THE CANCER LETTER INTERACTIVE

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

Oxaliplatin Regimen May Beat Standard For Advanced Colorectal Cancer, NCI Says

Drilling into the NCI clinical trials Web site, visitors may stumble across the following announcement:

"Oxaliplatin Combo May Be Better Treatment for Advanced Colorectal Cancer."

According to the news item, a study led by North Central Cancer Treatment Group found that a regimen containing oxaliplatin slowed the time to progression of advanced colorectal cancer, and produced better survival and toxicity than the current standard of care.

(Continued to page 2)

In Brief:

Martha Fewell, Assistant To Four Directors Since 1987, To Retire After 29 Years At NCI

MARTHA FEWELL, administrative assistant to four NCI directors since 1987, announced she plans to retire in June.

Fewell's calm, no-nonsense demeanor kept NCI Directors **Vincent DeVita**, **Samuel Broder**, **Richard Klausner**, and **Andrew von Eschenbach**, as well as interim directors **Edward Sondik** and **Alan Rabson**, on schedule. Anyone who had something to discuss with the director called Fewell first.

She and her husband Joe Fewell plan to move to Florida to be near their daughter, Dee Fewell, her sister, and her sister's grandchildren. Joe Fewell retired five years ago from NCI. "I planned to go then, but Dr. Klausner begged me to stay," Martha Fewell said.

After helping von Eschenbach settle into his new job over the past four months, Fewell said she decided "the time has come." She has worked 29 years at NCI, starting as an assistant to **Bill McGuire** in the Cancer Therapy Evaluation Program. In 1979, she became assistant to **Eli Glatstein**, who headed the Radiation Oncology Branch in the Clinical Oncology Program, Division of Cancer Treatment.

Working eight years in the Clinical Center was good preparation for the administrative hot seat in the director's office, Fewell said. When DeVita asked Fewell why he should select her to be his assistant, she answered, "If I could survive the Clinical Oncology Program, I can certainly handle the director's office."

"Working in the Clinical Center was the most rewarding time of my career, because everyone pulls together for the sake of the patients," Fewell said. "That's what NCI is all about— ultimately, to help patients."

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NCCTG Trial Data Embargoed Until ASCO Presentation

(Continued from page 1)

In fact, the NCCTG data and safety monitoring committee recommended closing the standard care arm of the study and switched the patients to the oxaliplatin regimen arm.

A new regimen for colorectal cancer that beats the standard of care would appear to deserve more than a subtle statement. Why not a big "rollout" downtown, with HHS Secretary Tommy Thompson opening a press conference with a heartwarming story about his native state?

Instead, on April 24, the news item was tucked into a not-very-noticeable place, on the NCI Clinical Trials Web site: http://www.cancer.gov/clinical_trials.

Releasing information from important clinical trials is rarely a straightforward and orderly process. In this case, NCI officials said they felt an obligation to inform the public about the findings, and American Society of Clinical Oncology officials said they wanted to allow time for reasonable peer review.

Also, reports of significant findings and their review are among top reasons for 25,000 people to attend the upcoming ASCO annual meeting in Orlando. The oxaliplatin data are under an embargo until their presentation on May 18.

"From our point of view, the process of releasing important trial results in a 'rolling' fashion has worked well in this case, and may be useful in other situations when a result emerges suddenly," said Richard Kaplan, chief of the NCI Clinical Investigations Branch.

"The ease and transparency of communication via the Web allows the outcome to be known right away, and then additional detail and perspective are progressively made available as soon as they are ready," Kaplan said. "NCI can ask everyone to 'watch this space' to get a full picture of the importance of the trial results. Meanwhile, those who have the most urgent need for information, study subjects and other patients and oncologists, can be informed of the direction of the trial outcome; they need not wait until a clean dataset is ready, or until opinion leaders have been able to view the data and put it into clear clinical perspective."

ASCO would have preferred to limit the release of information to trial participants and investigators, said Charles Balch, the society's executive vice president and CEO.

"The NCI and the investigators felt an obligation, which I think is correct, to inform the patients on the trial and the investigators," Balch said. "However, we were disappointed that they chose to put what they did on the public Web page."

Oxaliplatin, a drug sponsored by Paris-based Sanofi-Synthelabo, is not approved in the U.S., which makes the release of information less urgent, Balch said. "The drug is not available outside a clinical trial, so it's not a public health issue," he said.

At ASCO, the results of the trial, N9741, will be presented by investigators from NCCTG and critiqued by Leonard Saltz, the gastrointestinal oncologist whose regimen of CPT-11, 5-fluorouracil and leucovorin now appears to be inferior to oxaliplatin, 5-FU and LV.

"There will be discussion and debate about the context of this drug relative to other drugs, such as CPT-11, and that's part of discussion among peers that will occur at the ASCO meeting," Balch said. "Experts need to debate this."

Kaplan agreed that it would be premature to release data at this point.

"The impact of the N9741 results, like those of any trial, needs to be considered carefully not only within the context of the trial itself, but also in relation to data from other studies, the impact of second-line regimens, and the full scope of therapeutic options," he said.

"The data that led to the DSMB decision to

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unblind the results were from an interim (albeit planned) analysis at a point where a good deal of additional data were still rolling in quite quickly," Kaplan said. "A brief delay before ASCO allowed NCCTG to carry out what is always a critical step in preparing any trial for presentation—calling in outstanding data, performing quality checks, and locking the dataset."

Watch This Space

The NCI statement contained no data:

"Patients with newly diagnosed advanced colorectal cancer who received a multidrug regimen containing the investigational agent oxaliplatin appear to have fared significantly better than patients who received the current standard treatment, according to preliminary data from a randomized, phase III clinical trial sponsored by NCI.

"The preliminary analysis showed that patients receiving the regimen known as FOLFOX (oxaliplatin, together with infusional 5-FU and LV) had a significantly longer time to disease progression, significantly better overall survival, a significantly higher response rate, and lower toxicity than patients receiving a regimen known as IFL (CPT-11, together with bolus 5-FU and LV). IFL (also known as the Saltz regimen) has been the standard treatment for advanced colorectal cancer since April 2000.

"The data, although preliminary, appear to show a very strong trend in favor of the FOLFOX regimen. The trial, known as N9741, is coordinated by the North Central Cancer Treatment Group in collaboration with four other cancer research cooperative groups in the U.S. and Canada.

"The current analysis involves 795 patients with previously untreated metastatic colorectal cancer who enrolled in the study between March 1999 and April 2001.

"During a planned interim analysis of the trial last week, the independent monitoring committee charged with oversight of the trial reviewed the results to date and found the FOLFOX data promising enough to warrant significant changes to the trial.

"Consequently, enrollment onto the IFL arm of the trial has been discontinued. New patients will continue to be enrolled on the FOLFOX arm pending other arrangements for access to oxaliplatin. Patients on the other arms of the trial who at any point are not responding to their current treatment will be permitted to switch to the FOLFOX regimen. (In the non-FOLFOX arms of the trial, patients receive either IFL or a combined regimen consisting of [CPT-11] and oxaliplatin only. It's still too early to draw any conclusions about the effectiveness of the latter regimen compared with that of FOLFOX.).

" 'Patients and their doctors are being advised of these findings as quickly as possible,' said Richard Kaplan, of the NCI Cancer Treatment and Evaluation Program. 'Even though the data are preliminary and stem from a single randomized trial, the data monitoring committee felt that the apparent superiority of FOLFOX should be made known to patients and clinicians.

"Collection of all the trial data is now under way. Details concerning the magnitude of the differences between the two regimens are expected to be announced within the next few weeks. Meanwhile, discussions are under way between NCI and the maker of oxaliplatin, the French pharmaceutical company Sanofi-Synthelabo, to permit more patients with metastatic colorectal cancer to receive treatment with the investigational drug, which is currently not licensed for use in the U.S."

Two- To Three-Month Survival Advantage?

Sources said the data and safety monitoring committee overseeing the trial determined on April 10 that the oxaliplatin-containing regimen had surpassed the CPT-11-containing regimen.

With the data absent, colorectal cancer experts appear to be enjoying the guesswork.

"I can guess what the data shows, because the study was terminated abruptly," ventured one expert who performed this exercise on condition that his name would not be used. "It didn't terminate because of bad news. One arm had to have been doing better, and it wouldn't have closed for anything but survival, so one arm had to have had a survival advantage, and my guess it's the oxali arm. Otherwise, there wouldn't be so much excitement."

According to the protocol, in order to close an arm in the trial, the planned interim analysis had to find superiority in time to tumor progression with the p-value of less than .0005. Finding a survival advantage in a smaller study powered to detect time to progression means the survival advantage is substantial.

"It would have to be in the range of two to three months," the expert said.

The NCCTG trial is being rewritten to remain open, to serve as an expanded access program, sources said.

"This is a drug that may become available for use without any data available, outside an ASCO presentation," said an expert familiar with development of oxaliplatin.

The Eternal Question: Bolus Vs. Infusion 5-FU

Though N9741 shows a survival advantage for the oxaliplatin regimen, the trial's implications for the approval of oxaliplatin by FDA aren't clear cut:

—The trial was launched two years ago to compare progression-free survival in six treatments of colorectal cancer, rather than to provide a basis for approval of any drug or regimen. Ultimately, three of the trial's arms were dropped. One arm, 5-FU/LV, was dropped after it was surpassed by the Saltz regimen as the standard of care, and two other regimens were dropped because of toxicity problems.

—The trial compares regimens, not single drugs. FDA has required data on the contribution of all drugs contained in multidrug regimens.

—The trial isn't even in the same indication as the registration trials sponsored by Sanofi. While N9741 is conducted in the first-line setting, Sanofi is testing oxaliplatin as a second-line treatment.

—The oxaliplatin and CPT-11 regimens aren't using the same methods of administering 5-FU/LV. The oxaliplatin regimen uses infusion. The CPT-11 regimen uses bolus.

This distinction in the administration of 5-FU/LV may be significant, experts say.

"[Aimery] deGramont has previously published a randomized trial showing that infusional 5-FU produces significantly better time to progression and less toxicity than daily 5-FU/LV a-la-Mayo," said Richard Schilsky, associate dean for clinical research at the University of Chicago. "So, the infusional 5-FU could be an important contributor. Therefore, it would be nice to know how FOLFOX compares to [the Douillard regimen] CPT-11 and infusional 5-FU."

Schilsky said he has not seen the data from N9741.

—Selection of patients can be significant, too. For example, an imbalance in the number of patients with the performance status of ECOG 2, who generally don't benefit from treatment, can alter the result in either arm.

Approval for First and Second Line?

The full spectrum of news about oxaliplatin is appears to be broader than ASCO presentations reflect.

On April 29, five days after the NCI announcement of the NCCTG findings, a press release from Sanofi reported that FDA has granted fast-track review for the application for oxaliplatin as a second-line therapy for advanced colorectal cancer.

The company study (EFC 4584) tested the drug in patients whose disease progressed on the Saltz regimen or within six months after treatment.

The fast track designation doesn't amount to an inside track at FDA. It means that the drug has the potential to address an unmet medical need, that the sponsor would be allowed to submit the New Drug Application in parts, as a "rolling NDA," and that FDA would have to complete review of the application on an accelerated schedule, within six months.

"We are working very closely with the independent data and safety monitoring board for this trial to determine appropriate handling of data from a planned interim analysis of objective response rate, time to tumor progression, and reduction in tumor-related symptoms," said Mace Rothenberg, Ingram associate professor of cancer research at Vanderbilt University and the principal investigator on EFC 4584.

The best-case scenario for Sanofi may be that data from the NCCTG trial in the first-line indication and emerging data in the company-sponsored trials in the second-line indication, as well as pooled data accumulated in countries where oxaliplatin is approved, would support an across-the-board approval for oxaliplatin in advanced colorectal cancer.

"Ideally, these trials will provide complementary data addressing the role of oxaliplatin in first and second line, not necessarily limiting labeling to one setting or another," Rothenberg said. "One can say, let's not view this in isolation, but rather in the context of many completed and published phase III trials. The level of comfort regarding activity, toxicity, and tolerability may actually be greater because of these other trials."

This will be the second time oxaliplatin has been reviewed by FDA. In March 2000, the agency's Oncologic Drugs Advisory Committee recommended against approval of the drug. At that time, Sanofi and U.S. partner Eli Lilly & Co. sought approval based on European studies powered for response rate and progression-free survival. The company's survival assessment involved extensive statistical analysis that went beyond the simple log rank test (**The Cancer**

Letter, March 24, 2000).

Soon after ODAC nixed the drug, Eli Lilly dropped out of the U.S. development program, and oxaliplatin reverted to Sanofi.

In Congress:

Senate Confirms Bush Nominee Elias Zerhouni For NIH Director

The U.S. Senate on May 2 approved Elias Zerhouni, 51, to head the National Institutes of Health.

President Bush nominated Zerhouni, executive vice dean and chairman of radiology at Johns Hopkins University School of Medicine, in March to head NIH, which has a $27 billion annual budget.

Zerhouni, born and educated in Algeria, came to the U.S. in 1975 with his wife, Nadia, a pediatrician. He is an expert in medical imaging and biomedical engineering, and established the Institute for Cell Engineering, which conducts stem cell research at Hopkins.

At his confirmation hearing May 1, Zerhouni expressed strong support for federal funding for research on stem cells from human embryos.

"As executive vice dean at Johns Hopkins, I was instrumental in creating an institute for stem cell engineering primarily because I was concerned about the lack of any federal funding to advance the fundamental research still needed in this promising but fledgling field," he told the Senate Health, Education, Labor and Pensions Committee. "Without federal funding, it is hard for me to see how you develop a field of science in our country."

Last August, Bush allowed federally funded research on stem cell lines already in existence, from excess embryos from fertility clinics. Zerhouni called that policy "an important advance," because it allowed some federal funding.

If, in the future, that policy proves to be too limiting to research, Zerhouni said, "I'll be the first one to assemble that information."

Zerhouni said he would provide objective scientific advice on the controversial issue. "I believe disease knows no politics," he said. "The NIH and its director should not be or made to be factional but must always remain factual."

As NIH director, Zerhouni said he would promote faster translation of research results into clinical testing and greater interdisciplinary research. He said he also would work to increase diversity of grant recipients.

"We need to continue to train, recruit and retain the best talent in biomedical research because in the final analysis it is always the creative spark of the unique individual that leads to new knowledge and real progress," he said to the committee.

"Elias Zerhouni is a living example of the American dream," said Sen. Edward Kennedy (D-Mass.), committee chairman. "He arrived from Algeria with little else but his medical training and a desire to help his fellow human beings facing disease. I believe that all of us on this committee can agree that his contributions have been extraordinary."

HHS Secretary Tommy Thompson said he believed Zerhouni "will be a visionary and innovative leader as we work to cure and develop treatments for the world's most deadly diseases and chronic conditions."

Bush's nominee for surgeon general, Richard Carmona, also is expected to get Senate approval soon.

FDA Proposes Requirement For Electronic Submission

FDA this week issued a proposed rule that would require certain labeling submitted for review with new drug applications, certain biological license applications, abbreviated new drug applications, supplements, and annual reports to be submitted to the agency in electronic format.

The rule, when finalized, would be the first FDA regulation to require submission of information by electronic means.

In the proposal, the agency said the electronic format would enable more rapid and accurate review of the content of labeling.

Each year, FDA receives more than 1,000 proposed labeling changes for NDAs and BLAs and more than 2,600 proposed original and supplemental labeling changes for ANDAs. As part of the review process, FDA conducts word-for-word comparisons to ensure accuracy and currency of the information.

"Electronic submissions will allow computer matching that will greatly enhance the accuracy and speed of this part of the review," said Lester Crawford, FDA deputy commissioner.

The proposed rule was published in the May 3 Federal Register with a 90-day comment period.

Written comments may be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061,

Rockville, MD 20852. Electronic comments may be sent to http://www.fda.gov/dockets/ecomments.

Funding Opportunities:

AACR, Pancreatic Network Offer Early-Career Award

Application Deadline: Oct. 15, 2002

American Association for Cancer Research and the Pancreatic Cancer Action Network invite applications for the Career Development Award for early-career scientists engaged in pancreatic cancer research.

Candidates must be, by the start of the grant term (July 2003), in the first, second, or third year of a full-time faculty appointment at the level of instructor, acting assistant professor, assistant professor, or an equivalent full-time faculty appointment at an academic or medical institution within the U.S.

Research proposals are restricted to those basic, translational, or clinical research proposals with 100 percent applicability to pancreatic cancer. The two-year grant provides $50,000 per year for direct research expenses, 2003 and 2004 AACR Annual Meetings financial support for travel, and a waiver of registration fees. Application information and guidelines can be downloaded from http://www.aacr.org.

Inquiries: American Association for Cancer Research, Attn: Sheri Ozard, program coordinator, Public Ledger Bldg., Suite 826, 150 South Independence Mall West, Philadelphia, PA 19106-3483, phone 215-440-9300; fax 215-440-9372; e-mail awards@aacr.org.

RFAs Available

RFA CA-03-011: Community Clinical Oncology Program

Letter of Intent Receipt Date: June 24,

Application Receipt Date: July 22, 2002

Division of Cancer Prevention, NCI, invites domestic institutions to apply for new and currently funded Community Clinical Oncology Programs and research bases. The NCI-supported clinical cooperative groups and/or cancer centers serve as research bases for the CCOPs. The research bases design the protocols for the clinical trials in cancer treatment, prevention and early detection as well as evaluating interventions affecting quality of life, rehabilitation and symptom management associated with cancer and its treatment. The RFA seeks to build on the strength and demonstrated success of the CCOP network over the past nineteen years by: 1. continuing the program as a vehicle for supporting community participation in cancer treatment and prevention and control clinical trials through research bases (clinical cooperative groups and cancer centers supported by NCI); 2. expanding and strengthening the cancer prevention and control research effort; 3. utilizing the CCOP network for conducting NCI-assisted cancer prevention and control research; and 4) evaluating on a continuing basis CCOP performance and its impact in the community. The RFA will use NIH U10 award mechanism. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-03-011.html.

Inquiries: Lori Minasian, chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, NCI Executive Plaza North - Room 2017, 6130 Executive Blvd, MSC-7340, Bethesda, MD 20892-7340, phone 301-496-8541; fax 301-496-8667; e-mail lm145a@nih.gov

RFA CA-03-012: Minority-Based Community Clinical Oncology Program

Letter of Intent Receipt Date: June 24, 2002

Application Receipt Date: July 22, 2002

Division of Cancer Prevention, NCI, is continuing the established cancer control effort which involves practicing oncologists who serve large minority populations in the NCI clinical trials program. The Community Oncology and Prevention Trials Research Group, DCP, invites domestic institutions with the capability and intent to serve new cancer patients largely from minority populations to apply for cooperative agreements in response to this Minority-Based Community Clinical Oncology Program. Currently funded Minority-Based CCOPs are also invited to respond to this RFA. The NCI clinical trials program provides a network of support for clinical research in cancer centers, major university centers, and community programs. The program supports as a national resource those physicians involved in the care of minority cancer patients who are available for treatment and cancer prevention and control clinical trials research. Areas of research where minority involvement is especially needed include: cancer prevention and control, interventions to improve screening and early detection practices; methodological research on ways to increase the educational awareness of individuals at risk for cancer; and studies of barriers to prevention and treatment of cancer. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-03-012.html.

Inquiries: Worta McCaskill-Stevens, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, NCI Executive Plaza North-Rm 2017, 6130 Executive Blvd., MSC-7340, Bethesda, MD 20892-7340, phone 301-496-8541; fax 301-496-8667; e-mail wm57h@nih.gov

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In Brief:

The Voice On The NCI Director's Line, Martha Fewell, To Retire

(Continued from page 1)

In 1992, while working for Broder, Fewell was diagnosed with malignant melanoma. "Thanks to the wonderful medical staff at the NCI, I am a cancer survivor today," Fewell said.

Fewell's retirement plans are relaxed in comparison to the hectic pace of the director's office. "After moving to Florida, I hope to spend quality time with my family and enjoy the good life by the pool," Fewell said.

* * *

NIH and the **University of California at San Francisco** have signed a memorandum of understanding for research use of UCSF's two human cell lines that meet President's Bush criteria in his August 9, 2001 address. UCSF is the first university to enter into a stem cell agreement for distribution of human stem cell lines. In compliance with the NIH guidelines for the transfer of research materials, the agreement allows NIH scientists to publish the results of their research. NIH would retain its ownership to any intellectual property that might arise from the conduct of research in this area. UCSF will retain commercial rights to its material and will receive a fee to cover handling and distribution expenses. UCSF has agreed to make stem cell lines available for use by non-profit institutions that receive grants from NIH under the same terms and conditions as those available to NIH scientists, provided these institutions enter into a separate written agreement with UCSF. "We welcome these collaborative efforts because they provide the framework for future progress in this important scientific area," said **Ruth Kirschstein**, acting NIH director. . . . **NIH FUNDED** four resource infrastructure enhancement awards for human embryonic stem cell research. The awards, which provide $3.5 million over two years, will fund expansion, testing, quality assurance, and distribution of existing cell lines that meet the President's criteria for federal funding of this research. The awardees include **Cellsaurus**, a subsidiary of Bresagen, of Athens, GA; **ES Cell International Pte Ltd**, of Melbourne, Victoria, Australia; **UCSF**; and the **Wisconsin Alumni Research Foundation**. The four entities are listed on the NIH Human Embryonic Stem Cell Registry, http://www.escr.nih.gov, and have a combined total of 17 stem cell lines that will be available to basic scientists for research. . . . **KATHY RUSSELL,** deputy to the director and associate director for planning and administration at the Lombardi Cancer Center at Georgetown University Medical Center, has been appointed special advisor to the Georgia Cancer Coalition. Russell, who will be based in Washington, DC, will provide clinical and technical assistance on research, grants, operational and liaison matters for the GCC. Prior to her work at Lombardi, Russell served in the Clinical Oncology Program, the Biological Response Modifiers Program, and the Division of Cancer Treatment during her eight years with NCI. Created by **Gov. Roy Barnes**, the GCC brings together leading Georgia hospitals, universities, biotech firms, civic groups, and non-profit and government agencies to provide cancer research, prevention, detection and treatment. . . . **RICHARD KLAUSNER**, senior fellow and special adviser for counterterrorism at the National Academies and former director of NCI, received the inaugural Walther Prize at the Indiana Historical Society on April 26. The prize is an unrestricted cash award of $50,000 for cancer research. In his research, which focuses on the genetics and biochemistry of metals as essential but toxic nutrients for virtually all forms of life, Klausner created a detailed picture of post-transcriptional gene regulation; worked on the pathways by which molecules traffic and speak to each other within the cell; and described novel mechanisms by which tumor suppressor genes function. . . . **UNIVERSITY OF FLORIDA** Blood and Bone Marrow Program was chosen by NIH as part of the Blood and Marrow Transplant Clinical Trials Network. The award provides $2 million over five years and is sponsored by the National Heart, Lung and Blood Institute and NCI. **John Wingard**, professor in the College of Medicine division of hematology and oncology, and director of the UF Blood and Marrow Transplant Program, was selected chairman of the steering committee. His study will compare voriconazole to fluconazole. . . . **NATIONAL ACADEMY OF SCIENCES** elected two Dana Farber researchers to membershipin the academy: **Harvey Cantor,** chairman of the Department of Cancer Immunology and AIDS; and **Bruce Spiegelman**, professor of cell biology. . . . **CORRECTION:** The Lustgarten Foundation this year awarded $1.3 million in grants, not $6.5 million as reported in **The Cancer Letter** last week. The foundation's total grants funding since 1999 is $6.5 million.

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Business & Regulatory Report

Product Approvals & Applications:

Faslodex Approved For HR+ Metastatic Breast Cancer In Postmenopausal Women

FDA has granted marketing approval for Faslodex for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antioestrogen therapy.

The drug is sponsored by **AstraZeneca.**

The approval is based on two phase III trials that showed Faslodex to be at least as effective as the aromatase inhibitor Arimidex in tamoxifen-

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Deals & Collaborations:

Aventis To Provide $480M To Genta For Development Of Genasense

Genta Inc. (Nasdaq: GNTA) and **Aventis** (NYSE: AVE) said they have entered into an agreement to develop and commercialize Genasense (G3139), Genta's antisense compound.

The compound, Genasense, is in phase III trials in hematologic cancers and solid tumors. By inhibiting production of the Bcl-2 protein, Genasense targets apoptosis, making it easier for chemotherapy to kill the cancer cells, the company said.

The agreement will provide up to $480 million in cash, equity, milestones and convertible debt to Genta.

"We believe Genasense is one of the most promising late stage investigational oncology compounds currently under study," said Richard Markham, CEO of Aventis Pharma.

Also under the agreement, Aventis will fund 75 percent of all future NDA-directed development costs in the U.S., and 100 percent of all other development, marketing, and sales costs within the U.S. and elsewhere. Genta will receive royalties on all worldwide sales of Genasense.

The two companies will jointly develop and market Genasense in the U.S., and Aventis will have exclusive development and marketing rights to the compound in all countries outside of the U.S.

Genta will retain responsibility for global manufacturing and for regulatory filings within the U.S., while Aventis will assume all regulatory responsibilities outside the U.S.

Joint management teams, including representatives from both partners, will oversee the Alliance.

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FDA Approves Faslodex For Metastatic Breast Cancer

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resistant breast cancer in postmenopausal women, the company said.

Faslodex, an oestrogen receptor antagonist, has no known agonist effects, the company said. Unlike aromatatase inhibitors that reduce the amount of oestrogen in a woman's body, and tamoxifen, which blocks the oestrogen receptor, Faslodex targets and degrades the oestrogen receptors in breast cancer cells.

It is the only antioestrogen in general clinical use to have demonstrated efficacy following tamoxifen failure, indicating that it works in a different way from tamoxifen.

"Faslodex provides an effective, new treatment option for women with advanced breast cancer whose tumors have become resistant to tamoxifen," said C. Kent Osborne, the lead investigator from Baylor College of Medicine. "When you have a new drug like Faslodex that we can now add to that sequence of drugs, we may be able to control the breast cancer for a longer."

* * *

Dendreon Corp. (Nasdaq:DNDN) of Seattle said its therapeutic vaccine for multiple myeloma, Mylovenge, has been granted orphan drug status by FDA.

In receiving orphan drug status for the therapy, Dendreon is eligible for tax credits for related clinical development costs and assistance from FDA to facilitate the regulatory review and approval process, the company said.

"We will continue our ongoing efforts to explore the utility of the vaccine for treating B-cell malignancies such as multiple myeloma," said David Urdal, president and chief scientific officer of Dendreon.

Mylovenge is in phase II trials, the company said. Preliminary results of two recently completed trials suggest that Mylovenge treatment is safe, and that it may stimulate immune activity and cause disease regression or stabilization.

* * *

Merck KGaA of Darmstadt, Germany, said it would delay its filing application for European approval of cetuximab (Erbitux/C225) until the first half of 2003 for colorectal cancer and head-and-neck cancer.

"As the European regulatory system does not allow a rolling submission, we now plan to wait a few months and then file with a bigger and more robust data package based on the Merck colorectal-cancer trial data," said Matthew Emmens, head of the Merck Pharma Ethicals business sector.

The Europe-wide introduction of cetuximab is now scheduled to take place in 2004, a few months later than originally planned, but with a much more promising outlook for its oncology business because of the greater number of colorectal-cancer patients, the company said.

Enrollment in the European clinical trials on cetuximab for colorectal cancer is nearly complete, the company said. Merck said it has already completed its trial for head-and neck cancer and is compiling the data.

Cetuximab is an investigational monoclonal antibody designed to target and block the epidermal growth factor receptor, the company said.

Merck said it licensed the rights to develop and market cetuximab outside of North America from ImClone Systems of New York in 1998.

Merck had planned to submit its EMEA application in 2003 for both cancer indications, with data for the treatment of head-and-neck cancer from its own clinical trials and data from the ImClone System colorectal-cancer clinical trial. FDA, however, advised ImClone that it would not accept for filing in

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its current form the Biologics License Application of cetuximab for irinotecan-refractory colorectal cancer.

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Syncor International Corp. (Nasdaq:SCOR) of Woodland Hills, CA said it has completed delivery of the first commercial doses of Zevalin (ibritumomab tiuxetan), an FDA-approved treatment for relapsed or refractory low grade, follicular, or transformed B-cell Non-Hodgkin's Lymphoma.

While other therapies for treating lymphoma require weeks or months of treatment, Zevalin therapy is completed over a period of seven to nine days, the company said. The therapeutic regimen consists of Rituxan preceding Indium-111 Zevalin followed seven to nine days later by a second infusion of Rituxan prior to Yttrium-90 Zevalin.

Zevalin is the first product approved by the FDA that combines monoclonal antibody and radiopharmaceutical technologies, the company said

"It is a complex pharmaceutical requiring patient-specific compounding and ultra-precise dispensing accuracy," said Rod Boone, president and CEO of Syncor Pharmaceutical Services. "Our staff of over 450 nuclear pharmacists serve as consultants to thousands of other pharmacists and nuclear medicine and oncology specialists coast to coast. They will use their depth of clinical knowledge to help customers manage the complexities of using this product to provide care to very ill patients."

Deals & Collaborations:

Genta, Aventis In Agreement On Genasense Development

(Continued from page 1)

Genta will receive a total of $135 million in initial and near- term payments consisting of $10 million cash as a licensing fee and $40 million cash as development fees, $10 million in convertible debt, and $75 million pursuant to an equity investment upon achievement of a near-term clinical milestone. Genta will receive an additional $280 million in cash, and $65 million in convertible notes, pursuant to achievement of clinical and regulatory milestones.

"This collaboration brings together world-class leadership in oncology product development," said Raymond Warrell, Genta chairman and CEO. "Having followed the terrific work that Aventis has conducted with its leading oncology drug Taxotere, we believe this new collaboration is perfectly poised to maximize the blockbuster potential of Genasense on a worldwide basis. Genta's expertise in hematologic oncology, both in development and marketing, will be a key factor in the ultimate success of the product."

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Abbott Labs, AstraZeneca, Aventis Pharmaceuticals, Bristol-Myers Squibb Co., GlaxoSmithKline, Johnson & Johnson, and **Novartis** said they are collaborating on a consumer-friendly Together Rx savings card, which would allow Medicare enrollees savings on more than 150 commonly prescribed drugs.

Through the Rx Card, Medicare enrollees without public or private prescription drug coverage and with incomes of up to $28,000 ($38,000 for couples) would be able to save 20 to 40 percent off the price of prescription medicines at the pharmacy, directly from the manufacturers, the company said.

Enrollment by the sales force of each company has begun through participating pharmacies, physicians' offices, and community centers, the company said. The cards become effective in early June. During the enrollment process, individuals of more limited income who meet eligibility requirements for patient assistance programs provided by the individual companies or by foundations supported by each of the individual companies, will be notified by McKesson, the Together Rx Card administrator, that they may qualify for further savings, the company said.

"The lack of prescription drug coverage among Medicare beneficiaries is a serious national problem that no individual company can solve," said executives from the seven participating companies. "While the Together Rx Card is an excellent start, it is not the single long-term solution that is needed. We commend President Bush for his leadership in calling for the enactment of a comprehensive Medicare prescription drug benefit this year."

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Ardais Corp. of Lexington, MA, said **Abgenix Inc.**, **Aventis**, **CuraGen Corp.** and other biotech and pharmaceutical companies have licensed access to its Biomaterials and Information for Genomic Research Library and Suite of Bioinformatic Tools.

The desktop resource enables researchers to apply a portfolio of human tissue-based products and services in molecular profiling studies to identify and

validate drug targets, the company said.

"Access to specimens from patients who suffer from diseases of significant morbidity, mortality or poor quality of life is a key research element for the identification of novel therapies with improved clinical efficacy," said Greg Landes, vice president of product discovery at Abgenix, Inc. "To utilize the clinical reagents to make informed decisions in the drug development process, the specimens must exhibit excellent consistency and high quality to enable critical development correlations to be made."

The BIGR Library is a repository of tens of thousands of frozen tissue samples representing a diversity of disease, collected through the National Clinical Genomics Initiative, the company said.

The initiative, launched by Ardais in September 2000, includes collaborations with four leading medical centers.

Through the collaborations, tissue samples are collected and processed according to strict protocols to maintain the molecular and histological integrity for genomics-based research.

The tissue samples obtained through the collaborations are linked in the BIGR System with the structured, anonymized clinical information permitted by strict patient consent procedures, the company said.

The Ardais initial portfolio of clinical genomics resources includes formalin-fixed and frozen tissue samples and associated clinical information; standard or custom Tissue Microarrays for high throughput parallel analyses; and molecular derivatives, such as RNA, which are validated for research use through a battery of qualification procedures, the company said.

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Correlogic Systems Inc. of Bethesda, MD, said it has entered into a licensing arrangement with NIH and a research agreement with FDA and NCI.

The company signed an exclusive, worldwide licensing agreement with NCI for the shared invention of using patterns of protein expression to detect disease as well as other biological states, the company said.

Through a cooperative research and development agreement, FDA, NCI and Correlogic Systems will continue their joint research in the identification of patterns of protein expression, the company said.

A study conducted by the company, FDA and NCI revealed that it is possible to detect ovarian cancer, even at its earliest stage, by analyzing patterns of proteins from a small sample of blood, the company said.

The same process and technology may also be used to discover patterns or models—signaling other cancers and diseases.

The licensing arrangement provides for the commercialization of the intellectual property rights with the concept of patterns of molecular expression as a diagnostic tool, the company said.

The arrangement will allow Correlogic to enter into sub-licensing, joint venture and other agreements with for-profit and non-profit organizations and, importantly, will facilitate the rapid commercialization of the technology and the development of clinical diagnostic tests.

Research conducted under the CRADA would validate and expand the joint research by examining patterns of protein expression for the early screening and detection of diseases, the company said.

In addition to early cancer detection, researchers will apply the same technique to the investigation of drug toxicity, drug metabolism, prion diseases and viral agents.

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Duke Comprehensive Cancer Center and **Accelerate Brain Cancer Cure,** both of Durham, NC, said they have initiated a research collaboration to accelerate drug development.

"The goal of the collaboration is to rapidly move life-saving drugs from the laboratory to the clinic in an effort to save brain tumor patients, who have little time and few therapeutic options available to them," said Darell Bigner, director pro tempore of the Duke Comprehensive Cancer Center.

The protocol invites researchers from any venue—academia, corporations and government agencies—to submit compounds to Duke for immediate screening, free of charge.

"Such an offer is highly unusual in the drug research and development arena where funding is extremely scarce for so-called translational studies that advance drugs from the laboratory to the clinic," said Bigner.

"With the help of ABC2, we are filling a tremendous void in the drug discovery and development arena," said Bigner. "The partnership is unique because ABC2 is establishing a critical link between biotech and pharmaceutical companies and

academia to quickly evaluate compounds and move them into clinical trials."

The open invitation to researchers is expected to encourage pharmaceutical companies to submit their approved and experimental anti-cancer drugs (for breast, colon, lung cancer, etc.) to Duke for further testing for their potential utility against brain cancer, since there will be no cost to the companies.

"Typically, the drug testing process is long and laborious," said Henry Friedman, clinical co-director of the Brain Tumor Center at Duke. "Researchers can spend years testing a single compound in laboratory cell cultures, then in mice, just to find that it lacks the same effect in humans. The cost for such endeavors is huge. Few companies can afford to invest their research dollars on finding cures for rare diseases that affect small percentages of the population, as does brain cancer. Thus, funding sources are scarce and few compounds ever make it into the final stages of testing."

"The new partnership will enable the Duke team to rapidly screen and test new drugs in the lab, then move them into the clinic more quickly than traditional approaches — within 18 to 24 months after testing," Friedman.

Researchers from academia, corporations and government agencies will be invited to submit applications for their drugs to be screened at no cost to them, the company said.

A joint committee at Duke and ABC2 will review compounds prior to testing their utility in animal models. Applicants and their drugs will be selected throughout the year 2002 based upon parameters that will be posted on the ABC2 web site, http://www.abc2.org.

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Dako A/S of Copenhagen and **Cytomation** Inc of Fort Collins, CO, said they would combine their operations.

Dako Cytomation A/S will combine the Cytomation high-performance bioinstrumentation and software with Dako biotech and diagnostic applications, the companies said.

Jes Estergaard, president and CEO of Dako A/S will head the new company and Nigel Ferrey, president and CEO of Cytomation Inc will be responsible for the US operations and join the Corporate Management Group, the companies said.

In the private exchange offer expected in May 2002, shareholders of the two companies could exchange their respective shares for shares in the new company—Dako Cytomation A/S, the companies said.

Dako A/S is an in-vitro diagnostic company specializing in the identification of cancer markers on tissue samples obtained from biopsies and surgery, the companies said.

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Enzon Inc. (Nasdaq:ENZN) and **Micromet AG** said they have entered into a multi-year strategic collaboration to identify and develop the next generation of antibody-based therapeutics.

Under the agreement, the companies said they would combine their patent estates and expertise in single-chain antibody technology to create a platform of therapeutic products based on antibody fragments. The collaboration will benefit from a non-exclusive, royalty-bearing license from Enzon for PEGylated SCA products, the companies said.

A new R&D unit will be located at the Micromet research facility in Germany, the companies said. The unit would be staffed initially with 25 scientists and fully operational by the end of 2002.

During the first phase of the collaboration, covering a 30-month period beginning in the third quarter of this year, the unit will focus on the generation of two clinical product candidates in therapeutic areas of common strategic interest.

The partners will share the costs of research and development, and plan to share the revenues from technology licenses and from commercialization. In addition to the R&D collaboration, Enzon will make a US $8 million investment into Micromet.

SCAs combine the antigen binding regions of antibodies on a single polypeptide chain. They are considerably smaller in size than conventional antibodies, and can be produced conveniently on a commercial scale in microbial protein expression systems, providing significant cost-savings when compared to monoclonal antibodies, the companies said. They are highly versatile and can be genetically engineered to work in a variety of formats.

The formats include SCAs specific for cell-surface receptors for application as biological antagonists and agonists; SCAs designed to block the activity of cytokines and other soluble biological mediators; and SCA-fusion proteins, where cell-specific SCAs are armed with toxins, radionuclides, enzymes, or cytotoxic drugs for selective elimination of particular cell types, for example in cancer.

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Pittsburgh Life Sciences Greenhouse Inc. said it has attracted its first company and has secured $33.33 million in seed funding from the Commonwealth of Pennsylvania.

PLSG is a partnership of the University of Pittsburgh, Carnegie Mellon University, the biotechnology industry of the region, economic development organizations and state and local governments, the company said. It has been formed to position the region as a global leader in biotechnology and grew out of an original plan known as BioVenture developed by the University of Pittsburgh and Carnegie Mellon University to position the region as an international center in the biosciences.

The PLSG is designed to accelerate the growth of the life sciences sector in the Pittsburgh region, focusing on: drug discovery tools and targets, medical devices and diagnostics, tissue/organ engineering and regenerative medicine, and therapeutic strategies for neurological and psychiatric disorders, the company said.

"Not only have we secured the funding we needed from the Commonwealth of Pennsylvania so that we can begin to execute our plan, we have also attracted our first company, Renal Solutions," said Dennis Yablonsky, president and CEO of the PLSG.

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Morphotek Inc. of Exton, PA, and the **Ludwig Institute For Cancer Research** have entered into a collaborative research and development agreement to develop therapeutic monoclonal antibodies and antibody production strains for the treatment of cancer and other diseases.

Under the agreement, Morphotek will apply its patented Morphodoma technology to LICR cell lines producing humanized MAbs that specifically target proprietary cell surface cancer antigens. Application of the Morphodoma process to LICR's therapeutic MAbs will create second- generation manufacturing strains capable of producing commercial quantities of antibody with enhanced affinity and/or increased specificity to target antigens.

Morphotek and LICR will co-own and develop the improved antibodies through early-stage clinical trials with Morphotek having the right to exclusively license each MORPHODOMA-derived line.

"Application of our Morphodoma process to Ludwig's humanized antibodies will enable us to rapidly produce improved MAbs as therapeutic products for the treatment of human malignancies," said Nicholas Nicolaides, president and chief executive officer of Morphotek.

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Pharmacia Corp. has provided a $3.15 million grant to the **National Comprehensive Cancer Network** for the development and review of clinical oncology research protocols and trials in breast, gynecological and other forms of cancer.

The grant will provide funding for clinical research to identify treatment advances that improve patient survival and, ultimately, quality of life.

"We are pleased to partner with NCCN to advance rigorous studies of our key therapies to evaluate and determine their full therapeutic value for patients," said Gabe Leung, group vice president of Global Oncology Franchise, Pharmacia. "Progress in cancer treatment can be accomplished only through innovative research and clinical trials. Pharmacia's collaboration with NCCN will facilitate such exploration."

"NCCN's mission is to provide state-of-the-art cancer care through the study and evaluation of promising new treatments, and through programs that continuously explore the application of current and novel therapies across numerous cancer types. The grant from Pharmacia offers us a tremendous opportunity to meet both these objectives," said Bill McGivney, NCCN's chief executive officer. "Our collaboration will provide a forum for the open exchange of information to better define the clinical application for the use of two medications in a variety of cancer types."

NCCN will conduct the studies through the NCCN Clinical Trials Network. CTN was created to facilitate clinical research through the streamlining and centralization of site identification and initiation processes. A particular focus of NCCN's CTN is the establishment of collaborations with pharmaceutical and biotech companies.

Oncology Management:
UPMC, Varian Form Service To Provide IMRT In Western PA

UPMC Health System and **Varian Medical Systems (NYSE: VAR)** of Palo Alto, CA, announced the formation of D3 Advanced Radiation Planning Services, a joint venture that will provide intensity modulated radiation therapy, or IMRT in Western

Pennsylvania.

UPMC Health System is affiliated with the University of Pittsburgh Schools of the Health Sciences, and includes the UPMC Cancer Center.

D3 will enable UPMC to rapidly implement IMRT throughout its network of cancer centers. IMRT delivers precise and shaped doses of radiation while protecting surrounding healthy tissue.

Establishing IMRT services requires physics expertise and sophisticated treatment planning capabilities as well as linear accelerators to administer the treatment. The joint venture with the Pitt health system is the first of its kind for Varian.

Software from D3 will provide UPMC with patient treatment plans over a telecommunications network, as well as training and other medical physics services needed for IMRT, the health system said.

Under the agreement, Varian will supply equipment for all of the UPMC system. Economies of scale will be achieved by centralizing IMRT treatment planning through the D3 telecommunications network, the health system said.

"As the world's first radiation oncology telemedicine company, D3 is making it possible for medical institutions anywhere in the country to provide patients with highly sophisticated radiation therapy without having to buy treatment planning software," said Joe Nicholas, CEO of D3. "We will give clinics that lack physics resources or funding for new technology a means of implementing IMRT by combining centralized treatment planning with in-depth training on treatment delivery, verification and quality assurance protocols."

Clinics and hospitals working with D3 will use Varian's SomaVision software to identify tumors and transmit patients' diagnostic images and dose prescriptions to D3. D3 will then use Varian's Eclipse and Helios software to develop treatment plans that map out precise beam angles, beam shapes and exposure times needed to achieve the desired IMRT radiation dose intensities to the tumor. D3 will transmit the plans back to the clinics for approval by their radiation oncology staff, which administers treatment to the patient. Clinics will compensate D3 for treatment planning, and D3 will compensate Varian Medical Systems for the use of its software, on a pay-per-plan basis.

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Impac Medical Systems Inc, of Mountain View, CA, said it has entered into a partnership with **Cancer Care Ontario** to install its integrated oncology management system.

The first phase of the installation partnership covers the replacement of the CCO internal patient management system with Impac Multi-ACCESS oncology management system in two regional cancer centres: Northwestern Ontario Regional Cancer Centre in Thunder Bay and Northeastern Ontario Regional Cancer Centre in Sudbury, the company said.

In another development, Impac said it would renew its business relationship with **Siemens Medical Solutions** of Concord, CA, marking a ten year collaboration.

Since 1992, the companies have installed more than 1,000 oncology management systems worldwide and jointly developed software solutions to improve the process of delivering quality patient care, the companies said.

"Our strength is having all of the enablers for oncology care — from screening and diagnosis to treatment and follow-up, "said Ajit Singh, president of Siemens Oncology Care Systems. "The imaging and workflow solutions of the product portfolio augment the Impac patient management software with the necessary backbone for image guided radiation therapy."

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CancerConsultants.com, of Sun Valley, ID, said it has selected **ePharmaLearning Inc.** as its exclusive provider of customized eCollaboration and eLearning solutions.

By combining the ePL eCollaboration solutions with the CancerConsultants.com library in cancer research, pharmaceutical companies can deliver on-line meeting and eLearning sessions in a fraction of the time and cost of traditional methods, the company said.

"Our pharmaceutical clients want more insight into their clinical programs, and the ePL solutions deliver valuable project detail information on a site-by-site basis. They want to verify that the training provided at study launch and throughout the study was not only delivered, but also clearly understood. In the past, the only way to accomplish this was to fly the investigators, coordinators, and clinical team members to a face-to-face meeting and provide selective re-training, discuss project related issues, and identify potential solutions - a costly and time-consuming expectation of oncologists who are busy

treating patients.

"By partnering with ePharmaLearning, we can accomplish the same goals on-line without the current travel and time commitment," said Charles Weaver, CEO of CancerConsultants.com.

This year, pharmaceutical companies will spend close to half a billion dollars hosting face-to-face meetings to manage the geographically dispersed internal and external study staff responsible for conducting their clinical development programs, the company said.

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LifeMetrix of McLean, VA, said it has launched three information centers designed to facilitate discussions between doctor and patient.

Cancerpage.com, the LifeMetrix Web site, launched the Cancer Drug Center, Managing Side Effects Center, and the Medical Illustrations Center.

The Cancer Drug Center offers patients a single location where they can find information about chemotherapy agents or supportive care drugs used to treat cancer, the company said. The Managing Side Effects Center deals with the manifestations of treatment.

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OnCure Technologies Corp. (OTCBB: ONCU) of Oakdale, CA, said has **entered into a letter of intent** for the acquisition of all of the outstanding capital stock of **Coastal Radiation Oncology Medical Group Inc.** and its affiliates.

Coastal, a provider of radiation therapy services in California, owns, operates and manages eleven radiation cancer treatment centers, the company said. Following the acquisition, OnCure will operate twenty-four 24 cancer centers and will have estimated annual revenues of $45 million and assets of $78 million, the company said.

The purchase price is $34 million, 80 percent payable in cash and 20 percent payable in capital stock, the company said.

Clinical Trials:

Coley Begins Trial Of Drug For Renal Cell Cancer

Coley Pharmaceutical Group Inc. of Wellesley, MA, said it has initiated a multi-center open label, phase I/II trial of its lead product candidate, CpG 7909, for the treatment of stage IV renal cell carcinoma.

The phase I study will assess the safety and tolerability of escalating doses of CpG 7909, and a phase trial will assess overall tumor response and immunologic effects. Other endpoints of the phase II portion of the study include time to disease progression, duration of response and survival time, the company said.

"Because our CpG 7909 product candidate stimulates multiple aspects of immunity believed to impact tumor shrinkage, such as production of Interferon- alphas (IFN-alpha), Interleukin-2 (IL-2) and enhancement of natural killer cell activity, we are evaluating CpG 7909 in the treatment of this fatal cancer," said Robert Bratzler, Coley president and CEO.

In the phase I trial, three to six patients will be enrolled at dose levels ranging from 0.08 mg/kg to 0.16 mg/kg. All patients will receive weekly subcutaneous injections of CpG 7909 for a total of 24 weeks, the company said.

The phase II trial will initially enroll 12 patients treated weekly for 24 weeks with the dose previously determined in the dose escalation portion of the study. Based on the number and quality of responses in the 12 patients, 25 additional patients may be enrolled.

Six centers will participate in the U.S. study. They are: the Cleveland Clinic Cancer Center; Northwestern Memorial Hospital; Seattle Cancer Care Alliance; the Providence Portland Medical Center, and Winter Park Urology Associates of Orlando.

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Zycos Inc. of Lexington, KY, said it has begun a phase I/IIa trial of ZYC300, a drug for breast, ovarian, colorectal and prostate cancers. The trial, which will evaluate safety and measure immune responses, is being conducted at the Dana Farber Cancer Institute and other clinics in the U.S., the company said.

"CYP1B1 is one of the most promising cancer targets known today," said Lee Nadler, senior vice president for experimental medicine at Dana Farber. "There is a significant unmet medical need for cancer therapeutics that can effectively differentiate cancer cells from normal cells."

ZYC300 is designed to stimulate the immune response of cells expressing CYP1B1, a proprietary molecule in the Zycos portfolio of oncology targets, the company said. CYP1B1 is an abbreviation for cytochrome P450 1B1, a tumor-specific protein that is found expressed in nearly every major cancer but significantly limited in normal tissue.

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