THE CANCER LETTER

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

Amgen Announces Cochrane Findings: ESAs Increase Risk Of On-Study Death

By Paul Goldberg

Something was missing from a press release announcing the Cochrane Collaboration's preliminary result from a pooled analysis of ESA studies.

That something was comment from the investigators who conducted the patient-level meta-analysis.

The only quote belonged to Roger Perlmutter, executive vice president for Research and Development at Amgen Inc., one of the three companies that provided the randomized trial data for the pooled analysis.

It was, in fact, Amgen that issued the press release about the Cochrane findings.

The pooling project was funded by the German government and accepted no pharmaceutical funding. However, companies and institutions that submitted the data were apparently entitled to receive updates. Johnson

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In the Cancer Centers:

Adams-Campbell Joins Lombardi Center To Lead Community-Based Research

GEORGETOWN UNIVERSITY's Lombardi Comprehensive Cancer Center has recruited **Lucile Adams-Campbell** as associate director for Minority Health and Health Disparities Research. Her position, newly created by Lombardi Director **Louis Weiner**, will focus primarily on community outreach and community-based participatory research in Washington, D.C. Adams-Campbell, director of the Howard University Cancer Center for the past 13 years, is an internationally recognized expert on health disparities.

"Lucile's leadership in the District of Columbia and expertise in conducting health disparities research and interventions are unparalleled. I am thrilled to be able to welcome her to Georgetown and to Lombardi," Weiner said.

Adams-Campbell is an epidemiologist who specializes in community health research, interventions, and outreach. She played a leading role in bringing the Boston University Black Women's Health Study—the largest study of African-American women—to the District. Lombardi will soon join the 12-year national study under Adams-Campbell's leadership.

The District has high rates of obesity, diabetes, cancer, cancer death, and heart disease, all of which may be affected by diet and exercise, Adams-Campbell said. Through community-based interventions, she hopes

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Amgen Press Release Spins Cochrane Findings On ESAs

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& Johnson and Roche also submitted data.

Amgen officials announced that they had received a "preliminary summary" of the findings. "The Cochrane Collaboration's analysis corroborates important information already reflected in the recently revised ESA labeling, which physicians and patients should consider when making individual treatment decisions," Perlmutter said in the press release Sept. 30.

The study analyzed data from 53 randomized studies that enrolled 13,933 cancer patients. According to Amgen's press release, "none of these studies utilized ESAs according to current label guidance."

Sources familiar with the situation said the decision to release the data was made unilaterally by Amgen. "We don't understand why they did that," said a source who asked not to be identified by name because of not being authorized to discuss the matter. "By the time they had sent it to us, there was no chance to correct it or say that maybe we should word a few things differently."

For example, Amgen's assertion that none of the pooled studies was consistent with current labeling is technically true, but misleading, observers say. "Most of the studies adhered to whatever guidelines applied at the time, and some of them were more conservative than the current guidelines," a source said.

Also, technically, the study couldn't be identified as the work of the Cochrane Collaboration, an international group that performs meta-analysis of therapies. The project is performed by an international independent committee and was to be vetted by Cochrane. This has not yet occurred, sources said. Nonetheless, the protocol for pooling the studies is posted on the Cochrane website: www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007303/frame.html

Last year, Amgen faced criticism for failure to announce the results of a Danish head-and-neck cancer study that showed an increase of locoregional disease progression in patients receiving Amgen's ESA Aranesp (darbepoetin) (The Cancer Letter, Feb. 16, 2007).

However, the situation was very different, because the Danish study was eagerly awaited original research. The Cochrane study is a meta-analysis, which can be only confirmatory.

FDA doesn't make approval decisions based on meta-analyses, and even though it would have made sense to inform the agency, which Amgen has done, an update of this sort would have likely been kept confidential.

Last week, FDA's MedWatch announced that the agency is investigating reports of an excess in deaths among patients receiving epoetin alfa, an ESA, in a German study investigating the agent in the treatment of acute ischemic stroke. But that alert was based on a clinical trial, not a meta-analysis.

Moreover, this isn't the first meta-analysis to show a negative result for the ESAs. Earlier this year, the Journal of the American Medical Association published a study-level meta-analysis that showed statistically significant increases in mortality and venous thromboembolism in patients who received ESAs.

Considering that the oncology indication has been severely restricted, FDA would have had no reason to act. Securities laws require companies to release material information that may affect stock price.

While these regulations would likely apply to a negative outcome of a clinical study of an aggressively marketed product, it's not at all certain that they would extend to a statistical analysis of a drug that has been closely watched and severely restricted by FDA.

Why did Amgen release the findings?

"Amgen announced the top-line findings and their submission to regulators in an effort to provide the most updated information to physicians and patients," said Kelley Davenport, a company spokesman.

Howard Ozer, chief of hematology and oncology and Eson chair and professor of medicine at the University of Oklahoma Cancer Center, said the company may have been eager to control the story and present it as "old

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news" for the investment community.

"I don't see anything more significant than what the FDA has already pointed out on the label," said Ozer, who isn't involved in the meta-analysis. "I don't think they are any longer afraid of the FDA or doctors. "I think they are afraid of Wall Street. They may have an analyst meeting coming up, or something like that."

The meta-analysis shows an increase in on-study deaths among patients receiving ESAs, Amgen said in the press release. The hazard ratio for that finding was 1.17, and the 95 percent confidence interval was 1.06 to 1.30.

This statistically significant finding suggests that patients receiving ESAs were more likely to die due to acute events than patients in the control groups. Deaths occurring later might point to tumor promotion, but this information wasn't included in the press release.

The hazard ratio for the overall risk of death for patients on the ESA treatment arms was 1.06 (95% CI 1.00-1.12), just short of statistical significance. In a Cochrane analysis published in 2006 and cited in the ESA label, the overall survival result was HR: 1.08 (95% CI 0.99-1.18).

"I don't see any more significance than what FDA has already pointed out, or what eight [negative studies on the ESA label] pointed out," Ozer said. "It's confirmatory, and if confidence intervals get narrower and narrower, that helps you say these are real data."

An analysis of ESA use in patients undergoing chemotherapy (i.e., excluding patients treated for anemia of cancer) showed that ESAs increased on-study deaths HR: 1.10 (95% CI 0.98-1.24) and the overall survival HR: 1.04 (95% CI 0.97-1.11) compared to controls. This analysis was based on 38 studies with 10,441 patients.

"While neither of these [chemotherapy-induced anemia] results is statistically significant, they do not exclude the potential for adverse outcomes when ESAs are used according to the current label," Amgen acknowledged in the press release.

The release of "snippets of data" in a press release that quotes an Amgen executive and doesn't quote any of the investigators raises more questions than it answers, said Charles Bennett, a hematologist-oncologist at Northwestern University's Robert H. Lurie Comprehensive Cancer Center and principal investigator of the NCI-funded Research on Adverse Drug Events and Reports project.

Bennett is the lead author of an earlier meta-analysis and a former Cochrane participant who took part in the group's previous two ESA studies (The Cancer Letter, Feb. 29).

"Are these data based on short-term or long-term results?" Bennett asked. "Which studies are included? Which studies are excluded? Do these results reflect the study protocol listed on the Cochrane website? Which specific studies are included in the analysis? What are the risk ratios for patients with head and neck cancer? For breast cancer? For non-small cell lung cancer? For cervical cancer? For lymphoma—i.e, for cancers where safety signals were identified previously. My understanding is that the benefit of an individual patient level data analysis is that these kinds of analyses can be conducted. Yet. I haven't seen such information."

The rush to release study results can preclude orderly peer review and publication, critics say. But, like it or not, such pressure is a fact of life in today's medicine, said Arthur Caplan, director of the University of Pennsylvania Center for Bioethics.

"Once data is 'sent around,' it is going to be out there," Caplan said. "Firing up your 'spin' is, I guess, to be expected. It would be right to share the release with the PIs in the study in advance to let them know it is going to be out there, but despite the fact that press release science undermines the more orderly release and interpretation of data it is the world of biomedicine that we now live in."

The Cochrane Collaboration has published two papers monitoring the efficacy and safety of ESAs.

As recently as this spring, the sponsors of ESAs pointed to an earlier Cochrane meta-analysis as evidence of acceptable safety and efficacy of these products. Cochrane's studies were cited repeatedly in venues that included conference calls with Wall Street analysts, the meetings of the FDA Oncologic Drugs Advisory Committee.

Cochrane's results were also used to argue that another meta-analysis, conducted by Bennett and published in JAMA earlier this year, was unreliable.

When Bennett's paper was published in the Feb. 27 issue of the medical journal, Johnson & Johnson, the sponsor of the ESA Procrit (erythropoietin) said in a statement that the paper's conclusions "do not provide an accurate reflection of the safety profile of ESAs when used for the treatment of chemotherapy-induced anemia."

The company noted that, along with the other ESA manufacturers, it provided individual patient-level data to the Cochrane Collaboration to support a combined analysis of all available controlled studies with ESAs in oncology patients.

"This project will be the largest combined analysis of ESA safety data ever undertaken," J&J said in a

press release Feb. 26. "It will create a database of more than 15,000 patients treated in various clinical studies, which should inform the benefit:risk profile of ESAs by identifying patient subgroups that would benefit from further study."

The effort was also cited at the March 12-13 meeting of the FDA Oncologic Drugs Advisory Committee during its two-day session that considered placing further restrictions on the ESA label.

Addressing ODAC at a public hearing, Julia Bohlius, a researcher at the Cochrane Hematological Malignancies Group at the University of Cologne, said that the companies that submitted the data for patient-level meta-analysis would be allowed to review the data, but would have no control over its presentation.

"All companies and independent investigators who submitted data are members of the advisory board of this project," Bohlius said at the meeting. "The advisory board has the right to review the protocol and the results of the analysis and to make suggestions, however, the advisory board is not authorized to make any decisions regarding the analysis or publications."

Contacted by The Cancer Letter, Bohlius referred questions to Andreas Engert, principal investigator on the study. Engert didn't respond to an email by deadline.

Sources said the meta-analysis results have been submitted as a late-breaking abstract to the annual meeting of the American Society of Hematology.

Utilization of ESAs, once the single biggest-selling product in oncology, has dropped by about half and sales slid by a third since bad news about the agents started to emerge in early 2007. The current FDA label states that the drug is not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (The Cancer Letter, Aug. 8).

The sponsors are working with the FDA to finalize the Risk Evaluation and Management Strategy for these products.

Capitol Hill:

Bush Signs CR To Fund NIH At FY08 Level Through March 6

By Kirsten Boyd Goldberg

President Bush on Sept. 30 signed into law a $630 billion continuing resolution (Public Law 110-329) that would fund at current levels the budgets of most federal agencies until March 6.

The bill, which the House passed on Sept. 24 and the Senate approved on Sept. 27, includes $29.5 billion for NIH, the same amount as fiscal 2008. The supplemental funding that NIH received earlier this year wasn't included in the base.

Congress hadn't approved any of the 12 annual appropriations bills when the new fiscal year began on Oct. 1.

In a guidance to grantees on Oct. 2, NIH said that until the final FY 2009 appropriation is enacted, it would issue non-competing research grant awards at a level below that indicated on the most recent Notice of Award (generally up to 90 percent of the previously committed level).

"NIH will consider upward adjustments to these levels after the final appropriation is enacted, but expects institutions to monitor their expenditures carefully during this period," the statement said.

The institutes plan to post further instructions to grantees at http://grants1.nih.gov/grants/financial/index.htm.

"Unless the incoming 111th Congress eventually provides FY 2009 increases for NIH, NSF, and other science agencies, the federal research investment in 2009 could decline for the fifth year in a row in real (inflation-adjusted) terms," according to an analyses by the American Association for the Advancement of Science.

The White House's budget for 2009, which the president proposed in February, called for $29.5 billion for NIH, the same amount as FY 2008.

The Federation of American Societies for Experimental Biology, an umbrella group representing more than 20 scientific societies, has formed an NIH Advocacy Clearinghouse at www.nihadvocacy.org. The site includes information about NIH funding useful to members of scientific societies.

Under the Continuing Resolution, FDA will be allowed to count supplemental funding received on July 1 as part of its FY 2008 base. The effect is to provide the agency with about $150 million extra in FY 2009, if the CR level extends for the entire fiscal year.

"We consider this a significant step in strengthening FDA," said Diane Dorman of the National Organization for Rare Disorders and a director of the Alliance for a Stronger FDA. "We are grateful to Members of Congress and staff who once again pulled FDA out of the hundreds of government programs and gave special consideration to its needs."

NBCC Disappointed In Research Act

The Senate approved, by voice vote on Sept. 27, a bill to authorize $40 million for NIH-funded research

on the causes of breast cancer. The bill passed the House on Sept. 25.

The bill was intended to apply the funding model used by the Department of Defense Congressionally Directed Medical Research Programs to research on the environmental causes of breast cancer, but the bill was essentially gutted in the House.

The National Breast Cancer Coalition worked on the bill, the Breast Cancer and Environmental Research Act, for about eight years. "What we were trying to do was take a strategic approach and incorporate a new model into NIH based in part on the DOD program and do something innovative at NIH and show this new model can work," NBCC President Fran Visco said to The Cancer Letter. "The approach set forth in the original draft of the Breast Cancer and Environmental Research Act would have been a step toward a new direction at NIH."

The bill maintained its original intent after negotiations with NIH and passage by the Senate Health, Education, Labor and Pensions Committee. Then, the bill ran into opposition in the House.

"We had thought that a bill with 286 bipartisan House cosponsors, and with both sides of the aisle publicly praising the Senate HELP-passed version, could have resulted in an agreement that maintained the core principles of that legislation," Visco said. "We remain supportive of the Senate HELP-passed version of the bill that has the support of 70 senators, and is not opposed by NIH."

As it is now written, the bill establishes an Interagency Breast Cancer and Environmental Research Coordinating Committee in the Department of Health and Human Services to make recommendations and solicit proposals for breast cancer research.

"We were looking for a new model and NIH and what we got was a coordinating committee," Visco said. "We will certainly push in every way we can, but it just makes more layers of committees and further away from actually accomplishing something."

NCI News:

SAIC Awarded $5.2 Billion, 10-Year Contract For Frederick

NCI has awarded SAIC-Frederick Inc. a follow-on contract to provide operations and technical support to the institute's Federally Funded Research and Development Center in Frederick, Md.

The single-award contract has a three-year base period of performance, five one-year award-term options, and one two-year option, for an estimated value of $5.2 billion if all options are exercised.

SAIC-Frederick Inc. is a wholly-owned subsidiary of Science Applications International Corp.

SAIC has been the operations and technical support contractor for the FFRDC since 1995, and in 2000 formed SAIC-Frederick to continue the work. The contract is the largest single research contract awarded by the Department of Health and Human Services.

The center is one of only 38 national laboratories in the U.S. and the only one solely dedicated to cancer and HIV/AIDS research.

Under the new contract, SAIC-Frederick will provide operations and technical support to the overall mission of the NCI within three major focus areas: basic research, translational research and development, and preclinical research and development. SAIC-Frederick employs more than 1,700 scientific, technical, and support personnel, and manages advanced technologies in genomics, proteomics, nanotechnology, optical and electron microscopy, and high-performance biomedical computing.

Under the current contract, SAIC-Frederick supports more than 300 clinical trials, and manages a pilot program of community hospitals in 14 states studying how best to bring the latest, evidence-based cancer care to rural, inner-city, and underserved patients. It also operates two biopharmaceutical manufacturing facilities—one for NCI and the other for the National Institute of Allergy and Infectious Diseases' Vaccine Research Center. These facilities produce drugs, vaccines, and other biologics for use in clinical trials.

"We appreciate the confidence NCI has shown in SAIC over the past 13 years and look forward to continuing our work to help deliver preventive, diagnostic, and therapeutic products to cancer patients," said Charles Koontz, SAIC group president.

SAIC employs about 44,000 and had annual revenues of $8.9 billion for its fiscal year ended Jan. 31.

Professional Societies:

Ganz, Sledge Candidates For ASCO Presidency

Nominees for the 2009 ASCO Election have been selected and include 18 ASCO members running for nine open positions: President, treasurer, and several seats on the Board of Directors and Nominating Committee. ASCO members will vote starting Oct. 15.

Candidates for president-elect are:

—Patricia Ganz, professor in the Schools of Medicine and Public Health at University of California, Los Angeles. She is also director of the Division of Cancer Prevention and Control Research at the institution's Jonsson Comprehensive Cancer Center. Ganz was a recipient of ASCO's 2008 Statesman Award and the ASCO-American Cancer Society Award and Lecture. Her ASCO involvement includes serving on the Board of Directors as Specialty Editor for Clinical Cancer Advances, and Associate Editor of the Journal of Clinical Oncology. She is a member of the Long-Term Medical Care for Adult Cancer Survivors Expert Panel, the Special Awards Selection Committee, and Immediate Past Chair of the Quality of Care Committee.

—George Sledge, is the Ballve-Lantero Professor of Oncology at Indiana University School of Medicine and Simon Cancer Center. He also serves the institution as a professor of Pathology and Laboratory Medicine. Sledge's ASCO involvement includes serving as chairman for the Cancer Education Committee, Nominating Committee, and Personnel Committee. He was also a member of the Board of Directors, the Government Relations Council, and Post-Mastectomy Radiotherapy Expert Panel.

Candidates for treasurer are:

—Clifford Hudis, chief of Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center.

—W. Charles Penley, MD, is in private practice in Nashville with Tennessee Oncology, PLLC.

Board of Directors Candidates, for Community Oncologist:

—Leon Dragon, medical director of the Kellogg Cancer Care Center in Highland Park, Ill., and assistant professor at Northwestern University Medical School.

—Peter Paul Yu, a physician in practice at Palo Alto Medical Foundation, Mountain View, Calif.

For Non-U.S. Oncologist:

—Eduardo Cazap currently serves as president of the Latin American and Caribbean Society of Medical Oncology and the International Union Against Cancer.

—Jacek Jassem, a professor of Radiotherapy and Clinical Oncology, and head of the Department of Oncology and Radiotherapy at the Medical University of Gdansk, Poland.

For Pediatric Oncologist:

—Kenneth Cohen, director of Pediatric Neuro-oncology at Johns Hopkins University School of Medicine.

—Susan Lerner Cohn, director of Pediatric Clinical Sciences at Comer Children's Hospital in Chicago, and a professor of pediatrics at the University of Chicago.

For Undesignated Specialty (two positions):

—Mary (Nora) Disis, director of the Institute for Translational Health Sciences at the University of Washington.

—Lynn Schuchter, director of the Clinical Research Unit at the Abramson Cancer Center, recently appointed to lead the center's Melanoma Program.

—Everett Vokes, professor of medicine at the Center for Advanced Medicine and the University of Chicago Medical Center.

—Robin Zon, vice president and partner at Michiana Hematology-Oncology, P.C., in South Bend, Ind.

For Nominating Committee (two positions):

—Joseph DiBenedetto Jr., a hematologist, oncologist and physician of internal medicine at Oncology & Hematology Associates in Providence, R.I.

—Scott Lippman, chairman of the Thoracic/Head & Neck Medical-Oncology Department at the University of Texas M. D. Anderson Cancer Center.

—Barbara McAneny, CEO of New Mexico Oncology Hematology Consultants, Ltd.

—Monica Morrow, chief of Breast Service in the Department of Surgery at the Memorial Sloan-Kettering Cancer Center.

In the Cancer Centers:

Adams-Campbell Joins Lombardi Cancer Center

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to decrease obesity and mortality from these related diseases.

"Like Dr. Adams-Campbell, I believe that Lombardi has a responsibility to our neighbors and that we must work to address the health disparities and high cancer rates in our city," Weiner said.

* * *

JOHN HOSEI YIM was appointed associate professor of surgery at City of Hope. Yim specializes in treating patients with breast and endocrine tumors, including those of the thyroid, parathyroid and adrenal glands. He also conducts research into interferon regulatory factors—proteins that have been shown to kill breast and other cancer cells. He was an assistant professor of surgery at University of Pittsburgh's Department of Surgery. . . . **WILLIAM SHIH**, assistant professor of Biological Chemistry and Molecular Pharmacology at Dana-Farber Cancer Institute and

Harvard Medical School, has been named a recipient of a 2008 NIH Director's New Innovator Award. The grant provides $1.5 million in direct cost support over a five year period. Shih will use the funding to support his research to develop tools for atomic-resolution imaging of membrane proteins to enable structure-based drug design. . . . **KEN-ICHI NOMA**, assistant professor in the Gene Expression and Regulation Program at Wistar Institute, received an NIH Director's New Innovator Award. He is working to develop a new method of mapping the three-dimensional structure of the human genome. These efforts aim to identify the molecular basis for many diseases, including cancers, and may aid in the development of new diagnostic tests and treatments. . . . **GEORGE KLEIN**, professor emeritus and research group leader for the Microbiology and Tumor Biology Center in Stockholm, Sweden, was selected to receive the 16th annual Herbert and Maxine Block Memorial Lectureship Award for Achievement in Cancer at Ohio State University.

Foundations:

Love, Avon Recruit Women, Scientists, For Research

DR. SUSAN LOVE RESEARCH FOUNDATION and the Avon Foundation began the Love/Avon Army of Women, an initiative that will partner women with breast cancer researchers. The foundations seek one million healthy women of all ages and ethnicities to be available to take part in breast cancer prevention research.

Scientists apply to the Army of Women for the opportunity to recruit volunteers for their research. Their studies undergo a scientific, safety, and ethical review. An email about approved research is sent to the Army of Women "members" with information about the study, and those who are interested in participating and meet the criteria are instructed on how to contact the researcher or a designated Army of Women research center. Through this process, the Army of Women provides researchers access to these volunteers. That process may involve completing a questionnaire, providing blood or saliva samples, or other relatively simple levels of participation on the part of the volunteer. All information is kept strictly confidential, and the women participate on a purely voluntary basis.

"Women have repeatedly demonstrated through fundraising and advocacy their personal dedication to ending this disease," said Susan Love, clinical professor of surgery at the David Geffen School of Medicine at UCLA, author of "Dr. Susan Love's Breast Book," and president of the Dr. Susan Love Research Foundation. "This new initiative gives women the opportunity to take the next steps and be part of the research itself."

"Avon is itself an 'army of women,' and we are committed to being the company and the foundation for women," said Andrea Jung, chairman and CEO of Avon Products Inc. "The Army of Women is a perfect marriage of our global leadership in the breast cancer cause and our grassroots access to women across the country."

The National Breast Cancer Coalition and the American Association for Cancer Research have partnered with the Love/Avon Army of Women in support of the campaign. Further information is available at www.armyofwomen.org.

Industry:

Cephalon To Plead Guilty, Pay $425M For Off-Label Marketing Of Three Drugs

Cephalon Inc. will enter a criminal plea and pay $425 million to resolve claims that it marketed three drugs for uses not approved by FDA, the Justice Department said.

The lawsuits were brought by former Cephalon employees and filed under the qui tam provisions of the False Claims Act. The suits alleged that Cephalon engaged in a scheme to market Gabitril, Actiq, and Provigil for unapproved uses in violation of the Food, Drug and Cosmetic Act.

The suits against the company alleged that, as a result of Cephalon's off-label marketing campaign, false claims for payment were submitted to federal insurance programs such as Medicaid and the Federal Employee Health Benefits Program which did not provide coverage for such off-label uses. A criminal information also filed by the Justice Department alleges that, between about 2001 and 2006, Cephalon also promoted the drugs for uses other than what the FDA approved. The company is charged with one count of "Distribution of Misbranded Drugs: Inadequate Directions for Use," a misdemeanor offense.

FDA approved Actiq for use only in opioid-tolerant cancer patients. Between 2001 and 2006, Cephalon allegedly promoted the drug for non-cancer patients to use for such maladies as migraines, sickle-cell pain crises, injuries, and in anticipation of changing wound dressings or radiation therapy. Cephalon also promoted Actiq for use with patients who were not opioid tolerant.

Cephalon undertook its off-label promotional

practices via a variety of techniques, such as training its sales force to disregard restrictions of the FDA-approved label, and to promote the drugs for off-label uses.

The Actiq label stated that the drug was for "opioid tolerant cancer patients with breakthrough cancer pain, to be prescribed by oncologist or pain specialists familiar with opioids."

Using the mantra "pain is pain," Cephalon instructed the Actiq sales representatives to focus on physicians other than oncologists, including general practitioners, and to promote this drug for many uses other than breakthrough cancer pain.

"This settlement is further evidence of the department's willingness to prosecute cases involving violations of the FDCA and to recover taxpayer dollars used to pay for drugs sold as a result of illegal marketing campaigns," said Gregory Katsas, assistant attorney general for the Justice Department's Civil Division. "The department takes off-label marketing of drugs very seriously because of the potential for patient harm arising from promoting drugs for uses not approved by the FDA."

As part of the resolution of these allegations, the HHS Inspector General and Cephalon have entered into a five year Corporate Integrity Agreement, which requires Cephalon to send doctors a letter advising of this resolution, that it post payments to doctors on its web site and that its board and top management regularly certify that the company is in compliance with all applicable requirements.

The civil settlement resolves four qui tam actions filed in the Eastern District of Pennsylvania. Three of those cases were filed by former Cephalon sales representatives.

Funding Opportunities:

Pancreatic Research Grants

The Pancreatic Cancer Action Network is partnering with the American Association for Cancer Research on its 2009 research grants program.

Grant applications are now open for Pilot Grants, Career Development Awards, and a Fellowship Award. Applications must be directly relevant and applicable to pancreatic cancer and may be in any discipline of basic, translational, or clinical research. The deadline for submission is Nov. 10, at noon (Eastern).

Guidelines and application instructions are available at: http://pancan.org/Research/AACR_grants08.html.

NIH Roadmap Initiatives

RFA-RM-08-030: Studies of the Ethical, Legal, and Social Implications of Human Microbiome Research. NIH Roadmap Initiatives. R01. Letters of Intent Receipt Date: Nov. 3. Application Due Date: Dec. 3. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-030.html. Inquiries: Jean McEwen, 301-496-7531; mcewenj@mail.nih.gov.

RFA-RM-08-022: Patient-Reported Outcomes Management Information System Network Center. NIH Roadmap Initiatives. U54. Letters of Intent Receipt Date: Feb. 3. Application Receipt Date: March 3. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-022.html. Inquiries: Phil Tonkins Jr., 301-594-4979; tonkinsw2@mail.nih.gov.

RFA-RM-04-011: Patient-Reported Outcomes Management Information System Research Sites. NIH Roadmap Initiatives. U01. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-023.html.

RFA-RM-08-024: Patient-Reported Outcomes Management Information System Technology Center. NIH Roadmap Initiatives. U54. http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-024.html.

RFA-RM-08-025: Patient-Reported Outcomes Management Information System Statistical Center. NIH Roadmap Initiatives. U54. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-025.html.

Other Funding Opportunities

Small Business Innovation Research Program Contract Solicitation NOT-OD-08-094. Proposal Receipt Date: Nov. 3. http://researchportfolio.cancer.gov/initiativedetail.jsp?InitiativeID=3929. Inquiries: Ms. Mary Landi-O'Leary, ml186r@nih.gov.

PA-08-267: Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-267.html. Inquiries: James Tricoli, 301-496-1591; tricolij@mail.nih.gov.

RFP N02-RC-91002-56: Retroviral vector Encoding Anti-Tumor TCR Genes. Response Due date: Oct. 31. Full text: http://www.fbodaily.com/archive/2008/09-September/14-Sep-2008/FBO-01668919.htm. Inquiries: Michael Marino, 301-435-3801; marinomic@mail.nih.gov.

RFP S08-221: Chemical Biology Consortium. Full text: http://www.fbodaily.com/archive/2008/09-September/12-Sep-2008/FBO-01665991.htm. Inquiries: Melissa Borucki, cbcsubs@mail.nih.gov.

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THE CANCER LETTER

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Business & Regulatory Report

Oncology Management:

US Oncology Begins Service Division To Provide Evidence-Based Cancer Care

US Oncology Inc. of Houston said it has begun **Innovent Oncology**, a service division that allows oncologists and health plans to work together through integrated programs designed for cancer care.

The division offers payers and oncologists solutions that combine evidence-based treatment guidelines, patient support services and advance care planning to improve clinical outcomes while addressing costs, the network said.

"We've worked with oncologists and payers nationwide to develop

(Continued to page 2)

Clinical Trials:

Dendreon Begins Phase II Provenge Trial; Patients Randomized To Different Doses

Dendreon Corp. (NASDAQ:DNDN) of Seattle said it has begun the second of two, phase II trials of Provenge (sipuleucel-T), its investigational active cellular immunotherapy for advanced prostate cancer.

In the multicenter Prostate Active Cellular Therapy 120-patient, or ProACT trial, three cohorts will be randomized to receive Provenge manufactured with different concentrations of the immunizing antigen.

Three infusions of the drug will be administered, each two weeks apart, to study the effect of antigen concentration on CD54 upregulation, as well as immune response. Survival data will also be collected.

The company also said it has begun enrollment in a 40-subject, single-center Neoadjuvant Active Cellular immunotherapy, or NeoACT study, or P07-1, which is being conducted at UCSF Helen Diller Family Comprehensive Cancer Center.

Genta Inc. (BULLETIN BOARD: GNTA) of Berkeley Heights, N.J., said the independent Data Monitoring Board for AGENDA, a phase III trial of the Genasense (oblimersen sodium) Injection, has completed its review.

With more than half of the planned number of patients enrolled, the IDMB recommended that the trial continue to completion of full enrollment, the company said.

The study is a randomized, double-blind, placebo-controlled trial that supports global registration of Genasense in advanced melanoma. The study would confirm safety and efficacy results from a prior randomized trial

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US Oncology's Innovent To Offer Cancer Care Services

(Continued from page 1)

this program," said Marcus Neubauer, chairman of the US Oncology Level I Pathways committee and medical oncologist with Kansas City Cancer Centers. "The physicians affiliated with US Oncology developed evidence-based treatment pathways several years ago to reduce the high variability of drug utilization during treatment, but this program goes well beyond drug utilization in its quest for improved quality and reduced costs."

Innovent Oncology services have been in community-based application for more than three years within the US Oncology network of member practices, the network said.

In another development, **US Oncology Inc**. said it has appointed **Michael Sicuro** executive vice president and chief financial officer.

Sicuro will lead and manage the finance function and provide leadership on a range of financial, analytical, operational, and transactional issues, including accounting, financial reporting, treasury, tax, and financial planning and analysis, the company said.

Sicuro was senior vice president, chief financial officer at Asyst Technologies Inc., an automation and technology company.

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Supportive Oncology Services Inc. of Memphis said it has begun www.UnderstandingCancer.tv, a multimedia informational resource for cancer patients and caregivers.

UnderstandingCancer.tv contains diagnosis, treatment and possible side effects information that was developed, reviewed and approved by a national editorial board of community-based oncology professionals, the group said.

Clinical Trials:

NovaRx Begins Phase III Trial Of Lucanix In Lung Cancer

(Continued from page 1)

of Genasense combined with dacarbazine in patients identified by a biomarker and who have not received chemotherapy. The co-primary endpoints of AGENDA are progression-free survival and overall survival. A total of 300 patients are expected to enroll.

"We anticipate that accrual will complete in the first quarter of 2009," said Loretta Itri, president, pharmaceutical development of Genta.

Merrimack Pharmaceuticals Inc. of Cambridge, Mass., said initial dosing has begun in a phase I study of MM-121, a fully human monoclonal antibody and therapeutic that blocks signaling of the ErbB3 receptor.

The dose escalation study will evaluate the safety and pharmacokinetics of MM-121, the company said. Enrollment is underway at Fox Chase Cancer Center and two additional oncology sites are expected to participate in the trial later in this year.

Until now, computer simulation has not been widely applied toward understanding optimal therapeutic strategies for treating cancers driven by complex signaling pathways, the company said.

"ErbB3 is an important target in many types of cancer including lung, breast, colorectal, ovarian and others," said William Slichenmyer, senior vice president and chief medical officer at Merrimack. "Preclinical studies of MM-121 have demonstrated antitumor activity in a wide range of tumor types and a very favorable safety profile."

NovaRx Corp. of San Diego said it has begun a phase III trial of Lucanix (belagenpumatucel-L) in advanced non-small cell lung cancer.

The STOP study is named because of its expected endpoints: Survival; Tumor-free, Overall;

and Progression-free. The study is an international, multicenter, randomized, double-blind 700-patient trial that will conducted at 90 clinical sites in the U.S., Canada, India, and Europe, the company said.

In a phase II trial, two-year survival in stages IIIB and IV disease with Lucanix treatment was longer than that of treatment with the standard of care, the company said. A second, investigator-initiated phase II study supported these results.

NovaRx induces the immune system to target the cancer, the company said. In phase II studies, treatment side effects have included redness or soreness at the injection site, the company said.

"In medical research, you see something like this once in a lifetime," said John Nemunaitis, executive director at the Mary Crowley Medical Research Center in Dallas, and principal investigator of both the phase II Lucanix study and the investigator-initiated phase II trial.

"This is a very promising approach to cancer treatment, and results reported so far are beyond anyone's expectations.," said Lyudmila Bazhenova, principal investigator of the STOP trial at the Rebecca and John Moore's Cancer Center the University of California, San Diego. "Traditional chemotherapy for stage IV NSCLC still yields disappointing results."

In phase II testing, 50 percent with stable disease and Lucanix treatment following one frontline regimen of chemotherapy lived more than 44 months, compared to less than 10-12 months for treatment with standard of care, the company said. In addition, treatment with Lucanix for advanced disease after zero to five prior chemotherapy treatments demonstrated a one-year survival of 61 percent and a two-year survival of 41 percent. Such late-stage disease demonstrate one-year survival of less than 30 percent, the company said.

Lucanix consists of four non-small cell lung cancer cell lines that have been genetically engineered to shut off their immune suppressive properties, the company said. The cell lines are then modified to block transforming growth factor-beta, which is produced by cancer cells, allowing the immune system to mount an anti-tumor response.

Oncolytics Biotech Inc. (NASDAQ:ONCY) of Calgary said it has begun enrolment in a phase II trial using intravenous administration of Reolysin in combination with paclitaxel and carboplatin in advanced head and neck cancers.

Monica Mita of the Cancer Therapy & Research Center at The University of Texas Health Science Center is principal investigator, the company said.

Oncolytics also said it is beginning a phase II trial using intravenous administration of Reolysin in combination with paclitaxel and carboplatin in non-small cell lung cancer with K-RAS or EGFR-activated tumors.

Miguel Villalona-Calero, professor, Division of Hematology/Oncology and Department of Internal Medicine and Pharmacology at The Ohio State University Comprehensive Cancer Center, is principal investigator, the company said.

The treatment in the 36-patient, single arm, two-stage, open-label, study will consist of four to six cycles of paclitaxel and carboplatin in conjunction with Reolysin, at which time Reolysin may be continued as a monotherapy, the company said.

The primary objectives are to determine the objective response rate of Reolysin in combination with paclitaxel and carboplatin and to measure progression-free survival at 6 months, the company said. The secondary objectives are the median survival and duration of progression-free survival, and to evaluate the safety and tolerability of Reolysin in combination with paclitaxel and carboplatin in this population.

In another development, Oncolytics said NCI has begun enrolment in a phase II, 47-patient trial for metastatic melanoma using systemic administration of its proprietary formulation of the human reovirus Reolysin.

The trial is being conducted by the Mayo Phase II Consortium under the NCI Clinical Trials Agreement with Oncolytics, with clinical supplies of the agent supplied by Oncolytics, the company said. Evanthia Galanis, of the Mayo Clinic Cancer Center, is principal investigator.

The primary objectives are to assess the antitumor effects of the drug, as well as its safety profile. Secondary objectives include assessment of progression free survival and overall survival, the company said.

Treatment consists of systemic administration of Reolysin at a dose of 3x1010 TCID50 per day on days 1-5 of each 28 day cycle, with up to 12 cycles of treatment, the company said.

SpectraScience Inc. (BULLETIN BOARD: SCIE) of San Diego said it is shipping its WavSTAT Optical Biopsy System to Mayo Clinic and to the **University of California San Diego/VA** to study its clinical value as an adjunctive tool in identifying dysplasia or cancer in the esophagus.

This will be the final phase of the study, which has

been conducted over the past three years, the company said.

The approved WavSTAT System uses a low power, non-significant risk laser to scan tissue and determine whether small polyps are normal or pre-cancerous without removing the tissue, the company said. If the polyps are pre-cancerous, they are removed during the same procedure.

The hypothesis that the sensitivity of a WavSTAT-assisted endoscopic examination improves that of standard endoscopy alone will be tested. If this hypothesis is proven, the physician should be able to take fewer physical biopsies, decrease the duration of the exam and minimize the discomfort of the patient.

Telik Inc. (NASDAQ:TELK) of Palo Alto said the lead compounds of its Aurora kinase and VEGFR dual inhibitor program have met a preclinical development milestone.

Aurora kinase is a signaling enzyme required for cancer cell division, while VEGFR plays a role in tumor blood vessel formation, the company said. The Telik lead compounds prevented tumor growth in preclinical models of human colon cancer and human leukemia by inhibiting both Aurora kinase and VEGFR, the company said.

A development drug candidate is being selected, and a phase I study may be initiated, the company said.

Deals & Collaborations:

Firms Collaborate To Develop Robotic Radiosurgery System

Accuray Inc. (NASDAQ:ARAY) of Sunnyvale, Calif., and **IMPAC Medical System Inc.** said they collaborate to develop inter-operability between the CyberKnife Robotic Radiosurgery System and the MOSAIQ oncology information system.

Using DICOM standard interface protocols, both treatment plan and delivery information from the CyberKnife System will automatically feed into the IMPAC electronic medical record, the companies said.

The CyberKnife System produces treatment records to the comprehensive patient chart. The MOSAIQ electronic data exchange automatically coordinates with the CyberKnife System, eliminating the need for manual data entry. Additionally, the capability diminishes the need for paper charts, providing a single electronic source for information, the companies said.

Genasense inhibits production of Bcl-2, a protein that blocks a pathway of chemotherapy-induced cell death.

AstraZeneca (NYSE:AZN) of Singapore said it has entered into a partnership with **National Cancer Centre Singapore** and **National University Hospital** to develop anti-cancer compounds.

Under the Memorandum of Understanding, the collaborative agreement spans both clinical and pre-clinical development activities, the company said. Included in the partnership is a Training Program placement with the Manchester Cancer Research Centre, with whom AstraZeneca has a formal research alliance. Supported in part by the Singapore Economic Development Board, the program would train clinical research professionals for both private-sector and public-sector research labs.

Under the clinical development collaboration, two research institutions in Singapore, the NCCS and NUH, will be given access to AstraZeneca compounds which have already undergone clinical testing, the company said. Two compounds have been identified for clinical screening in inoperable HCC during 2008 and 2009. Compounds will be made available at a rate of one per year, for the duration of the partnership, which is in place until 2012.

Pre-clinical activities are also included in the partnership, under which the same institutions will be given annual access to up to six candidate drugs for appraisal of activity in the mouse in vivo primary HCC explant model, the company said.

For both clinical and pre-clinical activities, AstraZeneca said it retains the option to assume further development and marketing of drugs made available as part of the partnership.

BN ImmunoTherapeutics of Kvistgard, Denmark, said it has entered into a Cooperative Research and Development Agreement with NCI to develop immunotherapies in prostate cancer.

Under the CRADA, BN ImmunoTherapeutics said it has rights to exclusively license intellectual property that results from the collaboration.

Through the collaboration and a license agreement with the U.S. Public Health Service, the company said it has obtained rights to intellectual property rights covering a prostate cancer vaccine product candidate in late phase II clinical development. Data from clinical studies with this vaccine candidate are being evaluated.

BN ImmunoTherapeutics is a subsidiary of Bavarian Nordic.

Cryo-Cell International Inc. of Oldsmar, Fla., and **EndGenitor Technologies Inc.** of Indianapolis said they have entered into a research collaboration to co-develop a combined cellular platform therapeutic for rapidly forming vasculature in injured tissues for therapeutic applications including cancer.

The research will use ECFCs and MenSCs. ECFCs are cord blood-derived endothelial colony-forming cells and MenSCs, are primitive mesenchymal progenitor cells found in menstrual blood that are retrievable without invasive techniques, the companies said.

"Both ECFCs and MenSCs contribute to angiogenesis in vivo, which underscores the importance of further study into the synergy of the cells in the formation of vasculature," said Julie Allickson, vice president of laboratory operations and research and development at Cryo-Cell, which developed and maintains proprietary intellectual property on MenSCs. EndGenitor developed and maintains IP on ECFCs.

febit of Heidelberg, Germany, and **Translational Genomics Research Institute** of Lexington, Mass., said they have formed a collaboration in which TGen will evaluate Next-Generation-Sequencing equipment in conjunction with the febit proprietary Geniom Microarray Technology.

The febit HybSelect Technology enables selective DNA capture and elution, a method to preselect sequences for Next-Generation Sequencers, the companies said. HybSelect is based on the febit Geniom Technology and uses arrays within microfludic biochips for the selection process of targeted DNA. Geniom biochips are programmable and can contain a desired set of capture probes. The method combines the performance of latest sequencers with the selection capabilities of Geniom Technology, the companies said.

"The collaboration enhances the opportunities for TGen researchers to make a difference in research utilizing next generation sequencing," said Matthew Huentelman, TGen associate investigator and lead collaborator.

GeneGo Inc. of St. Joseph, Mich., said **M.D. Anderson** Cancer Center has become a certified GeneGo Center of Excellence.

M.D. Anderson researchers will have institution-wide access to the GeneGo MetaCore data analysis suite, training and advanced support. MetaCore will be used in research programs both as a central data repository, management and collaboration platform for clinical OMICs data and as an integrative pathway analysis suite, the company said,

"I have been using MetaCore for many years in my research into pathways and networks that control aggressive behavior in cancers," said Mary Edgerton, pathologist at M.D. Anderson. "I am using it to infer networks from analysis of gene expression array data for pathways in lung, brain, and breast cancer. I also use the curated pathways to formulate mathematical models of molecular networks that predict tumor behavior using multiscale modeling."

GeneGo Inc. develops systems biology technology such as compound based pathway analysis, cheminformatics and bioinformatics software for life science research, the company said.

OncoGenex Pharmaceuticals Inc. (NASDAQ: OGXI) of Bothell, WA, said it has granted **Eagle Pharmaceuticals Inc.** of Vancouver the exclusive worldwide rights to develop and commercialize Tocosol Paclitaxel.

Under the agreement, OncoGenex said it would be entitled to royalty payments from Tocosol Paclitaxel sales and a percentage of sub-licensing royalty and milestone payments received by Eagle Pharmaceuticals. Development expenses are the sole responsibility of Eagle Pharmaceuticals.

Tocosol Paclitaxel was developed by Sonus Pharmaceuticals prior to the combination of Sonus and OncoGenex Technologies, which occurred earlier this year. At that time, further development of Tocosol Paclitaxel had been terminated, OncoGenex said.

"We will focus our efforts on the deep pipeline we have in development, including OGX-011 which is completing five phase II studies in prostate, breast and lung cancers," said Scott Cormack, president and CEO of OncoGenex Pharmaceuticals. "Tocosol Paclitaxel was not part of that strategy, and we are pleased to be able to out-license the program to an organization with interest in continuing development of the product candidate."

QLT Inc. (NASDAQ: QLTI; TSX: QLT) of Vancouver said **QLT USA Inc**., its wholly-owned subsidiary, entered into an exclusive license agreement with **Reckitt Benckiser Pharmaceuticals Inc.** of the U.K. for its Atrigel sustained-release drug delivery technology.

Under the agreement and related asset purchase

agreement, QLT USA received an aggregate upfront payment of $25 million, the company said. As part of the transaction, Reckitt acquired 18 employees from QLT USA and will take over its corporate facility located in Fort Collins, Colorado.

"The licensing deal will bring our total proceeds from our announced non-core asset transactions to $240 million," said Bob Butchofsky, president and CEO of QLT. "Eligard, our leuprolide acetate for injectable suspension for advanced prostate cancer, is our remaining non-core asset which we hope to divest in the near future."

The Atrigel drug delivery system consists of biodegradable polymers dissolved in biocompatible carriers, the company said.

Rosetta Genomics Ltd. (NASDQ: ROSG) of Rehovot, Israel, said it has entered into a clinical validation study with **M. D. Anderson Cancer Center** using the Rosetta Genomics microRNA-based test that identifies the primary site of cancer of unknown primary.

The study will include 100 patients who are diagnosed with CUP at MDACC, and who meet the eligibility criteria. Rosetta Genomics said the test would be submitted for regulatory approval later this year.

CUP is a heterogeneous group of cancers that constitutes 3-5 percent of all cancers with a poor median survival of 6-10 months, the company said.

"The current gold standard diagnostic evaluation for CUP consists of a careful history and physical examination, laboratory tests, imaging studies, invasive studies when necessary, and thorough pathologic evaluation," said Gauri Varadhachary, of M D Anderson Cancer Center. "This process is lengthy and exposes the patient to unnecessary toxicities." The study would validate their assay as well as compare its performance with current tests for CUP."

Transgenomic (BULLETIN BOARD: TBIO) of Omaha said it has entered into a partnership with **Key Genomics** of Charlottsville, Va., to develop a molecular diagnostic test for ovarian cancer, powered by COXEN, the Key Genomics predictive algorithm.

Data from COXEN-derived genomic signatures trials demonstrate the test can distinguish responders from patients who do not benefit from a therapy, the company said.

The Transgenomics technologies for DNA mutation detection and analysis will work with COXEN, which combines genomic and pharmacological response data on a set of cancer cell lines to generate molecular signatures of patient response to specific anti-cancer agents, the company said.

"An algorithm that could quickly sort molecular information about a particular tumor, and then match this information with the right drug treatment would be a valuable medical breakthrough," said Tim Gallagher, CEO at Key Genomics. "COXEN could bring significant healthcare and economic value by personalizing cancer therapy by using such a method, an algorithm based on in vitro response to anti-cancer drugs."

VION Pharmaceuticals Inc. of New Haven said it has entered into an agreement with **HOVON** to conduct a phase III trial of laromustine (Cloretazine (VNP40101M)) with standard remission-induction therapy in untreated acute myelogenous leukemia and high-risk myelodysplasia.

The trial has been designed in two parts. Part A will determine the safety and preliminary effectiveness of laromustine administration at three dose levels in combination with cytarabine and idarubicin. Part A will also evaluate the pharmacokinetics and the clinical efficacy of the laromustine combination, the company said.

Part B would evaluate the clinical efficacy of the laromustine combination versus two cycles of cytarabine and idarubicin without laromustine with regard to clinical outcome, or event free survival, the complete remission rate, disease free survival, risk of relapse and overall survival, as well as the tolerance and toxicity, and pharmacokinetics of the combination, the company said.

"Laromustine is a promising agent for leukemia, " said Bob Lowenberg, chief investigator of HOVON.

The trial is expected to start this fall and will be conducted at sites in the Netherlands, Belgium, Switzerland and Norway, the company said.

HOVON is a Dutch-Belgian cooperative clinical trial group in hematology oncology with a clinical development program in leukemia, malignant lymphomas and multiple myeloma, the company said.

Product Approvals & Applications:

FDA Approves Alimta For First-Line NSCLC

Eli Lilly and Co. (NYSE: LLY) of Indianapolis said it received approval from FDA for Alimta (pemetrexed for injection) in combination with cisplatin, in the first-line treatment of locally-advanced and

metastatic non-small cell lung cancer with nonsquamous histology.

Alimta is not indicated for squamous cell non-small cell lung cancer, the company said.

The approval is based on a phase III, open-label randomized 1725-patient study that evaluated Alimta plus cisplatin (AC arm) versus Gemzar (gemcitabine HCl for injection) plus cisplatin (GC arm). The median survival was 10.3 months in the AC arm and 10.3 months in the GC arm [adjusted hazard ratio 0.94 (95 percent CI: 0.84, 1.05)]. The median progression-free survival was 4.8 and 5.1 months for the AC and GC arms, respectively [adjusted hazard ratio 1.04 (95 percent CI: 0.94, 1.15)]. The overall response rates were 27.1 percent and 24.7 percent for the AC and GC arms, respectively.

In a pre-specified analysis, the impact of NSCLC histology on overall survival was examined and clinically relevant differences in survival according to histology were observed, the company said. In the nonsquamous cell NSCLC subgroup, the median survival was 11.0 and 10.1 months in the AC and GC groups, respectively [unadjusted hazard ratio 0.84 (95 percent CI: 0.74, 0.96)]. However, in the squamous cell histology subgroup, the median survival was 9.4 versus 10.8 months in the AC and GC groups, respectively [unadjusted hazard ratio 1.22 (95 percent CI: 0.99, 1.50)]. The unfavorable effect on overall survival associated with squamous cell histology observed with pemetrexed was also noted in a retrospective analysis of the single-agent trial of pemetrexed versus docetaxel in stage III/IV NSCLC after prior chemotherapy, the company said.

Treatment with the Alimta regimen resulted in less hematologic toxicity, fewer blood transfusions and decreased use of growth factors compared to treatment with the GEMZAR regimen, the company said. The most common adverse reactions (incidence greater than or equal to 20 percent) for Alimta in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia and constipation, the company said.

Based on the same data, FDA also approved a change to the second-line indication. Alimta is indicated as a single agent for locally-advanced or metastic nonsquamous non-small cell lung cancer after prior chemotherapy.

Alimta is not indicated for treatment of squamous cell non-small cell lung cancer, the company said.

ImClone Systems Inc. (NASDAQ: IMCL) said it has submitted an application to FDA to broaden the use of Erbitux (cetuximab) to include first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck.

ImClone said it has requested Priority Review of the application, which, if granted, means the decision could come within six months. The FDA will notify ImClone whether it has accepted the submission by the end of October, the company said.

Erbitux was approved in 2006 for use in combination with radiation therapy for locally or regionally advanced SCCHN, and as a single agent for recurrent or metastatic SCCHN for which platinum-based therapy had failed. If approved, the submitted label would extend that use of Erbitux in the first-line setting.

Data from the phase III Erbitux in first-line Treatment of REcurrent or MEtastatic head and neck cancer or Extreme study, investigating the efficacy of Erbitux in combination with platinum-based chemotherapy in the first-line setting in recurrent and/or metastatic SCCHN, was conducted by Merck KGaA, of Darmstadt, Germany. The study showed that the agent, when added to standard platinum-based chemotherapy, increased the overall survival time, the company said.

The randomized 442-patient study consisted of treatment with either Erbitux plus platinum-based chemotherapy (cisplatin or carboplatin plus infusional 5-fluorouracil) or platinum-based chemotherapy alone, the company said.

The study met the primary endpoint of increasing overall survival. The median overall survival in the Erbitux plus platinum-based chemotherapy arm was 10.1 months, and 7.4 months for treatment with platinum-based chemotherapy alone (Hazard Ratio, 0.797 ($p = 0.036$)).

Erbitux plus platinum-based chemotherapy also conferred increased progression-free survival and a higher response rate compared with chemotherapy alone. The median PFS values were 5.6 months and 3.3 months (HR = 0.538 (p less than 0.0001)) and the response rates were 35.6 percent and 19.5 percent ($p = 0.0002$) treatment with Erbitux plus chemotherapy and chemotherapy alone, respectively.

Imclone also said treatment has begun in a phase II trial of IMC-1121B, its proprietary fully human IgG1 anti-vascular growth factor receptor-2 monoclonal antibody, in advanced ovarian cancer.

The multicenter, open-label single-arm 55-patient study in persistent or recurrent advanced ovarian, fallopian tube, and primary peritoneal epithelial cancers following at least one platinum-containing chemotherapy regimen, would evaluate efficacy and

safety of the antibody administered as an intravenous infusion every two weeks.

In another development, ImClone said it has begun enrollment in a multicenter randomized phase II trial of IMC-A12 in advanced breast cancer.

Patients whose disease had progressed on an antiestrogen therapy are being randomized to treatment with either IMC-A12 as a single agent or IMC-A12 in combination with same dose and schedule of the last antiestrogen therapy to which the disease became refractory, the company said.

The primary objective of the 90-patient study is efficacy of both IMC-A12 alone and IMC-A12 combined with the last antiestrogen therapy to which the cancer became refractory. The study will also characterize the safety of the antibody given alone and combined with antiestrogen therapy. IMC-A12 will be administered on an every-two-week schedule, the company said.

In 2007, Imclone completed enrollment in two phase I studies of IMC-A12. Data demonstrated favorable safety and pharmacokinetic profiles, as well as preliminary evidence of antitumor activity as a single agent when administered either weekly or every two weeks.

In addition to the phase II study of IMC-A12 in hormone expressing advanced breast cancer, phase II studies of IMC-A12 in soft tissue sarcoma and advanced prostate, pancreatic, colorectal, liver, head and neck cancers, as well as a series of phase I/II studies in pediatric malignancies and another evaluating the combination of IMC-A12 and temsirolimus, have begun enrollment, the company said.

Additional disease-directed studies of IMC-A12 sponsored by both ImClone and NCI under a development agreement are advancing towards initiation, the company said.

Novartis of East Hanover, N.J., said that Gleevec (imatinib mesylate) tablets were granted priority review status by FDA as the first therapy used after surgery in kit-positive gastrointestinal stromal tumors.

Similar regulatory submissions have been filed in the European Union and Switzerland and will be filed in other countries, the company said.

The submissions are based on ACOSOG Z9000, a phase III, double-blind, randomized, multicenter, international 700-patient study in GIST after surgical removal of the tumor. The results showed a 89 percent reduction in risk of kit-positive GIST returning after surgery with Gleevec versus placebo, the company said.

In 2007, the study met its primary efficacy endpoint, showing an advantage for Gleevec in recurrence-free survival. At that time, following the recommendation of the independent study data monitoring committee to stop the trial accrual early, the study investigators made public the interim results and offered Gleevec to patients receiving placebo.

The study compared the recurrence-free survival of GIST treatment with Gleevec 400 mg/day versus placebo for one year immediately following surgery. The results showed that 98 percent receiving Gleevec remained recurrence free at one year following surgery compared to 82 percent of those receiving placebo. As a result of adjuvant therapy with the drug, there was an 89 percent reduction in risk of GIST returning, the company said.

The study was conducted at cancer centers throughout the U.S. and Canada, under a Cooperative Research and Development Agreement between Novartis and NCI, and was led by the American College of Surgeons Oncology Group.

In another development, Novartis said RAD001 (everolimus) has been granted priority review by FDA in kidney cancer.

Novartis also said it filed marketing authorization applications for the agent with the European Medicines Agency and the Swiss Agency for Therapeutic Products.

The regulatory submissions are based on the REnal Cell cancer treatment with Oral RAD001 given Daily, or RECORD-1 trial. The data show the product more than doubled time without tumor growth and reduced the risk of disease progression by 70 percent, the company said. Safety findings in the RECORD-1 trial were consistent with those seen in prior phase II studies.

Ortho Biotech Products L.P. of Bridgewater, N.J., said it has submitted a supplemental new drug application to FDA for the combination of Doxil (doxorubicin HCl liposome injection) and Taxotere (docetaxel) for advanced breast cancer with prior anthracycline treatment.

Data from a completed randomized, parallel-group, open-label, multicenter phase III trial that evaluated time to progression of the disease with combination vs. monotherapy docetaxel treatment met its protocol-specified primary endpoint: the Doxil-docetaxel combination had a statistically significant improvement in TTP as compared to docetaxel alone, the company said. Secondary endpoints included overall survival, response rates and safety.