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Learning From Europeans, U.S. Oncologists Consider Role For Oxaliplatin, 5-FU Infusion

After four decades of seeking the optimal method for administration of 5-fluorouracil, oncologists treating colorectal cancer find themselves in the midst of transition into the new world of multiple therapies.

With these new therapies comes a multitude of unanswered questions.

The horizons in gastrointestinal oncology broadened beyond 5-FU in 1996, with the FDA approval of CPT-11 for advanced colorectal cancer that progressed on 5-FU.

In April 2000, two combinations of the Pharmacia drug CPT-11, 5-FU, and leucovorin moved to first-line treatment of advanced colorectal

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In Brief:

Bush Names Leffall Cancer Panel Chairman, Appoints Cyclist Lance Armstrong To Panel

PRESIDENT GEORGE W. BUSH made two appointments to the President's Cancer Panel recently. **LaSalle Leffall Jr.**, the Charles R. Drew Professor of Surgery at Howard University College of Medicine, replaces **Dennis Slamon**, chief of hematology-oncology at University of California, Los Angeles, for a term expiring Feb. 20, 2004. Leffall was appointed to serve as chairman of the panel for one year. Leffall also is chairman of the Susan G. Komen Breast Cancer Foundation Board of Directors. Bush appointed **Lance Armstrong**, professional cyclist and testicular cancer survivor, to a term expiring Feb. 20, 2005, replacing **Fran Visco**, president of the National Breast Cancer Coalition. **Harold Freeman**, chairman of the panel since his appointment by President George H.W. Bush in 1991, and reappointed by President Clinton in 1994, 1997, and 2000, will serve the remainder of his term to 2003. Freeman serves as director of the NCI Center to Reduce Cancer Health Disparities, and professor of clinical surgery at Columbia University and director of surgery at North General Hospital in New York City. The panel was created by the National Cancer Act of 1971 to monitor the National Cancer Program and report delays to the President. The panel meets at least four times a year. . . . **LÁSZLÓ TABÁR**, professor of diagnostic radiology at Uppsala University in Sweden, received the American Cancer Society Distinguished Service Award. Tabár, director of the Department of Mammography at Falun Central Hospital, has directed the Kopparberg arm of the Swedish Two-County Trial of Mammographic Screening. Tabár made contributions

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Some GI Oncologists Say Data Justify Switch To 5-FU Infusion

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cancer. Then, last April, FDA approved the Roche drug Xeloda (capecitabine), an oral equivalent of 5-FU.

Now, following presentation of new data on oxaliplatin at the 38th annual meeting of the American Society of Clinical Oncology in Orlando on May 18-21, GI oncologists are expecting a third active drug—oxaliplatin—to become available in the US.

Oxaliplatin is sponsored by Paris-based Sanofi Synthelabo, and is widely available outside the U.S.

The new data came from a study led by North Central Cancer Treatment Group, comparing several regimens used in first-line treatment of advanced colorectal cancer.

The trial, N9741, found a statistically significant survival advantage and a delay in time to disease progression in the arm combining oxaliplatin with infusional 5-FU and leucovorin.

The results of the trial appear to have the potential of changing everyday practice of GI oncology.

—Several prominent academic oncologists told **The Cancer Letter** that the new data has convinced them to switch from bolus administration of 5-FU to the infusional method. Oncologists, especially those in private practice, have been reluctant to switch to this more cumbersome technique.

—The standing of the FDA-approved Saltz regimen as the standard of care in the U.S. may be erode as oncologists, including the regimen's inventor Leonard Saltz, switch from bolus 5-FU to infusion. At the same time FDA approved the Saltz regimen, it approved the Douillard regimen, which uses infusional 5-FU.

The Saltz regimen is also known as IFL and the Douillard regimen, developed by French oncologist Jean-Yves Douillard, is known as FOLFIRI.

—If the new data on oxaliplatin leads to approval of the agent in the U.S., drug developers will have to think hard about pinpointing appropriate control regimens. At this time, experts are contemplating four-arm trials or two-arm trials comparing new agents with regimens containing oxaliplatin and CPT-11.

Uncertainty notwithstanding, for the first time, GI oncologists would be able to offer their patients several viable options for the treatment of advanced colorectal cancer.

"Based on our data, and on other studies, there are currently three agents—5-FU and its pro-drugs, CPT-11, and oxaliplatin—that are active in the treatment of metastatic colorectal cancer," said Richard Goldberg, coordinator of the NCCTG and Mayo Clinic Cancer Center GI Cancer Programs.

"We feel that the FOLFOX regimen [oxaliplatin, infusional 5-FU and LV] has notable activity and an advantageous toxicity profile in comparison to IFL [CPT-11, bolus 5-FU and LV]," said Goldberg, presenting the trial results at the ASCO conference May 18.

"These findings permit patients, their oncologists, and governmental regulatory bodies to evaluate the current therapeutic alternatives to determine the appropriate standard of care for first-line treatment of patients with advanced colorectal cancer," Goldberg said.

In the phase III trial, 71 percent of patients who received FOLFOX were alive a year after starting treatment, compared to 58 percent of patients who received IFL therapy.

The findings, published as ASCO abstract 511, were based on analysis of 795 patients who enrolled in the trial between March 1999 and April 2001. Patients who received the FOLFOX treatment lived an average of 18.6 months, compared to 14.1 months for patients who received IFL.

Time to disease progression was 8.8 months on

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FOLFOX and 6.9 months on IFL. Response rate was 38 percent on FOLFOX and 29 percent on IFL.

Patients on FOLFOX had fewer infections, less diarrhea and vomiting, and did not lose their hair as frequently.

"To maximize all results, all agents must be available to all patients, and while we've made a lot of progress, it's important for us to keep perspective on the situation: all currently available regimens for colorectal cancer remain inadequate," said Saltz, an oncologist at Memorial Sloan-Kettering Cancer Center, who was the discussant at the presentation of NCCTG results.

A Shift To Infusion

The NCCTG trial was designed to evaluate treatment regimens rather than to support registration of oxaliplatin.

The results could have been inadvertently skewed to favor oxaliplatin in part because patients who were randomized to FOLFOX as a first-line treatment had no trouble getting CPT-11 in second line.

By contrast, patients randomized to first-line IFL had difficulty obtaining FOLFOX as a second-line treatment since oxaliplatin is not approved in the U.S. and is available either in clinical trials or through the company's expanded access program.

The trial's relevance to the approval process is unclear. While Sanofi is seeking approval for oxaliplatin as a second line treatment, N9741 tested the drug in first line.

Critics note that the comparison of IFL and FOLFOX is imperfect because the two regimens use different approaches to administration of 5-FU.

However, this apparent quirk is the reason N9741 may end up altering clinical practice in the U.S.

The trial compared a popular European regimen with the U.S. standard treatment, and the European regimen won. Did this happen because of oxaliplatin's superiority over CPT-11 or because of the superiority of infusional 5-FU over bolus 5-FU?

Acknowledging that definitive answers to these questions will have to emerge from future trials, some GI oncologists are switching to infusion.

"I use the infusional 5-FU regimens as my routine default position when treating patients off-study," Saltz said to **The Cancer Letter**. "And I am designing my studies with the 48-hour infusional regimen."

In the past, Saltz would have defaulted to the FDA-approved IFL regimen also known the Saltz regimen.

"It was our best shot at the time, and for a while I think it was the best way to go," Saltz said. "Now, I think that at least in many cases there is something that has a modest advantage."

Saltz said he changed his approach after reviewing the data from that trial, in conjunction with earlier data.

"I think this study should change people's thoughts about practice," Saltz said. "I don't think it has to have regimented 'you must' connotations, but the purpose of studies is to force us to think about the data and decide where they apply."

Saltz acknowledges that the case for infusion isn't air-tight.

"Could somebody rigorously interpret these data differently? Yes, they could," Saltz said. "Is somebody free to do so? Yes, they are. Do I want to tell people that if they use a bolus regimen, they are wrong? Absolutely not. But what have I done since ASCO when I see new patients not on protocol? I start them on FOLFIRI, [a 48-hour infusion of 5-FU] with CPT-11."

Though studies comparing infusional and bolus regimens of 5-FU are numerous and inconclusive, Saltz said a relatively small study presented at the 2001 ASCO annual meeting by Christoff Tournigand comes closest to offering a comparison between oxaliplatin and CPT-11 regimens (Abstract 494).

In that study, 226 patients were randomized to regimens containing either oxaliplatin [FOLFOX] or CPT-11 [FOLFIRI], which are administered with infusional 5-FU and LV. When patients progressed on one arm, they crossed over to another.

"The curves were virtually overlapping," Saltz said. "The survival curves were virtually identical, the response rates were virtually identical, and the time to tumor progression were virtually identical. My impression is that even though this study was underpowered, it's very hard to look at it and believe that there would be a dramatic difference if that study was larger."

Saltz is not alone in switching to infusional 5-FU.

NCCTG's Goldberg abandoned the bolus 5-FU and leucovorin regimen in favor of infusion about three months ago.

Goldberg said his decision to abandon the administration method (which just happens to be called

the Mayo Clinic Regimen) was based on his experience with toxicity experience as well as the results of N9741, which were starting to trickle in.

"The Europeans have been trying to teach us this lesson for a long time," Goldberg said. "I think there is unequivocal data that the safety profile is advantageous, and that activity profile is also advantageous."

Though randomized studies don't show a survival advantage of infusion over bolus, "the safety advantage becomes noticeable when you combine [5-FU] with an additional drug that has toxicity," Goldberg said.

Mace Rothenberg, Ingram associate professor of cancer research at Vanderbilt University, said that he has been switching to infusional 5-FU or capecitabine as a single agent in ECOG Performance Status 2 patients over several years.

Rothenberg is the principal investigator in a phase III trial that oxaliplatin's sponsor Sanofi is using in its application for approval for second-line treatment of advanced colorectal cancer.

Academic oncologists who practice at large institutions are likely to be comfortable with switching to infusional 5-FU.

Their counterparts in private practice would be more resistant to such change, mostly because infusion pumps are cumbersome to operate, and when they malfunction, patients call and ask for help.

The FDA Oncologic Drugs Advisory Committee members noted their reservations about practicality of infusion during discussion of the Pharmacia application for CPT-11 for the first-line treatment of colorectal cancer (**The Cancer Letter**, March 24, 2000), and during discussion of toxicity of the IFL regimen (**The Cancer Letter**, Dec. 14, 2001).

"If you are in a three-physician group, every third week you get the infusion calls," said Goldberg. "And that's the main reason why Americans have been refractory to infusion."

Choice Based on Toxicity?

NCCTG's Goldberg said oxaliplatin offers a real survival advantage that can't be attributed entirely to the differences in the schedules for administration of 5-FU.

"I don't think the magnitude of the benefit we observed in N9741 can be explained by the comparison between bolus 5-FU and an infusional 5-FU regimen," Goldberg said.

Saltz disagrees. "Considering data available to date, there is no compelling evidence to support any one regimen as a clear standard of care," Saltz said.

If the drugs' efficacy is indeed similar, the treatment decisions could be based on toxicity, experts agree.

"You can say to people, there are a couple of different ways to approach your problem," Saltz said to **The Cancer Letter**. "The side effects that you will be at risk for are different, so let me discuss with you which side effects profile would be more acceptable to you as an individual."

Oxaliplatin poses a greater risk of neurotoxicity.

"If somebody is a surgeon or a concert violinist, that's going to be a consideration," Saltz said.

On the other hand, CPT-11 entails a higher risk of diarrhea, nausea, neutropenia, and hair loss.

"Those are going to be serious considerations for some of the people," Saltz said. "Which is better? Which is worse? Now, we will be able to say to our patients, Let me talk to you about who you are, and which of these is going to be most acceptable to you, and let's customize the care within the realm of viable options."

Goldberg said the toxicity profiles of the two drugs suggest a different strategy.

"With CPT-11, toxicity tends to occur early and require dose adjustments," Goldberg said. "In our study, 4.5 percent of patients died within 60 days of going on CPT-11. For the sort of patients put on a first-line clinical trial, this is a distinctly unusual circumstance."

While the toxicity of CPT-11 regimens affect all patients, regardless of whether they benefit from therapy, toxicity of oxaliplatin is more likely to occur in patients who respond to the regimen, Goldberg said.

"When you are talking about the neurotoxicity of oxaliplatin, you are talking about neurotoxicity that occurs late, so it affects only patients who benefit from the drug," Goldberg said. "And while it limits the amount of treatment the patient can take, it seldom limits their life expectancy."

Given these efficacy and toxicity profiles, it may be reasonable to use FOLFOX first, move to FOLFIRI as a second line, and return to FOLFOX as a third-line treatment, Goldberg said.

"This would be a reasonable strategy to expose the tumor to the most active drugs in our armamentarium," said Goldberg, attributing the FOLFOX-FOLFIRI-FOLFOX sequence to Aimery deGramont, a French oncologist who developed the FOLFIRI regimen.

The Mysteries Of Control

"We are in a very dynamic period," said Vanderbilt oncologist Rothenberg. "Things have not settled out, and they will not settle out over the next year or year-and-a-half."

Meanwhile, what's a drug developer to do?

"You want to cover all bases," said a scientist involved in development of a next-generation regimen for advanced colorectal cancer.

At this point, the scientist, who spoke on condition that his name would not be used, said he is leaning toward testing his therapy separately against an oxaliplatin regimen and against a CPT-11 regimen.

"We want to be in front line, and we want to be in second line, so we are talking four huge phase III trials," the scientist said.

Since the decision on approval of oxaliplatin is still months away, it may be appropriate to use the current approved regimen, IFL and FOLFIRI, some observers say.

However, at least for now, many pharmaceutical companies opt for IFL, a regimen that comes closest to the treatment administered to the majority of patients in the U.S.

"You can use IFL, but the ground is going to shift, and at least a percentage of patients—I would hazard more than 50 percent of patients with newly diagnosed colon cancer—are going to end up getting oxaliplatin as their first-line therapy once it's freely available," said Goldberg.

"You would want to combine your new agent with an oxaliplatin regimen, and not just a CPT-11 regimen to know exactly where it fits," he said. "It's unclear which of these will end up winning out as standard therapy. It may be that there will be two standard therapies."

Rothenberg said confusion stems from blanket acceptance of IFL as the standard of care in the U.S.

"People are confused, because they don't know how to [interpret] recent data that came out of the N9741 trial," Rothenberg said. "The gold standard didn't perform as well in that trial.

"There are a lot of more questions than answers in people's minds, but it only means that they should use their perspective," Rothenberg said. "You don't have to have a single gold standard. You could have an accepted treatment as a control arm, and simply design a trial to show that your drug is safe and efficacious for the indication requested.

"Drug development in oncology isn't that simple," he said. "Choice is a good thing. Our lives are more complicated, but they are more complicated for the right reason."

Sanofi Prepares for U.S. Market

In recent months, Sanofi has been putting together its U.S. marketing team, company officials said.

The Paris-based company said it plans to market oxaliplatin without a U.S. partner. Flying solo is a change of strategy for Sanofi. Two years ago, following an unsuccessful attempt to get oxaliplatin approved by FDA on the strength of European data, the French company parted with its U.S. partner, Eli Lilly & Co.

"As we said two years ago, after discontinuation of partnership with Lilly, we are not considering a new partnership," said Alain Herrera, head of the Sanofi corporate oncology franchise.

"We decided to develop the drug ourselves, and we established a completely new clinical development program in the U.S., and we completed this clinical program, and we will market the drug by ourselves," Herrera said to **The Cancer Letter**.

The company expects to complete its New Drug Application for the second-line indication by late June, which means FDA would be expected to act on the application in mid-September. At a later date, the company expects to seek the first-line indication.

"The results presented at ASCO by Rich Goldberg are the results of preliminary analysis," Herrera said. "[After] the results are reconfirmed by definitive analysis, we will pose a question to FDA, but we cannot anticipate the answer."

Meanwhile, NCI has arranged for FOLFOX to be available as a treatment option for patients not previously treated with chemotherapy for advanced colorectal cancer.

The regimen will be offered at all NCI-designated comprehensive and clinical cancer centers and other select health care institutions across the country, the Institute said.

According to NCI, the supply of the drug will be limited for the next several months. Up to 300 patients with advanced colorectal cancer who wish to receive the FOLFOX treatment will be randomly selected each month.

By early fall, sufficient supplies of the drug should be available to treat all patients who are eligible to receive it, NCI officials said. Further information is available at: http://www.sanofi-synthelabous.com/excellence/whitepaper.html.

Philanthropy:

HHMI Appoints 12 Physicians As Translational Investigators

Howard Hughes Medical Institute, in Chevy Chase, Md., selected 12 physician-scientists out of 138 nominations to be appointed as HHMI investigators in a new program to improve the translation of basic science discoveries to enhanced treatments for patients.

The Institute enters into long-term collaboration agreements with universities and other academic research organizations, where its investigators hold faculty appointments. Under these agreements, HHMI investigators, all of whom are employees of the Institute, carry out their research in HHMI laboratories located on various campuses. The 12 new investigators will join 324 current HHMI investigators across the U.S.

The Institute expects to provide initial research budgets of up to $1 million annually for each of its new investigators, plus payments to the host institutions for laboratory space.

The Institute's biomedical research expenditures this fiscal year will total about $450 million. In addition to conducting medical research, the Institute has a large grants program that supports science education in the U.S. and the research of a select group of biomedical scientists in other countries. HHMI grants will total more than $100 million during the current fiscal year.

The new HHMI investigators are:

Robert Darnell, of The Rockefeller University. Darnell studies paraneoplastic neurologic disorders, which are believed to arise when tumor cells abnormally produce proteins that are usually made only in neurons. In PND patients, the immune system produces antibodies and T cells that effectively attack the patient's own tumor. But the same immune cells can also attack healthy neurons.

One of the goals of Darnell's research is to learn more about the neuronal proteins that are attacked by the immune system. Using serum from patients with PND, Darnell's research team has identified a series of genes that encode previously undiscovered neuron-specific proteins. By studying the PND antigens, Darnell and colleagues have found that neurons are unique in the way they regulate gene expression through their processing of RNA. These findings are relevant for a number of diseases. For example, the Darnell laboratory recently discovered how the RNA binding protein associated with fragile X mental retardation might cause the range of cognitive and behavioral abnormalities characteristic of this disease.

A second goal is to understand the nature of the anti-tumor and autoimmune response, with the aim of developing new immunotherapies. By starting with the unique set of PND patients, the Darnell laboratory is working its way back toward understanding how people's immune system may normally suppress cancer as well as how autoimmune diseases, such as multiple sclerosis, arise—two pursuits that may lead to novel strategies for treating these life-threatening conditions.

Brian Druker, of Oregon Health & Science University. Working from the premise that the leukemia-cell-specific Bcr-Abl tyrosine kinase caused chronic myelogenous leukemia, Druker searched for a molecule that would block the action of this altered kinase without interfering with other normal kinases. His search led to scientists at Novartis, who provided a number of chemical compounds that Druker tested to see whether they blocked the activity of the wayward kinase. The studies turned up STI-571, a compound that Druker played a key role in shepherding through development from early experimental therapy to large-scale clinical trials in patients.

As the STI-571 studies have shown, tyrosine kinases make excellent targets for new cancer therapies. Druker and his colleagues are continuing to study how tyrosine kinases spur cellular transformation. His group is now studying the FLT3 tyrosine kinase, which is mutated in 30 percent of patients with acute myeloid leukemia. Using the STI-571 studies as a road map for drug development, Druker and his colleagues hope to design an effective FLT3 kinase inhibitor.

Todd Golub, of Dana-Farber Cancer Institute. Golub is addressing clinical problems in cancer medicine by studying primary patient material at the genetic level. He and his colleagues are developing diagnostic and prognostic tests for childhood leukemia based on the cloning of genes involved in chromosome translocations; they are devising strategies for predicting responses to chemotherapy based on DNA microarray gene expression patterns; and they are exploring novel therapeutic strategies based on whole genome analyses of patient samples.

Golub and his colleagues have shown that children with acute lymphoblastic leukemia carry a

rearrangement of the TEL gene. They demonstrated that 27 percent of patients they studied carried a specific TEL/AML1 fusion gene that can be used as a diagnostic marker to predict a favorable response to therapy. TEL/AML1 testing is now being used at some medical centers to tailor individual treatment plans for patients with ALL in the hope of reducing toxicity caused by chemotherapy.

Unlike acute leukemias, most adult solid tumors are characterized by more complex gene rearrangements. Golub is now taking a number of different approaches that will yield a more accurate picture of how these tumors develop by taking a "whole genome" look at cancer. His research team is bringing the power of genomic technologies to bear on clinical dilemmas in cancer treatment, with an eye toward developing more rational approaches to treatment planning and drug development.

Katherine High, of the Children's Hospital of Philadelphia. For the past 16 years, High has studied the molecular basis of blood coagulation, with an emphasis on hereditary bleeding disorders. In 1999, High's research team showed that gene therapy could achieve long-term improvement in a naturally occurring hemophilia that affects dogs. They carried out the first studies of parenterally administered adeno-associated virus vectors in humans. The clinical studies are continuing in patients with severe hemophilia B.

Helen Hobbs, of University of Texas Southwestern Medical Center. Hobbs and her colleagues have collected and characterized the plasma lipoprotein levels in over 500 families in which multiple family members have elevated plasma levels of lipoproteins. Hobbs is investigating why some individuals are more likely than others to develop high plasma cholesterol levels on a high cholesterol diet.

Brendan Lee, of Baylor College of Medicine. Lee is studying the developmental and biochemical pathways that regulate mammalian tissue and organ development. In studies on skeletal and kidney development, he has correlated human genetic disease phenotypes with mouse models to elucidate the regulators and targets of key transcription factors specifying unique developmental programs. These basic and translational studies are linked with clinical research from the Texas Children's Hospital Skeletal Dysplasia Clinic.

Emmanuel Mignot, of Stanford University School of Medicine. Mignot and his colleagues are studying narcolepsy. In 1999, Mignot's research team and another group led by HHMI investigator Masashi Yanagisawa at the University of Texas Southwestern Medical Center converged on a faulty neuropeptide system that induced narcolepsy in dogs and mice. Mignot showed that molecules, which they called hypocretins, were absent in the brain of patients with narcolepsy. Mignot is now investigating whether narcolepsy is exacerbated by an autoimmune response against specific cells in the brain.

Charles Sawyers, of Jonsson Comprehensive Cancer Center, University of California, Los Angeles. Sawyers is investigating how molecular abnormalities in leukemia and prostate cancers lead to abnormal growth and cellular transformation. In collaboration with Brian Druker, Sawyers designed and conducted the phase I-II clinical trials of STI-571 for treatment of CML. Sawyers recently showed that resistance to STI-571 occurs through mutation or amplification of the Bcr-Abl gene. Sawyers is developing kinase inhibitor therapy for other cancers. He is studying how the PTEN tumor suppressor gene restricts access to the Akt pathway, which regulates growth signals. When PTEN is mutated, the Akt pathway promotes rapid cell growth, which may lead to cancer. Since 1997, Sawyers and his colleagues have learned critical information about how PTEN and Akt interact. The studies may help identify the molecular changes that accompany glioblastoma and prostate cancer.

Robert Siliciano, of Johns Hopkins University School of Medicine. Siliciano's laboratory is searching for ways to prevent or treat HIV infection through the development of new vaccine or drug therapies. Siliciano and his colleagues have shown that HIV-1 can persist in a silent form in a long-lived population of memory T cells. Since this reservoir of HIV-1 decays very slowly, latent infection of these so-called memory CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective antiretroviral therapy.

Edwin Stone, of University of Iowa College of Medicine. Stone's research interests are in inherited eye diseases. He established the Molecular Ophthalmology Laboratory at the University of Iowa in 1987 to facilitate the diagnosis and treatment of human eye diseases. Since1990, Stone has collaborated with HHMI investigator Val Sheffield at the University of Iowa in identifying the chromosomal location of genes that cause 14 different eye diseases and over 70 different mutations that cause a range of disease.

Bruce Walker, of Harvard Medical School.

Walker is investigating the cellular immune response to human viral pathogens, particularly HIV-1, HIV-2, and hepatitis C virus. Walker's group has focused their research efforts on persons in the earliest stages of HIV infection to determine how the immune system fights the virus during the initial encounter.

Christopher Walsh, of Harvard Medical School. Walsh is interested in the causes of mental retardation and epilepsy in children. Increasingly, children with mental retardation and epilepsy are being discovered to have abnormal development of the largest structure of the human brain, the cerebral cortex. By identifying the genes that are mutated in patients with disorders of brain development, Walsh and his colleagues are learning what proteins are involved, as well as where and how they function.

Funding Opportunities:

RFA Investigators Meeting

Notice ES-02-010: Pre-Application Meeting for the RFA on Centers for Population Health and Health Disparities

Pre-application meeting: June 10, 2002, 12:30 p.m.-3:30 p.m., Rm 5034, 6116 Executive Blvd, Bethesda, MD 20892. Application Receipt Date: Aug. 29, 2002.

National Institute of Environmental Health Sciences, NCI, and National Institute on Aging will hold a pre-application informational meeting for investigators planning to submit applications in response to RFA-ES-02-009, Centers for Population Health and Health Disparities. Staff will be available to discuss the intent and requirements of the RFA. Potential applicants are not required to attend the pre-application meeting. A written transcript of the meeting will be posted at http://dccps.nci.nih.gov/communicationcenters/index.html as a public document as soon as possible after the meeting.

Inquiries: Suzanne Heurtin-Roberts, NCI, Division of Cancer Control and Population Sciences, 6130 Executive Blvd., EPN 4054, Bethesda, MD 20892, phone 301-594-6655; fax 301-435-7547; e-mail sheurtin@mail.nih.gov

In Brief:

ACS Honors Tabar; CTEP's Cheson Moves To Lombardi

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to the technology of mammography, pioneering work in mammography positioning and promoting new extended film processing, microfocus magnification, spot compression and other concepts to improve the quality of images, ACS said. His methods and procedures have been part of the training for a generation of radiologists and are part of the formal recommendations of the American College of Radiology's Mammography Accreditation Program and the Mammography Quality Standards Act of 1992. . . . **BRUCE CHESON**, head of the Medicine Section in the NCI Cancer Therapy Evaluation Program since 1984, will become professor of medicine, head of hematology, and director of hematology research at the Lombardi Cancer Center at Georgetown University on July 1. Cheson also has served as editor of the ASCO Daily News, the official newspaper of the American Society of Clinical Oncology annual meeting, since the paper's inception. . . . **OLEH HALUSZKA**, director of GI endoscopy and assistant professor of medicine at the University of Maryland, has joined the Fox Chase Cancer Center medical oncology staff as director of gastrointestinal endoscopy. He was medical consultant for the White House medical department form 1998 to 2000. Haluszka will see high-risk patients in the Gastrointestinal Tumor Risk Assessment Program, which is designed to provide health education, genetic counseling, molecular diagnostics and screening guidelines to those at increased risk of colorectal, esophageal, pancreatic and other GI tumors.

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Business & Regulatory Report

Uninsured More Likely To Die Prematurely Than Insured, Institute Of Medicine Finds

Americans without health insurance are more likely to have poorer health and die prematurely than those with insurance, according to a report from the National Academies' Institute of Medicine.

Uninsured patients with colon or breast cancer face up to a 50 percent greater chance of dying than patients with private coverage. Uninsured victims of trauma also are more likely to die from their injuries. Being uninsured for even a year appears to diminish a person's general health.

"Because we don't see many people dying in the streets in this

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Clinical Trials:

IDM Gets FDA Approval For Phase III Trial Of Osiderm For Stage III Ovarian Cancer

Immuno-Designed Molecules, S.A. of Paris, France, and **IDM Inc**., its U.S. subsidiary, said they have received an FDA investigational new drug agreement for a phase III trial of the cell drug Osidem (IDM-1) for ovarian cancer.

The IDM study will be carried out in association with a number of U.S. teams of cell therapy specialists led by Ken Hatch and Evan Hersh, of the Arizona Cancer Center in Tucson, the companies said.

Other U.S. clinical and cell preparation centers will begin including patients in the coming months, with the support of IDM North American clinical research team, based in Montreal, the company said.

The cellular immunotherapy treatment would eliminate residual tumor cells after surgery and chemotherapy, the companies said.

Osidem is comprised of monocytes-derived activated killer cells associated with a bi-specific anti-HER-2/neu antibody developed by IDM partner Medarex Inc, of Annandale, NJ, the company said.

The phase III trials for stage III ovarian cancer are underway in Europe, Canada and Australia, the companies said.

The aim of the studies is to prolong remission after a positive response to a standard protocol consisting of surgery followed by two chemotherapies, the companies said.

* * *

Genetronics Biomedical Corp. (AMEX and TSX: GEB) announced results from a survey of the subjects in its phase II clinical trials in the U.S. and Canada for the treatment of recurrent squamous

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Uninsured Cancer Patients Die Sooner, IOM Study Says

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country, we assume that the uninsured manage to get the care they need, but the evidence refutes that assumption," said Mary Sue Coleman, co-chairman of the committee that wrote the report, and president, Iowa Health System and University of Iowa, Iowa City. "The fact is that the quality and length of life are distinctly different for insured and uninsured populations."

The committee examined the consequences of being uninsured for people with cancer, diabetes, HIV infection and AIDS, heart and kidney disease, mental illness, traumatic injuries, and heart attacks. It focused on the roughly 30 million—one in seven—working-age Americans without health insurance. This group does not include the population over 65 that is covered by Medicare or the nearly 10 million children who are uninsured in this country. A future report will look at how the lack of health insurance affects children and pregnant women.

Adults with public coverage, such as Medicaid, are a distinct group as well since they tend to be in significantly worse health than those with private insurance and even in somewhat worse health than those with no insurance. Adults qualify for Medicaid because they are poor or have already incurred unaffordable medical expenses. Low-income adults eligible for Medicaid often do not apply for it until they are sick.

Uninsured cancer patients die sooner than people with insurance do, largely because of delayed diagnosis, the report said. The uninsured are less likely to receive timely screening services such as mammograms, Pap tests, and colon exams. By the time cancer is diagnosed in uninsured patients, it is more likely to be at an advanced stage.

Uninsured adults with hypertension or high cholesterol are less likely to monitor their blood pressure or stay on drug therapy—if they are fortunate enough to be screened at all, the report said. Uninsured adults with HIV infection or AIDS are less likely to receive drugs that have become standard treatment in the past five years. When they do get drug therapies, their wait to receive treatment has been an average of four months longer than that of patients with private insurance. Providing health insurance to HIV and AIDS patients has been shown to significantly reduce death rates.

"It wasn't difficult for us to conclude that if the uninsured became insured on a continuous basis, their health would improve and they would live longer," said committee co-chairman Arthur Kellermann, professor and chairman, department of emergency medicine, and director, Center for Injury Control, Emory University School of Medicine.

Studies that have monitored the health of people who had no insurance or temporarily lost it for a period of one to four years show that a person's overall well-being suffers during the time they lack coverage. The decline in health caused by a lack or loss of coverage is most profound for adults between 55 and 65 years old, the report says. Symptoms of worsening health might include high blood pressure, greater difficulty climbing stairs or walking, or a decline in general self-perceived wellness.

Health insurance strategies that target the entire uninsured population would be more likely to produce greater health benefits and increase life expectancy than "rescue" programs aimed only at the seriously ill, the committee said. Being uninsured magnifies the health risks for chronically sick and mentally ill patients, as well as for groups that are already at greater risk of poor health, such as racial and ethnic minorities and adults with low incomes, the committee said. It added that increasing health insurance coverage would reduce some, but not all, of the disparities in health care experienced by racial and ethnic minorities.

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The committee noted that the research literature on which it based its findings probably understates the differences in health outcomes between insured and uninsured adults. The studies cannot account for the experiences of those who do not seek treatment, and uninsured adults are less likely to seek treatment.

The study is sponsored by the Robert Wood Johnson Foundation. Copies of the report, "Care Without Coverage: Too Little, Too Late," are available at http://www.nap.edu.

Clinical Trials:

Head & Neck Cancer Responds To EPT+Bleomycin, In Phase II

(Continued from page 1)

cell carcinoma of the head and neck.

Subjects in Genetronics' phase II clinical trial, at the time of the initial survey, had a median survival time of 5.4 months. The longest survival for a subject treated with the EPT+intralesional bleomycin was two years and 11 months. The data were published in the Program/Proceedings handbook at the 38th annual meeting of the American Society of Clinical Oncology in Orlando, Fl.

Genetronics' phase II trials were designed to evaluate the use of the company's proprietary Electroporation Therapy (EPT) system, consisting of the application of EPT+intralesional bleomycin for the treatment of recurrent SCCHN.

At the time of submission of the abstract, survival results were unknown in 19% of the cases. For these subjects, survival results were conservatively counted as the last date of contact plus one day. Subsequent to submission of the abstract, survival results of additional subjects were obtained. The additional subjects increased the median survival time to 6.4 months. According to information released during the FDA's Oncologic Drug Advisory Committee meeting of Sept. 10, 2001, the median survival time for subjects with a comparable stage of disease, as those in Genetronics' phase II trial, is about three months.

In Genetronics' North American multi-center phase II clinical trial, 51 SCCHN tumors on 42 subjects were treated with EPT+intralesional bleomycin. Those subjects demonstrated a 57% objective response rate in the tumors treated, consisting of 24% complete responses and 33% partial responses (defined as tumor reduction of 50% or greater). The company announced the launch of its phase III clinical trial for the treatment of recurrent SCCHN earlier this month.

"The data gathered from the phase II study suggest that utilizing electroporation with intralesional bleomycin can significantly extend a subject's survival time," said Paul Goldfarb, medical advisor for Genetronics. "The EPT treatment represents an important step forward in the battle against head and neck cancer."

MGI PHARMA Inc., (Nasdaq: MOGN) of Minneapolis, and its partner **Helsinn Healthcare SA**, a Swiss pharmaceutical group, said phase II results demonstrating the potential efficacy of their investigational agent palonosetron in the prevention of acute chemotherapy-induced nausea and vomiting in patients who received highly-emetogenic chemotherapy.

The study results, which were presented at the annual meeting of the American Society for Clinical Oncology in Orlando, showed palonosetron was effective in the prevention of CINV during the initial 24-hour period and for several days beyond.

Palonosetron is a potent, highly selective 5-HT_3-receptor antagonist with an extended half-life (nearly 40 hours) and a strong receptor-binding affinity, in development for the prevention of chemotherapy-induced nausea and vomiting, which is estimated to occur in 85 percent of cancer patients undergoing chemotherapy. If untreated, CINV can result in a delay or even discontinuation of chemotherapy treatment. A New Drug Application submission for palonosetron is expected in the third quarter of 2002.

"These phase II results with palonosetron are most encouraging," said Richard Gralla, associate director, Herbert Irving Comprehensive Cancer Center, Columbia University. "Patients often receive chemotherapeutic agents that are associated with nausea and vomiting that can continue for several days after the administration of chemotherapy. While they can receive follow-on treatment for delayed nausea and vomiting, there is a need for agents that can provide enhanced control and convenience over an extended period of time. We look forward to the results of the well-planned phase III studies with palonosetron."

In the phase II study, dose ranging was performed to determine the clinical efficacy relationship among a range of different doses of palonosetron. Clinical efficacy in the 161 patients

studied was assessed by a complete response rate, defined as the percentage of patients who did not experience vomiting or receive rescue medication. Patients received highly-emetogenic chemotherapy, primarily cisplatin.

During the first 24-hours following chemotherapy treatment, across the dose ranges evaluated (0.3-1 mcg/kg through 90 mcg/kg), patients treated with a single IV dose of palonosetron achieved complete response rates up to 50 percent without concomitant corticosteroid administration.

Encouraging complete response rates were also observed through the fifth day following the administration of a single intravenous dose of palonosetron. Adverse events associated with palonosetron, the most common being headache, were similar to those seen with other 5-HT_3-receptor antagonists.

* * *

Wilex AG and the **Technical University of Munich** said they have begun a phase III trial of 540 high risk patients with primary breast cancer, sponsored by **Wilex** and **Aventis Pharma Deutschland GmbH**.

The randomized multicenter trial coordinated by the Departments of Gynecology at the Technical University of Munich and the Ludwig Maximilians University of Munich will be conducted in up to 40 clinical sites across southern Germany under the leadership of Marion Kiechle and Harald Sommer.

The adjuvant docetaxel vs. epirubicin based regimen trial will investigate the efficacy of docetaxel, a taxane by Aventis Pharma, in sequential application after anthracycline containing adjuvant chemotherapy, the company said. The study would provide data on chemotherapy regimens that may be combination therapies for the Wilex uPA inhibitor WX-UK1, which is in phase I clinical development.

Research shows that high risk patients, according to their uPA/PAI-1 status, benefit from adjuvant systemic chemotherapy and combination chemotherapy regimens leads to improved patient outcome and prolonged survival in breast cancer, the company said. The study would serve to evaluate the predictive value of the levels of urokinase-type plasminogen activator and plasminogen activator inhibitor type-1 in the primary tumor with respect to docetaxel containing chemotherapy regimens.

A secondary objective is to look for new therapy response markers and targets, the company said. This clinical-translational part of the trial will be supervised by Nadia Harbeck, a breast cancer specialist and member of the ADEBAR scientific steering committee, and Manfred Schmitt, head of clinical research group, both from the Department of Gynecology at the Technical University of Munich.

"High risk breast cancer patients can be identified by their uPA/PAI-1 levels in the primary tumor," said Harbeck. "It is of utmost importance for these patients to find out whether they benefit from addition of docetaxel to the standard anthracycline containing adjuvant chemotherapy. The study offers the unique possibility due to the funding by Aventis and Wilex to combine interesting clinical questions with up-to-date translational research."

Patients with high levels of uPA and/or PAI-1 have a considerably poorer prognosis than patients with low tumor levels, the company said. uPA and PAI-1 are the first novel tumor biological factors in breast cancer that have recently reached the highest level of evidence for clinical utility due to successful completion of a clinical trial and a meta analysis, the company said.

Deals & Collaborations:

Cancer Society To Use Firm's Clinical Trial Referral System

EmergingMed and the **American Cancer Society** said they are entering into a three-year collaboration to incorporate EmergingMed's clinical trial matching and referral system into the ACS Web site, http://www.cancer.org, and call center.

The ACS cancer information specialists, who answer calls to the society's toll-free number, also will use EmergingMed's system to prescreen and guide cancer patients over the phone to researchers conducting government-funded as well as privately sponsored cancer clinical trials throughout the U.S.

"The American Cancer Society is strongly committed to helping people with cancer find and gain access to clinical trials," said Harmon Eyre, the society's chief medical officer. "In a clinical trial, patients receive either the current standard of care or are given investigational treatments that may be even more effective, and they will be part of the research that helps tomorrow's patients get better care."

Beginning this summer, ACS plans to offer the clinical trials matching and referral service to any of its 100,000 monthly callers and 350,000 monthly Web site visitors.

"The integration of EmergingMed's unbiased matching and referral system and the American Cancer Society's commitment to providing families with the most up-to-date information on cancer and treatment options creates an unprecedented bridge between cancer researchers and cancer patients," said Courtney Hudson, EmergingMed's CEO and founder.

New York based EmergingMed is a private health service and application service provider. Founded in January 2000, the company's 17 clients include Aventis Pharmaceuticals, SuperGen, Genentech, AntiGenics, and the University Pennsylvania Cancer Center. Its database of 2,200 cancer clinical trials and 4,000 physician-researchers also is available to patients and health care professionals on the company's Web site, http://www.emerging.med.com, or by calling 877-601-8601.

* * *

Amgen (Nasdaq: AMGN), said its stockholders approved the issuance of shares of Amgen common stock in connection with the company's proposed acquisition of **Immunex Corp**. (Nasdaq: IMNX) at Amgen's annual meeting of stockholders.

Upon the completion of the acquisition, Immunex shareholders will receive 0.44 of a share of Amgen common stock and $4.50 in cash for each share of Immunex common stock that they own.

Wyeth (formerly American Home Products Corp.), which beneficially owns approximately 41 percent of Immunex's outstanding shares, previously agreed to vote all of its shares in favor of the transaction.

"We are very pleased by Amgen's stockholders' overwhelming support for the transaction," said Kevin Sharer, Amgen chairman and CEO. "With this acquisition, Amgen, the world's largest biotechnology company, will acquire the Seattle-based biotechnology company, Immunex. Upon the close of this transaction, we look forward to adding Enbrel, a proven blockbuster in the treatment of inflammation, to Amgen's portfolio of blockbuster medicines."

In addition to Immunex shareholder approval, the close of the transaction remains subject to certain customary regulatory approvals, as well as other customary closing conditions.

* * *

Hitachi Ltd. (TSE: 6501, NYSE: HIT, "Hitachi") said it has acquired an 80 percent stake in AccSys Technology Inc., (AccSys) to expand its proton beam therapy systems business.

Through the acquisition, Hitachi will apply AccSys's ion linear accelerator (linac) technology to its in-house developed proton beam therapy system (PROBEAT). The move will enable Hitachi to aim for the top share in this market.

AccSys is the only commercial supplier in the world that has patented compact linac systems used for proton beam therapy. This product is incorporated into the synchrotron-accelerator as an injector for initial acceleration of the proton beam and also has applications in other devices, including neutron generators.

* * *

Cytogen Corp. (NASDAQ: CYTO) and **DRAXIMAGE Inc**., the radiopharmaceutical subsidiary of DRAXIS Health Inc. (TSX: DAX; NASDAQ: DRAX), said it has begun to market a palladium version of brachytherapy implant for the treatment of localized prostate cancer in the U.S.

This next-generation form of brachytherapy, called BrachySeed Pd-103, is immediately available to patients in the U.S.

BrachySeed Pd-103 is the second next-generation implant developed by DRAXIMAGE for the treatment of prostate cancer and other localized tumors.

BrachySeed I-125, which contains radioactive iodine, was launched in 2001 by Cytogen.

"We are pleased to be working with DRAXIS, one of only a few companies that produce both palladium-103 and iodine-125 versions of brachytherapy implants," said H. Joseph Reiser, Cytogen's president and CEO. "Having the ability to provide both iodine and palladium seeds helps us to further establish this next-generation product as the premier therapy for prostate cancer that is confined to the gland."

BrachySeed Pd-103, which incorporates a more energetic radiation from palladium-103, is believed to be suitable for certain more aggressive forms of prostate cancer and is preferred by some oncologists over iodine-based seeds.

* * *

Ilex Oncology Inc. (Nasdaq:ILXO) of San Antonio and **Abgenix Inc.** (Nasdaq:ABGX) of Fremont, CA, said they are entering into a licensing agreement to develop a fully human monoclonal antibody therapy against the antigen MUC1 for cancer.

The collaboration is part of the Ilex effort to further develop the core MUC1 patent rights and

technology licensed exclusively to Ilex by the Dana-Farber Cancer Institute last year, the company said.

Under the collaboration, Abgenix said it would use its XenoMouse and XenoMax technologies to generate fully human antibodies against the antigen supplied by Ilex. Ilex would have the right to obtain an exclusive product license to commercialize an antibody product to MUC1. Abgenix would receive an upfront research license fee, and could receive additional license and milestone payments and royalties on any future product sales by Ilex. Ilex would be responsible for product development, manufacturing and commercialization of any product developed through the collaboration. The collaboration would accelerate the identification of therapeutic leads that target the MUC1 protein at the extra cellular level closest to the cell surface, the companies said.

"Ilex believes that MUC1 is an important anticancer target, as it's highly overexpressed on the surface of most cancer cells, including those of the lung, breast, prostate, pancreas, ovary and bowel" said Jeffrey Buchalter, president and CEO of Ilex.

Research has shown that MUC1 functions like a receptor and contributes to the development of tumors, the companies said. Of the 1.2 million tumors diagnosed in the U.S. each year, more than 700,000 overexpress the MUC1 protein, the company said.

In another development, Ilex Oncology Inc. said it has filed a supplemental biologics license application with FDA for Campath (alemtuzamab).

The request is based on two-year follow-up data in patients who had been treated with alkylating agents and failed fludarabine, the company said.

"Now that we have the final study data, we are committed to updating the Campath label in order to provide community-based oncologists and hematologists with the most current data available," said Buchalter.

* * *

Impac Medical Systems Inc of Mountain View, CA, said it has acquired **Intellidata Inc.**, a clinical laboratory information system supplier for medium-to-large multi-site clinics, small-to-midsize hospitals, and independent reference laboratories.

The acquisition will extend the Impac Multi-ACCESS oncology management system to include IntelliLab, the Intellidata LIS, capable of interfacing to laboratory devices, the company said. The result is the seamless reporting of laboratory results in the Impac electronic medical record, and an LIS solution that addresses both the clinical and business needs of the cancer specialist, the company said.

The company said it would continue to support the import of lab data from any LIS via the HL7 format; however IntelliLab provides Impac customers with an integrated LIS solution and immediate access to critical lab values at the point-of-care.

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MacroGenics Inc. of Rockville, MD, said it is licensing a therapeutic target induced by Epstein-Barr virus, the cause of infectious mononucleosis and certain lymphomas, from **EBVax Inc.** and **Tufts University**.

Building on the findings of Brigitte Huber and David Thorley-Lawson, professors of pathology at Tufts University School of Medicine and Tufts-New England Medical Center and founders of EBVax, MacroGenics said it would launch a research program to identify treatments to reduce morbidity for the acute and chronic consequences of EBV infection.

Huber and Thorley-Lawson reported that EBV induces a superantigen protein that may be responsible for clinical complications of mono and contribute to the development of lymphomas, the company said. MacroGenics will develop therapeutic antibodies that block or eliminate cells expressing the superantigen to treat diseases such as mono, post-transplant lymphoproliferative disorder a complication of solid organ transplantation, and some forms of Hodgkin's and non-Hodgkin's lymphoma.

* * *

Novuspharma SpA (Nuovo Mercato: NOV.MI) of Bresso, Italy, said it is entering into a research and development collaboration with **Cephalon Inc.** (Nasdaq:CEPH) to discover and develop cancer drugs based on the Cephalon proprietary proteasome inhibition technology.

Under the three-year agreement, Novuspharma would use its pre-clinical research to optimise the Cephalon proteasome inhibitors that exhibit anti-cancer activity, the company said. Discoveries of compounds would be jointly owned by the two companies. Clinical candidates would be developed by Novuspharma until proof of concept is achieved, the company said. The two companies would jointly support subsequent development, the companies said.

Cephalon would retain marketing rights in the Americas and Japan, whereas Novuspharma would retain rights in Europe, the companies said.

Financial terms were not disclosed, the companies said.

The proteasome is a naturally-occurring cellular protease complex that regulates the expression and activity of proteins involved in cell cycle progression, cell survival and tumor growth, the companies said.

Cephalon identifies, assays and develops proprietary compounds specific for the inhibition of the proteasome, believed to be involved in certain cancers, the company said. The main effects of proteasome inhibition are the induction of apoptosis through suppression of NF-kB mediated survival pathways, the inhibition of degradation of proteins involved in cell cycle regulation and the increase of levels of cell cycle inhibitors, the companies said.

Product Approvals & Applications:

FDA Clears CA19-9 Test For Pancreatic Cancer

Fujirebio Diagnostics Inc. of Malvern, PA, said it has received FDA marketing clearance for the CA19-9 Radioimmunoassay, which monitors pancreatic cancer patients.

The CA 19-9 RIA laboratory test enables physicians to evaluate and monitor the effectiveness of treatment and is the first blood test cleared for use in pancreatic cancer, the company said.

"Recent reports, mainly from Europe, have shown that serial measurements of serum CA 19-9 can reflect the response of patients to chemotherapy," said Herbert Fritsche, professor, biochemist and chief of clinical chemistry at M.D. Anderson Cancer Center in Houston. "The availability of the CA 19-9 test in the U.S. will give us a new tool for early assessment of the effectiveness of the many new drugs that are becoming available for the treatment of metastatic cancer of the pancreas."

An in-vitro tumor marker, such as CA 19-9, enables a physician to evaluate whether there is a need for immediate, additional imaging tests and more aggressive treatment because the disease is progressing, or whether the disease has stabilized and the current therapy should be continued, the company said. A decrease in CA 19-9 assay values correlates with a positive response to therapy. An increase in CA 19-9 values may indicate progressive disease and thus aid the physician in assessing treatment regimens.

"CA 19-9 is an extremely useful marker of disease status, especially when assessed frequently since, in conjunction with clinical assessment, it enables clinical decisions with respect to treatment options to be made earlier to the benefit of the patient," said Jules Harris, Judd and Majorie Weinberg Presidential Professor of Medicine, professor of immunology and microbiology at Rush Medical College in Chicago.

Polymedco Inc. of Cortlandt Manor, NY, is the exclusive distributor of CA 19-9() RIA and will provide front-line technical and customer service support, the company said.

* * *

Genentech Inc. (NYSE: DNA) and **OSI Pharmaceuticals Inc**. (Nasdaq: OSIP) said FDA has designated Tarceva (erlotinib HCl, OSI-774) a fast track product for the treatment of chemotherapy-naïve stage III/IV non-small cell lung cancer patients.

Tarceva is a small molecule EGFR inhibitor being developed by Genentech, OSI, and Roche.

"Lung cancer remains one of the most devastating forms of cancer, with a five-year survival rate of only 3 percent for patients with metastatic disease," said Susan Hellmann, Genentech's executive vice president, development and product operations, and chief medical officer. "Designation of Tarceva as a fast track product recognizes the seriousness of the condition and unmet medical need in lung cancer. We are currently enrolling approximately 1,000 chemotherapy-naïve non-small cell lung cancer patients into a randomized phase III clinical trial evaluating Tarceva with chemotherapy with survival as the primary endpoint."

Tarceva is a small molecule designed to target the epidermal growth factor receptor (EGFR) pathway, which is critical to cell growth in many cancers. EGFR, also known as HER1, is a key component of the HER signaling pathway, which is often involved in the formation and growth of numerous cancers. Tarceva is designed to inhibit specifically the tyrosine kinase activity of EGFR/HER1 thereby blocking the signaling pathway with the intent of potentially inhibiting tumor cell growth.

Tarceva is being studied in non-small cell lung cancer and in pancreatic cancer through randomized and controlled phase III studies with survival as the primary endpoint. Also, the NCI Cancer Therapy Evaluation Program is planning to conduct numerous Tarcevatrials in solid tumor types such as ovarian, metastatic colorectal, head and neck, renal cell carcinoma, and pancreatic, the companies said. It is anticipated that more than 3,000 patients will participate in the phase III clinical trial program for Tarceva.

* * *

MGI Pharma Inc. (Nasdaq:MOGN) of Minneapolis, and its partner **Helsinn Healthcare SA**, of Lugano, Switzerland, said a pre-new drug application meeting has taken place with FDA for palonosetron, their investigational agent in late-stage development for chemotherapy-induced nausea and vomiting..

Submission of the NDA is expected in the third quarter of 2002, the companies said. Marketing of the drug is subject to complete NDA review and approval by FDA.

"This milestone, along with the preliminary analysis of the phase III trial data of palonosetron, which met the targeted efficacy endpoints, are important achievements in advancing the product candidate," said Lonnie Moulder, executive vice president of MGI.

In the phase III trials, Palonosetron met the 24-hour complete response primary efficacy endpoint, which was defined as no vomiting and no rescue medication for 24 hours following administration of chemotherapy, the companies said. In addition, the complete response rate for the 24-120 hour (days 2 through 5) time period favored palonosetron over the comparator agents, which are marketed 5-HT3 antagonists, the companies said.

Palonosetron is a highly selective 5-HT3-receptor antagonist with an extended half-life (nearly 40 hours) and a strong binding affinity, the companies said.

More than 2,700 subjects have participated in clinical trials of the drug, the companies said. Adverse events associated with palonosetron, the most common being headache, are similar to those seen with other 5-HT3-receptor antagonists.

Last year, MGI and Helsinn signed an agreement granting MGI the exclusive U.S. and Canadian licensing and distribution rights to the agent, the companies said.

* * *

NeoPharm Inc. (Nasdaq: NEOL) said its investigational tumor-targeting agent IL13-PE38 was granted the European designation of orphan drug status for the treatment of gliomas, including glioblastoma multiforme and anaplastic astrocytoma, by The European Commission on the recommendation of the Committee for Orphan Medicinal Products (COMP).

Orphan drug designation in the European Union is available for medical treatments and drugs that show promise in diagnosing, treating or preventing rare, life-threatening or chronically debilitating conditions.

IL13-PE38 is in phase I/II clinical trials in the U.S. and has received orphan drug designation from the U.S. Food and Drug Administration in November 2001 and fast track drug development program status from the FDA in May 2002.

NeoPharm has exclusively licensed IL13-PE38 from the National Cancer Institute and the FDA, and is developing the agent under a Cooperative Research and Development Agreement with the FDA's Center for Biologics Evaluation and Research.

The company said it plans to initiate phase I/II trials of IL13-PE38 in Germany and Israel in 2002.

With orphan drug status in Europe, NeoPharm has been granted incentives designed to enhance and facilitate the research and development process for IL13-PE38 so that it can be brought to market more quickly to help address an unmet medical need for malignant glioma.

NeoPharm can request protocol assistance from the Scientific Committees of the European Agency for the Evaluation of Medicinal Products at all stages during the initial development of the compound prior to the submission of the application for marketing authorization, as well as receive potential reductions in marketing application fees and additional financial incentives.

Orphan drug status designation also entitles NeoPharm to receive a 10-year marketing exclusivity in the designated indication once the compound has been approved. This protection prevents the community or a member state from subsequently issuing a marketing authorization for a similar medicinal product and for the same indication.

Patents:

Idun Receives 100th Patent

Idun Pharmaceuticals Inc. of San Francisco said it has received its 100th patent related to apoptosis, covering rev-caspases used for screening and identifying caspase inhibitors and enhancers.

Caspases are a component of the apoptosis pathway and controlling them is the basis of a wide range of drug development opportunities, the company said. The human apoptotic pathway is associated with cancer, heart disease, stroke, sepsis and chronic neurodegenerative diseases like Alzheimer's, ALS and Parkinson's, the company said.

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