THE CANCER LETTER

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Two Research Teams Link Response To Iressa To Mutations In EGF Receptor

By Paul Goldberg

Two teams of researchers at Massachusetts General Hospital and Dana-Farber Cancer Institute have found specific mutations associated with response to the AstraZeneca lung cancer drug Iressa.

Working separately, the teams analyzed samples from patients treated at their institutions, finding somatic mutations of the epidermal growth factor receptor gene that correlate with response to the oral therapy.

One paper on the findings was published online by the journal Science,

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In Brief:

Amgen Names PhRMA Exec Rodger Currie Vice President for Government Relations

RODGER CURRIE has been named vice president for government affairs at Amgen Inc., of Thousand Oaks, Calif. He will work with **David Beier**, senior vice president, global government affairs at Amgen, to design the company's legislative strategy. Currie was senior vice president for federal affairs and law at the Pharmaceutical Research & Manufacturers of America, where he led PhRMA's efforts to enact the Best Pharmaceuticals for Children Act and the Prescription Drug User Fee Act in 2002. Currie also led the association's efforts to pass $400 billion free market Medicare prescription drug coverage legislation, including House and Senate passage of the PhRMA-supported bill. The Hill named him "Top Lobbyist" in 2002, 2003, and 2004. Prior to joining PhRMA, Currie worked as majority counsel for the House Committee on Energy & Commerce and as an attorney in private practice. "With the ongoing importance of Amgen's relationship to legislative bodies and elected officials, Rodger will be the key asset in the management of our Washington, D.C. office's Federal Government Affairs program, a vital initiative and a strategic imperative for Amgen," said Beier. Currie replaces **Rita Norton**, who is retiring from Amgen. Norton will remain on staff over the next several months, and has agreed to continue working with Amgen's Government Affairs team in a consulting role. . . . **ROBERT HALL** was appointed director of government relations for the National Coalition for Cancer Survivorship. Hall was legislative counsel to **Sen. Mark Dayton** (D-MN), where he managed health care, labor, education, pensions, and appropriations policy. "Bob knows Washington, D.C., and the politics of patient advocacy from various vantage points as

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Dramatic Responses Spurred Discovery In The Laboratory

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and another was released early on the Web page of the New England Journal of Medicine. The publications punctuated the end of a dizzying week, which began April 25, with the announcement by Genentech Inc. and OSI Pharmaceuticals Inc. that Tarceva, another drug that blocks the EGF receptor, extended survival in late-stage non-small cell lung cancer.

Closing the phase III trial, the Tarceva sponsors refrained from announcing its finding, saying that the data would be presented at the annual meeting of the American Society of Clinical Oncology, which begins in New Orleans June 5.

In an explosion of emails and telephone conferences, cancer experts appear to have linked the two news items, and are hammering out a research agenda for Iressa (gefitinib), Tarceva (erlotinib HCl), and other drugs that block EGF receptors.

"The email activity on this has been extraordinary," said Roy Herbst, a lung cancer expert at M.D. Anderson Cancer Center, who served as the principal investigator on one of the Iressa trials. "There is a rapid effort to try to explore this in as many patients as possible."

While researchers are lining up tumor blocks from patients who received Iressa, a group of six institutions that hold NCI Specialized Program of Research Excellence grants are asking the Institute for $50,000 to support retrospective analysis of the gene mutation in the tissue samples they have.

"That's why the NCI director and the NIH director like to have some discretionary money," said Paul Bunn, director of the University of Colorado Cancer Center. "Because stuff happens."

The Iressa findings point to an Achilles heel in lung cancer, said Brian Druker, director of the Leukemia Center at Oregon Health Sciences University, who found a similar vulnerability in chronic myelogenous leukemia and gastrointestinal stromal tumor. "People still had some doubts as to whether this approach would work with breast, or prostate, or lung, or colon," Druker said. "But here is the proof that it does."

The Power of Unexpected Response

Iressa has been something of a mystery in oncology.

Two rigorously designed trials of the agent in conjunction with chemotherapy as a first-line therapy came out negative. A phase II single-arm study in previously treated relapsed NSCLC patients that led to the agent's approval by FDA demonstrate a response rate that lingered around 10 percent, just a bit above statistical noise.

Meanwhile, doctors who treat lung cancer could tell stories of responses that seemed to border on the miraculous. Dramatic responses tended to occur in women, non-smokers, patients with adenocarcinomas or bronchoalveolar carcinomas, as well as in the Japanese. Before the drug was approved, the company set up an expanded access program that gave the agent to 20,000 patients in the U.S.

To FDA-watchers, Iressa became emblematic of loosening of criteria for drug approval and the dangerous merging of data and anecdote. While a nightmare for biostatisticians, the lukewarm data and powerful anecdotes of the drug's activity seemed to persuade clinicians, who comprise the overwhelming majority of the FDA Oncologic Drugs Advisory Committee, and, ultimately, the agency staff (**The Cancer Letter**, Sept. 28, 2002; Nov. 8, 2002; May 9, 2003).

When Iressa was approved in the U.S. last May, the words "targeted therapy" were conspicuously absent from the label. Claims that the agent could bring about stabilization of disease were missing, too.

Still, doctors in the U.S. have written 64,000 prescriptions for the drug, which costs about $2,000 a month, industry figures show. Global sales of Iressa added up to $228 million in 2003, with the U.S. contributing $102 million to that total, and Japan,

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where the drug was approved earlier, contributing $101 million.

On Nov. 24, 2003, the Boston Globe ran a story about a lung cancer patient who did exceedingly well on Iressa. The newspaper article crossed the desk of Daniel Haber, director of the MGH Center for Cancer Research.

Intrigued, Haber, a cancer geneticist, contacted Thomas Lynch, an MGH oncologist who treated the patient.

"Dan Haber said, 'Gosh, there must be something more going on here. I wonder if this is an activating mutation," Lynch recalled. "I gave him samples of people who had these dramatic responses, and he started sequencing the gene. And we found these mutations."

Later, Jeff Settleman, head of a laboratory at MGH, joined the project, "to figure out what the mutation did, and showed that the mutation conferred exquisite sensitivity to both EGFR and inhibition with gefitnib," Lynch said.

The paper was submitted to the Journal in late March, and went out to reviewers on March 24.

At the same time, researchers at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and the Broad Institute at MIT and Harvard, were sequencing mutations in tyrosine kinase.

"Matt Meyerson and Bill Sellers had a several-year effort to consistently sequence mutations in the tyrosine kinase as a method of gene discovery," said Bruce Johnson, an oncologist who had observed several dramatic responses to Iressa at Dana-Farber and Brigham and Women's. "That was an active and ongoing program here. And as part of this, they were sequencing EGFR, and we had proposed to them that we sequence our responders." Meyerson and Sellers are scientists at Dana-Farber and the Broad Institute.

The team, which included scientists from Nagoya City University Medical School, also obtained a series of pathology samples from Japan.

According to Science, the paper was submitted on April 16, accepted for publication five days later, and published online on April 29. The Journal paper was expected to appear in the May 20 issue, but was released online apparently in order to keep up with the early release of the Science paper. That paper will be published in Science at a later date.

"One of the things that we did, despite our two groups pursuing this in parallel, is that we did think the results were important enough that we got together and discussed it, and shared the results before it was published, and decided to release it together, because it's too important to let it go independently," Johnson said.

The two teams searched for mutations in primary tumors from patients who received Iressa at their institutions and demonstrated a response. The Massachusetts General team also looked at a series of patients who didn't have a response and patients who hadn't been exposed to the agent. Their analysis of the specimens included expressing the protein in cultured cells.

Researchers identified somatic mutations in the tyrosine kinase domain of the EGFR gene in eight of the nine responders they tested. By comparison, none of the seven non-responders had the mutations. "Mutations were either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pockets of the tyrosine kinase domain," the paper states.

After examining the tumors of 25 NSCLC patients who hadn't received Iressa, the MGH team detected similar mutations in two of those patients. "In vitro, EGFR mutants demonstrated enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to inhibition by gefitinib," the paper states.

The Dana-Farber and Broad Institute team compared the tumors of five patients who responded to Iressa with four who didn't, finding mutations in all the responders and no mutations in non-responders. Also, researchers found mutations in tumors of 15 of 58 unselected patients who were treated at Nagoya and in only one of the 61 patients treated at Brigham and Women's.

The Journal paper is posted at http://content.nejm.org/cgi/content/abstract/NEJMoa040938, and the Science paper is posted at www.sciencemag.org/cgi/content/abstract/1099314, where it's available to subscribers.

"Around the time of the approval of Iressa, there was a lot of emphasis placed on a small fraction of patients that appeared to have truly remarkable responses," said Druker, who isn't involved in these studies. "My take on that was that there was something very real there, and that at some point we would figure out who those patients were and why they responded. And here it is.

"What's really interesting about these mutation is that they are more sensitive to Iressa than the wild-type receptor," Druker said. "Iressa may not completely shut down the wild-type receptor at clinically achievable doses, but these mutations are actually more sensitive than wild-type. You almost have an ideal situation,

where you have an even greater selectivity for the tumor, because the mutation is more sensitive to your drug than the wild-type. What more ideal situation could you imagine than that?

"Not only do you get targeted, but you actually get tumor-specific," Druker said.

In the Clinic…

The tests used by the two teams aren't exotic. "These tests are done by DNA sequencing machines," said Bunn. "It would be cheaper to do it by PCR. You could probably develop about 10 PCRs that would cover almost all the mutations, and I am sure people are doing that. This is not a test that—when its commercialized—each person will be doing in their lab."

However, it's possible that other testing methods could yield additional results. "It could be the combination of FISH and mutation analysis would be a way to go," Bunn said.

While mutational analysis can show that a cell contains the information to make an aberrant receptor, Fluorescent In-Situ Hybridization, FISH, assay shows that the cell produces the aberration. In other settings, including Herceptin, FISH and mutational analysis are used to gauge the probability of a patient's response to treatment.

"In my opinion, the leading technology for doing this is the proteomics work by Dave Carbone's group," said Dana-Farber oncologist Johnson. "They have been doing some work using mass spectroscopy of tissue specimens, trying to identify relatively sensitive lung cancers to gefitinib treatment." Carbone is a medical oncologist at Vanderbilt-Ingram Cancer Center.

Ultimately, these findings may influence the way drugs are developed, approved and reimbursed, experts say.

Clinical implications of these findings were limited, but immediate. Physicians familiar with the new data agreed that it may now be reasonable to give Iressa earlier to a patient who has the mutation:

--"What these studies tell me is that if I could show someone had an activated mutation in the tyrosine kinase, particularly in exons 18 through 24, that person might be reasonable for therapy with Iressa upfront," said Fadlo Khuri, a lung cancer expert and chief medical officer at Emory University's Winship Cancer Institute.

--"If a patient is mutation-positive, I would consider strongly treating them with drugs earlier than later," Lynch said. "I wouldn't necessarily wait till third-line therapy to treat them with Iressa. I think with mutation-negative patients, I will probably do exactly what I am doing right now until we have more information, which is save Iressa till third-line."

--"What it means is that if you have this mutation, you probably ought to get one of these drugs," said Bunn. "It doesn't tell you when you should get them, but you probably should get one."

The rest is uncertain. Should a male smoker who doesn't have the mutation be a candidate for Iressa?

"Response rate for male smokers is low, but it's not zero," said Bunn. "I don't think it's a good way to exclude somebody. My belief is we are going to have biologic tests to tell us with pretty good certainty that a response rate is going to be less than 5 percent, and those patients obviously should get something else. My suspicion is this is going to end up being half of the patients, not 90 percent of the patients. There is going to be a group where we can define that the response rate is very high, but then there is going to be another group where the response rate is higher than 15 percent but less than 50.

"You are going to have to treat those people," Bunn said.

Stable disease, too, poses a ticklish question. Though oncologists often cite data on symptom improvement and radiographic response as evidence that about a third or more patients achieve stabilization of disease, the Iressa label doesn't mention this endpoint. The agency hasn't recognized this endpoint in cancer, and it would be unlikely to recognize it for an agent that receives an accelerated approval based primarily on a single-arm study due to the lack of a concurrent comparator.

"How do these new data fit with the finding that more than 30 percent of patients who received gefitinib in the large phase II trials had stable disease?" asked Mark Green, a lung cancer expert at the Hollings Cancer Center at the Medical University of South Carolina, in an editorial that accompanies the Journal paper. "Did those trials really show an effect of gefitinib, or were we overinterpreting noncomparative phase II data?"

Patients who have stable disease may not have the mutation, Green said in an interview.

"They might; or they might not," he said. "Stable disease might be a global impact, where this is one of many drivers, and where there happens to be enough benefit that the disease stays stable for a while, but that's probably not going to be a setting where you might want to take it upfront. It might still be a setting where you would use it third-line. Or it might be that we would see something intermediate. This is what you

want. You want to be able to understand the level of the biology of the genotypic subgroups, but also how they are going to behave.

"And we are getting closer," Green said.

In many cases, demand for Iressa is driven by patients, Khuri said.

"People are requesting it," he said. "It's not quite like the EPO phenomenon, where patients are coming to us and saying, 'Why aren't you treating my anemia,' or 'Why aren't you treating my fatigue?' But Iressa or Tarceva are often the first names on their lips."

AstraZeneca officials said the finding of the mutation isn't yet relevant in the clinic. "Further studies will be needed, as this mutation has not been correlated with all patients that currently benefit from Iressa, only those that have the most dramatic results," the company said in a statement.

"Currently, the best way for most lung cancer patients to see if Iressa will be effective for them is to have a short trial of therapy," the company said. "Within the first two months of treatment, those who are likely to respond to continuing treatment will show clinical benefit from Iressa in terms of symptom improvement or tumor shrinkage. In clinical studies, symptom improvement was evident from around eight to 10 days, and 90 percent of tumor shrinkage was evident by eight weeks of treatment. Therefore, trial of therapy will remain important especially in second- and third-line disease."

INTACT: What Went Wrong?

The findings may shed light on one of the great mysteries of Iressa: its failure to improve survival when combined with chemotherapy in two phase III trials.

"You are going to see a repetition of the trials with chemotherapy in advanced disease in this subset of patients," said Bruce Chabner, clinical director of the MGH cancer center. "Also, you are going to see a drug like this alone or with chemotherapy in early disease to prevent recurrence."

The mutation could have skewed the two 1,000-patient trials that tested paclitaxel and carboplatin with and without Iressa, agrees M.D. Anderson oncologist Herbst, who was the principal investigator on one of the negative trials, INTACT 2.

"That's one of my major thoughts right now: let's start looking at the INTACT trial," he said. "We don't know why that trial was negative. It could be because there weren't enough patients with the target, which would make a lot of sense. If it's only a 10-percent gene, and the trial enrolled 1,000 patients, only 100 of them had it. If we didn't stratify for it, and if it's such a low number, it may not have been enough to influence the whole cohort. And there might be an inherent interaction between these drugs and chemotherapy. I think we need to look at some of the INTACT data.

"The key thing now is we have a new marker we can use as we design clinical trials," Herbst said.

It's unclear whether reanalysis of the INTACT trials would produce a conclusive answer. Tissue can be found for about 40 percent of patients who were enrolled in these trials. A smaller number of tumors are available for the phase II IDEAL trial that led to approval of the agent.

Nonetheless, researchers seem to find themselves in a situation where retrospective studies are generating as much excitement as prospective trials.

"This is hot; everyone is doing this," said Bunn. "We have about 200 cases from expanded access that we are doing right now. We have a postdoc from Italy who came with 120, which we've combined with our own."

Sources said Memorial Sloan-Kettering Cancer Center is processing its massive series of cases, the University of Texas Southwestern is getting ready to start work on 200 cases obtained from Japan, and Vanderbilt scientists are preparing to run an analysis of tissues from INTACT.

"The next study we will be doing is take an enriched population of women with adenocarcinoma, treat everybody with it, sequence it, and find out what the relationship between the mutation and the response and the duration of the response are," said Dana-Farber oncologist Johnson. "The trials to validate these observations should take place very quickly, and in places where they can do the sequencing. I think the next thing to do is to do a single-agent trial, where you sequence everybody, and that could be done in just a few institutions. That trial could be done in six months."

Some answers may come from the Tarceva studies, experts say. Since the drug shares a molecular target with Iressa, researchers are eager to run it through the same series of tests to determine the correlation between this investigational agent with the newly discovered EGFR mutation.

"In the Tarceva vs. palliative care trial, you could compare the outcome of patients with similar histology," said Chabner.

Of course Tarceva doesn't necessarily equal Iressa. "It has the same target, but whether it acts in the same way, we don't know," Chabner said. "The early analysis of the data from the Tarceva trial is interesting. It shows

a survival advantage, and there is a real possibility that it was affecting more than the small percentage of patients with the mutation. In order to get a statistically significant survival advantage, there is a possibility that there is a lesser positive effect on other patients."

Bunn is similarly intrigued. "I haven't seen the statistical analysis of the Tarceva study, but a study that helps 10 percent of people that has 600 patients in it, is unlikely to show a survival benefit," he said. "And the Tarceva study shows a survival benefit, which would indicate to me that a lot more than 10 percent of patients benefiting."

"Behind the Eight-Ball"

While for now the activity swirls around the cancer centers and SPOREs, the cooperative groups, too, may have a role to play.

"This is the time to understand the enormous value of the cooperative groups," said Green. "I would certainly think that the groups would provide a resource, a platform, a structure in which to actualize the studies that should come out of this."

The group tissue banks contain samples that will show prevalence of the EGFR mutations and correlate these findings with outcomes. Though the groups haven't taken on Iressa studies, they have been collecting tissue for as many as 80 percent of participants in lung cancer trials.

"Do tumors that have these mutations have a worse prognosis or a more favorable prognosis? Do they have a better or worse response to conventional cytotoxic chemotherapy?" said Richard Schilsky, associate dean for clinical research at the University of Chicago, and chairman of the Cancer and Leukemia Group B. "We can actually begin to sort through these questions using available specimens in the cooperative groups tissue banks.

"You have to understand the impact of the mutation on the natural history of the disease," Schilsky said. "Let's say that tumors that have this EGFR mutation have a more indolent clinical course. One could easily conclude, since these people get treated with Iressa, that Iressa is producing the stable disease, when in fact it may be simply that people who are candidates for Iressa by virtue of having this mutation have a tumor that is biologically less aggressive and is more likely by virtue of this natural history to be stable."

Tissues stored by CALGB can help explore prognostic value of the mutations, Schilsky said.

"For example, in our CALGB adjuvant study, we have a large, randomized, clinical trial of patients who got chemo versus observation following surgical resection of NSCLC, if it turns out that harboring one of these EGFR mutations is associated with a worse or perhaps a more favorable prognosis, it would be possible to sort that out, because we have the blocks, and we have the outcomes on the patients," he said. "And we have an untreated control group. So we would be able to easily look at the prognostic importance of these mutations, and we might be able to determine if the mutation has any predictive importance with respect to benefit from conventional chemotherapy."

The trial results will be presented at the ASCO annual meeting.

Last year, the groups proposed to begin studies with Iressa, but were precluded from doing so by the NCI Cancer Therapy Evaluation Program (The Cancer Letter, May 9, 2003).

"There was a time some months ago when CTEP declared that they would not support any more phase III studies with Iressa in the cooperative group program until the biology is better worked out," Schilsky said. "So now, the biology is better worked out.

"The unfortunate thing is that we are behind the eight-ball, because had CTEP not made the decision they made, we would have trials that are ongoing right now. These would be prospective, randomized clinical trials with tissue block collection," Schilsky said.

"Instead of now being in a position of just having to start a new generation of trials, we would already have trials ongoing that could have been used to validate these preliminary results."

Funding Opportunities:

RFAs Available

RFA-CA-05-012: Community Networks to Reduce Cancer Health Disparities

Letter of Intent Receipt Date: June 14, 2004

Application Receipt Date: July 13, 2004

NCI Center to Reduce Cancer Health Disparities invites cooperative agreement grant applications U01 for Community Networks to Reduce Cancer Health Disparities Through Education, Research, and Training (Community Networks Program).

The CNP would conduct community-based participatory education, training, and research among racial/ethnic minorities (e.g., African Americans, Hispanics, Asians, Pacific Islanders, and Native Americans/Alaska Natives) and underserved populations (e.g., Appalachian, rural, low socioeconomic status and other underserved populations). The program would

improve access to and utilization of cancer interventions in communities with cancer health disparities, thereby reducing these disparities.

The RFA will use the NIH cooperative agreement U01 award mechanism. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-012.html.

Inquiries: Kenneth Chu, Center to Reduce Cancer Health Disparities, phone 301-496-8589; fax 301-435-9225; e-mail KC10D@NIH.GOV

RFA-CA-05-015: Minority-Based Community Clinical Oncology Program

Letter of Intent Receipt Date: June 15, 2004

Application Receipt Date: July 15, 2004

NCI Division of Cancer Prevention invites domestic institutions that serve minority populations to apply for cooperative agreements in response to the RFA. The NCI clinical trials program provides a network of support for clinical research in cancer centers, major university centers, and community programs.

The RFA will use the NIH U10 award mechanism. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-05-015.html.

Inquiries: Worta McCaskill-Stevens, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, phone 301-496-8541; fax 301-496-8667; e-mail wm57h@nih.gov.

RFA-CA-05-014: Community Clinical Oncology Program

Letter of Intent Receipt Date: June 14, 2004

Application Receipt Date: July 14, 2004

NCI Division of Cancer Prevention invites domestic institutions to apply for cooperative agreements in response to the CCOP.

The CCOP: 1) provides support for expanding the clinical research effort in the community setting; 2) stimulates quality care in the community through participation in protocol studies; 3) fosters the growth and development of a scientifically viable community cancer network able to work closely with NCI-supported clinical cooperative groups and cancer centers; 4) supports development of and community participation in cancer prevention and control intervention research, which includes chemoprevention, biomarkers, early detection, symptom management, quality of life, rehabilitation, and continuing care research; 5) involves primary care providers and other specialists in cancer prevention and control clinical trials; and 6) increases the involvement of minority and underserved populations in clinical research.

Combining the efforts and expertise of community physicians and other health care professionals with those of the NCI-funded cancer treatment and prevention and control clinical trials groups provides opportunities for transfers of the latest research findings to the community level.

The RFA will use the NIH U10 award mechanism. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-05-014.html.

Inquiries: Lori Minasian, chief, Community Oncology and Prevention Trials Research Group, DCP, phone 301-496-8541; fax 301) 496-8667; e-mail lm145a@nih.gov.

In Brief:

Karmanos Cancer Institute Joins NCI CaBIG Project

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a former Hill staffer, as a lawyer and as a government relations expert," said **Ellen Stovall**, president of NCCS. "He will elevate NCCS' advocacy efforts and his skill set will strengthen NCCS' ability to advance policy issues that will improve the quality of care for people with cancer. . . . **BARBARA ANN KARMANOS** Cancer Institute has been selected by NCI to participate in the pilot phase of its cancer Biomedical Informatics Grid initiative. Karmanos will work with 49 other NCI-designated cancer centers on the $20-million per year informatics network. The network would link cancer research data, tools, individuals, and organizations around the world. "The sheer volume of post-publication data that is distributed between the cancer centers is overwhelming," said **Richard Rauscher**, chief information officer for the Karmanos Cancer Institute. "This project has the ambitious goal of bringing all of the intellectual capital and tools together to focus on curing cancer." . . . **THE NATIONAL ACADEMIES** received a $20 million grant from the Bill & Melinda Gates Foundation to help African academies of science develop and strengthen their policy-making and public discourse. The 10-year initiative will support efforts to improve human health issues, including HIV/AIDS, chronic malnutrition, malaria, and diarrheal diseases. "Understanding the critical importance of basing decisions on sound science and incorporating it into the policy-making process could be an important step forward for many African nations," said **Bruce Alberts**, president, National Academy of Sciences. "The goal of integrating scientific advice and public policy can best

be accomplished by boosting both the capacity and the credibility of the institutions that represent the scientific and medical communities in individual countries." . . . **MITCHELL MACHTAY** was named vice chairman and director of clinical research, Department of Radiation Oncology at Thomas Jefferson University Hospital and the Kimmel Cancer Center of Thomas Jefferson University. He was also appointed the Walter J. Curran Jr. Associate Professor of Radiation Oncology at Jefferson Medical College. Machtay was associate professor of radiation oncology at the University of Pennsylvania Medical Center. He has been a principal investigator of various studies in the Radiation Therapy Oncology Group since 1994, and has served as deputy group chairman since 2000. . . . **THOMAS JORDAN**, president of Tom Jordan Consulting, was honored by Cancer Care of New Jersey for his contributions to the field of oncology over the past 30 years. Jordan was head of the Bristol-Myers Squibb Co. global franchise. . . . **LOVELL JONES**, of the Department of Gynecologic Oncology at M. D. Anderson Cancer Center, was appointed to the Scientific Advisory Board of the Uniformed Services University of the Health Sciences. The university has been directed by Congress to fund a gynecologic cancer initiative to address the needs of the military in this area. The role of the SAB is to review and critique the program. . . . **KAVITA SHARMA** was appointed the first Arthur G. James American Cancer Society Algology and Palliative Medicine fellow at The Ohio State University's Medical Center and The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute Comprehensive Cancer Center. Sharma, a specialist in internal medicine and geriatrics, was associate director of geriatric medicine at New York Medical College. She will study under the direction of **Costantino Benedetti**, director of pain and palliative medicine at Ohio State. The fellowship is funded by the Ohio Division of ACS. . . . **UNIVERSITY OF PITTSBURGH** Medical Center and the Heritage Valley Health System announced the opening of the UPMC/HVHS Cancer Center. Working in collaboration with the University of Pittsburgh Cancer Institute, the new center will offer cancer patients exceptional care and state-of-the-art treatments close to home. The center is one of more than 40 UPMC Cancer Centers being established throughout the tri-state region. Oncologists at the center will work in tandem with more than 2,000 physicians, scientists, administrative staff and other health care professionals at UPCI and patient care at UPMC Cancer Centers.

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Business & Regulatory Report

Clinical Trials:

Bayer, Onyx Compound On Fast Track, In Phase III For Renal Cell Carcinoma

Bayer Pharmaceuticals Corp. (NYSE: BAY) of West Haven, Ct. and **Onyx Pharmaceuticals Inc.** (Nasdaq: ONXX) said BAY 43-9006 has been granted Fast-Track status by U.S. FDA for metastatic renal cell carcinoma, or advanced kidney cancer.

The compound, which is in phase III testing, is an RAF kinase and VEGF inhibitor that prevents tumor growth by combining two anticancer activities: inhibition of tumor cell proliferation and tumor angiogenesis,

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Deals & Collaborations:

EU Approves $60 Billion Sanofi Takeover For Aventis After Novartis Drops Bid

The European Union approved Sanofi-Synthelabo's •51 billion ($60.6 billion) cash and shares takeover bid for Aventis, after finding no reason to investigate the role of the French government in the deal.

The French government played a key role in bringing Sanofi and Aventis to negotiations, after which Sanofi increased its offer by 14 percent. The move also prompted competitor Novartis to drop its effort to purchase Aventis.

"The Commission has authorized, under the Merger Regulation, the proposed acquisition of Aventis by subject to a number of conditions intended tosafeguard competition and hence the interests of European consumers on a number of markets," a commission statement said.

The purchase will create the third larges drug company in the world, behind Pfizer and GlaxoSmithKline.

* * *

Amgen Inc. (Nasdaq:AMGN) of Thousand Oaks, Calif., and **Tularik Inc**. (Nasdaq:TLRK) of South San Francisco, said they have signed a definitive merger agreement whereby Tularik will become a wholly-owned subsidiary of Amgen in a stock-for-stock transaction valued at $1.3 billion.

The acquisition will combine the Amgen cellular and molecular biology and medicinal chemistry with the Tularik gene regulation, the companies said.

Under the agreement, Amgen, in a tax-free transaction, will exchange Tularik common stock for Amgen common stock in a ratio that fixes the Tularik value at $25 per share based on the average Amgen stock price

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IDM Begins Phase II/III Trial Of Bexidem For Bladder Cancer

(Continued from page 1)

the companies said.

In clinical studies, BAY 43-9006 demonstrated both anti-proliferative and anti-angiogenic properties in two important anticancer activities, the companies said. In preclinical models, the agent inhibited tumor cell proliferation by targeting the RAF/MEK/ERK signaling pathway at the level of RAF kinase. The agent also exerted an antiangiogenic effect by targeting the receptor tyrosine kinases VEGFR-2 and PDGFR and their associated signaling cascades.

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IDM of Paris said it has begun a phase II/III trial of Bexidem, its cell therapy product candidate bladder cancer.

The randomized trial will be carried out in Europe, primarily in France, Belgium, Luxembourg and Germany, the company said. Half of the patients will receive 12 intra-bladder instillations of Bexidem over a period of 6 months. The other half will receive Bacillus Calmette-Guerin, the standard treatment for superficial cancers of the bladder.

Bexidem is a cell therapy product comprised of activated macrophages obtained from the white blood cells of the patient, the company said.

In a phase II 17-patient pilot trial for superficial cancer of the bladder with a high probability of cancer recurrence, 112 instillations of Bexidem were administered without any serious adverse reactions attributed to the product candidate. The total number of recurrences decreased from 34 the year before treatment to 8 during the year of administration.

The trial has received approval from the French and Belgian drug regulatory agencies as well as the ethics committee at Necker Hospital where the French trial will take place under Nicolas Thiounn, coordinating investigator.

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FASgen Inc. of Baltimore said it has received $2.4 million grant from NCI for a phase II study of its compounds (fatty acid synthase inhibitors) for their anti-tumor efficacy in ovarian cancer.

During phase I of the research, the company said it identified six potent small molecule FAS inhibitors that provided a firm scientific basis for formal drug development. The compounds were effective in treating human cancer xenografts in athymic mice, a commonly used pre-clinical test model, the company said.

FASgen Inc. said it has a sponsored research agreement with the Johns Hopkins University and is coordinating its research with the JHU Oncology Center, where the trial will take place.

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Ligand Pharmaceuticals Inc. (Nasdaq: LGND) of San Diego said it has agreed with FDA to a final statistical plan with a modification for its two phase III studies of Targretin (bexarotene) capsules in front-line combination therapy for non-small cell lung cancer.

The two randomized trials, known as SPIRIT I and II (studies providing investigational research in Targretin), are being conducted at 265 sites worldwide, the company said. They are evaluating whether adding Targretin to front-line cisplatin/vinorelbine and carboplatin/paclitaxel chemotherapy extends survival of advanced stage IIIB with pleural effusion or stage IV NSCLC.

For both studies, the primary endpoint is overall survival with a secondary endpoint of projected two-year survival, the company said. Enrollments were completed in August and September 2003, respectively. No efficacy results, preliminary or otherwise, from either study are known, nor would the current state of maturation of the data provide any meaningful predictive analysis, the company said.

The final statistical plan as modified specifies the analysis trigger to be at 456th death event or 18

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months of follow-up from the date the last patient was entered into each study, whichever occurs later, the company said.

"This modification should result in the majority of patients having between 1.5 and 2.5 years of follow-up observation based upon SPIRIT I and II accrual rates," said Andres Negro-Vilar, executive vice president of research and development and chief scientific officer at Ligand. " We also expect the assessment of projected two-year survival, the study secondary endpoint, to be enhanced by the revised statistical plan."

The studies are powered to show a 30 percent improvement in median survival among Targretin-treated patients compared to those who receive combination chemotherapy only, the company said.

In another development, Ligand and **Organon** of Roseland, N.J., said they would expand their combined AVINZA (morphine sulfate extended-release capsules) primary care sales force calls by more than 50 percent and establish a targeted sales force to cover the long-term care/hospice segment of the $3.6 billion sustained-release opioid chronic moderate-to-severe pain market.

"AVINZA performed well in 2003 in both prescription market share growth and net sales," said David Robinson, president and CEO at Ligand. "However, the opportunity in primary care representing more than half of all SRO prescriptions and in long-term care and hospice estimated at 15-20 percent of the value market remains to be more fully developed. It is the overall growth opportunity of agent and in these particular segments which has motivated the partners to announce plans to expand AVINZA sales force calls and to increase the year-end five-year market share target of AVINZA to 15 percent of overall SRO prescriptions."

FDA granted marketing approval for the drug for the once-daily treatment of moderate-to-severe pain where continuous, around-the-clock opioid therapy for an extended period of time is required. Ligand launched the product in mid-2002.

* * *

NeoRx Corp. (NASDAQ:NERX) of Seattle said it has begun enrollment in a phase III trial of Skeletal Targeted Radiotherapy for refractory multiple myeloma.

NeoRx is developing STR for use with high-dose chemotherapy and autologous stem cell transplantation for multiple myeloma and other cancers that arise in or spread to the bone and bone marrow.

The 240 evaluable patient phase III trial is a multi-center, randomized, controlled study, designed to evaluate the safety and efficacy of STR for refractory myeloma where a partial response to conventional therapy has failed and where treatment occurred for less than 18 months, the company said.

The one-half on the experimental arm will receive STR at a dose of 750 mCi/m2 plus the chemotherapy drug melphalan at 200 mg/m2, followed by autologous stem cell transplantation, the company said. The control arm will receive melphalan only, followed by transplantation. Both study arms will be evaluated for response to treatment six months after transplantation, using an immunofixation assay to detect myeloma protein in samples. Sample analysis will be conducted at a central laboratory, and blinded results will be reviewed by an independent panel of experts. The primary endpoint is complete response, as determined by the complete disappearance of myeloma protein at six months post-transplant, the company said.

STR, an injectable drug that may be administered on an out-patient basis, is a targeted cancer therapeutic that delivers radiation directly in the bone and bone marrow, the company said. It is composed of a bone-targeting molecule, DOTMP, in a stable complex with the radioactive substance, holmium-166. When injected into the bloodstream, it binds to bone mineral to treat the bone and bone marrow with a brief, intense dose of radiation to destroy cancer cells in the

In a related development, NeoRx Corp. said it has executed an agreement with **University of Missouri-Columbia Research Reactor Center**, under which MURR will manufacture and supply to NeoRx the radioisotope holmium-166 for the NeoRx phase III trial of skeletal targeted radiotherapy.

Financial terms of the agreement were not disclosed, the company said.

NeoRx said it uses holmium-166 in the formulation of STR, its cancer therapeutic candidate.The company said it plans to initiate a phase III trial of STR for primary refractory multiple myeloma.

NeoRx is developing STR for use with high-dose chemotherapy and autologous stem cell transplantation for multiple myeloma and other cancers that arise in or spread to the bone and bone marrow, the company said.

STR is composed of a bone-targeting molecule, DOTMP, complexed with the beta-emitting radioisotope holmium-166, the company said. When injected into the bloodstream, STR binds to bone mineral, bringing holmium-166 in direct proximity to the bone marrow to destroy cancer cells. STR that does not bind to bone is rapidly eliminated by the kidneys shortly after administration.

The high-energy and relatively long path-length of the beta particles emitted by holmium-166 allow penetration and uniform irradiation of marrow and bone disease sites, the company said. The short half-life of holmium-166 allows treatment on an out-patient basis, and minimizes the time required between STR administration and stem cell transplantation, which is performed to restore bone marrow function after treatment with STR and high-dose chemotherapy.

In another development, NeoRx said it has acquired the worldwide exclusive rights from **AnorMED Inc.** (TSX:AOM), excluding Japan, to develop, manufacture and commercialize AMD473, a platinum-based anti-cancer agent.

In phase I and II trials, the agent demonstrated anti-cancer activity in a range of tumors and had a manageable safety profile, the company said. NeoRx said it would begin clinical studies of AMD473 in one or more cancer indications in the second half of this year.

Under the agreement, NeoRx paid AnorMED a one-time upfront milestone payment of $1 million in NeoRx common stock and $1 million in cash, the company said. The agreement also provides for additional milestone payments to AnorMED of up to $13 million, payable in cash or a combination of cash and NeoRx common stock. Upon regulatory approval, AnorMED would receive royalty payments of up to 15 percent on product sales.

Under the agreement, NeoRx said it has acquired an exclusive license, under a portfolio of issued patents and patent applications, to develop, manufacture and commercialize AMD473. The patent portfolio relates to composition of matter, formulations and methods of use of AMD473 and related analogs and compounds, and includes issued patents and patent applications in major countries. The agreement also transfers to NeoRx certain know-how pertaining to AMD473, including clinical and manufacturing data, regulatory submissions, and related information. Also under the agreement, AnorMED will transfer to NeoRx an inventory of finished AMD473 suitable for use in clinical studies.

In phase I studies of AMD473 as a single agent and in combination with other cancer therapeutics, anti-tumor activity was observed in a broad range of cancers, the company said. In phase II monotherapy studies, objective responses were observed in hormone-resistant prostate cancer, and in second-line ovarian, breast, and lung cancers, including platinum-resistant and platinum-sensitive cancers. Existing platinum agents such as cisplatin and oxaliplatin exhibit nephrotoxicity and/or neurotoxicity. No clinically significant nephrotoxicity or neurotoxicity has been observed with AMD473 to date. Moreover, AMD473 has shown oral bioavailability and anti-tumor activity with oral administration in preclinical studies, and has the potential to be the first platinum agent with both intravenous and oral formulations, the company said.

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OSI Pharmaceuticals Inc. (NASDAQ:OSIP) of Melville, N.Y., said it has initiated a phase II study of the monotherapy Tarceva (erlotinib HCl) versus standard chemotherapy for previously untreated non-small cell lung cancer with a poor performance status.

Tarceva blocks tumor cell growth by inhibiting the tyrosine kinase activity of the HER1/EGFR receptor, thereby blocking the HER1/EGFR signaling pathway inside the cell, the company said. The monotherapy is being developed in a global alliance among OSI, Genentech and Roche.

The multi-center, open-label, randomized study of up to 102 patients, would evaluate in parallel the efficacy and safety of the drug. and of a standard chemotherapy, such as a combination paclitaxel and carboplatin, the company said. The primary endpoint is progression-free survival and secondary endpoints include disease-related symptom benefit, tumor response and overall survival. Tarceva will be administered at 150mg/day.

The performance status of a patient is measured by the Eastern Cooperative Oncology Group Performance Scale, the company said. The scale ranks the global function according to level of activity and symptoms from PS0 to PS4 with PS0 patients being fully ambulatory and asymtomatic. To be eligible for the trial, patients need to have moderately impaired performance status graded as 2 (PS2). A PS2 rating is defined as capable of self-care but unable to carry out any work activities; up and about more than 50 percent of waking hours, the company said.

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Seattle Genetics Inc. (Nasdaq:SGEN) of Bothell, Wash., said it has initiated a phase I trial of

SGN-40, a humanized monoclonal antibody that targets the CD40 antigen, for multiple myeloma.

The study would evaluate the safety, pharmacokinetic profile and antitumor activity of a multi-dose regimen of SGN-40, the company said.

The single-agent, open label study will enroll up to 24 patients at four U.S. cancer centers, the company said. The company said it would begin a clinical trial of SGN-40 for refractory non-Hodgkin's lymphoma in the second half of 2004.

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ZymoGenetics (Nasdaq:ZGEN) of Seattle said it received agreement from FDA for a phase I study with Interleukin 21 (IL-21).

IL-21 is a recombinant human protein being developed by ZymoGenetics for metastatic melanoma and renal cell carcinoma, the company said.

The company said it would open enrollment and begin the study within the next several months. The trial will evaluate the safety and pharmacokinetics of recombinant human IL-21.

"Metastatic melanoma and metastatic renal cell carcinoma represent significant unmet medical needs," said Bruce Carter, president and CEO of ZymoGenetics. "For melanoma, each year there are 56,000 new cases and 8,000 deaths in North America alone. We believe that the ultimate potential of IL-21 could be much larger, presenting opportunities in a number of other cancers."

Deals & Collaborations:

Amgen To Purchase Tularik In Deal Worth $1.3 Billion

(Continued from page 1)

set prior to the close of the transaction, the companies said. The value of the transaction as of closing date would be $1.3 billion, net of estimated cash to be acquired and net of the Amgen existing ownership of Tularik of approximately 21 percent. In addition, there will be a one-time charge related to in-process research and development affecting GAAP earnings per share in the period during which the deal closes.

The transaction is expected to close in the second half of 2004, the companies said.

Amgen said the agreement would represent an incremental increase of $100 million per year in its investment in research and development for the next several years.

David Goeddel, founder and CEO of Tularik, will become site head of Amgen San Francisco, the companies said. The boards of directors of Amgen and Tularik have approved the transaction, which is subject to the approval of the stockholders of Tularik and other customary closing condition, the companies said.

* * *

Baylor Research Institute of Dallas received a $1.3 million **NIH** grant to study JC virus, a virus suspected to play a role in causing colon cancer.

C. Richard Boland, chief of gastroenterology at Baylor University Medical Center at Dallas, will lead the study.

Approximately 80 percent of healthy people carry the virus in their colons, and show no obvious ill effects.

"Since most of us carry the virus, the virus itself is not the culprit," Boland said. "It seems to exist in a latent state in most people. But when the virus replicates, it can make mistakes or mutate. We think it very likely causes a problem called chromosomal instability and could be a trigger that starts the process that leads to colorectal cancer."

If the study can determine the role of the JC virus, clinical trials will be proposed to develop an immunization strategy for colon cancer, Boland said. The trials would be conducted in collaboration with Jacques Banchereau, director of the Baylor Institute for Immunology Research in Dallas.

"Ultimately, we hope to develop a vaccine that might delay or prevent the emergence of neoplastic lesions in the colon," Boland said. "Our success could have significant implications for public health."

* * *

BTG (LSE: BGC) of West Conshohocken, Pa., said it has signed a license agreement with **Cougar Biotechnology** of Los Angeles by which Cougar is granted worldwide exclusive rights to develop and commercialize abiraterone acetate for advanced prostate cancer.

BTG said it would receive an upfront cash payment and will benefit from further development milestones and a royalty on sales.

Detailed financial terms were not disclosed, the company said.

Abiraterone was first synthesized at The Institute of Cancer Research in the UK as part of a BTG-funded program to discover a selective, orally active drug to inhibit the enzyme in testosterone synthesis, 17a hydroxylase/C17,20-lyase, the company said. Suppression of testosterone synthesis was subsequently demonstrated in prostate cancer.

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DxS of West Conshohocken, Pa., and **BTG** (LSE: BGC) of Manchester, U.K., said they have signed an exclusive license with **AstraZeneca** to commercialize Amplification Refractory Mutation System DNA diagnostic technology.

ARMS detects gene mutations and single nucleotide polymorphisms, the companies said.

Under the agreement, BTG and DxS said they will assume certain rights to the intellectual property and will commercialize the technology within the diagnostic and research markets. The licensing campaign will maximize the commercial value for the ARMS technology through companies that offer products and services which relate to the detection of genetic variation, companies that are currently using ARMS technology as part of their in-house research activities, as well as encouraging new applications for the technology.

The $1 billion nucleic acid diagnostic market includes testing for infectious and genetic diseases, as well as cell/tissue typing, cancer genetics and personalized medicine, the companies said.

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Gene Logic Inc. (Nasdaq:GLGC) of Gaithersburg, M.d., said it has entered into a multi-year agreement with NCI, Division of Cancer Treatment and Diagnosis, for preclinical safety and pharmacology studies in cancer, AIDS and AIDS-related illnesses.

The seven year contract could achieve up to $6.9 million in revenue based on studies and services requested by the agency over the life of the agreement, the company said.

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Immunomedics Inc. (Nasdaq:IMMU) of Morris Plains, N.J. and **Amgen Inc.** (Nasdaq:AMGN) of Thousand Oaks, Calif., said Amgen has returned to Immunomedics all rights for epratuzumab, the humanized CD22 monoclonal antibody therapeutic licensed to Amgen by Immunomedics in December 2000, including rights to second generation molecules and conjugates.

As part of the transaction, Immunomedics said it has agreed to issue to Amgen a 5-year warrant to purchase 100,000 shares of the company's common stock with a strike price equal to $16.00 per share. Amgen will receive a final payment of $600,000 from Immunomedics if epratuzumab is approved for commercialization in the U.S. for non-Hodgkin's lymphoma therapy.

There are no other financial obligations between the parties as a result of the agreement, the companies said.

"Phase II data demonstrate that epratuzumab is active against NHL)," said Roger Perlmutter, executive vice president of research and development at Amgen. "Epratuzumab was also shown to be safe and well-tolerated when administered as a single agent or in combination with rituximab (Rituxan). Our transfer of preclinical and clinical data to Immunomedics will aid their efforts to develop epratuzumab."

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Matria Healthcare Inc. (NASDAQ:MATR) of Marietta, Ga., said its subsidiary, **Quality Oncology Inc**., is providing comprehensive disease management services nationwide for Delta Air Lines employees and their family members with cancer.

The cancer disease management program, which began in January, includes 24-hour-a-day, seven-day-a-week phone access to a QO team of experienced cancer nurses, the company said.

"Our nurses are experienced specialists who are able to anticipate family and patient needs and see that those needs are met, " said Dan McCrone, chief medical officer of Quality Oncology. "The treating doctor remains the primary medical resource for the patient and family, but many patients have found that our nurses add valuable and timely assistance."

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North American Scientific Inc. (Nasdaq: NASI) of Chatsworth, Calif., said it has entered into an agency agreement with **NOMOS Corp**. that will allow each party to act as an independent agent to begin selling the other's radiation therapy products, prior to the closing of the proposed acquisition of NOMOS.

In 2003, North American Scientific signed a definitive agreement to acquire NOMOS Corp. in a deal that is expected to close at the end of the year, the company said.

Under the agreement, NOMOS could begin selling the NAS Prospera I-125 and Pd-103 brachytherapy sources, the company said. NAS would add the NOMOS suite intensity modulated radiation therapy and image-guided radiation therapy technologies to its product line, including PEACOCK, an IMRT planning and delivery system, which includes CORVUS and the NOMOS multileaf collimator, MIMiC, able to shape or conform radiation to fit the size and shape of a tumor target while

reducing exposure to nearby healthy tissue.

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Targeted Molecular Diagnostics LLC of Chicago said it has entered into a research collaboration with Eli Rosenbaum and David Sidransky of **Johns Hopkins University**, and with Yosef Yarden of the **Weizmann Institute of Science** to identify the role of Epigen, a ligand in the clinical behavior of prostate cancer.

Studies performed by Yarden and Bacus made use of Epigen to the ErbB cell surface receptors, and detected Epigen expression in the majority of prostatic cancer specimens, the company said. The expression of epidermal growth factor-like ligands is coordinately up-regulated in androgen-independent prostate tumors, and similarly mammary cancers exhibit expression of multiple EGF-like ligands. Whether Epigen plays a role in the clinical behavior of prostate cancers will be the subject of the collaborated study. TMD said it would test the prostate cancer tissues for expression of Epigen and will correlate it to the outcome of the patients from John Hopkins Hospital.

Product Approvals & Applications:

Germany Approves 3-Month Formulation of Pamorelin

Debiopharm S.A. of Lausanne, Switzerland and **CNS** said Pamorelin long acting 11.25mg, a three month formulation, was granted final marketing authorization in Germany by the Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM) for prostate cancer.

Pamorelin LA is manufactured at Debio R.P., the Debiopharm FDA-inspected production site in Martigny, Switzerland. A one-month formulation of Pamorelin is already registered in Germany.

CNS is an independent drug-development company specializing in oncology, endocrinology, and niche diseases.

Debiopharm said it conducted the formulation, scale-up, optimization, GMP, clinical trials and registration work for the development of Pamorelin LA. Debio R.P. will supply its partner Ipsen S.A. with commercial quantities of Pamorelin LA, to be marketed in Germany. Debiopharm will receive milestones for the registration and royalties on sales of the product, the companies said.

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ILEX Oncology Inc. (Nasdaq:ILXO) of San Antonio said it has submitted to FDA the final section of its new drug application for clofarabine for refractory or relapsed acute leukemia in children.

The filing was based on data from two acute lymphoblastic leukemia and acute myeloid leukemia phase II trials, the company said.

The drug had been granted orphan drug designation for adult and pediatric ALL and AML, the company said

Clofarabine is a second generation of the drug class purine nucleoside analogs and inhibits DNA production necessary for cancer cell growth, the company said.

Bioenvision Inc. (Amex: BIV) granted ILEX the right to develop clofarabine 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.

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INEX Pharmaceuticals Corp. (INEX; TSX:IEX) of Bridgewater, N.J. and **Enzon Pharmaceuticals Inc**. (Nasdaq: ENZN) of Vancouver have submitted the final section of a rolling NDA submission for marketing approval of Onco TCS as a single-agent for relapsed aggressive non-Hodgkin's lymphoma previously treated with at least two combination chemotherapy regimens.

Inex said it has requested the NDA be granted a priority review as it is a product for an unmet medical need.

In the completed multi center pivotal phase II/III trial for the agent, 119 patients with aggressive NHL were treated who had not responded to previous therapy or had responded and subsequently relapsed, the company said. After treatment, an overall response rate of 25 percent was attained.

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Ivax Corp. (AMEX: IVX) (LSE: IVX.L) of Miami said it has received approval from the European Commission to extend the indication of the existing marketing authorization for its proprietary injectable paclitaxel (Paxene) to include metastatic breast cancer and metastatic ovarian cancer in the E.U.

Ivax said it entered into an agreement with Mayne Group Ltd. for the marketing and distribution of Paxene in Belgium, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Sweden, the U.K., and Norway.

Ivax said it will be distributing on its own or with additional partners in Austria, Denmark, Greece and Spain.

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Maxim Pharmaceuticals (Nasdaq: MAXM) (SSE: MAXM) of San Diego said its treatment protocol Ceplene in combination with interleukin-2 (IL-2), has been approved by the U.S. FDA for advanced malignant melanoma.

The treatment protocol allows Maxim to provide expanded access of Ceplene to patients in the U.S. while investigation of the drug continues in the confirming phase III trial.

The data show that Ceplene/IL-2 investigational therapy may provide a survival benefit for advanced malignant melanoma, the company said. FDA agreed expanded access of Ceplene to critically ill patients with limited treatment options. FDA has also approved reimbursement for study medication, which allows Maxim to recover costs associated with providing qualified patients access to Ceplene therapy.

FDA specifies four criteria for approval of a treatment protocol. These criteria require that the disease be serious and life threatening, that no satisfactory alternative treatments are available, that the drug is under investigation in a controlled clinical trial under an existing IND and that the sponsor is actively seeking marketing approval.

The treatment protocol will be available in the U.S., the company said.

The company said it will expand the protocol to additional qualified treatment centers over subsequent months. The net cost of making the treatment protocol available to patients will be approximately $1.5 million in the current fiscal year, the company said.

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R2 Technology Inc. of Sunnyvale, Calif., said it has received an approvable letter from the U.S. FDA for its ImageChecker computed tomography lung CAD system.

The system is the first CAD system to receive an approval recommendation from a FDA Advisory Panel and an approvable letter for the detection of suspicious lung nodules using CT as an imaging modality, the company said.

A panel of radiologists at the European Congress of Radiology said the CAD application could provide a significant advance in detection of suspicious lung nodules, the company said. Early clinical studies have shown an increase in radiologists performance, according to the panel.

"CAD will prove a significant advance in the interpretation of CT lung exams," said Philippe Grenier, of the University of Paris. "The new technology could provide a tremendous aid in helping to detect lung nodules due to many diseases, including lung cancer. In many cases, the CAD system has found lung nodules that were missed in initial clinical review. We believe that the combination of CAD and the radiologist is a more powerful combination than the radiologist alone."

CAD acts as a second pair of eyes for the radiologist and is used after the radiologist first conducts a standard review, the company said. The CAD algorithms automatically detect areas of interest to increase physician accuracy by decreasing observational oversights. Providing workflow-enhancing tools, including automatic measurement and characterization information of the detected lung nodules, the ImageChecker CT system is designed to improve radiologist efficiency in reviewing chest CT exams and to improve accuracy in lung nodule detection, the company said.

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Seattle Genetics Inc. (Nasdaq:SGEN) of Bothell, Wash., said FDA has granted

orphan drug designation to its product candidate SGN-30 for T-cell lymphomas.

SGN-30 is a monoclonal antibody in phase II trials for the treatment of anaplastic large cell lymphoma and Hodgkin's disease, the company said. FDA granted SGN-30 orphan drug designation for Hodgkin's disease in July 2003, the company said.

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SightLine Technologies of Haifa, Israel, said it received U.S. marketing approval from FDA for ColonoSight for diagnosis and treatment of colorectal cancer.

The ColonoSight system is operated using a miniature video camera and light source that is inserted into the colon to locate polyps and growths, the company said. The system uses proprietary IntraPull technology, which pulls the device into the colon, as compared with a standard colonoscopy examination, in which the operator is required to push the device to obtain results. Consequently, both the discomfort to the patient and the likelihood of puncturing the colon is reduced, the company said. The amount of anesthesia required for the procedure is also lessened. The ColonoSight device uses a disposable sheath, reducing the likelihood of infection. The disposable sheaths eliminate the need for disinfection between procedures. The system also enables swift treatment of growths in the colon, and can be used to remove polyps.

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