THE CANCER LETTER

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Lilly Drug Misses The Target, But Wins ODAC Endorsement For Lung Cancer

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee unanimously recommended accelerated approval for Alimta (pemetrexed) as a single agent for second line treatment of locally advanced or metastatic non-small cell lung cancer.

In a 13-0 vote at a meeting July 27, ODAC recommended approval of the supplemental New Drug Application for the Eli Lilly & Co. antifolate drug. Earlier this year, Alimta was approved in combination with cisplatin

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In Brief:

Rep. Greenwood To Become President Of Biotechnology Industry Association

REP. JAMES GREENWOOD (R-Penn.) stepped down as chairman of the House Oversight and Investigations Subcommittee last week after announcing that he would become president of the Biotechnology Industry Association, effective Jan. 5. He will complete his term in Congress. **Rep. Joe Barton** (R-Texas), chairman of the House Energy and Commerce Committee, will become acting chairman of the subcommittee for the remainder of the session. Vice Chairman **Greg Walden** (R-Ore.) is expected to serve as chairman of many of the subcommittee's hearings. Greenwood has been investigating possible conflicts of interest by NIH and FDA employees who consulted with industry. Earlier this year, **Carl Feldbaum**, BIO president since the group began in 1993, said he would step down in December. "Jim Greenwood has the broad social perspective, the passion, ability, and experience to lead BIO superbly," Feldbaum said. BIO represents more than 1,000 companies. "After a comprehensive search from a pool of top-level candidates, Jim Greenwood was the Board of Directors' unanimous choice to lead BIO because of his commitment to improving people's lives through science and technology and his personal leadership skills," BIO Chairman and Alkermes CEO **Richard Pops** said. Greenwood has represented Pennsylvania's Eighth District since 1993, serving as chairman of the subcommittee since 2001. "I passionately believe in the promise of biotechnology to find cures and treatments for the diseases that force parents to watch their children suffer and die, and children to endure their parents' disintegration into the clutches of Parkinson's and

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Accelerated Approval Lets FDA Sidestep Non-Inferiority Muddle

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for the treatment of malignant pleural mesothelioma.

Though Lilly failed to demonstrate Alimta's superiority or its "non-inferiority" to docetaxel, the committee decided that the Lilly agent's toxicity profile, response rates, and progression-free survival provided sufficient justification for an accelerated approval.

ODAC deliberately sidestepped the technical, statistical issues involved in demonstrating non-inferiority, and instead made a clinical judgment, said committee member Otis Brawley, who chaired the meeting.

"When statisticians look at non-inferiority, they are asking the question, 'Does Drug A produce the same response as Drug B?'" said Brawley, an oncologist and associate director for cancer control at Emory University Winship Cancer Institute. "What ODAC did was say that Drug B can have slightly less activity than Drug A, but can still be non-inferior because it has less toxicity."

Now, the Alimta recommendation gives the agency flexibility to approve drugs that demonstrate favorable toxicity, but fail to show superior efficacy or non-inferiority to approved therapies. "For accelerated approval, an improvement over available therapy must be demonstrated and may utilize a surrogate endpoint 'reasonably likely to predict clinical benefit,'" Richard Pazdur, director of the FDA Division of Oncology Drug Products, said at the ODAC meeting. "A more favorable safety profile could constitute an improvement over available therapy.

"This decision requires considerable clinical judgment, and is not merely an exercise in adding up grade 3 and 4 toxicities and declaring a winner," Pazdur said. "The importance of selected toxicities in patient management, toxicity duration, and overlapping toxicities may direct your clinical opinion. With regards to the surrogate endpoint for accelerated approval in this application, the agency has used response rates of similar magnitude and duration, as demonstrated in this Alimta trial for past accelerated approvals."

The committee enthusiastically accepted these surrogate endpoints for accelerated approval of Alimta, but voted 8-5 against regular approval, which requires a demonstration of patient benefit.

FDA has been struggling with the question of interpretation of non-inferiority trials for the past four years. The question came to light in the context of the Bristol-Myers Squibb application for UFT, an oral equivalent of 5-fluorouracil. Like Alimta, UFT received a unanimous endorsement from ODAC, but, in an unusual move, the agency disregarded the committee's advice. This triggered a Congressional investigation, but ultimately the controversy waned (**The Cancer Letter**, July 21, 2000).

With the agency issuing no guidance documents for the drug industry, the approval standards for demonstration of non-inferiority remain a mystery. The most recent cancer therapy to get approval based on such a claim was the Roche Pharmaceuticals oral drug Xeloda (capecitabine). FDA approved the agent for metastatic colorectal cancer in April 2001. ODAC was not consulted on that decision, which some observers said was inconsistent with the decision on UFT.

Uncertainty of FDA standards appeared to benefit the sponsors of drugs like Taxotere in the lung cancer indication. The trial that led to the drug's approval for lung cancer in November 2002 randomized 104 patients to Taxotere versus best supportive care.

"Although sufficient data existed to approve docetaxel in this setting, the FDA believes that there is not a reliable and reproducible characterization of the docetaxel effect to use in a non-inferiority analysis,

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Member, Newsletter and Electronic Publishers Association

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

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

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

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constancy assumptions cannot be verified, and inter-study variability is unknown," Pazdur said at the meeting. The text of Pazdur's remarks appears on page 5.

The absence of standards gave sponsors the perverse incentive to conduct smaller trials, experts say. Ambiguous results made it more difficult for potential competitors to claim non-inferiority. In cases where it cannot be clearly demonstrated that Drug A is better than placebo, potential competitors knew they would have difficulty demonstrating patient benefit in a non-inferiority trial of Drug A vs. Drug B.

"You are rewarding somebody for being first, allowing them to have a small study, and then closing the door on drugs that are not much better than the original drug, in terms of efficacy," said Donald Berry, chairman of the Department of Biostatistics and Applied Mathematics at M.D. Anderson Cancer Center.

In the case of Taxotere, the slim database from its lung cancer trial makes later non-inferiority comparisons problematic, said ODAC member Ralph D'Agostino, professor of mathematics and statistics at Boston University.

"There is a term they use in this field, non-inferiority trials, 'Biocreep,'" D'Agostino said at the meeting. "If you allow this to sneak in with a small database, and the next one uses an even smaller database, because it's now pegged on this one, there is a real concern. It's not just a matter of being a cruel statistician."

Still, Alimta was approved largely because it appeared to produce the same survival as Taxotere, said Berry, who advised Lilly in preparation for ODAC. "If the response rates and the progression-free survival were similar, but the survival curves were not, they wouldn't have gotten accelerated approval," Berry said to **The Cancer Letter**.

Missing The Endpoints

Lilly conducted a single phase III trial of Alimta. The trial, which randomized 571 previously treated patients with locally advanced or metastatic non-small cell lung cancer, was designed to show superiority or non-inferiority.

The study failed to demonstrate superiority, and the agency said the non-inferiority claim was not convincing, because it was unclear whether the active control—Taxotere—produced a survival advantage.

The study showed a similar survival benefit for the two drugs. Median survival for Alimta was 8.3 months, compared to 7.9 months for Taxotere. Tumor shrinkage was 9.1 percent for Alimta, compared to 8.8 percent for Taxotere. Progression-free survival was the same: 2.9 months.

Patients on Alimta experienced less grade 3 or 4 neutropenia, less neutropenia with fever, less diarrhea, fewer hospitalizations due to adverse events, and less hair loss. However, Alimta was associated with higher rates of grade 3 or 4 elevations of liver function tests.

At the meeting, committee members and company experts sparred with FDA medical reviewer Martin Cohen, whose presentation included the following claims:

—Patients treated with Alimta received folates and vitamin B12, while patients on the Taxotere arm didn't. "Whether these supplements, which were not given to docetaxel-treated patients, would have ameliorated docetaxel's toxicity is not known," Cohen said.

—Patients on Alimta experienced greater weight loss.

—Patients who failed Alimta crossed over to Taxotere, and lived longer. "Post-study chemotherapy confounds the survival analysis," Cohen said. "With post-study chemotherapy, there are two issues. The first issue is the crossover of 85 Alimta-treated patients to docetaxel treatment… While median survival of these patients is similar to the median survival of patients receiving other chemotherapy regimens, such survival analyses do not take into account possible prognostic differences between the various treatment groups. The second issue is that patients who didn't receive post-study chemotherapy had a shorter survival than those who did receive that treatment. There were 30 more docetaxel-treated patients than Alimta-treated patients who didn't receive post-study chemotherapy."

ODAC member Michael Perry said Cohen's statement on the potential role of dietary supplements missed the point. The use of the folates and B12 with Alimta is supported by data, he said.

"You made a comment that the B12 and folate supplementation might have had an effect if it were given to people on the docetaxel trial," said Perry, director of the Division of Hematology and Medical Oncology at the University of Missouri Ellis Fischel Cancer Center. "Is there any evidence anywhere in medical oncology that vitamin B12 and folate supplementation decreases toxicity in any group of compounds other than the antifolates?"

COHEN: "No, there is no evidence… but there is no reason to exclude that possibility, either. "

PERRY: "Yes, I think there is every reason to exclude it. It hasn't been done, but you could say that these people didn't get yogurt, either, and that didn't have an effect. I think it's an invalid point to bring up. It's the antifolates that have the vitamin B12 supplementation effect. Not the taxanes, not the alkylating agents, not any other class of drugs."

COHEN: "I guess we disagree."

Lilly biostatisticians and consultants disputed Cohen's claim that Alimta was associated with greater weight loss. ODAC member Perry added that even if Alimta produced greater weight loss, clinical significance of this finding would have been unclear.

"I think the weight loss issue here is a real red herring," Perry said. "You have to remember that the people on docetaxel are getting an enormous dose of Decadron, which causes fluid retention, and therefore artificial weight gain. We are talking about 16 times the normal dose of prednisone equivalent that one makes per day, versus eight times in the Alimta arm. I don't think weight loss is something we can discuss reasonably. I do think that there is less neutropenia in the Alimta arm."

Cohen's claim that the findings were confounded by crossovers from Alimta to Taxotere was challenged by Lilly's experts. Response rates in third-line treatment for non-small cell lung cancer hover around two percent, and median survival is less than four months, said Frances Shepherd, a lung cancer expert at the Princess Margaret Hospital in Toronto, "There is nothing that suggests that third-line chemotherapy contributes to survival," she said.

Even if such impact were real, the results would have made the Alimta arm look worse, Shepherd said, speaking for the company

"If you look carefully, more patients on the docetaxel arm received Iressa in the third-line setting," Shepherd said. "The only treatment that has been known to prolong survival—an EGFR inhibitor—and four times as many patients on the docetaxel arm actually received that kind of treatment. So, if anything, that would have favored docetaxel, not Alimta."

Also speaking for Lilly, Paul Bunn said Cohen's claim was erroneous. "People who got chemotherapy in the third line did live longer, but that's just a diagnostic group," said Bunn, director of the University of Colorado Cancer Center. "It's just like saying that responders live longer than progressive disease. It doesn't mean that the treatment made them live longer. "

Scott Emerson, professor of biostatistics at the University of Washington, agreed. "We certainly can say that those people who survived long enough to get post-study chemo survived longer than those who didn't survive long enough to get post-study chemo," said Emerson, testifying for the company. "The grouping is true. There is longer survival among those who got post-study chemo. But that's not quite as strong as what Dr. Cohen said when he said that the post-study chemo made people live longer. "

Lilly officials said the company's post-approval plans include a study of Alimta in combination with chemotherapy as a front-line treatment of NSCLC.

Last month, the European Committee for Medicinal Products for Human Use issued a recommendation for dual cancer indications for Alimta. Marketing authorization by the European Commission is expected later this year, the company said.

Decision On Alimta Requires Clinical Judgment, Pazdur Says

The text of FDA Division of Oncology Drug Products Director Richard Pazdur's comments at the July 27 meeting of ODAC follows:

I would like to preface today's presentations with a few comments to focus your attention on key issues.

This NDA highlights some unique challenges in developing oncology drugs, especially regarding non-inferiority trial design and analysis. Survival as an endpoint for regular approval has been well-established endpoint for clinical benefit and regular approval.

In oncology trials, test drugs have generally demonstrated survival improvements compared to active controls. Alternatively, an effect on the survival endpoint may be accomplished by demonstrating a non-inferior survival effect.

Non-inferiority ensures that a survival advantage, the control effect, would not be lost by a new agent. To determine the control effect, external information from multiple controlled trials is generally required. A certain proportion of the control effect, known as the margin, should be preserved to demonstrate non-inferiority.

The active control in a non-inferiority trial should have an effect that is of substantial magnitude and

that can be precisely estimated with estimates relevant to the setting.

The ICH E9 guidance states that an acceptable active comparator… "could be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well-designed and well documented superiority trials and which can be reliably expected to have similar efficacy in the contemplated active control trial." The active control effect should preferably be derived from multiple studies with a large, consistent drug effect suitable for a convincing meta-analysis to be performed.

Constancy assumptions must be addressed in designing a non-inferiority trial ensuring that the active control effect should be the same as in the historical trials. These considerations ensure that the population enrolled in the historical trials is similar to the population in the proposed trial with respect to baseline characteristics, supportive care, additional available therapies, and observational frequencies.

The Alimta trial's primary objectives were not achieved. Neither superiority nor non-inferiority to docetaxel were adequately demonstrated. The FDA believes that Alimta's non-inferiority for overall survival cannot be demonstrated for two reasons. First, only a single, small historical study exists to estimate the docetaxel treatment effect.

This study randomized a total of only 104 patients to either docetaxel or best supportive care. A second study was used in the docetaxel's approval consideration. This study compared docetaxel to either ifosphamide or vinorelbine—neither agent has a demonstrated survival effect in this setting. This second trial failed to demonstrate an overall survival benefit associated with docetaxel, however, there was improvement in one-year survival.

Although sufficient data existed to approve docetaxel in this setting, the FDA believes that there is not a reliable and reproducible characterization of the docetaxel effect to use in a non-inferiority analysis, constancy assumptions can not be verified, and inter-study variability is unknown.

An additional concern is the existence of crossover in the present study. Over 30 percent of patients randomized to receive Alimta subsequently received docetaxel at disease progression. Crossover obscures the differences between treatments; hence, in superiority trials crossover may lead to a false-negative conclusion potentially denying an active drug a marketing claim. The use of a time-to-progression endpoint—an analysis occurring prior to crossover—may be preferred in settings where significant crossover is expected.

In contrast to superiority trials, crossover in non-inferiority trials may lead to a false-positive conclusion. This crossover confounds our interpretation of survival since the observed survival in both arms can theoretically be attributed to the control drug—in this case, docetaxel.

Similarly, data integrity problems—trial "sloppiness"—either in trial data collection or execution—may obscure the observation of differences leading to false positive non-inferiority trials. The agency has strongly recommended two trials to support a non-inferiority claim in an attempt to ascertain a true effect.

For regular approval of a drug, the sponsor must demonstrate that the drug is safe and effective in adequate and well-controlled trials. The effectiveness must be demonstrated on an endpoint that the agency believes represents clinical benefit—usually survival, disease symptom amelioration or an established surrogate for these. The sponsor is not obligated to show that the drug is safer and/or more effective than an approved drug.

Many other therapeutic areas conduct placebo-controlled trials—Drug A versus placebo— ensuring that superiority can be easily demonstrated. It is more difficult to demonstrate superiority in active control superiority trials—Drug A versus Drug B. The test drug must possess the entire activity of the active control on the endpoint plus an additional incremental effect.

The agency has frequently recommended "add-on trials"—A + B vs. B. This design was used in the approval of Alimta plus cisplatin in mesothelioma. In the add-on design, the test drug plus active control combination is compared to the active control alone or, alternatively, active control plus placebo.

This design ensures that all patients receive the active treatment, yet isolates the test drug's effect. To demonstrate superiority, the test drug must only possess an incremental advantage over the active control rather than possess the increment plus the control's entire effect on the endpoint.

We will be asking the committee to consider this application for accelerated approval. For accelerated approval, an improvement over available therapy must be demonstrated and may utilize a surrogate endpoint "reasonably likely to predict clinical benefit."

A more favorable safety profile could constitute an "improvement over available therapy." This

decision requires considerable clinical judgment, and is not merely an exercise in adding-up grade 3 and 4 toxicities and declaring a winner. The importance of selected toxicities in patient management, toxicity duration, and overlapping toxicities may direct your clinical opinion.

With regard to the surrogate endpoint for accelerated approval in this application, the agency has used response rates of similar magnitude and duration as demonstrated in this Alimta trial for past accelerated approvals.

In making a regulatory decision we must consider all available data—a comprehensive drug evaluation, including any past approvals. As noted, Alimta in combination with cisplatin was approved for a mesothelioma indication earlier this year. An improvement in overall survival advantage was demonstrated.

In contrast to other accelerated approval applications that commonly use single-arm studies in refractory disease populations, the sponsor has provided a large, randomized trial.

Randomized trials always provide greater information. We have comparative response rate and toxicity data and the ability to examine time-to-event endpoints, although we believe formal non-inferiority analyses can neither be performed on TTP nor survival.

The sponsor is conducting large randomized trials in earlier stage lung cancer that can serve as confirmatory studies for clinical benefit if accelerated approval is granted.

The statistical analysis and design of non-inferiority trials is an evolving field and represents considerable challenges. Non-inferiority trials are difficult. They take considerable resources in planning, designing, and executing the trial and usually require considerable patient resources.

"Winning" is always better than "tying"…the demonstration of superiority is always better than that of non-inferiority—it moves the field forward by identifying new agents and treatments. However, a "win" may not only be an efficacy improvement, but may also be a safety improvement, especially in a field where toxicity concerns may dictate treatment choices. However, as we would like you to discuss later this morning, this regulatory decision must be weighed against the clinical relevance of any potential survival loss.

I hope these comments will focus your attention and deliberations on essential issues.

Cancer Policy:

Medicare To Cut Payments For Cancer Drugs By 2-8%

The Centers for Medicare and Medicaid Services released a proposed physician fee schedule for 2005 that would cut between 2 percent and 8 percent in reimbursements to oncologists for the medications they administer in their offices.

The July 27 proposal, ordered under the Medicare Modernization Act of 2003, will result in at least a $500 million cut in total reimbursement for cancer care, the American Society of Clinical Oncology said earlier this week.

"ASCO supported the reform of Medicare and fixing the imbalance in payments for chemotherapy and patient support services," said ASCO President David Johnson, of Vanderbilt University. "But, we fear that patients and their families may be deprived of critical community-based cancer care as a result of these substantial cuts."

The proposal doesn't provide oncologists with reliable information upon which to make decisions about their practices in 2005 and beyond, ASCO said. The CMS data provides inadequate information about reimbursement levels in 2005 and does not include a complete list of cancer drugs affected, the society said.

More than 80 percent of cancer patients receive treatment in doctor's offices, and not in hospitals. ASCO said the cuts could cripple the ability of oncologists to provide quality cancer care, including appropriate patient support services, in community-based practices.

ASCO said it supports maintaining 2004 net reimbursement levels for cancer treatment during 2005 and 2006, while three government-mandated studies on the effect of the MMA on cancer care are completed.

"If our worst fears are borne out, we would hope that Congress will take the necessary steps to ensure that cancer patients continue to receive the quality care that they need," Johnson said.

CMS is seeking comment on the proposed rule, which is scheduled to be published in the Aug. 5 Federal Register.

Comments will be accepted until Sept. 24. CMS plans to publish the final rule by Nov. 1, with an effective date of Jan. 1.

The text of the proposed rule is available at www.cms.hhs.gov/regulations/pfs/2005/1429p.asp.

Obituary:

Richard Bloch, NCAB Member, Patient Advocate, Dead at 78

By Kirsten Boyd Goldberg

Richard Bloch, co-founder of the H&R Block Inc. tax preparation service, who spent the last 25 years of his life helping cancer patients access information on the disease and its treatment, died of heart failure July 21 at his home in Kansas City, Mo. He was 78.

Bloch is credited with the expansion of the tax service in the 1960s and 1970s. In 1978, Bloch was told he had terminal lung cancer, when, in fact, his disease was curable with appropriate treatment.

Convinced that his experience was not atypical, Bloch decided he would help other survivors obtain information about treatments and clinical trials. He and his wife Annette started the R.A. Bloch Cancer Foundation.

"I am not fighting for what treatments a patient receives or from whom," Bloch wrote in a letter on the foundation's Web site, www.blochcancer.org. "All I care about is that the patient is entitled to make an informed decision. Being told that nothing can be done, that surgery is required tomorrow, or take these pills and come back in 90 days, is not making an informed decision."

In 1982, President Ronald Reagan appointed Bloch to the National Cancer Advisory Board. In his six-year term, he supported NCI's effort to build the Physician Data Query online database of peer-reviewed treatment and clinical trials information. In the pre-Internet era, when many physicians resisted the idea of patient access to medical information, Bloch was a much-needed advocate for the program.

Bloch saw PDQ's potential to empower patients to play a role in their own care. "My goal was to open PDQ to patients, to make patients aware of it, so they would take the information to their physicians," Bloch said in a 1996 interview (**The Cancer Letter**, Oct. 11, 1996, Vol. 22 No. 39).

"Really good physicians know they don't know everything. I'm not worried about them," Bloch said. " I'm worried about the Americans who don't go to top doctors. We know that many people are dying though they do not have to, because their physician is unaware of what is available."

When NCI needed more office space for the International Cancer Information Center, which would operate PDQ, Bloch donated the major portion of the $1.4 million purchase price for a building across the street from the NIH campus. The building was named the R.A. Bloch International Cancer Information Center.

When PDQ went online in 1983, the NCAB decided to limit access to physicians only, a choice that disappointed Bloch. In February 1984, he commended NCI for starting PDQ, but acknowledged that the system "is not what I dreamed it would be."

In the early 1980s, NCI had difficulty striking deals with companies to make PDQ available online. One problem was the requirement that companies block access by non-physicians.

Compuserve, then owned by H & R Block, wanted to distribute PDQ as a public service. To pave the road for that deal, Bloch severed his ties with the company and sold his shares of stock, he said. "[After the sale] no one could say I was promoting PDQ for my personal benefit," Bloch said to **The Cancer Letter** in 1984.

After a year of debate, NCAB's Committee on Information, which Bloch chaired, recommended that NCI make PDQ available to patients at the request of their physicians. Finally, in 1986, the NCAB voted to remove all restrictions on PDQ.

Ten years later, Bloch still didn't feel that PDQ's promise had been fulfilled. "PDQ has not had nearly enough promotion," Bloch said to **The Cancer Letter** in 1996. "PDQ should be nearly mandatory for every newly diagnosed cancer patient. That would take a tremendous amount of publicity. I don't think NCI has the resources to do that."

In 1996, NCI and FDA began an campaign to encourage pharmaceutical companies to list their clinical trials on PDQ. Bloch said he was surprised to learn that some companies might not want to list their trials.

"I don't know anyone in this field who isn't interested in helping human beings," Bloch said. "If a company were talked to properly, I would think they would be totally in favor of sharing the knowledge."

Bloch also founded the R.A. Bloch Cancer Management Center and the R.A. Bloch Cancer Support Center at the University of Missouri-Kansas City. In 1990, he dedicated a park to cancer survivors in Kansas City.

Bloch is survived by his wife, Annette, and three daughters, Linda Lyon, of Kansas City, Mo.; Barbara Stanny, of Port Townsend, Wash.; and Nancy Linsley, of Corona Del Mar, Calif.; and two brothers, Henry and Leon, both of Kansas City, Mo.

Funding Opportunities:

Program Announcements

PAR-04-133: Clinical Trials: Oral Complications of Cancer Therapy

National Institute of Dental and Craniofacial Research and NCI invite applications on the prevention and/or management of symptoms and lesions in the oral cavity and pharynx resulting from cancer therapies. Applications are for pilot data grants leading to phase III trials. The pilot data grant applications may involve limited pilot testing of novel experimental hypotheses, design-driven development of new or novel techniques or technologies, and/or the acquisition of a body of data that could have high-impact on the reduction of mucositis and other oral complications related to chemotherapy, radiation or other cancer therapies.

Also, data may include but is not limited to: collection of preliminary data for establishing measures of effectiveness and/or safety; testing and documenting recruitment mechanisms and their effectiveness; short-term studies to address questions to optimize the design of the phase III trial; small studies to refine an intervention strategy (e.g., dosage, duration, delivery system, etc.); and, the development and testing of participant inclusion criteria and data collection and outcome instruments. The PA will use the NIH Exploratory/Developmental R21 award. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PAR-04-133.html.

Inquiries: For NCI—Roy Wu, Clinical Grants & Contracts Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment & Diagnosis, phone 301-496-8866; fax 301-480-4663; e-mail rw51j@nih.gov.

PA-04-134: Pilot Studies: Oral Complications of Cancer Therapies

NIDCR and NCI recognize that developmental, exploratory, and/or pilot studies in epidemiology, behavioral/social sciences or other areas of clinical research may be needed to accelerate scientific progress in addressing this topic. The studies would collect preliminary data leading to R01 level clinical research grants. The PA will use the R21 award. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-04-134.html.

Inquiries: See the preceding PA.

Cancer Research Small Grants Program R03

NCI Division of Cancer Prevention invites applications that address developmental research in chemoprevention agent development, biomarkers, early detection, nutrition science, and clinical studies that focus on specific target organs. The PA is available at http://deainfo.nci.nih.gov/concepts/cancerresearch.htm.

Inquiries: Harold Seifried, NCI, Division of Cancer Prevention, phone: 301-496-8573; e-mail hs41s@nih.gov.

In Brief:

STAR Completes Enrollment; NCI Forms Pediatric CIRB

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Alzheimer's diseases," Greenwood said. "The research and the science that BIO's members represent hold so much potential: regenerative medicine to enable us to repair our organs and spinal cords, biotech crops and foods which can help feed the hungry, and biofuels to help save the environment." . . . **STUDY OF TAMOXIFEN AND RALOXIFENE** completed enrollment of 19,000 women in June, a month ahead of schedule, the National Surgical Adjuvant Breast and Bowel Project said. In the study, women are randomized to either tamoxifen or raloxifene for five years to determine which agent is more effective in preventing breast cancer. Initial results are expected by the summer of 2006. STAR began in 1999 and some women have completed five years of treatment. "It's a remarkable achievement," said **Norman Wolmark**, chairman of the NSABP and the Department of Human Oncology at Allegheny General Hospital. "Women at increased risk for developing breast cancer chose to be proactive about finding options to prevent the disease. We owe a debt of gratitude to these women who are leading the charge in preventing breast cancer." . . . **PEDIATRIC CENTRAL IRB** was formed by NCI to simplify review of cooperative group treatment studies. PedCIRB will act as the clearing IRB for pilot, phase II, and phase III trials conducted by the Children's Oncology Group. Local institutional review boards at the 238 COG institutions will decide whether to accept PedCIRB decisions. PedCIRB includes 10 physicians with pediatric subspecialty expertise, two nurses, a bioethicist, four patient advocates, a pharmacist, and a statistician. **Vita Land** is the executive director. The group plans to begin review of COG protocols in November. . . . **LANCE ARMSTRONG**, a member of the President's Cancer Panel, won the Tour de France for the sixth consecutive time on July 25. The cyclist and testicular cancer survivor will again ride in the Bristol-Myers Squibb Tour of Hope, a cross-country bike ride from Los Angeles to Washington, DC., later this year, to bring attention to cancer research. . . . **DANIEL SCHULTZ** was named director of the FDA Center for Devices and Radiological Health. Schultz held managerial positions at FDA and has a background in general and pediatric surgery, and family practice.

THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

Corixa Files sBLA For Accelerated Approval Of Bexxar For Non-Hodgkin's Lymphoma

Corixa Corp. (Nasdaq:CRXA) of Seattle said it has filed a supplemental biologics license application with FDA requesting accelerated approval for expanded use of the Bexxar therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) for relapsed or refractory low grade, follicular, or transformed CD20 positive non-Hodgkin's lymphoma where disease has relapsed following chemotherapy.

The request for expanded use is based on a multicenter, single-arm, open-label study of 60 chemotherapy refractory patients, the company

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Deals & Collaborations:

Merck, Vertex, To Collaborate On VX-680 Development For Oncology Indications

Merck & Co. Inc. (NYSE:MRK) of Whitehouse Station, N.J, and **Vertex Pharmaceuticals Inc**. (Nasdaq:VRTX) of Cambridge, Mass., said they have entered into a global collaboration agreement to develop and commercialize VX-680, the Vertex Aurora kinase inhibitor.

Under the agreement, Vertex would receive a $20 million upfront payment and an additional $14 million in research funding over the next two years, the companies said. In addition, Vertex could receive as much as $350 million in milestone payments, including $130 million for the successful development of VX-680 in the first oncology indication and additional milestone payments for development of the inhibitor and follow-on compounds in subsequent major oncology indications. Merck would be responsible for clinical development and commercialization of VX-680 worldwide and would pay Vertex royalties on product sales.

Also, the companies said they would conduct a joint research program to characterize the activity of the product across a broad range of cancer types as well as to identify follow-on drug candidates directed at Aurora kinases, using molecular profiling approaches and microarray technologies pioneered by Merck.

Merck would fund research conducted jointly, and lead the clinical development of VX-680 and any subsequent compounds selected from the joint research program, with development input from Vertex, the companies said. Vertex could negotiate a co-promotion agreement with Merck prior to commercialization. Vertex could earn additional milestone payments for the development of Aurora kinase inhibitors outside the

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

Corixa Files sBLA For Bexxar Treatment In Refractory NHL

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said. Patients enrolled had not responded to prior therapy or had responded with a duration of response of less than or equal to six months. The median number of prior chemotherapy regimens was four, ranging from two to 13.

The primary endpoint for the study was a comparison of the number of patients with a longer duration of response (greater than 30 days) following the therapeutic regimen to the number of patients with a longer duration of response following their last qualifying chemotherapy regimen. The results were confirmed by an independent panel.

Twenty-six patients had a longer duration of response following the therapeutic regimen while only five had a longer duration of response following their last qualifying chemotherapy regimen (p less than 0.001), the company said. Secondary endpoints included response rate and duration of response.

Bexxar pairs the targeting ability of a monoclonal antibody (Tositumomab) and the therapeutic potential of radiation (Iodine-131), the company said. Combined, the agents form a radiolabeled monoclonal antibody regimen that is able to bind to the target antigen CD20 found on B-cells, including normal cells and those that become cancerous in non-Hodgkin's lymphoma, thereby delivering the dose of radiation. Bexxar, which is given in four visits over one to two weeks, is specifically dosed based on drug clearance rate of the individual, allowing the delivery of a pre-determined amount of radiation, the company said.

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IDM of Paris, France, said the European Commission has granted Mepact orphan medicinal product designation for osteosarcoma.

Designation was granted following the approval of the European Medicines Agency and its Committee for Orphan Medicinal Products, the company said

Mepact is an immune system stimulant that destroys cancer cells by activating macrophages, the company said.

Statistical analysis from a randomized phase III 800 patient trial, where surgical resection of the tumor has occurred, indicates the agent provides a significant increase in disease free survival, as well as a significant increase in overall survival with Mepact versus with chemotherapy alone, the company said.

IDM said it is completing its application to regulatory authorities to market the agent in the European Union and the U.S.

Mepact obtained orphan drug status in the U.S. in June 2001.

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ILEX Oncology Inc. (Nasdaq:ILXO) of San Antonio said FDA has will grant six months of extended market exclusivity to clofarabine under the Best Pharmaceuticals for Children Act.

Clofarabine is under priority review for refractory or relapsed acute leukemia in children, the company said. If approved, the treatment would be the first drug to be labeled or pediatric leukemia in more than a decade.

"This is an important milestone for children with cancer and for the FDA because children are usually an afterthought in oncology drug development," said Susan L. Weiner, president, Children's Cause for Advocacy. "Hopefully this good news will set a precedent for other companies to make children with cancer a priority in their drug development plans."

Clofarabine was granted orphan drug designation for adult and pediatric acute lymphoblastic leukemia and acute myeloid leukemia, the company said.

Clofarabine is of the drug class purine nucleoside analogs which all inhibit DNA production necessary for cancer cell growth, the company said.

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Bioenvision Inc. (AMEX:BIV) sub-licensed ILEX the right to develop and market clofarabine for cancer indications in the U.S. and Canada. Bioenvision is entitled to milestone payments tied to the development of the compound and is entitled to royalties on North American sales, the company said.

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ImClone Systems Inc. (NASDAQ:IMCL) of New York, N.Y., and **Bristol-Myers Squibb Co.** (NYSE:BMY) of Princeton, N.J., said they have established a plan with FDA to file a supplemental biologics license application for Erbitux (Cetuximab) Injection, an IgG1 monoclonal antibody, as a single agent and in combination with radiation in squamous cell carcinoma of the head and neck.

The sBLA would be submitted in the second quarter of 2005 with a priority review request, the companies said. at the time of filing.

FDA has provided written notification that the following clinical trials could form the basis of an sBLA together with other supportive data: a randomized, international phase III trial (IMCL-9815) conducted by ImClone Systems and Merck KGaA examining the impact of combining the agent with radiation on locoregional control and overall survival in 424 patients with locally advanced SCCHN; and a multicenter phase II trial (EMR-016) conducted by Merck evaluating the response rate of Erbitux as a single agent in 103 patients with advanced recurrent and/or metastatic SCCHN not suitable or further local therapy and who have failed platinum-based chemotherapy, the companies said.

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PharmaMar of Madrid, Spain, said FDA has accepted an IND, allowing for two phase II trails to begin in the U.S. for Aplidin.

Two phase II trials would run under the IND, one in multiple myeloma EU and U.S., another in prostate cancer in the U.S, the company said.

Aplidin is in clinical development in Europe and Canada for solid tumors, hematological malignancies and pediatric tumors, the company said. Phase II trials are ongoing for melanoma, colorectal, renal, lung, medullary thyroid, head and neck and pancreatic carcinomas. The product is also in phase I in pediatric trials for solid and hematological tumors.

Aplidin is a novel antitumour agent derived from the marine tunicate Aplidiu albicans, the company said. It induces rapid and persistent activation of apoptosis combined with blocking of cell division in the G1/G2 phase of the cell cycle in tumor cells. It also inhibits the secretion of vascular endothelial growth factor.

In a related development, PharmaMar said FDA has granted orphan drug status to Aplidin(a), its second marine-derived compound in clinical development for acute lymphoblastic leukemia .

The designation would grant PharmaMar a special seven-year period of market exclusivity in the US for the indication, subject to successful marketing authorization, the company said. Aplidin was awarded orphan drug status for ALL by the European Commission in July 2003.

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3M Pharmaceuticals of St. Paul, Minn., said FDA has approved Aldara (imiquimod) Cream, 5 Percent, for superficial basal cell carcinoma.

The cream, a topical immune response modifier, treats biopsy-confirmed, primary sBCC in adults with normal immune systems, the company said. The cream was FDA approved for certain types of actinic keratosis (clinically typical, nonhyperkeratotic, nonhypertrophic) on the face or scalp in adults with normal immune systems, the company said.

Both AK and sBCC are skin conditions caused by chronic sun exposure, the company said.

In phase III sBCC studies, 82 percent of patients treated with Aldara Cream achieved histological clearance and 75 percent achieved composite clearance, defined as clearance confirmed by both biopsy and visual inspection, the company said.

"It is imperative for the medical community to continue striving toward new and better options for treating nonmelanoma skin cancer," said Darrell Rigel, clinical professor of dermatology, NYU School of Medicine. "Aldara Cream, an immune response modifier, is a unique, nonsurgical treatment advance for patients with certain types of BCC. It is already being used successfully in treating actinic keratosis."

The approval is based on results from two double-blind, placebo-controlled clinical trials involving 364 patients with primary sBCCs. Those with one biopsy-confirmed sBCC tumor were enrolled and randomly assigned to receive Aldara Cream or placebo cream once daily, five times a week for six weeks, the company said.

Clinical studies showed that 75 percent treated with Aldara Cream achieved composite clearance compared with two percent in the placebo group, the company said. In addition, the histological (confirmed through biopsy) clearance rate was 82 percent for

those treated with Aldara compared to three percent in the placebo group. Histological and composite clearance rates were assessed at 12 weeks post treatment.

Aldara Cream is indicated for sBCC tumors with a maximum diameter of 2.0 cm, on certain areas of the body, only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured, the company said. The safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types.

In clinical studies, the most frequently reported adverse reactions were local skin reactions, including flaking/scaling, in duration, edema, erythema, scabbing/crusting, erosion, and itching and burning at the application site.

Deals & Collaborations:

EU Marketing Approval Granted To Erbitux For Colon Cancer

(Continued from page 1)

area of oncology.

An IND application for VX-680 has been filed with FDA by Vertex to support clinical development in the U.S., the companies said. Merck and Vertex said they expect phase I studies of VX-680 to begin by the end of the year.

Preclinical results for VX-680 demonstrated that a compound targeting the Aurora mechanism could induce tumor regression in human models of solid tumor cancers, the companies said.

In another development, Merck KGaA of Darmstadt, Germany, said the European Commission has granted EU marketing approval for Erbitux (cetuximab), for metastatic colorectal cancer.

Erbitux is the first monoclonal antibody specifically targeting the epidermal growth factor receptor to gain marketing authorization, the company said. It is licensed for use in combination with irinotecan for EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Erbitux would be available for supply in all 25 member states of the European Union as well as Iceland and Norway in accordance with local legal regulations, the company said.

The use of Erbitux is supported by clinical study data showing consistent efficacy in EGFR-expressing colorectal tumors in combination with chemotherapy, the company said. The licensed indication is supported primarily by data from the Bowel Oncology and Cetuximab Antibody study, which showed that Erbitux, when used in combination with irinotecan, benefited more than half of the patients. The combined treatment shrank tumors by more than half in 23 percent and stopped tumor growth in an additional 33 percent, the company said. Erbitux is the first EGFR inhibitor proven to enhance tumor response in combination with chemotherapy even when this chemotherapy alone is no longer effective, the company said.

"The data supporting Erbitux are robust," said David Cunningham, head of the Gastrointestinal and Lymphoma Units at the Royal Marsden Hospital in London and Surrey, U.K., and lead investigator in the BOND study. "Erbitux has shown efficacy in the most difficult to treat category of patients—those who have metastatic disease and previous treatment failure. The effectiveness of the Erbitux/irinotecan combination is not influenced by the number or type of previously administered chemotherapy regimens."

Erbitux has been approved in Switzerland, the U.S. and, most recently, in Argentina, Chile and Mexico, the company said.

Merck KGaA licensed the right to market Erbitux outside of the U.S. and Canada and the co-exclusive right to market Erbitux in Japan from ImClone Systems Inc., of New York, in 1998.

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AGT Biosciences Ltd. (ASX:AGT) of Melbourne, Australia, and **ChemGenex Therapeutics Inc**., of Menlo Park, Calif., said they have completed their merger transaction to form **ChemGenex Pharmaceuticals Ltd.**

The new company would continue trading on the Australian Stock Exchange under the present stock symbol of AGT, which would soon be changed to CXS, the companies said.

"The merger creates a genomics-driven global biotechnology company with two products in phase II clinical development, and discovery and development capabilities in oncology, diabetes, obesity and depression," said Greg Collier, CEO of ChemGenex Pharmaceuticals.

Ceflatonin (homoharringtonine), the first product, is in phase II development for leukemia, the company said. In past trials high response rates in both chronic and acute leukemia have been observed.. The product would be developed as a

single agent for chronic myeloid leukemia, the company said. Future studies would focus on myelodysplastic syndrome and acute myeloid leukemia.

The second company product, Quinamed (amonafide dihydrochloride), is beginning phase II development for solid tumors, the company said. Phase I data on 32 patients validated the use of genotyping to determine the most efficacious dose. In addition, evaluable responses were observed in three patients who had failed prior chemotherapy. The ongoing phase II trial would use genotyping to determine dose and is designed to confirm anti-tumor activity in a number of indications including colon, breast and prostate cancers, the company said.

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BioWa Inc., of Princeton, N.J., said it has granted a commercial license to **Biogen Idec Inc.** for its Potelligent Technology that enhances antibody-dependent cellular cytotoxicity.

The agreement provides Biogen Idec with the right to reserve for itself exclusive commercial rights to develop antibodies for an undisclosed number of targets, the companies said. In return, BioWa would receive a signing fee, and could receive milestone payments and royalties on products developed by Biogen Idec.

BioWa is a wholly owned subsidiary of Kyowa Hakko Kogyo Co., Ltd., of Japan.

* * *

CancerVax Corp. (Nasdaq:CNVX) of Carlsbad, Calif., said **Tarcanta Inc**., and Tarcanta, Ltd. of Ireland, its wholly owned subsidiaries, have obtained the exclusive rights to complete the clinical development of three active immunotherapeutic product candidates that target the epidermal growth factor receptor pathway for cancer.

Under the agreements, CancerVax rights include commercialization of product candidates within the U.S., Western Europe, Canada, Japan, Australia, New Zealand, and Mexico, the company said.

Data from early phase I and II studies of SAI-EGF suggest the product was well tolerated and may increase the survival of advanced stage non-small-cell lung cancer, the company said.

In addition to the phase II product candidate, SAI-EGF, which targets epidermal growth factor, the licensing agreements also include rights to SAI-TGF-alpha, which targets transforming growth factor-alpha that binds to and activates EGFR, and SAI-EGFR-ECD, which targets the extracellular domain of EGFR, both of which are in preclinical development, the company said.

Under the agreements, CancerVax would provide upfront access fees, technology transfer fees, development and commercialization milestones and royalties upon commercial sales, the company said. CancerVax said it is obligated to make access and technology transfer payments of $6 million over the next three years. If the three product candidates are approved for commercialization in the U.S., Europe and Japan, CancerVax is also obligated to pay additional milestone payments, up to a maximum of $35 million, based upon meeting specified regulatory, clinical and commercialization milestones, and royalties on future net sales of product.

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Cellomics Inc., of Pittsburgh, said it has entered into a non-exclusive, worldwide patent license agreement for its core HCS patent portfolio with **GE Healthcare.**

In parallel, Cellomics and GE Healthcare have also entered into a limited term, exclusive agency agreement, which gives rights to GE Healthcare to broker sublicenses of the Cellomics HCS patent portfolio to pharmaceutical companies.

"The agreements with Cellomics help us to enable customers to ask complex biological questions using our cellular sensors and, in turn, interpret the answers, said Michael Evans, vice president of marketing and Strategy, discovery Systems.

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Confirma, of Kirkland, Wash., and **GE Healthcare**, of Waukesha, Wis., said it has signed a strategic alliance for GE to distribute the Confirma CADstream software to GE MRI customers worldwide.

"Our relationship with GE Healthcare is focused on enhancing breast MRI analysis and reaching more healthcare providers and patients with state-of-the-art technology for diagnosing breast cancer," said Max Lyon, president and CEO, Confirma. "Together, GE Healthcare and Confirma would offer the most advanced breast imaging solutions available."

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Ergomed Clinical Research Ltd., of Frankfurt, Germany, said it has acquired, through a subsidiary, the operating assets of the **Ilex Oncology Inc.** (Nasdaq:ILXO) clinical research and regulatory service office in Guildford, UK.

The office was owned and operated by Ilex Services Ltd., a subsidiary of Ilex Oncology Services

Inc., of San Antonio.

Under the asset transfer agreement, Ergomed would become a preferred provider of services to Ilex and would continue to provide site management, monitoring and project management services for ongoing clinical studies outside the U.S.

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Agensys Inc., of Santa Monica, Calif., said it has signed a collaboration and license agreement with **Genentech Inc.** (NYSE:DNA) for the research, development and commercialization of two of the Agensys proprietary therapeutic and diagnostic cancer targets.

The agreement provides Genentech with exclusive worldwide licenses under the Agensys patent rights to develop therapeutic products and associated diagnostic applications, the company said. Genentech also acquires rights to monoclonal antibodies developed at Agensys and provides Agensys financial incentives to collaborate on developing additional antibodies to both targets, which would then fall under the license.

Under the agreement, the development and launch of antibody products to each target would trigger milestone payments that could exceed $90 million, the company said. Agensys would also receive royalties on the sales of therapeutic products and a share of the profits from diagnostic products. The development of non-antibody products would prompt additional comparable milestone and royalty payments.

Genentech will be responsible for the development and commercialization of all therapeutic and associated diagnostic products, except for vaccine products and certain diagnostic applications, which rights were retained by Agensys, the company said. In addition to an upfront licensing payment, Genentech has made an equity investment in Agensys preferred stock.

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General Electric Co. (NYSE:GE) through GE Global Research of Niskayuna, N.Y, along with **Celera Genomics Group** (NYSE:CRA) of Rockville, Md., and **Celera Diagnostics,** of Alameda, Calif., a joint venture between Celera Genomics and the Applied Biosystems Group (NYSE:ABI), said they have entered into a research collaboration to develop products for personalized, or targeted, medicine.

The first project in the collaboration supports the GE development of cancer imaging agents that target cell surface proteins identified by Celera Genomics associated with cancer, the companies said. The cell surface proteins are also the basis for complementary drug discovery programs undertaken by Celera Genomics and its partners.

Under the agreement, GE would have exclusive access to protein targets for research and development of medical imaging agents, the companies said. The parties would share responsibilities and costs associated with research and development, as well as value from commercial products from the project.

A second collaborative project related to bioinformatics would support the development of algorithms and tools to advance the diagnostic and/or therapeutic programs of the collaboration partners.

Personalized medicine encompasses in vivo and in vitro diagnostics and assesses disease risk, identifies and characterizes disease, monitors patients for disease onset, and selects therapy and measures therapeutic response, the companies said. In vivo imaging agents would target differentially expressed cell surface proteins that are found on diseased cells.

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Geron Corp. (Nasdaq:GERN) of Menlo Park, Calif., and **Kyowa Hakko Kogyo Co., Ltd.** said Kyowa Hakko has returned Asian territory development and marketing rights for the Geron telomerase inhibitors.

"Kyowa has made a decision to focus on other oncology platforms in the future, including monoclonal antibodies, and are consequently relinquishing our rights to the drugs to Geron," said Kenichi Fukuhara, executive officer of Kyowa Hakko.

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Immusol, of San Diego, said it has begun a collaboration with **Affymetrix Inc.** (Nasdaq:AFFX) to advance drug discovery for cancer therapies.

The aim of the program is to elucidate transformation pathways and to acquire and validate therapeutic target candidates, the company said. Immusol would retain all rights for any discoveries.

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MathWorks, of Natick, Mass., said **Infinity Pharmaceuticals Inc.**, of Cambridge, Mass., is using its MATLAB, the Statistics Toolbox, and the Curve Fitting Toolbox, for data analysis.

By integrating MATLAB into their data analysis applications, Infinity was able to cut development time and save $100,000 annually, the companies said.

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MGI PHARMA INC. (Nasdaq:MOGN) of Minneapolis, said it has entered into a three-year promotion agreement with **Alpharma Inc**. to promote the Alpharma sustained release morphine sulfate product, Kadian for moderate to severe cancer pain.

Under the agreement, MGI PHARMA will market Kadian in the U.S., the companies said.

Initially, MGI PHARMA and Alpharma will equally share profit contribution on sales of Kadian for oncology applications, the companies said.

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North Shore-Long Island Jewish Research Institute of Huntington, N.Y, and **Correlogic Systems Inc**., of Bethesda, Md., said they would collaborate on a blood test for the early detection of ovarian cancer.

Blood samples would be collected from several hundred women over the next two years, the groups said. Samples would be analyzed immediately to expand validation of the blood test, and in subsequent months to provide additional information that may help extend clinical use of the test.

North Shore-LIJ Health System, the parent of the North Shore-LIJ Research Institute, which has access to large patient populations, would invite all women undergoing specific gynecologic surgery, women at high risk who are not undergoing surgery, and women who have been diagnosed with ovarian cancer to participate in the research effort by providing blood samples for scientific evaluation, the groups said.

"Upon validation, this blood test can dramatically change the lives of women at high risk for ovarian cancer," said John Lovecchio, and lead investigator and chief of gynecologic oncology for the North Shore-LIJ Health System. "When caught very early, the survival rate can be as high as 90 percent. Unfortunately, most of these cancers are caught only after the disease has progressed to the later stages, when the survival rate is only about 25 percent."

The collaboration was brought about by Rep. Steve Israel, of Huntington, co-chairman of the House Cancer Caucus, who introduced a Congressional resolution promoting research on the technology and calling for federal and private insurance coverage of ovarian cancer tests based on the technology, the groups said. The resolution was approved in the House in July 2002.

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Seattle Genetics Inc. (Nasdaq:SGEN) of Bothell, Wash., and **CuraGen Corp.** (Nasdaq:CRGN) of New Haven, said they have signed an antibody drug conjugate agreement.

CuraGen licensed the Seattle Genetics proprietary ADC technology for use with its proprietary antibodies for cancer, the companies said. CuraGen would pay an upfront fee of $2 million for the ADC technology for one of its proprietary antibody programs. CG also has an option to access the ADC technology for a second CuraGen proprietary antibody program in exchange for an additional fee.

Under the multi-year agreement, Seattle Genetics would receive up to $28 million in milestone payments for two antibody therapeutics employing ADC technology and would receive royalties on net sales of resulting products, the companies said. CuraGen is responsible for research, product development, manufacturing and commercialization of all products under the collaboration. CuraGen would pay maintenance and material supply fees as well as research support payments for any assistance provided by Seattle Genetics in developing ADC products.

In another development, Seattle Genetics Inc. said it has entered into a preferred provider agreement with **Albany Molecular Research Inc.** (Nasdaq:AMRI) for the manufacture of its proprietary drug-linker system.

The system, comprised of cell-killing drugs and stable linkers, is used in the Seattle Genetics antibody-drug conjugate technology, the company said. The arrangement secures rights for the Seattle Genetics ADC licensees to work directly with AMRI on manufacturing campaigns to obtain cGMP supplies of drug-linker units to support future clinical trials of products using the ADC technology.

Seattle Genetics also licensed ADC technology to Genentech, Celltech Group, Protein Design Labs, and CuraGen.

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Teva Pharmaceutical Industries Ltd. (Nasdaq:TEVA) of Jerusalem said pursuant to its 2004 supply and distribution agreement with **Bristol-Myers Squibb Co**., its subsidiary **Sicor Inc.** has begun commercially shipping carboplatin injection (50 mg, 150 mg, 450 mg) and carboplatin aqueous solution injection (50 mg/5 ml, 150 mg/15 ml, and 450 mg/45 ml).

Carboplatin injection and carboplatin aqueous solution injection are generic-labeled versions of the Bristol-Myers Squibb cancer treatment Paraplatin, which had U.S. sales of $769 million in 2003.

Clinical Trials:

Adherex To Begin Phase I Trial Of Exherin, Cadherin Antagonist

Adherex Technologies Inc. (TSX:AHX) of Research Triangle Park, N.C., said FDA has cleared its IND application for Exherin, a cadherin antagonist, tumor vascular targeting compound, allowing a U.S.-based, phase I trial to begin.

David Stewart, professor of thoracic/head and neck medical oncology at M.D. Anderson Cancer Center, is principal investigator for the study.

The study would also use Dynamic-MRI imaging techniques to assess the time-course of activity of the drug on a tumor and its blood supply. The study is expected to begin in July and would enroll up to 20 patients.

Exherin is a tumor vascular targeting agent and is a small peptide molecule that disrupts the blood vessels of cancers through inhibition of the cell adhesion protein, N-cadherin, that is a structural component of some tumor blood vessels.

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Point Therapeutics Inc. (NASDAQ:POTP) of Boston, said it has initiated a phase II trial of the compound, talabostat (PT-100), for advanced chronic lymphocytic leukemia.

The study would evaluate the anti-tumor activity of the compound in combination with Rituxan in advanced CLL where a fludarabine/rituximab-containing regimen has failed.

The primary clinical endpoint of the single-arm, two-stage, 54-patient study is overall tumor response, the company said. At mid-point, tumor response rates would be compared to historical response rates of current therapies to determine whether the trial should be continued. Other secondary study endpoints include complete response rate, duration of tumor response, time to disease progression and survival.

"Our first two phase II trials are studying talabostat in combination with Taxotere in stage IIIB/IV non-small cell lung cancer and in combination with cisplatin in patients with advanced metastatic melanoma," said Don Kiepert, president and CEO of Point Therapeutics.

The company also began a phase II trial of talabostat PT-100 for advanced metastatic melanoma. The study is designed to evaluate the anti-tumor activity of the product as a single-agent, the company said.

The trial design is a single-arm, two-stage study in up to 30 patients, the company said. The primary clinical endpoint would be overall tumor response. At mid-point of the study, tumor response rates would be compared to historical response rates of current therapies to determine whether the trial should be continued. Other secondary study endpoints include complete response rate, duration of tumor response, time to disease progression and survival.

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Praecis Pharmaceuticals Inc. (NASDAQ: PRCS) of Waltham, Mass., said it has received FDA approval to resume its phase I trial of PPI-2458 in non-Hodgkin's lymphoma.

FDA had issued a clinical hold based on a preliminary neuropathological finding in an animal safety study, the company said.

PPI-2458 inhibits the enzyme, methionine aminopeptidase type 2, thought to be involved in the growth of a spectrum of cancers, the company said. The company said it has developed a proprietary pharmacodynamic assay for clinical studies to assess the level of inhibition of MetAP2 achieved by PPI-2458. In addition to the inhibition of MetAP2, PPI-2458 preclinical data have demonstrated the inhibitor blocks angiogenesis.

* * *

Sunesis Pharmaceuticals Inc. of South San Francisco, said it has initiated the first of two phase I studies of SNS-595, an anti-cancer small molecule drug.

The open-label multi-center, dose-escalation study examines the safety, tolerability, and pharmacokinetics of the drug to establish optimal dosing regimens, the company said.

SNS-595 is a first-in-class cell cycle modulator that kills proliferating cancer cells by inducing apoptosis, the company said.

Enrollment has begun at four centers in the U.S for advanced malignancies, the company said. In the first trial, SNS-595 would be administered as a single dose followed by a 21-day observation period for up to six treatment cycles.

In vivo animal studies of the drug demonstrate robust activity, as well as marked potency, in comparison to marketed cytotoxic drugs such as paclitaxel and irinotecan, the company said. In addition, SNS-595 shows activity in drug-resistant tumor models.

Sunesis said it would begin a second, multi-dose phase I study in the third quarter. Phase II studies in a variety of tumor types are expected to begin in 2005.

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