with the company. The primary endpoint was the mean percent change in the number of colorectal polyps, and secondary endpoint was the mean percent change in the duodenal plaque-like areas. The population was heterogenous, representing a range of ages. Some of the patients had colectomies.

According to the FDA analysis, in the 400 mg arm, mean percentage in colorectal polyps decrease by about 28 percent, compared to placebo. Treatment didn't result in a statistically significant reduction in duodenal polyps.

The agency reviewers said the percentage change in rectal polyps in one area does not appear to predict changes in the entire rectum. The agency also concluded that durability of the effect of the drug could not be assessed because of the short duration of the trial.

"Without a complete regression of all colorectal polyps, reduction in polyps may not result in a decrease in colorectal cancer incidence in FAP patients," FDA said in its review. The committee voted 13-0 with two abstentions that a reduction in colorectal polyp count reasonably predicted patient benefit. Accelerated approval was recommended in a 14-0 vote with one abstention.

Taxotere sNDA For SCLC

ODAC's decision to recommend approval for Taxotere for locally advanced or metastatic non-small-cell lung cancer after failure of prior chemotherapy was based on the results of two multicenter studies involving over 500 patients, the first phase III trials ever conducted in advanced NSCLC patients in the second-line setting.

In one phase III trial, 204 patients who had previously failed platinum-based chemotherapy were randomized to Taxotere or best supportive care. Originally, patients received 100 mg/m^2 of Taxotere. However, after the dose produced unacceptable toxicity, the dose was lowered to 75 mg/m^2.

According to FDA analysis of the company data, patients treated with Taxotere, 75 mg/m^2, had a median survival of 7 months versus 4.6 months in patients who received BSC.

Another trial, designed to demonstrate superiority, randomized 373 platinum-resistant patients to one of the two doses of Taxotere or vinorelbine or ifosfamide. In that trial, median survival remained unchanged across the three arms.

According to the FDA analysis of Taxotere versus BSC, the time to disease progression was 12.3 weeks in the treatment arm, and seven weeks in the control arm. The one-year survival rate was 37 percent in the Taxotere arm, versus 12 percent for BSE.

Quality of life was assessed using the Lung Cancer Symptom Scale and the European Organization for the Research and Treatment of Cancer QOL questionnaire. The clinical-benefit analysis showed that patients treated with Taxotere, 75 mg/m^2, used less radiotherapy and pain-relieving medications and had less weight loss, the company said.

The three-arm study found that the one-year survival rate in patients treated with 75 mg/m^2 of Taxotere was 30 percent, compared to 20 percent in patients treated with either vinorelbine or ifosfamide.

The major side effects of Taxotere, 75 mg/m^2, in both studies were neutropenia, fatigue, hypersensitivity and alopecia.

The committee voted 12-0 for approval of the drug.

Recently, the Committee for Proprietary Medicinal Products recommended approval for Taxotere in the European Union for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy.

The drug was approved in the U.S. for the treatment of advanced breast cancer after failure of anthracycline-based therapy.

Targretin For CTCL

The committee voted 13-2 with one abstention to recommended Targretin (bexarotene) capsules in the advanced-stage CTCL.

However, in a 6-5 vote with five abstentions, the committee declined to recommend approval in the early-stage CTCL.

The NDA is based on the results from two multi-center, multinational clinical trials involving 152 patients with CTCL.

In a review, FDA officials noted protocol violations involving 75 percent and 90 percent of patients in the company's studies. These violations included failure to take full body photographs, as well as eligibility problems.

In two cases, FDA noted that while some photos showed regression of lesions, other lesions on the same patients continued to progress. The agency also questioned discrepancies in the company's quality of life measurement

The agency said potential benefits of the drug include a decrease in tumor involvement of the body surface area in 37 percent of early disease patients and 33 percent of advanced disease patients. Demonstrable improvement in index skin lesions was noted in 29 percent of patients with early stage disease and 35 percent of patients with moderately advanced disease.

The company said it will continue to seek the early stage indication. "We look forward to continuing to work with the FDA to address requirements for approval in the early-stage disease patient population as well as commencing our dialogue on the recently submitted Targretin gel NDA in early-stage disease," said Richard Yocum, Ligand senior medical director and physician team leader for the CTCL project.

Ligand submitted a Marketing Authorization Application with the European Medicines Evaluation Agency seeking marketing clearance for Targretin capsules for CTCL. The company is also conducting phase II trials for moderate to severe plaque psoriasis and for advanced breast cancer.

NCI Programs:

Unequal Cancer Outcomes Result Of Unequal Treatment; NCI To Raise Awareness

NCI officials plan to meet with representatives from professional organizations next month to consider developing a national education campaign aimed at health professionals to raise awareness about unequal treatment of minorities with cancer, NCI Director Richard Klausner said last week.

The action was spurred by a research study and an editorial published in the Nov. 17 issue of the Journal of the National Cancer Institute on outcomes for cancer treatment, Klausner said. The study, by investigators with the National Surgical Adjuvant Breast and Bowel Project, found that in five randomized clinical trials of patients with colon cancer, black and white patients who had the same treatment experienced the same outcome.

In an accompanying editorial, Otis Brawley, director of the NCI Office of Special Populations Research, and Harold Freeman, of the North General Hospital in New York City, and chairman of the President's Cancer Panel, wrote that the study, and others like it, demonstrate that "equal cancer treatment yields equal cancer outcome between blacks and whites."

Yet, age-adjusted colorectal cancer death rates are higher for blacks than for whites. "A number of researchers have postulated that biologically more aggressive tumors in blacks offer the most reasonable explanation for this disparity," Brawley and Freeman wrote. "However, recent data from numerous controlled clinical trials, including the current study on colon cancer, have convincingly shown that unequal treatment of blacks at curable stage of disease provides the fundamental explanation for such disparities.

"The finding raises deep ethical and moral questions concerning how the research community, the American health care system, and society as a whole will move toward providing remedies for this unacceptable reality," the editorial concluded.

Klausner said NCI will continue to support research to understand disparities in treatment. "There is much we need to learn about the 'whys' of this unequal treatment and unequal access, but we believe that the body of evidence that has already been developed compels us to speak to this issue more definitively and directly to raise awareness by all who treat individuals with cancer," Klausner said to the National Cancer Advisory Board at its Dec. 7 meeting.

An educational campaign "cannot alone address issues of economic disparity, or insurance, but can raise awareness about what may be very complex and unconscious processes in the interaction between patients and physicians or patients and health care systems that result in unequal treatment," Klausner said.

NCI also plans to increase funding for special populations research this year, Klausner said.

The Institute plans to nearly double the funding for a new grants program, called Special Populations Networks, designed to create a new infrastructure for cancer control research by linking minority institutions to NCI research and information resources, Klausner said.

NCI had expected to fund about eight of these networks for about $30 million over five years. However, the Institute received 52 grant applications, of which 30 received priority scores in review last month, Klausner said to the National Cancer Advisory Board at its meeting Dec. 7.

Because of the "overwhelming response," NCI will instead commit between $50 million and $60 million to fund about 17 grants, Klausner said.

"We think this will be the largest program we have ever engaged in of this sort," Klausner said. "Many of these [grant applications] really are quite superb, and allow us to create these infrastructures in communities that we've not touched before in this sort of way."

NCI also plans to increasing funding for its programs for professional training of minority researchers by 37 percent, Klausner said. This will include a 38 percent increase in grant supplements; funds will be supplied to 185 grants specifically to support minority researchers.

K01 grants for minority researchers will receive an increase of 62 percent. NCI will begin a program of supplemental funds to cancer centers for minority training, and the Institute plans to expand its R25 and K12 grant programs for minority training, Klausner said.

Health Organizations:

ACS, In Statement, Will Support Human Stem Cell Research

The American Cancer Society will "accept and support" research grant proposals involving human pluripotent stem cells, conditional on compliance with "minimum requirements" for guidelines that it urged NIH to put in place.

The statement, approved by the National Board of Directors last month, said ACS "concludes that human pluripotent stem cells research holds significant promise to eradicate or ameliorate many diseases, including cancer. The Society believes that such research may be conducted in a moral and ethical manner using cells derived from human embryos that were not being used and would otherwise be discarded, as well as stem cells derived from fetal germ cells obtained from elective or spontaneous abortions."

The statement called on NIH to "establish and promulgate guidelines, at the earliest possible time, for the oversight of federally funded research projects using human pluripotent stem cells so that studies on this promising line of research may begin. Such guidelines shall include, at a minimum:

"—federal regulatory oversight mechanisms to promote accountability, with regular reporting of results;

"—reports on the source of cells from all derived stem cell lines approved for use in federally-funded research;

"—stringent peer review by NIH review panels and Institutional Review Boards;

"—donor informed consent standards;

"—prohibition and legal recourse against payments or incentive transactions with donors, in vitro fertilization clinics responsible for disposal of excess embryos, or their agents;

"—prohibition against designating embryos for a specific research purpose; and

"—adaptation and application of existing NIH guidelines on the conduct of research using fetal tissue to research with human embryonic stem cells derived from fetal germ cells."

In the statement, ACS urged NIH and the private sector to "resolve questions about the prospects, efficacy and comparability of related stem cell research modalities. Further, resources should be directed immediately for the support of comparative trials on the promise, adequacy, and efficacy of research using stem cells derived from a variety of animal and human sources (including umbilical, bone marrow, embryo and fetal) and to address questions of cell line compatibility and supply."

Funding Opportunities:

RFA Available

RFA AI-00-008: Small Business Innovation Research: Animal Models of HIV Infection

Letter of Intent Receipt Date: Jan. 24, 2000

Application Receipt Date: Feb. 24, 2000

This is a multi-Institute solicitation targeting the development/identification of one or more small animal models of hepatitis C infection and disease progression including acute and chronic states, fibrosis/cirrhosis, and liver tumor development, not necessarily all in the same model. The RFA invites grant applications for Small Business Innovation Research projects with award duration and amounts greater than those routinely allowed under the SBIR program. Information on the SBIR program is available at: http://grants.nih.gov/grants/funding/sbir1/SBIR.HTM.

Approximately 10 awards will be made in FY2000,

and $3.2 million from the SBIR set-asides of the participating Institutes will be designated for this purpose.

Inquiries: For NCI, John Cole, Division of Cancer Biology, NCI, Executive Plaza North, Room 540, Bethesda, MD 20892-7209, phone 301-496-1718; fax 301-496-2025; e-mail jc121b@nih.gov

RFA LM-00-001: Internet Connection for Health Institutions

Letter of Intent Receipt Date: Feb. 20

Application Receipt Date: March 14

National Library of Medicine is offering grants to support institution-wide Internet connections. Funds available for this RFA are approximately $600,000.The number of awards to be made is estimated to be between 10 and 16.

Inquiries: Frances Johnson, Division of Extramural Programs, NLM, Rockledge One Bldg., Suite 301, 6705 Rockledge Dr., Bethesda, MD 20892, phone 301-594-4882; fax 301-402-2952; e-mail: FJOHNSON@NLM.NIH.GOV

Program Announcement

PAR-00-025: Cancer Prevention Research Small Grant Program

Application Receipt Date: March 20, July 20, Nov. 20

The NCI Division of Cancer Prevention invites applications that address developmental research in chemoprevention agent development, biomarkers, early detection, and nutrition science. New, as well as experienced, investigators in relevant fields and disciplines may apply for small grants to test ideas or do pilot studies.

Support will be through NIH Small Grants Program, R03. Total budget may not exceed $100,000 in direct costs for the entire project. The direct costs in any one year must not exceed $50,000. The total project period may not exceed three years. The small grant is not renewable.

Inquiries: Barry Portnoy, Division of Cancer Prevention, NCI, Bldg., 31, Room 10A49, Bethesda, MD 20892, phone 301-496-9568; fax 301-496-9931; e-mail: bp22z@nih.gov

NCI SPORE Grant Guidelines

NCI SPORE grants use the NIH P50 Specialized Center grant mechanism to support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer or a highly related group of human cancer types. SPOREs are open to any scientific approaches that can have an impact on the disease and are dependent upon team approaches in the design and implementation of the research.

The guidelines for SPORE grants can be accessed at the following URL: http://deainfo.nci.nih.gov/awards/spore.htm.

Inquiries: Jorge Gomez, Organ Systems Branch, Office of Centers, Training, and Resources, Office of the Deputy Director for Extramural Science, NCI, 116 Executive Blvd., Room 7008, MSC 8347, Bethesda, MD 20892-8347, phone 301-496-8528; e-mail: jg1w@nih.gov

RAID Addendum

This notice announces a change to the NCI program, Rapid Access to Intervention Development, effective immediately:

Requests for support should provide evidence of feasibility for the preparation of any product proposed for clinical trial. For more information concerning this new requirement, guidelines for submitting requests for support, and information on previously supported requests, visit the web site, http://dtp.nci.nih.gov/.

RAID will make available to academic investigators, on a competitive basis, the preclinical development contract resources of the NCI Developmental Therapeutics Program. RAID is not a grant program to originating investigators. The goal of RAID is the rapid movement of novel molecules and concepts from the laboratory to the clinic for proof-of-principle clinical trials. RAID will assist investigators who submit successful applications by providing any or all of the preclinical development steps that may be obstacles to clinical translation. They may include, for example, production, manufacture of products using current Good Manufacturing Practices, formulation, and toxicology. Suitable agents for RAID include small molecules, biologics, or vaccines.

The original notice is available at: http://grants.nih.gov/grants/guide/notice-files/not98-070.html.

Inquiries: James Drake, Coordinator, RAID Program, Special Assistant to the Associate Director, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, NCI, 6130 Executive Blvd., Room 843, Bethesda, MD 20892, Rockville, MD 20852 (for express/courier service), phone 301-496-8720; fax 301-402-0831; e-mail drakej@dtpax2.ncifcrf.gov.

In Brief:

Simons To Direct Winship Cancer Institute At Emory

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Simons has lead the way in the use of human gene therapy to create clinically measurable immune responses against metastatic prostate cancer, the Institute said. Simons is director of the Molecular Pharmacology Program and Cancer Gene Therapy Laboratory at Johns Hopkins University School of Medicine, where he is associate professor of both oncology and urology. The appointment enables

Emory to move ahead on a $56 million, 226,000-square-foot comprehensive cancer building. About four floors will be devoted to outpatient clinical care and three for research, the Institute said. . . . **GEORGE CANELLOS** was given the 1999 Key to the Cure Award by the Cure for Lymphoma Foundation. The editor-in-chief of the Journal of Clinical Oncology, Canellos is the William Rosenberg Professor of Medicine at Harvard Medical School, a member of the senior staff at Dana-Farber Cancer Institute, Brigham and Women's Hospital and Massachusetts General Hospital. . . . **JOSEPH TESTA,** a cancer geneticist who directs the human genetics program at Fox Chase Cancer Center, received a 1999 Irving J. Selikoff Award for Cancer Research. Testa was honored for his "outstanding contributions in understanding the origins of mesothelioma." by the Ramazzini Institute for Occupational and Environmental Health Research on Dec.3. **WILLIAM ROM**, of New York School of Medicine, received a Selikoff Award for Cancer Research for his work in lung cancer. . . . **EDWARD BENZ** was named president of the American Society of Hematology. Benz is Sir William Osler Professor and Director, Department of Medicine, and professor of molecular biology and genetics, at Johns Hopkins University School of Medicine. He is also physician-in-chief at Johns Hopkins Hospital. . . . **SUSAN B. KOMEN** Breast Cancer Foundation presented two 1999 Brinker International Awards for Breast Cancer Research. **Mary-Claire King** received the Basic Research Award for genetic work in breast cancer. **Nancy Davidson**, professor of oncology and Breast Cancer Research Chair at Johns Hopkins School of Medicine, was presented the Clinical Research Award for her work with estrogen and steroid receptors in breast cancer growth. Davidson is the principal investigator for an NCI-sponsored clinical trial of chemotherapy with or without hormonal therapy for management of pre-menopausal breast cancer. . . . **OHIO STATE UNIVERSITY** received $1 million grant from NCI for Arthur G. James Cancer Hospital and Richard J. Solove Research Institute to study the causes and find treatments for central nervous system lymphoma. **Michael Caligiuri**, whose laboratory developed an animal model for studying the process for CNS lymphoma development, is associate director for clinical research at the James and principal investigator for the study. . . . **OFFICE OF CANCER SURVIVORSHIP** at NCI has expanded its Web site. OCS Director **Julia Rowland** said the site can be reached at http://dccps.nci.nih.gov by clicking the "survivorship research" button. . . . **NIH** awarded a Cooperative Research and Development Agreement through 2004 to **BioSpace.com**, of San Francisco, to oversee the further development of the NIH IntraMall, an e-commerce site for procuring laboratory supplies and equipment. The site was piloted in August 1997 by NCI prior to its adoption throughout NIH in June 1998. NIH spends in excess of $1 billion each year for laboratory supplies and equipment. Suppliers will be able to post their products on the site without up-front fees, the company said. "We chose BioSpace.com because of its capacity for customization, and the breadth and flexibility of its supplier base," said **MaryAnn Guerra**, NCI deputy director for management. "Although the initial design for the IntraMall was technically excellent, we want to rapidly expand the breadth of suppliers and dramatically increase NIH end-user participation."

Best Wishes For The New Year

The Cancer Letter editors and staff send their best wishes to readers for the holiday season and New Year.

This is the final issue for 1999. The next issue, Vol. 26, No. 1, will be published Jan. 7.

Beginning in 2000, there will be 46, rather than 48, issues of **The Cancer Letter** each calendar year. The newsletter will continue to be published weekly on Fridays, with the exception of the month of August and the last two weeks of December.

Should important news events take place during the publication breaks, the editors will consider publishing extra editions. There has been no increase in the standard subscription price for 2000.

The two additional non-deadline weeks will give the staff more time for professional growth.

In the past two years, **The Cancer Letter** has begun an electronic edition, **The Cancer Letter Interactive**, redesigned its business section, **Business & Regulatory Report** (formerly Cancer Economics), and published special reports on media coverage of science (Vol. 24, No. 19, May 15, 1998), clinical trials of antineoplaston (Vol. 24, No. 36, Sept. 25, 1998), and the future of cancer centers (Vol. 25, No. 18, May 7, 1999). The newsletter won three journalism awards for the antineoplaston special report, and an award for articles in 1997 on mammography screening for women aged 40 to 50.

THE CANCER LETTER

Vol. 14 No. 12
December 1999

Business & Regulatory Report

Formerly "Cancer Economics"

Oncology Management:

Targeted Cryoablation In Use At 10 Centers For Treatment Of Prostate Cancer

Endocare Inc. (Nasdaq: ENDO), of Irvine, CA, said 10 of the leading U.S. cancer centers are launching or have established cryosurgery programs featuring targeted cryoablation procedure, a minimally invasive prostate cancer treatment that uses extreme cold to freeze and destroy cancerous tissue in and around the prostate gland.

Targeted cryoablation is an FDA-cleared prostate cancer treatment that is reimbursed by Medicare nationwide.

Among the leading institutions that have adopted Endocare's targeted cryoablation procedure are: University of Texas M. D. Anderson Cancer

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Clinical Trials:

Agouron Begins Phase II Trial Of MMI Prinomastat For Glioblastoma Multiforme

Agouron Pharmaceuticals Inc. of La Jolla, CA, said it has initiated a pilot phase II clinical trial for patients with glioblastoma multiforme.

The trial will evaluate the matrix metalloprotease inhibitor prinomastat in combination with chemotherapy for patients with newly diagnosed glioblastoma multiforme following surgery and radiation therapy, the company said.

In this multi-center pilot study, patients with newly diagnosed glioblastoma multiforme that have undergone resection surgery and radiation therapy will be randomized to receive prinomastat or placebo in tablet form in combination with Temodar (temozolomide).

Prinomastat is an orally active, small synthetic molecule designed to selectively inhibit matrix metalloproteases involved in tumor angiogenesis, invasion and metastasis. In preclinical models, prinomastat has been shown to inhibit angiogenesis tumor invasion, and metastasis, the company said.

Aguron said the most common side effects of prinomastat have been joint stiffness, swelling and mobility of certain joints, most often in the shoulders and hands. All were reported reversible and managed by treatment rests and dose reductions, the company said.

* * *

Celsion Corp.(OTC BB:CELN) of Columbia, MD, said Harbor UCLA Medical Center is recruiting patients for phase I trials of its breast cancer treatment system. Additional phase I testing began in October at a Columbia/HCA member hospital in Florida to expedite patient accrual

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Targeted Cryoablation In Use At 10 Cancer Centers

(Continued from page 1)

Center; Mayo Clinic; University of Michigan Medical Center; the UCLA Jonsson Cancer Center; Cleveland Clinic; Stanford University Medical Center; Emory University Hospital; Medical Center Harper Hospital in Detroit; and H. Lee Moffitt Cancer Center in Tampa.

"Targeted cryoablation is an effective, minimally invasive treatment for prostate cancer that offers patients a short recovery time and fewer side effects than some other therapies," said Richard Babaian, professor of urology at M. D. Anderson. "M. D. Anderson implemented a cryosurgery program because we are committed to helping our patients fight prostate cancer and feel that targeted cryoablation is an important and effective treatment option for men suffering from this disease."

In the July issue of the journal Urology, a comparative study of 163 patients treated with two different methods of cryoablation shows that 97.6 percent treated with targeted cryoablation were cancer-free after six months.

The success rate of targeted cryoablation is comparable to other prostate cancer treatments, such as radiation therapy, but unlike other surgical treatments, targeted cryoablation can be repeated if cancer recurs, the company said.

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Targeted cryoablation uses cryoablation in combination with ultrasound and temperature monitoring to precisely destroy cancer cells in and around the prostate gland.

During targeted cryoablation, a patient is first treated with epidural anesthesia; he is awake and can talk to the physician, but feels no pain during the procedure. A thin catheter that circulates warm fluid is placed in the urethra to protect it from cold temperatures. Next, slender cryoprobes are inserted through small incisions into the prostate gland. Liquefied argon gas, which is contained within the cryoprobe tips, freezes and destroys the cancer and tissue that reaches -40 degrees Celsius. After 10 minutes, the physician completes the first freeze cycle and then immediately administers another treatment to help ensure that all cancer cells are killed. The entire procedure lasts about one to two hours.

* * *

Surgical Information Systems said it has agreed to give its perioperative software system to the **University of Texas M.D. Anderson Cancer Center**. The system will enable the center to retain a clinical and financial record from the time surgical treatment is scheduled until a patient is released from recovery.

The data will be used to create a database of treatment information for research and anlysis to promote the development of surgical protocols, the company said.

* * *

US Oncology (Nasdaq: USON) of Houston, announced the resignation of Ed French, CEO, effective December 1999.

French was president and CEO of Physician Reliance Network Inc., Dallas, prior to the merger with American Oncology Resources Inc., which created US Oncology.

"Ed French has decided to execute a provision within his preexisting employment agreement that would expire at the end of this year." said R. Dale Ross, chairman and CEO of US Oncology. "Ed has made tremendous contributions to US Oncology during the merger transition process, and we wish Ed continued success in his future endeavors."

"US Oncology is a great organization that will make an even more significant impact on the availability and quality of cancer care in the U.S. in the years to come," said French.

He did not elaborate on his future plans.

Study Of G3139 With Irinotecan For Colorectal Cancer Begins

(Continued from page 1)

and accelerate the trials, the company said.

The phase I studies underway in California and Florida are evaluating the safety of the focused heat treatment system, which is designed to destroy cancerous tumors and viable cancer cells using heat alone. The device is designed to be a non-surgical, minimally invasive treatment that is non-toxic and side effect free, the company said.

* * *

Genta Inc. (Nasdaq: GNTA) of Lexington, MA, said NCI has begun a phase I-II study of G3139 in combination with irinotecan (Camptosar, **Pharmacia & Upjohn**) for the treatment of relapsed colorectal cancer.

The study is being conducted under a Cooperative Research and Development Agreement between Genta and NCI.

G3139 was designed to reduce the bcl-2 protein level in cancer through an "antisense" mechanism that specifically targets the messenger-RNA produced by the bcl-2 gene. In many human cancers, the bcl-2 protein is believed to be a major factor in inhibiting apoptosis, or programmed cell death, and in contributing to resistance of those cancers to treatment with anticancer drugs. The rationale for using G3139 in this disease is based on several reports showing frequent expression of the bcl-2 protein in colorectal cancers, and preclinical studies showing enhanced anticancer effects when G3139 is combined with various types of chemotherapeutic agents.

"This is the first of a series of studies pursuant to the CRADA with NCI that represents the company's refocused strategy of using G3139 to enhance the cancer-killing actions of selected, major chemotherapeutic drugs," said Raymond Warrell Jr., president and CEO of Genta.

The lead investigator for the study is Anthony Tolcher of the Institute for Drug Development in San Antonio, and co-author of laboratory studies with G3139 published in the October 1999 issue of Clinical Cancer Research. The study is also being conducted at Case Western University.

* * *

Fred Hutchinson Cancer Research Center said researchers presented data on an experimental agent, CMA-676, for acute myeloid leukemia at the American Society of Hematology meeting in New Orleans earlier this month.

CMA-676, an antibody-drug conjugate that delivers treatment directly to the leukemia cells, induces remission in a significant proportion of patients with few serious side effects. CMA-676 represents the first successful application of antibody-targeted chemotherapy, the center said.

Researchers at the Hutchinson Center, in collaboration with scientists from eleven leading leukemia centers, including University of Chicago Medical Center, M.D. Anderson Cancer Center, and University of Pennsylvania Cancer Center, are working with Wyeth-Ayerst Research and Celltech Chiroscience PLC to study CMA-676.

Promising results continue to emerge from a phase II trial in the U.S., involving patients who experienced a relapse following initial AML chemotherapy. CMA-676 given alone produces remission among 34 percent of patients—a rate comparable to that of standard combination chemotherapy regimens. The data also indicate CMA-676 has several important advantages over standard agents, the center said.

* * *

ImClone Systems Inc. (Nasdaq: IMCL) of New York, said it has begun a phase II clinical trial evaluating its cancer therapeutic, C225, in combination with gemcitabine for pancreatic carcinoma.

C225, a monoclonal antibody, targets and inhibits the epidermal growth factor receptor (EGFr), associated with tumor cell growth and repair in a number of EGFr-positive solid tumors, the company said.

Preclinical data from M.D. Anderson Cancer Center and ImClone on the use of C225 in combination with gemcitabine in a mouse model of pancreatic cancer showed combined administration of C225 plus gemcitabine resulted in a 90 percent reduction in pancreatic tumors, compared with a 27 percent reduction using gemcitabine alone.

When administered alone, C225 demonstrated significant tumor regression and destruction of liver metastases when compared to treatment with gemcitabine, the company said.

ImClone said it has begun two phase III clinical trials evaluating C225 in combination with radiotherapy and with chemotherapy in patients with advanced squamous cell head and neck carcinoma. ImClone said it began a phase II trial evaluating C225 in combination with cisplatin in patients with refractory advanced squamous cell head and neck

carcinoma and a second phase II trial evaluating C225 in combination with irinotecan in patients with refractory colorectal carcinoma.

* * *

Immunomedics Inc. (Nasdaq: IMMU) of Morris Plains, NJ, said interim results of its phase I/II clinical trial of Epratuzumab, a humanized antibody against the CD22 marker expressed by most B-cell lymphomas (including non-Hodgkin's lymphomas), were presented by Weill Medical College of Cornell University and New York Presbyterian Hospital at the annual meeting of the American Society of Hematology, in New Orleans.

"We are enthusiastic about our findings during a dose-escalation trial of this new antibody drug for the treatment of NHL, because we found only minimal toxicity (only transient grades 1 and 2), compared to what has been shown for other antibody products, with similar potential efficacy, so far," said Morton Coleman, director of the Center for Lymphoma and Myeloma at the Weill Center and study author.

"Objective responses (partial and complete remissions) were achieved in almost 70% of patients with indolent NHL at the optimal doses given once weekly over 4 weeks, while responses were also observed in aggressive NHL, including a complete response for more than 13 months," said John Leonard, director of Clinical Research at the Center and senior author of the Cornell study.

* * *

Isis Pharmaceuticals (Nasdaq: ISIP) of Carlsbad, CA, said it would begin phase III clinical trials of ISIS 3521, an antisense inhibitor of protein kinase C-alpha (PKC-alpha) expression, for non-small cell lung cancer based on promising data from a phase I/II study presented at the NCI-EORTC-AACR meeting last month in Washington, DC.

Results show that of 15 patients with non-small cell lung cancer, 13 have benefited from the drug through objective responses or stable disease lasting from more than 2 months to more than 13 months thus far. Eight of the 15 (53%) patients have experienced partial responses. Survival results from the study show that 7/15 (47%) patients have lived 1 year or more with the longest survival at 21 months following study entry. After an average of 8 months of follow-up, 90% of the patients are alive and continuing to be evaluated. Isis said it is continuing to enroll patients in its current trials until the phase III study is launched.

"The data from ISIS 3521 in non-small cell lung cancer are promising," said Alan Yuen, assistant professor of medicine at Stanford University Medical Center. "The response rates and survival observed in this early analysis appear better than would be expected with carboplatin and Taxol alone."

PKC-alpha is a member of a multi-gene family of signal transduction proteins that regulate information flow in and out of cells and modulate cellular responses to environmental stimuli. PKC-alpha has been implicated in the growth of a range of solid tumors.

* * *

MGI Pharma Inc. (Nasdaq: MOGN) of Minneapolis, said it began a phase I human safety study of its novel anti-cancer compound irofulven (also referred to as MGI 114) on a weekly dosing schedule that is designed for more convenient use with other anti-cancer drugs.

The dosing regimen being investigated is a five-minute infusion, once a week for three weeks, repeated every four weeks. The study is expected to determine the maximum tolerated dose of irofulven, when administered on this schedule to patients with advanced solid tumors.

The company recently announced preliminary results from a phase I drug-combination study of irofulven with CPT-11 (Camptosar). In the study, one patient with non-small cell lung cancer experienced a 47% reduction in measurable tumor mass and has remained in the study for more than nine months. Irofulven has demonstrated additive or synergistic activity with a number of marketed anti-cancer drugs in preclinical animal studies, the company said.

* * *

NeoRx Corp. (Nasdaq:NERX) of New Orleans, said 12 of the 27 patients experienced complete disappearance of all evidence of myeloma cancer tumors in a phase II clinical trial of skeletal targeted radiotherapy.

Safety data on the 45 patients treated thus far with escalating doses of STR, showed no serious toxicity. The safety profile led researchers to raise the age limit of study participants in future studies.

"We have completed response evaluation of 27 patients so far. As more patients are treated and evaluated, we have found continued support for our initial observations of safety and efficacy," said Richard Champlin, chairman of the department of Blood and Bone Marrow Transplantation at M.D. Anderson Cancer Center, and a principal investigators of the study.

"The ability to deliver safely up to 40Gy to the bone marrow provides an additional potent weapon without increasing the side effects of treatment. We have observed complete responses even in patients who did not respond to initial chemotherapy and in those that had relapsed after responding. Moreover, many of these responses are at lower STR doses, as most of the patients treated at the highest doses have not yet been evaluated for response,"said Camplin.

STR is a small molecule that carries a radionuclide, holmium-166, to bone. This is designed to deliver radiation therapy selectively to the site of the disease and avoid toxicity to normal tissue. In the phase II trial STR is administered in increasing doses to groups of 4 or more patients along with standard high dose therapies and stem cell support. Patient data has shown that STR goes to bone and is eliminated in the urine with negligible accumulation in other organs.

* * *

Pharmacyclics Inc. (Nasdaq: PCYC) of Sunnyvale, CA, said it has begun a phase I clinical trial of Xcytrin (motexafin gadolinium) Injection for treating children with intrinsic pontine glioma.

The study is being conducted by the Pediatric Phase I Consortium of the Children's Cancer Group, and sponsored by NCI under a Cooperative Research and Development Agreement with Pharmacyclics.

Pharmacyclics said the goals of the phase I dose-ranging study are to determine the dose and administration schedule that can be given safely with radiation, and to evaluate localization of Xcytrin in the affected tumors using MRI.

Xcytrin Injection augments the activity of radiation through a unique mechanism of action. Although some cancer patients have benefited from radiation therapy, it has many drawbacks, including harmful side effects and limited efficacy. Preclinical and clinical data indicate that Xcytrin, after repeated injections, accumulates selectively in cancerous tumors. The drug appears to enhance the effectiveness of X-rays in destroying diseased cells, without increasing damage to surrounding healthy cells.

"We are very excited about the potential of treating childhood gliomas with Xcytrin, which has so far shown promise in treating brain metastases in recently-completed and ongoing clinical trials," said Gregory Reaman, chairman of the hematology and oncology department at the Children's National Medical Center in Washington, DC, and associate chair of the CCG's new agent studies. "Until now, radiation has been the only way to treat these children. Xcytrin has been shown to enhance the effects of radiation without causing collateral damage, making it an ideal candidate to test in this disease."

Information about the study is available by contacting the NCI Cancer Information Service at 1-800-4-CANCER or by visiting the National Childhood Cancer Foundation at http://www.nccf.org.

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Valentis Inc. (Nasdaq: VLTS) of Burlingame, CA, said it began a phase IIa clinical trial of Interferon-a gene medicine for the treatment of malignant angioendothelioma, a rare form of vascular tumor.

The trial, under the direction of Laurence Baker at the Comprehensive Cancer Center at the University of Michigan, will enroll 12 to 15 patients and will run through December 2000, the company said.

"Interferons are thought to downregulate the genes that control new blood vessel formation, or angiogenesis. Angiosarcomas are believed to occur due to faulty regulation of blood vessel growth and, therefore, may be good candidates for an anti-angiogenic therapy using IFN-a," said Baker.

IFN-a gene medicine incorporates the company's polymer-based PINC (Protective, Interactive, Non-Condensing) gene delivery system. The resulting gene medicine is formulated as a stable, single vial, lyophilized product that is administered by injection into the tumor. Based on animal models of cancer, the IFN-a gene medicine is expected to result in local expression of the IFN-a protein within the tumor over a period of days. Valentis said it expects to induce an effective anti-tumor response without the serious side effects seen with systemic administration of the protein.

Valentis currently has a gene medicine incorporating IL-2 in a phase IIb clinical trial, and IFN-a and IL-12 gene medicines in phase IIa clinical trials for the treatment of head and neck cancer in collaboration with Roche Holdings Ltd. The company also recently released positive interim results from a phase IIb trial of a VEGF(165) gene medicine for restenosis, and has completed a phase IIa trial incorporating the CFTR gene for cystic fibrosis in which the plasmid-based delivery system did not generate any evidence of inflammation.

* * *

Vasogen Inc. (AMEX:MEW) of Toronto, said

results of pre-clinical research in the prevention of graft-versus-host disease support regulatory submissions to begin a clinical trial of VAS981 cell processing technology.

The results showed VAS981-treated cells produced much lower levels of the inflammatory cytokines that are associated with GvHD. The in vitro changes seen in these laboratory studies on human cells closely mirrored those seen in vivo in the pre-clinical models, where they were associated with a dramatic reduction in GvHD, the company said.

* * *

The Weill Medical College of Cornell University Center for Lymphoma and Myeloma and **New York-Presbyterian Hospital** said interim results of a study conducted at Weill using radioimmunotherapy in combination with Fludarabine, show it is safe and increases the rate of complete response for low-grade or follicular non-Hodgkin's lymphoma.

The study was designed to evaluate the safety and efficacy of a sequential regimen of fludarabine followed by tositumomab, iodine I 131 tositumomab.

The study enrolled 38 patients with previously untreated low-grade or follicular non-Hodgkin's lymphoma.

All patients achieved a response with Bexxar (tositumomab, iodine I 131 tositumomab) in combination with fludarabine. The addition of Bexxar to fludarabine increased the rate of complete response five-fold, as compared to initial treatment with fludarabine alone, with the rate of complete response continuing to increase over time, the Weill said.

Patients received three cycles of fludarabine (25 mg/m2 x 5 d every 5 weeks) followed six to eight weeks later by tositumomab, iodine I 131 tositumomab.

Fourteen of the 38 patients were evaluable for response at least six months after treatment with Bexxar. Ninety-three percent of patients (13 out of 14) had Stage IV NHL at the time of treatment; one patient had Stage II NHL. All of the patients in the study achieved a response to treatment with fludarabine followed by Bexxar. With the addition of Bexxar, after six months of follow-up, the rate of complete response increased five-fold as compared to initial treatment with fludarabine.

Following initial treatment with fludarabine, 14 percent of patients (two out of 14) experienced a complete response. At the thirteenth week, following treatment with tositumomab, iodine I 131 tositumomab, the rate of complete response increased to 43 percent (six out of 14 patients). At approximately six months, 71 percent of patients (10 out of 14) had experienced a complete response. Multicenter studies using Bexxar in combination with fludarabine are scheduled to begin next year, Weill said

Treatment with fludarabine in combination with Bexxar was well tolerated. The principal side effects were hematologic, including a decrease in blood counts, which was reversible. Non-hematologic side effects experienced with tositumomab, iodine I 131 tositumomab were mild-to-moderate, including nausea, fatigue, headache and rhinitis. Due to the immunosuppressive effect of fludarabine, only one patient developed human anti-mouse antibodies, Weill said.

The results were presented at the annual meeting of the American Society of Hematology in New Orleans.

Product Approvals & Applications:

Study Of Prostatic Stent For Use In BPH To Continue

Endocare Inc. (Nasdaq: ENDO), of Irvine, CA, said FDA has approved its investigational device exemption application to complete a multi-site clinical study of Horizon Prostatic Stent for the relief of acute urinary retention. The study will treat and review 20 patients initially and expand to 80 patients in total.

The device is designed to provide men suffering from benign prostatic hyperplasia with temporary relief of bladder outlet obstructions.

The stent is made of nitinol and has a unique shape-memory feature designed for quick and easy introduction and removal through a minimally invasive procedure. After placement, the stent is designed to expand at body temperature and open the prostatic urethra to provide immediate relief to the patient for up to 30 days. The stent is intended to complement existing thermal therapies available for treatment of BPH.

* * *

Guilford Pharmaceuticals Inc. (Nasdaq: GLFD) of Baltimore, said it has submitted an Investigational New Drug application to begin phase I clinical testing of Paclimer Microspheres, an injectable biopolymer-based formulation of paclitaxel (Taxol) for the treatment of ovarian cancer.

The phase I clinical trial is a dose escalation

safety, tolerability and pharmacokinetic study of Paclimer Microspheres in women with advanced ovarian cancer. The trial, conducted by the Gynecologic Oncology Group, will enroll approximately 30 patients, the company said.

The paclitaxel-loaded microspheres are suspended in fluid and injected directly into a patient's abdominal cavity. Once administered, they are designed to slowly dissolve over an extended period to provide controlled and continuous delivery of paclitaxel directly at the tumor site, the company said.

In a related development, Guilford Pharmaceuticals Inc. said it received a $5 million milestone payment from partner, **Amgen** (Nasdaq: AMGN), for collaboration in the clinical developments of neuroimmunophilin. The payment was earned when Amgen filed an Investigational New Drug application in the U.S.

Neuroimmunophilin ligands are a new class of orally active drugs, which, in animal experiments, demonstrated that they were able to gain access to the central nervous system and promote the re-growth and repair of damaged nerves.

* * *

ImClone Systems Inc. (Nasdaq: IMCL) of New York, said it has filed an Investigational New Drug application with FDA to initiate phase I clinical testing of its anti-angiogenesis agent, IMC-1C11. IMC-1C11 is a chimerized antibody that targets the KDR receptor on vascular endothelial cells by inhibiting binding of the essential ligand, vascular endothelial growth factor, to its receptor. KDR is a key receptor associated with tumor angiogenesis.

Use of IMC-1C11 results in the inhibition of tumor growth and death of tumor cells by apoptosis, the company said. Furthermore, as KDR is present preferentially in tumor vasculature, this receptor is a preferred target for the development of anti-angiogenesis therapeutics.

ImClone said it is engaged in a major effort to develop a therapeutic that targets the KDR receptor by inhibiting the action of VEGF. In preclinical studies, the company said it has demonstrated that inhibition of the VEGF receptor flk-1 (the mouse equivalent of KDR) in mice results in a potent inhibition of angiogenesis, tumor growth and metastasis.

In addition to IMC-1C11, ImClone said it has two other oncology programs, which are in advanced clinical development. C225, is being developed to treat cancers that are positive for the epidermal growth factor receptor (EGFr), associated with tumor cell growth and repair in a number of solid tumor cancers.

The company said it is conducting two phase III clinical trials evaluating C225 in combination with radiotherapy and with chemotherapy in patients with advanced squamous cell head and neck carcinoma.

Also, ImClone is conducting a phase II trial evaluating C225 in combination with cisplatin in patients with refractory advanced squamous cell head and neck carcinoma, and a second phase II trial evaluating C225 in combination with irinotecan in patients with refractory colorectal carcinoma. Also underway is a phase II study evaluating C225 in combination with the anti-cancer agent gemcitabine in patients with pancreatic cancer.

* * *

Lorus Therapeutics Inc. (Nasdaq:LORFF) of Toronto, said it has filed an investigational new drug application with FDA for the antisene drug, GTI 2040.

The company said GTI 2040 demonstrated strong anti-tumor properties when tested with a wide range of human tumors in animal models, including tumors derived from colon, liver, lung, breast, kidney and ovary.

* * *

Matritech Inc. (Nasdaq: NMPS) of Newton, MA, said an FDA advisory panel has unanimously recommended approval, with two conditions, of NMP22 Test Kit for the expanded claim of testing previously undiagnosed individuals who have symptoms or are at risk for bladder cancer.

FDA already approved NMP22 for monitoring the recurrence of bladder cancer in the U.S.

Deals and Collaborations:

Abgenix, CuraGen To Develop Human Antibody Drugs

Abgenix (Nasdaq: ABGX) of Fremont, CA, and **CuraGen Corp.** (Nasdaq: CRGN) of New Haven, said they have formed a five-year alliance to develop and commercialize genomics-based antibody drugs using XenoMouse technology.

The companies said the alliance was established to identify up to 120 fully human antibody drug candidates intended for treating a broad range of complex diseases including cancer and autoimmune disorders. Antibodies to cancer antigens in the CuraGen database will be generated exclusively with the Abgenix XenoMouse technology during this alliance. Under the terms of this agreement, Abgenix will purchase $15 million of CuraGen common stock

and CuraGen will provide research support payments of $1.5 million per year. Both companies will receive reciprocating milestone and royalty payments for products resulting from this alliance.

* * *

Biomedical Diagnostics, LLC, of Ann Arbor, MI, a jointly funded venture between **Biotherapies Inc.** of Ann Arbor and **BioLabs Inc**. of New York, has been formed to develop cancer screening products for routine medical testing to indicate risk of developing breast cancer, the companies said.

Biomedical Diagnostics is focused on development of an assay based on the level of Mammastatin in serum. BioLabs provided initial funding of $1.5 million, the companies said.

FDA gave approval to Biotherapies for phase I/II testing that began last June at M. D. Anderson Cancer Center.

* * *

EntreMed Inc. (Nasdaq: ENMD) of Rockville, MD, said it has signed a letter of understanding with **Chiron Corp**. for the contract manufacturing of bulk Endostatin protein.

Chiron will produce EntreMed's bulk Endostatin protein in its licensed manufacturing facilities. This manufacturing campaign is designed to ensure that a sufficient quantity of Endostatin protein is available for the continued expansion of EntreMed's clinical trial program, the company said.

Both EntreMed and its initial contract protein manufacturer, Covance Biotechnology Services, use the Pichia pastoris yeast expression system and EntreMed's protein purification procedures to produce GMP recombinant human Endostatin protein and Angiostatin protein for clinical testing. Chiron will also use this system and EntreMed's purification procedures.

In a related development EntreMed Inc. said it has exercised its option to repurchase 291,667 shares of its common stock from Bristol-Myers Squibb Co. at a price of $13.143 per share. BMS will continue to hold 583,332 shares of EntreMed common stock as required by the terms of its agreement.

* * *

OXiGENE Inc. (Nasdaq: OXGN; Sweden) of Boston and Sweden, said it has signed a letter of intent with **Bristol-Myers Squibb Co.** (NYSE: BMY) for the development and commercialization of the OXiGENE Combretastatin technology, including the lead compound, Combretastatin A4 Prodrug, an anti-tumor vascular targeting agent.

The letter of intent provides for an exclusive period for completion of a definitive agreement.

OXiGENE is conducting three phase I clinical trials of CA4P in the U.S. and Europe.

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Pangea Systems Inc. of Oakland, CA, said **Sugen Inc.** has licensed its Clustering and Alignment Tools. The scientific computational tools enable companies to quickly cluster and align high volumes of expressed sequence tags and partial gene sequences into full length gene sequences suitable for gene indexing and other applications for drug discovery.

* * *

SuperGen Inc. (Nasdaq: SUPG; SUPGW; SUPGZ) of San Ramon, CA, said it has extended to eight years its research agreement with the **Stehlin Foundation for Cancer Research** at St. Joseph's Hospital in Houston**.**

The company said it has secured the global rights to other camptothecins and additional anticancer compounds, one of which, rubitecan, has demonstrated marked antitumor activity and is expected to have a favorable safety profile. Also, reductions will be made with respect to SuperGen's royalty payments for sales of rubitecan above $500 million. Rubitecan is in phase III clinical testing for the treatment of pancreatic cancer and in phase II testing for the treatment of 11 additional tumor types.

* * *

Viragen Scotland Ltd., of Plantation, FL, a subsidiary of **Viragen Europe Ltd.** (OTC Bulletin Board: VERP) and the research arm of **Memorial Sloan-Kettering Cancer Center** announced a collaboration on a human monoclonal antibody for the treatment of melanoma and other cancers.

Viragen and Memorial will produce and manufacture the antibody which Memorial will test in clinical trials, Viragen said. Memorial has agreed to coordinate phase I and phase II trials, Viragen said.

Patents:

Myriad Wins MTS2 Gene Patent

Myriad Genetics Inc. (Nasdaq: MYGN) of Salt Lake City, said it has been awarded patent number 5,994,095 by U.S. Patent and Trademark Office for the DNA sequence of the MTS2 gene (commonly known as p19) as well as primers, probes and vectors relating to use of the p19 gene in diagnostic and therapeutic products.

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