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Study Finds No Benefit From CT Screening; Advocacy Group Alleges "Delaying Tactic"

By Paul Goldberg

An analysis of three single-arm studies of spiral computed tomographic screening for lung cancer showed a three-fold increase in the number of new lung cancer cases and a tenfold increase in surgeries, but no change in advanced lung cancers or deaths from the disease.

The paper, published in the March 7 issue of the Journal of American Medical Association, used a statistical model to analyze data from 3,246 current or former smokers who were enrolled in three separate single-arm trials, conducted at the Istituto Nazionale dei Tumori in Milan, the Mayo Clinic, and the Moffitt Cancer Center.

"This was a very disappointing result to us," said Peter Bach, a

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EPO Controversy:

CMS Removes Obstacles For Contractors To Deny EPO Coverage For Cancer Anemia

By Paul Goldberg

The Centers for Medicare and Medicaid Services March 8 informed its contractors that they may be able to expedite "local coverage decisions" to exclude payment for erythropoietin agents for anemia of cancer.

The CMS email, which wasn't intended to be made public, stated that the agency's regional offices may be able to grant waive the 45-day public comment period usually required for such changes, said sources who have seen the document.

Observers said that the email indicates that the agency is trying to bring about a quick succession of "local coverage determinations" to eliminate payment for this use of Amgen's Aranesp. The agency's actions may also extend to reimbursement for another version of EPO, Johnson & Johnson's Procrit.

The CMS email was sent out three days after Noridian Administrative Services LLC, a company which administers the Part A and Part B Medicare programs, became the first CMS contractor to announce that it would no longer pay for Aranesp in this off-label indication.

"We felt that we needed to act for the benefit of the beneficiary population," Noridian medical director William Mangold said to The Cancer Letter. "I concede that a valid option would be to wait and tread water, and see what everyone else does, but we just decided that we would err on the side of being a little more conservative."

A recent study showed that Aranesp decreased survival in anemia

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Study Finds Overdiagnosis, No Benefit, From CT Screening

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pulmonologist and a researcher at the department of epidemiology and biostatistics at Memorial Sloan-Kettering Cancer Center, the lead author of the study. "We were all optimistic that CT screening, because it could detect smaller nodules than chest x-ray, would actually successfully intercept those cancers that had high malignant potential."

Though far from definitive, the study produced evidence of overdiagnosis and overtreatment, and raised questions about reliability of another single-arm study, by the International Early Lung Cancer Action Program, which claimed an 88 percent 10-year survival for patients with stage I disease. The I-ELCAP study was published in the New England Journal of Medicine Oct. 26, 2006.

"Perhaps the best explanation for the contrasting results… is the difference in the primary outcome measures of the two studies: mortality in the study by Bach et. al. vs. survival in the I-ELCAP study," Dartmouth researchers William Black and John Barron wrote in an editorial that accompanied the JAMA paper.

The two studies appear to agree that CT screening can increase survival. However, the Bach study then moves on to consider whether survival translates into a decline in mortality.

"The I-ELCAP results are nested in ours," Bach said to The Cancer Letter. "They found a lot of early-stage cancers, and survival is excellent. We had those findings also." Indeed, in the Bach study, the 4-year lung cancer-specific survival of the 81 individuals who were diagnosed with stage I lung cancer and who underwent surgery was 94 percent.

"We went on to the next step, which was to say, 'Well, does that translate into benefits for patients?'" Bach said. "And we saw that we didn't save lives, that we didn't prevent advanced disease."

While supporters of the I-ELCAP study argue that the time has come for mass screening of former smokers and are lobbying Congress to provide funds for these interventions, Bach and the authors of the editorial that accompanies his paper argue that data from randomized trials would be needed to inform health policy on screening.

"Randomized controlled trials are the most reliable method for obtaining accurate assessments of the benefits and harms of screening in the underlying population," Black and Barron wrote. "Although expensive and time-consuming, rigorous trials of cancer screening are far more cost-effective that what might be the alternative—widespread adoption of costly screening intervention that cause more harm than good."

The Lung Cancer Alliance, a patient group, issued a press release describing the Bach paper as "another delaying tactic to deny people at high risk for lung cancer the chance to have it detected at an early, treatable stage."

"This is not productive," Laurie Fenton, president of the alliance, said in a statement. "We have heard these same statistical arguments used for years to delay screening for breast cancer, and there are many in the medical community who are still debating mammograms for women in their 40s even after eight trials have been completed."

"Why is lung cancer being held to a different standard?" said Fenton, who argues that CT screening has been shown to increase detection of small nodules. "We are talking about a high risk population, and no one argues that CT scans can detect lung cancer at a very early stage, not even the authors of the [JAMA] article. The issue is how to manage the suspicious nodules once they are found."

In their campaign to bring about mass screening, the alliance and I-ELCAP principal investigator Claudia Henschke argued that the ongoing NCI-sponsored trial comparing CT screening with standard chest X-ray is unethical, because half the patients are randomized to a less sensitive screening method (The Cancer Letter,

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Henschke didn't return calls and didn't respond to an e-mail from The Cancer Letter.

"This is a superbly qualified group of investigators who have carefully constructed the analysis of screening benefit based on observations from three cohort studies, compared to predictions of no screening using a previously validated model," said Denise Aberle, the national co-principal investigator for the National Lung Screening Trial and professor of radiological sciences, and director of thoracic imaging at UCLA Medical Center.

"They fully disclose all assumptions made, the sources upon which they base their assumptions, and the modifications made to the original lung cancer model," Aberle said. "They acknowledge the limitations of their research.

"What is so important here is that this work places the issue of CT screening smack dab within the appropriate framework, which is: (a) is there benefit from screening based on a legitimate endpoint: lung cancer mortality; (b) are there potential harms from screening; and (c) how do current optimistic predictions of screening benefit stack up, meaning: what do survival predictions really tell us?

"These are core questions that need to be addressed. Their results underscore the value of the NLST that, with over 53,000 participants, will be large enough and have the necessary control arm to answer the question of CT benefits versus harms. Finally, this group studied a small combined cohort; yet, these observations are based on data from more annual screenings than was the I-ELCAP report, the median follow-up of participants was 3.9 years--longer than that of the I-ELCAP, and they followed all 3,246 participants, not just those with lung cancer.

"In effect, the cumulative person-years of observation far exceeds that of the I-ELCAP," Aberle said. "I would expect no less from these guys. I hope we find they are wrong, but we will find out."

David Johnson, Cornelius Abernathy Craig Professor of Medical and Surgical Oncology and Director of the Division of Hematology/Oncology at Vanderbilt-Ingram Cancer Center, describes the LCA statement as "regrettable."

"Dr. Bach's paper has interjected a note of caution into the debate vis-à-vis the value of screening," said Johnson, a lung cancer expert who serves on the LCA medical and scientific advisory board, but who wasn't consulted about the statement.

"I certainly don't see it as a 'delaying tactic,' but simply an attempt to provide another perspective on this important issue," said Johnson. "Obviously, this is an emotional issue, and it's important to point out that there is no right or wrong. All parties want the same thing, namely the eradication of lung cancer and the suffering it causes.

"But importantly, before we expend huge amounts of our limited resources we need to await the results of the NLST and the NELSON trial [in Europe]. I think we can all agree that we do not want to see limited resources used injudiciously. I have the utmost respect for Laurie and her group. They have done much to shine a bright light on a heretofore ignored disease. I admire the group's passion and desire to do everything possible to eradicate lung cancer. However, on this issue, I do not agree with the position LCA has espoused."

Andrew Turrisi, another member of the alliance's medical and scientific advisory board, said that it's "unfair" to characterize the JAMA paper as a delaying tactic.

"The harsh words are due to the emotional position of advocacy," said Turrisi, chairman of the Department of Radiation Oncology at Wayne State University School of Medicine and chief of radiation oncology at the Barbara Ann Karmanos Cancer Institute and the Detroit Medical Center. "Lung cancer is awful, and the treatment is not great. Screening now has two conflicting studies, each imperfect. Throwing stones at either will not settle the dispute."

I-ELCAP had overestimated the benefit of screening, Turrisi said. "I believe that early detection will be better," said Turrisi. "Not as good as we would like, but better. The best would be prevention. Tobacco gone would cut lung cancer incidence by 90 percent--in 30 years."

The Bach paper is far from conclusive, in part because its entire argument turns on 38 lung cancer deaths, Turrisi said.

"In the context of 170,000 deaths per year, this hardly moves me to say there is no inkling of benefit," he said. "And it takes Mayo, Memorial, and Milan to find 38 cases? The science will need to await better trials rather than models."

Turrisi said he is skeptical about NLST. "I find the 50,000-patient study of chest x-ray vs. CT facetious," he said in an e-mail. "We all know that a CXR is poor at detection. The issue of prevalence—removing the extant cases 'incidentally' found—versus screening, subsequent imaging after the extant cases are dealt with makes the study confounded by design--the CT group will pick up some earlier cases and introduce lead time

bias for those found at prevalence testing.

"Fewer cases will be picked up by the CXR, and they will grow—the 'we don't need to find' cases will shake out, but the real cancers, and I think these are more the issue, will be allowed to grow and metastasize. By this paradigm, I forecast that CT screening will look better than it is--both groups should have had CTs to extract the prevalence cases, and then the screening would look at early detection versus delayed detection, and relative stage migration.

"The cost and problem is that 50,000-patient studies is like herding cats--do you look at intention to treat [or] screen, or how the patients are actually followed? Many randomized to either will decide to not return, and some on the CXR arm will decide that it is time for a CT."

Aberle said she reserves judgment on the value of chest x-ray until conclusion of the NCI-funded Prostate-Lung-Colorectal-Ovarian trial.

"I disagree with Dr. Turrisi, as have many in the scientific community who are awaiting results from the ongoing PLCO trial, one component of which is to determine the mortality benefits of CXR screening vs. no screening," Aberle said in an e-mail. "We have never had a trial with sufficient numbers of patients to know whether CXR can reduce lung cancer mortality.

"I do agree that CXR will detect fewer lung nodules than CT, and fewer lung cancers. However, we have no idea whether this will translate into a mortality benefit with CT, or simply represents length and overdiagnosis in CT-screened patients.

"Dr. Turrisi raises an interesting alternative methodology to the NLST, in which all individuals would undergo CT screen and then be randomized to receive either CXR or CT-screening thereafter. This asks a slightly different question than what is being asked by the NLST.

"We (NLST) do not assume that mortality benefit from either test will occur only at incidence screens—mortality benefit might occur at prevalence and/or incidence screens, so, to subject all participants to CT screening would confound this and force from analysis all subjects in whom prevalent cancers were diagnosed.

"Finally, the NLST has carefully factored into their sample size the issues of compliance and cross-over to which Dr. Turrisi refers," Aberle said. "We are adequately powered to address the question of lung cancer mortality in face of these expected events. And yes, NLST is an intention-to-treat trial, although we are capturing crossover events as well as compliance. I would discourage the metaphor of herding cats; it's more a matter of carefully maintaining contact with all of our participants over time to determine health outcomes."

Though Bach never presumed that his analysis of single-arm studies could be a substitute for a large randomized trial, he did hope to "scoop" NLST.

"We were hoping that we would scoop the NLST and be the first ones to demonstrate, using a comparative design, that CT screening effectively reduced the mortality rate from lung cancer, or at least produce suggestive evidence of that. We were very excited to beat them to the punch," Bach said. "Instead we saw the other set of results, which was that CT screening looks a lot like chest x-ray screening, able to uncover small growths that appear histologically like lung cancer, able to drive an increase in surgical treatment, which carries its own risk, but not able to intercept the cancers that are going to go on to become advanced, or to cause deaths in the near term."

EPO Controversy:

Two Contractors Deny AOC Payment Effective Immediately

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of cancer patients (The Cancer Letter, Feb. 2). The finding triggered a Dear-Doctor letter from Amgen and a MedWatch alert from FDA.

According to industry estimates, Amgen sells about $500 million worth of Aranesp for the treatment of anemia of cancer.

Noridian, a company that administers the federal program in 12 states, was able to deny coverage because earlier this month the U.S. Pharmacopeia struck this indication of Aranesp from its compendium. The anemia of cancer indication for Aranesp has never been listed by the AHFS Drug Information Compendium. Under law, CMS has to pay for treatments listed in at least one of these approved compendia.

Noridian's new policy, which became effective immediately, without a public comment period, is posted at https://www.noridianmedicare.com/macj3a/news/updates/parta.html.

Another contractor, NHIC, announced that effective March 9, it would no longer pay for either Aranesp or Procrit for the treatment of anemia of cancer.

Since Procrit retains its listing for anemia of cancer in both compendia, Noridian will continue to pay for it, Mangold said. "Frankly, we would not give any push-back if something came out from CMS sanctioning coverage as a class rather than for the drug, but we didn't feel that we had the authority as a regional

contractor to go beyond the strict coverage of that trial and its results," said Mangold. "Even though we might be able to infer that all members of the class would have the same result, we didn't feel that we could jump out in front of that data."

FDA has been treating the EPO agents as a single class, and industry sources said the agency is formulating a "black box" warning that would be placed on the labels of both Aranesp and Procrit.

In May, the FDA Oncologic Drugs Advisory Committee is expected to review recent data suggesting that EPO agents may trigger adverse events, accelerate progression of disease, and decrease survival.

Mangold said his company will revisit the issue after the ODAC meeting. "We felt totally justified in what we did based on the trial, but we didn't feel like we could extrapolate to the whole class," he said.

Noridian will use the standard CMS-1500 claims form to make certain that Aranesp is administered only in conjunction with chemotherapy.

"Every time I think something in this Medicare line of business is straightforward, I am usually brought up short when somebody demonstrates to me that it wasn't as simple as I thought it was," Mangold said. "But in this case, it seems pretty straightforward to me in terms of implementing it and people following it."

The standard CMS form requires doctors to include the ICD-9 code, which in this case would be 285.22, "anemia in neoplastic disease," and to state whether the drug is being used as part of chemotherapy. If it is, doctors note another code, a V-code, usually V58.11, "encounter for antineoplastic chemotherapy."

"Anybody using Aranesp now will only be paid if they used the 285.22 plus the V-code that says that this patient is undergoing chemotherapy," Mangold said. "If the V-code wasn't there, it would say to the system, 'Oops, they are not on chemo.' Therefore, they are just being treated with Aranesp with no chemo. Therefore, it would be denied."

Mangold said that in cases when Aranesp is given between courses of chemotherapy, the claims would still be paid. "If it is within a course of therapy, thus between cycles, I believe that would fall within the chemotherapy-related coverage," he said. "Obviously, some amount of time passing would constitute no longer being on chemo, but we have not yet addressed what that timeline might be."

The boundary between chemotherapy-induced anemia and anemia of cancer isn't always clearly defined, experts say. It's also an area where Mangold hopes to get some guidance from FDA or ODAC, when it meets to consider the EPO agents in May.

Mangold, who is a surgeon, serves as the medical director for Medicare Part B program in Arizona, Nevada, Utah, and Montana. The group also administers the Part B program in Alaska, Washington, Oregon, Hawaii, Wyoming, the Dakotas, Iowa and Colorado.

Lee Newcomer, head of oncology services for United Healthcare, said national standards, as opposed to "local coverage decisions" by Medicare contractors would be needed.

"A local health plan may be able to write those rules successfully," Newcomer said. However, "rules like that are tough to enforce unless they are national standards."

It would be difficult for oncologists to keep track of the changing rules. "Often the drug is given off-cycle from the chemotherapy," Newcomer said. "The physician office will have to remember to use the code for payment."

As different payers require different levels of documentation, confusion could ensue. "I have about 8,000 contracted oncologists and I represent less than 5 percent of their practice to the vast majority," he said.

Starting in April, United Healthcare will require physicians to document the patients' hematocrit level prior to initiation of EPO, and claims for treatment of patients whose hematocrit is above 36 percent would be denied.

Current CMS forms require documentation of hematocrit or hemoglobin levels in nephrology, but not in oncology. However, starting next January, this information will likely be required on oncology forms as well. The Tax Relief and Health Care Act of 2006, which was passed by Congress and signed into law, states:

"Each request for payment, or bill submitted, for a drug furnished to an individual for the treatment of anemia in connection with the treatment of cancer shall include (in a form and manner specified by the Secretary) information on the hemoglobin or hematocrit levels for the individual."

NCI News:

Cancer Research Budget Cuts Cause "Missed Opportunities," NCI Director Tells Advisors

By Kirsten Boyd Goldberg

NCI's budget, at $4.8 billion, has been held essentially flat since FY 2004 and is falling behind the rate of inflation in biomedical research, leaving the institute with 12 percent less purchasing power than it

had just four years ago, NCI Director John Niederhuber said.

The Biomedical Research and Development Price Index, which calculates the cost of doing research, shows that NCI's $4.8 billion FY04 appropriation is worth about $4.3 billion today, Niederhuber said to the institute's Board of Scientific Advisors and Boards of Scientific Counselors on March 5.

"One has to do across-the-board decreases as well as make tough decisions about certain things that just can't be done or done at a reduced rate," Niederhuber said at the meeting. "As all of you know who have grants, your grants have been decreasing."

In response to a request by BSA Chairman Robert Young, president of Fox Chase Cancer Center, Niederhuber provided the boards with a list of the cuts NCI has made to many of its programs over the past few years.

"It is relatively easy to count projects, trials, and patients affected," Niederhuber said. "It is far more difficult to account for missed opportunities and ideas lost." He also said he is pessimistic about the outlook for the budget in coming years.

Niederhuber's list of items NCI couldn't fund follows:

—In FY06, NCI didn't fund 179 R01 grant applications that were scored within the 20th percentile. First-year cost to fund these grants would have been $58 million.

—Funding for grant applications submitted in response to Requests for Applications has been cut nearly in half in two years, from $44.5 million in FY05 to $24.3 million in FY07. Some of the RFAs that NCI divisions have cancelled or not brought forward include:

Division of Cancer Treatment and Diagnosis: Cooperative Breast Cancer Tissue Resource, $1.013 million.

Division of Cancer Biology: Tumor Stem Cell Biology ($3 million) and Systems Genetics ($5 million).

Division of Cancer Prevention: Prevention of Cancer in Former Smokers RFA and Prevention of Hormonally Non-Responsive Breast Cancer.

Division of Cancer Control and Population Sciences: Cancer Care Outcomes Research and Surveillance Consortium, first year set-aside $6 million.

—Specialized Programs of Research Excellence took an $8 million, or 8 percent, cut in FY06, and further cuts may be necessary this year.

—Cancer Centers program non-competing grants have been flat for the past three years. Reductions of 10 percent may be necessary this year. Two new centers will be funded at capped ($1.5 million) levels.

—Clinical and translational trials may have to take a cut of 10 percent. This would result in a $16.5 million reduction to the clinical trials cooperative groups, causing the postponing or cancellation of 30 to 35 phase III trials and 60 phase II trials, potentially affecting 2,600 patients. The Community Clinical Oncology Program would potentially be cut by $12 million, resulting in a reduction of 1,500 patients in treatment trials and 1,000 patients in prevention and control trials.

These proposed cuts may be alleviated if NCI can find money from other programs to move around, Niederhuber said. The NCI Executive Committee plans to meet March 20 to review budgets for the SPORE program, cancer centers, and clinical trials cooperative groups.

—Cancer control budget line has fallen from $531 million in FY05 to $510 million in FY07. Examples of the cuts include: $6.5 million reduction to the Tobacco Control Research Branch from FY04 to FY07; $7.1 million reduction to the Quality of Cancer Care Program; $1 million reduction to the Cancer Survivorship Program; $760,000 reduction to Risk Factor Monitoring/Energy Balance in FY06.

—Intramural Research Program has dropped from $711 million in FY05 to $686.6 million in FY07, as a result of reviews by the Boards of Scientific Counselors. Examples of cutbacks in the Division of Cancer Epidemiology and Genetics in FY07 include: $1.8 million cut to the Bladder Cancer Whole-Genome Association Study; $400,000 cut to Translational Genomic Research; $1.5 million reduction to Identifying Genetic Determinants of Cancer Risk Factors; $1.5 million cut to Kidney Cancer Whole-Genome Association Study; $900,000 cut to NIH-AARP Study; $300,000 cut in the Chernobyl Research Program; $225,000 cut in second cancers following radiotherapy study; and $400,000 cut in LC/MS Technology for Hormone Measurements.

—NCI Center for Cancer Research patient accrual has fallen from 4,210 in FY04 to 3,795 in FY06. "We are shrinking down because we don't have the resources," Niederhuber said. "This is a number I would hope would be slowly increasing. I think it really supports the work in drug development on the extramural side."

—NCI-Frederick Cancer Research & Development Center took an $8 million, or 10 percent cut. This included a reduction of 40 scientific and support staff,

saving $2.9 million; a $2.7 million reduction in advanced technologies capital equipment; and $2.4 million cut in facilities repairs and maintenance. The facility provides a large amount of support to extramural researchers, including supplying live vaccines, and computing support, Niederhuber said.

—NCI Office of the Director took a 10 percent across-the-board cut. This included merging the Office of Communications and the Office of Education and Special Initiatives (The Cancer Letter, Dec. 8, 2006). MITRE Corp. is conducting a review of the merger to further downsize the office and help it provide better service to the divisions, Niederhuber said.

Some of the projects affected include: the Cancer Information Service cut 20 percent from its regional contracts; a mid-stream contract bid was halted for a savings of $750,000; the NCI Exhibit Program took a 14 percent cut; NCI will save $20,000 by not sending its staff writers to the American Society of Clinical Oncology annual meeting; and a contract supporting the Enterprise Vocabulary System was cut 33 percent.

Also, the NCI Executive Committee reviewed data on readership of the NCI Cancer Bulletin and decided to reduce its number of issues from 48 to 24 per year, starting April 3, and halt a printing contract for the publication. This will save $400,000.

"The System Is Broken"

BSA members expressed dismay about the potential for long-term damage to the biomedical research enterprise from declining funding.

"For the first time in my 40-year career in science, the bright and best are leaving biomedical research in droves," said BSA member Robert Weinberg, of the Whitehead Institute for Biomedical Research. "This will not affect the course of biomedical research in the next five years, but 10 or 15 years down the road, we will all of a sudden be conducting biomedical research with people who are different from the best and the brightest, because they are going off and becoming stock analysts, or lawyers, or biotech execs. This is, in the long run, going to have disastrous consequences. The work that they would be doing would not be done in biotech, it would not be done in large pharma. It can only be done in small, investigator-initiated laboratories by bright, young, innovative people, and we are losing them by the hundreds, by the thousands."

"I worry just like you do about this," Niederhuber replied. He said he recently talked to high school students in New Jersey about the opportunities in research, and he discusses his concerns with members of Congress.

"I talk every time I can when I'm down on the Hill, that we can't have a stable workforce if the budget goes up and down," Niederhuber said. "If we want a stable workforce in this country, then we have to support that with a budget that grows at least with inflation. That's the message I keep giving. It's the message I encourage our various advocacy groups to give."

Niederhuber said NCI's special program for new investigators, called "star R01s" (*R01), funds grant applications about six or eight points above the regular R01 payline. "At end of year I look at that group of *R01s not funded and in September I look for exceptions that are bright young people, with good proposals and a likelihood of being successful. I am confident that we are funding every good young investigator grant. There weren't good grants from young people that didn't get funded."

Joe Gray, of the Lawrence Berkeley National Laboratory, said pharma and biotech should begin to provide matching funds to NCI. "The system is clearly broken at this point," Gray said. "Now might be the time to be a bit more creative than we are being in how we go out and get money…. Now is the time to think seriously about how we could engage the private sector at a serious level, billions of dollars. It is in the private sector's interest to keep the NCI happy and successful."

Paul Allen, of Washington University School of Medicine, said he was concerned that NCI wasn't replacing people in the intramural program.

"We are looking at specific areas we could build," including stem cell biology, and a new center for excellence in genomics, Niederhuber said.

Hoda Anton-Cluver, of University of California, Irvine, asked whether NCI has any new projects this year. Niederhuber said NCI's only new projects in FY07 are the intramural stem cell biology work, the center for genomics, and the $9 million NCI Community Cancer Centers Program.

"That is very worrisome," Anton-Culver said. "People on the Hill… need to see the reality that we are reducing the budget to maintain what is going on, and in a way that isn't fully functional."

Richard Schilsky, of University of Chicago, said the cooperative groups worked to publicize the funding cuts to their programs, but the groups have already been affected. "What people may still not realize, is that even if some of the cuts aren't as deep as we feared, a lot of the damage is already done, at least in the clinical trials arena," he said. "There are clinical trials that have been stopped and that will not be resumed. There are committees addressing whole areas of research that have

been disbanded that are not likely to be reformed. What cutting at a lower level than 10 percent may do is that it may stop some of the bleeding, but it's not likely to actually restore some of the reduction in activity that has already occurred, because the cooperative groups and others have had no choice but to take action in anticipation of budget cuts."

H. Shelton Earp III, director of the UNC Lineberger Comprehensive Cancer Center, urged Niederhuber to be more optimistic about the prospect for budget increases. "I think we need to be hopeful, and I know you are," Earp said. "We just got a terrific signal from Congress, one that people worked a long time for. They reallocated $10 billion. Ten percent of that went to research infrastructure for NIH and NSF. That is an amazing signal. It is a new day. So I think we need to be hopeful and positive."

NIEDERHUBER: "I hope you're right. I guess my pessimism comes from working with the budget people that interact with OMB and with the department, and recognizing how many black holes there are in that discretionary budget. Some of those black holes are created because they know they are going to create enough pain to get the money. It's a game that's played between the executive branch and the legislative branch. There's a lot of demand, and not a lot of billions of dollars to fill all those holes."

EARP: "I am sure that if I had to deal with OMB, I would be taking Zoloft."

Lynn Matrisian, of Vanderbilt University, asked how NCI sets budget priorities. "It seems clear that if we want to make advances, and have new initiatives, that something has to give to make the budget balanced," she said. "In industry, they have a term they call zombies—things that are... not growing and expanding. Can you give us any insight into how you make that prioritization?"

NIEDERHUBER: "I make it and then I run and hide under my desk. For everything, there is unbelievable advocacy. Any little thing that I might touch, they come out of the woodwork and I'm the worst person in the world. If this were industry... we wouldn't be having this discussion. These are four- or five-year ongoing programs, with people out there in universities that depend on these programs. A lot of what's on that [list] is looked upon by the community as entitlement—'We've got a right to have this SPORE. We have a right to have this cancer center.' Programs within our own intramural side, there are FTEs there. The FTEs aren't going to go away. They are going to continue to be there as government employees. That's the bulk of the expense—it's salaries."

MATRISIAN: "Do we have metrics for success?"

NIEDERHUBER: "The metrics are peer review. Whether it's BSC review in intramural, or its peer review committees reviewing extramural activities. We need to apply those metrics rigorously, and we need in certain instances to make the peer review the priority. So it's quality science, and it's peer review—those are the two things that help us make those decisions."

Funding Opportunities:

RFA-RR-07-002National Gene Vector Biorepository and Coordinating Center. P40. Letters of Intent Receipt Date: June 11; Application Receipt Date: July 10. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RR-07-002.html. Inquiries: Daniel Rosenblum, 301-435-4051; rosenblumd@mail.nih.gov.

PAR-07-244: Avon-NCI Progress for Patients Awards for Early Phase Clinical Interventions and Biomarkers in Breast Cancer for P30 Cancer Center Support Grants. Letters of Intent Receipt Date: March 27, Oct. 15. Application Receipt Date: April 27, Nov. 15. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-244.html. Inquiries: Jaswant Bhorjee, 301-496-8531; bhorjeej@mail.nih.gov.

PAR-07-245: Avon-NCI Progress for Patients Awards for Early Phase Clinical Interventions and Biomarkers in Breast Cancer for P30 Cancer Center Support Grants. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-245.html. Inquiries: Igor Kuzmin, 301-496-8428; kuzmini@mail.nih.gov.

PAS-07-240: Technology Development for the Detection and Evaluation of Chemical and Biological Carcinogens. SBIR R43/R44. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAS-07-240.html. Inquiries: Phillip Daschner, 301-496-1951; pd93u@nih.gov.

PAS-07-241: Technology for the Detection and Characterization of Low Abundance Proteins, Peptides, or micro RNAs. SBIR R43/R44. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAS-07-241.html. Inquiries: J. Randy Knowlton, 301-435-5226; knowltoj@mail.nih.gov.

PAS-07-242: Technologies and Software to Support Integrative Cancer Biology Research. SBIR R43/R44. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAS-07-242.html. Inquiries: Jennifer Couch, 301-435-5226; couchj@mail.nih.gov.

PA-07-318: Occupational Safety and Health Research. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-318.html. Inquiries: Mukesh Verma, 301-594-7344; vermam@mail.nih.gov.

RFQ-NCI-70036-NG Special Studies Institutional Review Board NCI. Response Due Date: April 6. Full text: http://www.fbodaily.com/archive/2007/03-March/08-Mar-2007/FBO-01244431.htm. Inquiries: Malinda Holdcraft, holdcram@exchange.nih.gov.

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Business & Regulatory Report

Clinical Trials:

Satraplatin Improved PFS In Refractory Prostate Cancer, Phase III Trial Finds

Pharmion Corp. (NASDAQ:PHRM) of Princeton, N.J., and **GPC Biotech AG** (NASDAQ: GPCB) said final progression-free survival results for the double blind, randomized satraplatin phase III registrational trial, the SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial, are available.

The study is evaluating satraplatin plus prednisone versus placebo plus prednisone in 950 patients with hormone-refractory prostate cancer who have failed prior chemotherapy, the company said.

The data show that satraplatin reduces the risk of disease progression using the protocol-specified log-rank test, the company said. The hazard ratio of 0.6 (95 percent CI: 0.5-0.7, p<0.00001) was adjusted for nine pre-

(Continued to page 2)

Deals & Collaborations:

Access Pharmaceuticals To Buy Somanta; Products Include PB For CNS Cancers

Access Pharmaceuticals Inc. (Bulletin Board: ACCP) of Dallas and **Somanta Pharmaceuticals Inc.** (Bulletin Board: SMPM) of Irvine, Calif., said they have signed a letter of intent for Access to acquire Somanta.

Somanta has four anti-cancer compounds in development. Sodium Phenylbutyrate, or PB, is in phase II development. In NIH-sponsored trials, PB has demonstrated the greatest activity in CNS cancers, several of which are orphan indications such as glioblastoma multiforme, the companies said. Data suggest PB also may be an effective therapy for blood cancers and other solid tumors.

Other drug candidates include Alchemix, Prodrax and Angiolix. Alchemix, a pan-target inhibitor, is effective in tumor cells resistant to conventional chemotherapy by targeting and irreversibly binding to DNA, the companies said. Prodrax, a technology platform, is part of a family of prodrugs that enables compounds to remain inert until they reach the hypoxic region of tumors where they become toxic, thus targeting tumor cells which are difficult to kill. Angiolix, a humanized monoclonal antibody, induces cell death selectively to tumor blood vessels using a different mode of action than VEGF-oriented therapies. Somanta said it has prepared clinical development plans for all preclinical projects.

Somanta preferred and common shareholders will receive an aggregate of 1.5 million shares of Access common shares, which would represent

(Continued to page 5)

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GPC Biotech Begins Expanded Access For Satraplatin In U.S.

(Continued from page 1)

specified prognostic factors. Using a more conservative analysis, which adjusted only for the three pre-specified stratification factors, the hazard ratio is 0.67 (95 percent CI: 0.57-0.77, p=0.0000003). The hazard ratio numbers correspond to a reduction in relative risk of disease progression of 40 percent and 33 percent, respectively, the companies said.

In accordance with the recommendation of the independent Data Monitoring Board for the SPARC trial, patients who have not progressed will continue to be treated and all will be followed for overall survival.

"As there are no approved therapies for hormone-refractory prostate cancer which has failed on one chemotherapy regimen, satraplatin could address a mounting area of unmet medical need," said Daniel Petrylak, associate professor of medicine at Columbia University College of Physicians & Surgeons, director of the Genitourinary Oncology Program at New York-Presbyterian Hospital/Columbia, and a principal investigator. "The data show statistically significant results in progression-free survival in favor of treatment with satraplatin. The results are consistent no matter what the prior chemotherapy treatment, including Taxotere."

PFS at the median demonstrated a 14 percent improvement with satraplatin plus prednisone (11.1 weeks) compared to prednisone plus placebo (9.7 weeks), the companies said. The improvement in PFS with satraplatin increased over time. PFS at the 75th percentile showed an 81 percent improvement in the satraplatin arm (34.6 weeks) versus in the placebo arm (19.1 weeks). At six months, 30 percent in the satraplatin arm had not progressed, compared to 17 percent in the control arm. At twelve months, 16 percent who received satraplatin had not progressed, compared to 7 percent in the control arm, the companies said.

The median number of cycles was four for the satraplatin group compared to two for the control group, the companies said. 40 percent treated with satraplatin received five or more cycles of treatment compared to 20 percent in the control arm.

The improvement in PFS in the satraplatin arm was not affected by the type of prior chemotherapy; importantly, the improvement was similar with Taxotere (docetaxel) treatment, as well as other types of chemotherapy treatments, the company said. Fifty-one percent had been treated with Taxotere. The hazard ratio for treatment with Taxotere was 0.67 (95 percent CI: 0.54-0.83; p=0.0006, adjusted for the pre-specified stratification factors) and therefore numerically equivalent to the entire study population.

GPC Biotech said it has begun the Satraplatin Expanded Rapid Access protocol in the U.S. Expanded Access Programs, to give patients investigational drugs for serious or life-threatening diseases or conditions for which there are no adequate therapies. Under the SPERA program, satraplatin will be provided free of charge.

GPC Biotech AG said it has completed the rolling submission of a New Drug Application to FDA for satraplatin for androgen independent hormone refractory prostate cancer, which failed chemotherapy. The third and final portion of the NDA—the clinical section, is based on data from the SPARC phase III registrational trial. The trial, which enrolled 950 patients, showed highly statistically significant results for prolonging progression-free survival, the company said.

* * *

Bayer HealthCare of Leverkusen, Germany, and West Haven, Conn., said it has decided to end three clinical studies of Trasylol (aprotinin injection) on transfusion requirements and blood loss for elective spinal fusion surgery, pneumonectomy or esophagectomy for cancer, and radical or total cystectomy in bladder cancer.

The Trasylol labeling that was approved in the U.S. and is in the approval process in the European Union and other countries, includes a recommendation that in order to manage possible anaphylactic reactions, the

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drug should be administered only in surgical settings where cardiopulmonary bypass can be rapidly initiated, the company said.

Bayer said its decision to discontinue the trials was not made based on any safety findings in the non-CABG studies. In November, an independent data monitoring committee reviewed safety data for the first 120 patients randomized and based on its review of the safety data, the committee concluded, "the three clinical trials could continue as planned without modification."

"We believe that Trasylol can continue to provide important benefits for CABG surgery patients and, therefore, fills an important role for their cardiac surgeons," said Paul Mac Carthy, vice president, medical affairs Bayer Pharmaceuticals Corp.

Trasylol is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion for cardiopulmonary bypass in the course of coronary artery bypass graft surgery where there is an increased risk for blood loss and blood transfusion, the company said. The effects of Trasylol use in CPB involve a reduction in systemic inflammatory response to surgery, which translates into a decreased need for allogeneic blood transfusions, reduced bleeding and decreased mediastinal re-exploration for bleeding.

Trasylol administration may cause fatal anaphylactic or anaphylactoid reactions, the company said. Fatal reactions have occurred with an initial test dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial test dose was tolerated. The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to Trasylol administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. Trasylol should be administered only in operative settings where cardio-pulmonary bypass can be rapidly initiated. The benefit of Trasylol in primary CABG surgery should be weighed against the risk of anaphylaxis associated with any subsequent exposure to aprotinin, the company said.

* * *

Biomira Inc. (NASDAQ:BIOM) (TSX: BRA) of Edmonton said it has begun enrollment in the global phase III START (Stimulating Targeted Antigenic Responses To NSCLC) trial, assessing the efficacy and safety of Stimuvax (BLP25 liposome vaccine) in unresectable stage III non-small cell lung cancer.

The trial is being conducted by Merck KGaA of Darmstadt, Germany, and its U.S. affiliate EMD Pharmaceuticals Inc. under the terms of collaboration between Biomira and Merck. Under the agreement, Biomira would receive a milestone payment from Merck upon enrollment of the first patient.

The 1,300-patient randomized, double blind, placebo-controlled study is designed with the scientific advice from the European Medicines Agency and was agreed upon with FDA through a Special Protocol Assessment, the company said.

"Patients with advanced lung cancer are in need of new therapies that effectively target cancer cells while providing better safety and tolerability," said Frances Shepherd, director of medical oncology at Princess Margaret Hospital and lead investigator. "Therapeutic vaccines such as Stimuvax may help the immune system identify and destroy cancer cells without targeting normal, healthy cells."

Stimuvax induces an immune response to cancer cells that express MUC1, a protein antigen that is over expressed in cancers such as lung, breast and colorectal cancer, the company said.

A randomized phase IIb trial was conducted in 171 patients with stage IIIb and IV NSCLC with response or stable disease after first line therapy, the company said. While the overall study results were not statistically significant, in the randomization stratum with stage IIIb locoregional disease, Stimuvax showed a median survival of 30.6 months versus 13.3 months in the control group—an improvement of 17.3 months. Side effects were limited to mild-to-moderate flu-like symptoms, GI disturbances, and mild injection site reactions.

* * *

GlaxoSmithKline of Barcelona said it has begun an international phase III trial of Tykerb (lapatinib) for squamous cell carcinoma of the head and neck.

The adjuvant study will compare the effectiveness of oral lapatinib versus placebo given in high-risk patients following surgery, the company said.

"The trial represents another step towards understanding the role of lapatinib in other tumor types beyond breast cancer," said Jean Bourhis, head of the Department of Radiation-Oncology, Institute Gustave Roussy, France, and principal investigator. "There is a significant group who are at high-risk of disease recurrence following surgery, and they need treatments that can be combined with standard chemoradiation therapy."

The trial seeks to enroll 680 high-risk patients who will receive, within four to seven weeks after surgery,

either lapatinib (1500 mg) or placebo tablets once-daily with radiotherapy and cisplatin for seven weeks. They would continue with either lapatinib or placebo treatment for one year. The principal objective is length of time without disease symptoms, and overall survival with other clinical factors also to be measured.

Results from a phase I dose-escalation study of the drug—doses ranged from 500 mg to 1500 mg—plus chemoradiation in 31 head and neck cancer patients, identified 1500 mg of lapatinib taken once-daily with chemotherapy and radiotherapy as the optimal dose for the combination. Also, 89 percent of patients had a tumor response to the combination treatment, the company said. Common side effects were mouth ulcers (87 percent), radiation skin injury (65 percent), nausea (61 percent), swallowing difficulties (52 percent) and vomiting (52 percent).

Lapatinib blocks the activation of two receptors, EGFR and HER2, associated with increased growth and development of this type of head and neck tumor, the company said.

* * *

Rigel Pharmaceuticals Inc. (NASDAQ:RIGL) of South San Francisco said its partner **Merck Serono** has begun a phase I study evaluating the safety and tolerability of R763, an orally available multi-Aurora kinase inhibitor, for hematological malignancies.

The open-label, dose-escalation study would consist of two different dosing regimens, the company said. Fifty-four subjects with acute or chronic myeloid leukemia or myelodysplastic syndrome will be enrolled in each regimen and dosed orally with R763.

R763, also known as AS703569, has exhibited anti-tumor activity against a broad panel of cancer cell lines, the company said. Leukemia cells, lung, breast, pancreas, ovarian and cervical carcinoma cells, and histiocytic cells are particularly sensitive to R763.

* * *

Threshold Pharmaceuticals Inc. (NASDAQ: THLD) of Redwood City, Calif., said it has initiated enrollment in a phase II trial evaluating the dosing, safety and activity of glufosfamide for platinum-resistant ovarian cancer.

"There are very few drugs that will effectively treat platinum-resistant disease," said David Alberts, director of the Arizona Cancer Center, University of Arizona, and clinical investigator for the trial. "We are extremely interested in the therapy as it may provide an additional treatment option."

The 45-patient trial will evaluate two dosing schedules of glufosfamide, a once weekly schedule and a schedule of every three weeks, the company said. The study would explore the administration of slightly higher aggregate doses utilizing the weekly schedule as compared to every three week dosing. Treatment may consist of up to six 21-day cycles.

In addition to safety, the trial is investigating the efficacy of the treatment as determined by response rate, duration of response and progression-free survival based on changes in the serum tumor marker level CA-125 and based on tumor assessments and overall survival, the company said.

* * *

VION Pharmaceuticals Inc. (NASDAQ: VION) of New Haven, Conn., said it would proceed to the second stage of accrual in the phase II trial of Cloretazine (VNP40101M) in previously untreated patients at least 60 years of age with de novo poor-risk acute myelogenous leukemia.

The CLI-043 trial is evaluating the product as a single agent in the following additional risk factors: unfavorable cytogenetics; an ECOG performance status of 2 or greater; or a co-morbid condition that precludes receiving cytotoxic therapy with cytarabine and an anthracycline, the company said. Subjects over the age of 70 with de novo AML who do not have favorable cytogenetics are also eligible. The primary endpoint is the complete response rate. Secondary endpoints include overall survival, disease-free survival and progression-free survival. The trial would continue to a total accrual of 85 patients if there have been at least nine responses in the first 42.

Cloretazine, an alkylating agent, also is being evaluated in a phase III trial in combination with cytarabine in relapsed acute myelogenous leukemia, the company said. A trial of Cloretazine as a single agent in small cell lung cancer is also underway.

* * *

YM BioSciences Inc. (AMEX:YMI) of Mississauga, Ontario, said the independent Data Safety Monitoring Board has completed its third planned safety and efficacy analysis of the phase III trial of tesmilifene for metastatic or recurrent breast cancer.

The DSMB advised the company to stop the trial based on an interim analysis of 351 events, indicating it is very unlikely significant differences in overall survival will be shown between treatment arms as the data mature, the company said.

YM BioSciences said the trial was not stopped due to safety concerns relating to the product and it would submit data to an appropriate medical meeting after the company completes its review.

"We extend high praise to YM BioSciences," said Joyce O'Shaughnessy, breast cancer researcher, oncologist and the designated safety officer of the DSMB, and Lee-Jen Wei, chairman and statistician of the DEC Trial Data Safety Monitoring Board. "The DSMB is of the opinion that the trial was well-conducted and well-executed."

The trial compared survival of treatment with tesmilifene combined with epirubicin/cyclophosphamide to epirubicin/cyclophosphamide alone for rapidly progressing metastatic and/or recurrent breast cancer, the company said. The study, which completed enrollment of 723 patients in September 2005, was the subject of a Special Protocol Assessment and a Fast-Track designation for advanced breast cancer by FDA.

The trial was conducted according to a sequential design that permitted a number of planned interim analyses until one of two specific statistical conditions was satisfied, the company said. At each analysis, survival for the tesmilifene-containing treatment arm and the control arm was calculated and then reviewed by the DSMB. The trial was to be concluded if either the tesmilifene-containing treatment arm was superior to the control by a specified margin or it was determined that such evidence was not going to be found. After the third planned analysis, the DSMB concluded that the trial was highly unlikely to achieve a pre-specified survival benefit.

Tesmilifene is a small molecule that selectively targets multiple-drug resistant tumor cells, sensitizing them to chemotherapy, the company said.

Deals & Collaborations:

Mayo, Biodesign Institute To Collaborate On Vaccine

(Continued from page 1)

13 percent of the combined company, the companies said.

* * *

Biodesign Institute at Arizona State University of Tempe and **Mayo Clinic** are collaborating on a cancer vaccine.

Research by Stephen Johnston, director of the Center for Innovations in Medicine, Biodesign Institute, suggests common themes in the protein signatures that tumors produce, the groups said.

"This idea of identifying signatures unique to cancer suggests the possibility of preventive vaccines," said Laurence Miller, director of research and deputy director of the Mayo Clinic Cancer Center. "The approach could avoid many of the problems associated with trying to treat an established tumor."

The project is the first initiative undertaken under an umbrella partnership called the Mayo Clinic/ASU Center for Cancer-related Convergence, Cooperation and Collaboration.

* * *

Champions Biotechnology Inc. (BULLETIN BOARD: CSBR) of Arlington,Va., said it acquired patent rights for two Benzoylphenylurea sulfur analog compounds for prostate and pancreatic cancer cell lines.

The antimitotic inhibitors target MAPT (Microtubule-Associated Protein Tau) deficient tumors, a feature of solid tumors, have performed better than Docetaxel (Taxotere) in xenograft models of pancreatic cancer, the company said.

In exchange for 550,000 restricted shares of its common stock, the company said it was assigned all the rights in the U.S. and in foreign countries to the applications for the inhibitors developed at Johns Hopkins University by their inventors Saeed Khan, Gurulingappa Hallur, Manuel Hidalgo and Antonio Jimeno.

* * *

Debiopharm Group of Lausanne, Switzerland, said it has signed an exclusive research and development and commercialization agreement with **Kirin Brewery Co. Ltd.** for Debio-0719, an inhibitor of lysophosphatidic acid, for early preclinical development of local as well as metastatic cancer.

Under the agreement, Debiopharm said it would manage and fund the development of the agent before licensing to sales and marketing partners in all territories outside of Asia, where Kirin will maintain development and commercialization rights. Kirin would receive milestone payments, as well as royalties based on the Debiopharm revenues from worldwide sales.

Debio-0719, formerly named Ki16425/Ki16198, was discovered by Kirin in a screen for small molecule inhibitors of LPA receptors, the company said.

* * *

GW Pharmaceuticals plc (AIM: GWP) of London and Princeton, N.J., and **Otsuka Pharmaceutical Co. Ltd.**, of Tokyo said they have signed an exclusive license and development agreement for Otsuka to develop and market the GW product Sativex in the U.S.

The companies also said they are in discussions about a cannabinoid research collaboration in central nervous system disorders and cancer treatment.

Financial terms include total milestone payments

to GW of up to $273 million as well as a long term commercial supply price and royalty, the companies said. Otsuka would pay GW a signature fee of $18 million. Otsuka would bear the costs of all U.S. development activities for Sativex in cancer pain, additional indications, and future formulations.

Last year, FDA permitted the drug to enter directly into late stage development in the U.S. for advanced cancer pain not relieved by opioid medications, the company said.

"A phase III study showed that Sativex achieved a statistically significant improvement in pain relief in terminally ill cancer patients, said Russell Portenoy, chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center and principal investigator of the first planned U.S. Sativex study. "There are 3.9 million cancer patients in the U.S., of which 2.5 million suffer pain. Although opioids are highly effective analgesics, studies suggest that as many as one-third of patients with pain due to advanced cancer do not obtain adequate relief and new treatments are needed."

Under the proposed cannabinoid research collaboration, Otsuka would fund the evaluation of a range of cannabinoids as drug candidates within the field of CNS and cancer treatment, the companies said. Products selected for commercialization would be the subjects of a license from GW. Under the license, Otsuka would fund the global development of selected products and GW would receive commercially reasonable financial terms, the companies said.

* * *

ImClone Systems Inc. (NASDAQ: IMCL) of New York said it has opted out of its development agreement with **UCB S.A.** for CDP-791 to develop IMC-1121B, the ImClone Systems proprietary antibody product candidate targeting vascular endothelial growth factor receptor-2.

Data from an ongoing phase I study of IMC-1121B of 23 patients with advanced cancer, found that two have experienced confirmed partial responses and seven others had stable disease for at least six months, with the most severe adverse events--Grade 3—reported anemia, increased blood amylase, headache, hypertension, proteinuria and vomiting, the company said.

Under the agreement with UCB, ImClone Systems said it has the right to receive a royalty on CDP-791 sales, should the antibody be commercialized, and UCB retains freedom to operate rights for CDP-791 and certain of the ImClone Systems intellectual property pertaining to VEGFr-2.

* * *

Walter and Eliza Hall Institute of Medical Research of Melbourne, Australia, said it has entered into an exclusive global collaboration agreement with **Genentech Inc.** to discover, develop, manufacture and commercialize cancer therapeutics.

Under the agreement, Genentech would make upfront and research program payments, the institute said. The agreement centers on regulating the activity of proteins that control the normal and healthy process of apoptosis, the institute said.

"Every day, about 10 billion of our old and damaged cells die and are replaced by about 10 billion new cells," Jerry Adams, cancer researcher at WEHI. "Sometimes the process of apoptosis goes awry and inadvertently protects damaged cells from dying. When that happens, the rogue cells may multiply uncontrollably and give rise to tumors. Our research at WEHI has produced an encouraging series of small molecule drug candidates that stimulate apoptosis and aid cancer treatment."

The research teams at WEHI also include those led by Peter Colman, Suzanne Cory, Andreas Strasser and David Huang, Keith Watson, Ian Street and Jonathan Baell, the institute said.

Product Approvals & Applications:

Fosodine Receives Orphan Status In EU For Lymphoma

BioCryst Pharmaceuticals Inc. (NASDAQ: BCRX) of Birmingham, Ala., said the Committee for Orphan Medicinal Products of the European Medicines Agency has granted Orphan Drug status to Fosodine for cutaneous T-cell lymphoma.

This is the second indication for which the EMEA has granted Orphan Drug status to the agent following regulatory submissions by Mundipharma, the BioCryst European Fodosine partner, the company said. Last year, the EMEA granted Orphan Drug designation for T-cell acute lymphoblastic leukemia.

In 2005, FDA granted Orphan Drug designation to Fodosine for three indications: T-cell non- Hodgkin's lymphoma, including CTCL; CLL and related leukemias including T-cell prolymphocytic leukemia, adult T-cell leukemia, and hairy cell leukemia; and for B-ALL, the company said. The FDA has granted Fast-Track status to develop the drug for elapsed or refractory T-cell leukemia.

Fodosine is a transition-state analog inhibitor of the target enzyme purine nucleoside phosphorylase.

BioCryst said it entered into a strategic collaboration

with Mundipharma International Holdings Ltd., last year to develop and commercialize Fodosine for oncologic use in markets across Europe, Asia, and Australia.

* * *

Exelixis Inc. (NASDAQ:EXEL) of South San Francisco said it has submitted an investigational New Drug Application to FDA for XL418, an anticancer compound.

XL418 is an inhibitor of protein kinase B and S6 Kinase, components of the phosphoinosotide-3 kinase signaling pathway, the company said. Activation of the kinases promotes cell growth, survival and resistance to chemotherapy and radiotherapy in tumors.

* * *

Genta Inc. (Nasdaq: GNTA) of Berkeley Heights, N.J., said it would appeal the non-approvable notice from the FDA Office of Oncology Drug Products of its New Drug Application for Genasense (oblimersen sodium) Injection plus chemotherapy for chronic lymphocytic leukemia.

The appeal will be filed pursuant to the Formal Dispute Resolution process that exists within the FDA Center for Drug Evaluation and Research, the company said. Genta said it filed notice reserving the rights to appeal in December and would complete the filing this quarter.

* * *

Ikonisys Inc. of New Haven, Conn., said it has received FDA clearance to market its oncoFISH bladder diagnostic application in the U.S for bladder cancer.

The diagnostic application works with the Ikonisys proprietary robotic digital microscopy platform, which enables automated testing of cells in urine specimens, the company said.

* * *

Pharmion Corp. (NASDAQ:PHRM) of Boulder, Colo., said it has received approval from FDA for its new drug application supplement to add intravenous use as a route of administration to the instructions in the approved prescribing information for Vidaza, its DNA demethylating agent.

Vidaza may now be administered intravenously over a period of 10 to 40 minutes in a clinic or hospital setting, the company said.

With IV administration, the dosing for the agent remains the same as the approved subcutaneous administration at 75 mg/m2 daily, for seven days, every four weeks, the company said.

The approval was based on data from the original NDA, an uncontrolled phase II study and a bioavailability study, as well as data from an in-use stability and compatibility study and a pharmacokinetic modeling study completed by Pharmion, the company said.

Vidaza, which is part of a class of drugs called demethylation agents, is approved for Myelodysplastic Syndromes, the company said. FDA also approved the drug for all five MDS subtypes, including refractory anemia or refractory anemia with ringed sideroblasts if accompanied by neutropenia or thrombocytopenia or requiring transfusions; refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

In another development, **Pharmion Corp.** said it submitted a marketing authorization application with the European Medicines Agency for Thalidomide Pharmion in untreated multiple myeloma in the European Union.

The submission includes details of the Pharmion Risk Management Programme as a condition of supply following the approval of Thalidomide Pharmion, the company said.

The application is based upon a clinical data package comprised of four studies in more than 1400 patients, the company said. The studies include IFM 99-06, a three-arm study conducted by IFM, which demonstrated the superiority of melphalan/prednisone plus Thalidomide over standard therapy of melphalan/prednisone or a combination of chemotherapies (vincristine/adriamycin/dexamethasone, or VAD) followed by melphalan and transplantation (MEL 100) newly diagnosed elderly multiple myeloma.

The study randomized 444 patients to one of the three treatment arms. Following an interim analysis, recruitment was stopped on the recommendation of the Data Safety Monitoring Board, the company said. The median overall survival in the MPT arm was 53.6 months, compared to 32.2 and 38.6 months, respectively, for the MP and MEL 100 arms, the company said. Thalidomide treatment was well-tolerated by the majority, the company said. The Thalidomide combination was associated with more venous thrombosis and pulmonary embolism. Patients taking thalidomide were also at greater risk of peripheral neuropathy, neutropenia and constipation.

A study conducted by the Italian research group Gruppo Italiano Malattie Ematologiche dell'Adulto also demonstrated the superiority of melphalan/prednisone plus Thalidomide compared to melphalan/prednisone alone, the company said. In the randomized study of MPT versus MP alone in 255 elderly patients, MPT had

a superior response rate and a higher two-year event-free survival rate (54 percent versus 27 percent), the company said.

MM-003, a phase III, multi-national, placebo controlled, randomized study of 470 patients, sponsored by Celgene Corp. and supported by Pharmion, compared Thalidomide plus dexamethasone versus dexamethasone and placebo in the newly-diagnosed, the company said. In 2005, an Independent Data Monitoring Committee reviewed the data as part of a pre-specified interim analysis and concluded that the study should be stopped as it had reached its efficacy stopping rule of $p<0.0015$ for the primary endpoint of time to disease progression.

At the final analysis there was also a significant ($p=0.001$) improvement in response rate of Thalidomide plus dexamethasone of 69.4 percent, compared to dexamethasone and placebo of 51.1 percent. Of the Thalidomide treated patients, 43.8 percent experienced very good or complete response compared to 15.8 percent in the placebo arm ($p<0.0001$). Time to disease progression was 97.7 weeks versus 28.3 weeks, the company said.

A 200-patient phase III study conducted by the Eastern Cooperative Oncology Group compared Thalidomide plus dexamethasone compared to dexamethasone alone, the company said. The study demonstrated a statistically significant difference in response rates of 61.6 percent versus 39.6 percent ($p=0.001$) at four months with Thalidomide plus dexamethasone compared to dexamethasone alone, the company said.

Pharmion said it is seeking approval for the following indications: Thalidomide Pharmion in combination with melphalan and prednisone for untreated multiple myeloma aged 65 years or older or ineligible for high dose chemotherapy and Thalidomide Pharmion in combination with dexamethasone for induction therapy prior to high dose chemotherapy and bone marrow transplant, for untreated multiple myeloma. Thalidomide Pharmion must be prescribed and dispensed through the Pharmion Risk Management Programme.

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Pfizer Inc of New York said FDA has approved new labeling of Sutent (sunitinib malate), which includes first-line treatment of advanced renal cell carcinoma.

The drug was approved in January 2006 for advanced kidney cancer under the accelerated approval provision, based on partial response rates and duration of response. With the new labeling, the accelerated approval has been converted to regular approval.

In a large, randomized phase III trial, 750 treatment-naive patients with metastatic RCC received either Sutent or the comparator interferon-alfa, the standard of care. Findings include: Treatment with Sutent achieved a median progression free survival of 11 months--more than double the 5-month median progression free survival observed with IFN infinity; Treatment with the agent resulted in a 5-fold higher objective response rate compared with IFN infinity in first-line RCC treatment--27.5 percent vs. 5.3 percent; Overall, Sutent was generally well tolerated with fewer discontinuations from treatment than IFN infinity. Fewer discontinued the medicine because of treatment-emergent non-fatal adverse events (9 percent vs. 12 percent), the company said.

"To have such a high percent respond to the treatment is remarkable and a sign of the significant benefit Sutent may bring to patients fighting this deadly cancer," said Robert Motzer, lead investigator of the trial and attending physician at Memorial Sloan-Kettering Cancer Center.

In the trial, the most common treatment-related adverse events of any grade were fatigue, diarrhea, nausea, altered taste, mucositis/stomatitis, hypertension, anorexia and bleeding.

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Pharmacyclics Inc. (NASDAQ:PCYC) of Sunnyvale, Calif., said it received a refuse to file letter from FDA for its new drug application for Xcytrin (motexafin gadolinium) Injection for non-small cell lung cancer with brain metastases.

In the letter, FDA stated the application is not sufficiently complete to permit a substantive review based on clinical studies that failed to demonstrate statistically significant differences between treatment arms in the primary endpoints, the company said.

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Poniard Pharmaceuticals Inc. (NASDAQ: PARD) of South San Francisco said it has filed an Investigational New Drug application with FDA for an oral formulation of picoplatin.

In preclinical studies, the drug has demonstrated up to 40 percent oral bioavailability and a higher therapeutic index and efficacy against platinum-sensitive and -resistant tumor variants than marketed platinum-based therapeutics, the company said.

Poniard said it received Orphan Drug designation in 2005 for the treatment in SCLC and entered into a Special Protocol Assessment agreement with FDA in January 2007 for the SPEAR trial.