THE CANCER LETTER

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

PFS Is A Benefit "In The Right Context," Pazdur Says In Q&A On Avastin Approval

The Cancer Letter asked Richard Pazdur, director of the FDA Office of Oncology Drug Products, to comment on the agency's decision last week to approve the Genentech drug Avastin (bevacizumab) for front-line treatment of metastatic breast cancer.

The agency's action was something of a regulatory cliff-hanger that was watched closely by drug developers and patient advocates.

Genentech's application was based on a cooperative group trial that was not initially intended to support registration. That study, called E2100 showed a highly statistically significant improvement in PFS, but no improvement in overall survival in a setting where FDA has historically demanded a survival advantage.

In December, the agency's Oncologic Drugs Advisory Committee voted 5-4 against approval, and two weeks before the regulatory deadline

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ESA Controversy:

Meta-Analysis Finds ESA Use In Oncology Associated With Increases In VTE, Mortality

By Paul Goldberg

A meta-analysis published in the Feb. 27 issue of the Journal of the American Medical Association found that the use of erythropoiesis-stimulating agents in oncology is associated with statistically significant increases in venous thromboembolism and mortality.

The paper comes to nearly identical conclusions as the findings the same lead author presented at a poster session at last year's meeting of the American Society of Clinical Oncology (The Cancer Letter, June 1 and June 8, 2007).

However, at that time, the analysis included fewer studies, and relied on a cut-point to separate studies performed before 2003 from those performed subsequently.

The JAMA paper analyzes studies that have been reported through last month, and doesn't make use of a cut-point.

"When you put all these studies together, there is a 10 percent increase in relative risk of death and a 57 percent relative risk of VTE," said Charles Bennett, an oncologist at the VA Chicago Center for Management of Complex Chronic Care and an oncologist at Northwestern University Feinberg School of Medicine.

The mortality findings are based on pooling the results of 51 clinical

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FDA Will Require Survival Data For Avastin's Regular Approval

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for the agency's action, another trial, called AVADO, conducted by Roche, appeared to have confirmed the results of E2100.

The interview with Pazdur was conducted via email earlier this week, following the agency's Feb. 22 decision to approve the supplemental Biologics License Application for Avastin in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

TCL: Why is this an accelerated approval? What sort of data are you looking for to convert it to a regular approval?

PAZDUR: The final rule in 1992 stated that "accelerated approval" may be considered when approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival pending completion of studies to establish and define the degree of clinical benefit.

Most examples of accelerated approval in oncology have focused on the surrogate endpoint aspect of the provision. An improvement in PFS in some settings is a clinical benefit (see below).

Since this is the first time we are accepting PFS in a first-line metastatic breast cancer setting as the basis for approval, we wanted further information on Avastin's effect not only on PFS, but also survival and other endpoints to further define the degree of clinical benefit.

Since this is the first time we used PFS in a first-line breast setting, FDA desired further information on Avastin's effect on PFS, survival and other endpoints to be submitted. Although we had the top-line results of the AVADO trial, we did not have the data to review and the sponsor is now obligated to provide us this data.

In addition to the AVADO trials, an additional phase III trial (AVF369Fg) in patients with untreated metastatic breast cancer will be submitted. These two trials are required under the accelerated approval.

Additional trials the sponsor has agreed to conduct and report include a phase III trial in previously treated breast cancer, a phase III trial evaluating Avastin with trastuzumab and docetaxel, and a phase III trial of endocrine therapy alone or with Avastin.

TCL: Is the use of PFS precedent-setting?

PAZDUR: The agency has accepted PFS as a primary registration endpoint in the past. Recent approvals for renal cell cancer (Nexavar), multiple myeloma (Revlimid), GIST (Sutent), ovarian cancer (Gemzar), and breast cancer (Taxol, Ixempra, and Tykerb) have all been based on PFS as a primary endpoint for registration.

The three breast cancer approvals were in more heavily pre-treated patients. As stated above, this Avastin approval is the first time we used PFS as the primary registration endpoint in first-line metastatic breast cancer. PFS was the pre-defined primary endpoint of the trial.

CL: Does PFS constitute a clinical benefit?

PAZDUR: We have had many meetings on this subject. Considerable discussions have occurred both within the agency, with international regulatory agencies, at ODAC meetings, and in workshops held in conjunction with ASCO, AACR, and ASH examining endpoints in a variety of malignant diseases.

I have heard vocal advocates for both positions. The December ODAC discussions on Avastin mirrored this division.

Our European counterpart, the EMEA, has long advocated the use of PFS in the first-line setting, citing PFS as a more proximal evaluation of the drug effect to its endpoint than overall survival.

There are concerns that post-progression therapies—either crossover or new therapies—may confound a survival analysis. After disease progression, we usually have limited information on

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

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

Subscriptions/Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
General Information: www.cancerletter.com

subsequent therapies and their doses and duration—all of these factors could theoretically confound a survival analysis.

Whether PFS is a clinical benefit is a judgment. I appreciate arguments on both sides of the issue. Any discussion about PFS as an endpoint assumes that methodological issues in assessing and measuring the endpoint have been adequately addressed.

PFS is a clinical benefit in the right context. In this case, a robust delay in progression accompanied by a doubling of response rate was considered a benefit to patients facing a progressive, incurable disease. All data—other trials, secondary endpoints, prior regulatory history—should be brought into the regulatory decision-making process. The efficacy data should be weighed against the drug's adverse event profile.

Skeptics cite that PFS has not been linked to symptom benefits or quality of life. These relationships are difficult to prove. Most oncology trials are unblinded; hence, the evaluations of symptoms and health-related quality of life may be unreliable.

Good performance status patients, unlikely to experience symptoms during the evaluation period, are entered on most oncology trials, making a link from an improvement in PFS to amelioration and/or delay of symptoms quite difficult.

TCL: What role did the AVADO trial play in the agency's decision?

PAZDUR: At the December ODAC meeting, data from two trials in women with breast cancer were presented.

One first line trial (Trial 7 or E2100) demonstrated a robust effect on PFS when Avastin was combined with paclitaxel. Another trial (Trial 8) failed to improve PFS and overall survival when Avastin was combined with capecitabine in a more refractory disease setting.

The agency asked the sponsor for the top-line results of the AVADO trial, since they were available close to our action date. The results supported our decision.

TCL: Does the acceptance of PFS bring you in alignment with the EMEA? Does the accelerated approval on the PFS endpoint now constitute an acceptable endpoint for biologics in the front-line setting? If so, does this hold for chemotherapeutics?

PAZDUR: The EMEA approved the Avastin application a year prior to our decision. They have routinely used PFS in first-line settings for many applications over the years.

In contrast, EMEA usually requests the demonstration of an improvement in overall survival in refractory settings for approval. With this approval, we have now used PFS in the first-line setting.

Data on overall survival should be collected irrespective of the primary endpoint of the trial. We have asked sponsors to ensure that trials are adequately sized to examine overall survival.

Since survival is both a safety and efficacy endpoint, we must have assurance that there is no detrimental survival effect.

We do not differentiate endpoints based on class of products—biologic versus drug.

TCL: What would you say to people who believe that acceptance of PFS constitutes a lowering of the bar of cancer drug approvals?

PAZDUR: We have to demonstrate flexibility in providing drugs to patients with advanced malignancies.

To state that we would never approve a drug unless it demonstrated a statistically significant effect on overall survival is overly rigid.

Although all agree that an improvement in overall survival is the "gold standard," many—including patients, oncologists, and drug regulators—have voiced that a delay in progression, as noted above, may be of clinical benefit.

FDA examined the totality of evidence in formulating the Avastin decision. This is a supplemental BLA with two prior approvals demonstrating improvements in overall survival both in metastatic lung and colorectal cancer.

The breast cancer trial met its primary endpoint ($p<0.0001$) with a hazard ratio of 0.48. The effect of the drug was supported by an improvement (doubling) of response rate. Multiple sensitivity and subgroup analyses corroborated the drug effect.

There was close agreement between investigator-assessed endpoints—both PFS and response rate—and the independent radiographic facility (IRF). Analyses examining "missing data" did not support the introduction of systematic bias.

We were provided results of a second trial (AVADO) in the first-line setting that met its primary endpoint of improving PFS. There is an extensive database of clinical trials and post-marketing safety data.

The total body of evidence for the approval of this supplement was consistent with other supplemental BLA/NDA approvals in oncology.

TCL: Does taxane plus bevacizumab now become the standard of care or an acceptable

comparison arm in the front-line setting? What are the toxicities?

PAZDUR: As stated above, we are approving a supplemental BLA. "Standards of care" are set by the practice of medicine. Avastin may be an appropriate choice for some patients; it may not be for others. There is a choice.

The adverse events for Trial E2100 are clearly described in the product label. The addition of Avastin to paclitaxel resulted in an increase in Grade 3 to 5 AEs.

There were no differences between paclitaxel and Avastin plus paclitaxel in treatment-related discontinuation of therapy. FDA and the sponsor agreed that fatal adverse reactions occurred in 1.7% (6/363 patients) of the Avastin-treated patients; this statement is in product labeling.

The sponsor contended that despite these deaths there was a 7% absolute improvement in survival at 1-year associated with Avastin, and that the increased AEs should be viewed in the context that Avastin-treated patients received more therapy (median 10 cycles) compared to those treated with paclitaxel alone (median 6 cycles). Patients need to discuss these risks and benefits with their oncologists.

Since Avastin was an approved drug, many patients with breast cancer were being treated with the drug "off-label." FDA has long held that a reason to encourage sponsors to submit supplemental BLAs/NDAs is provide both the patient and physician with prescribing information that the agency has reviewed.

The Avastin prescribing information now includes FDA-reviewed safety and efficacy data for breast cancer. With this specific approval, we also wanted patients to be aware of the "negative" breast cancer trial conducted in more refractory disease patients. Hence, this trial was included as well as a specific statement in INDICATIONS—"Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy for metastatic disease."

Regarding future trials—The use of Avastin plus paclitaxel would be an appropriate comparator for a registration trial. However, we would not say that it must be the comparator.

TCL: Does this approval set a precedent for drugs that may have had trouble getting through the regulatory process?

PAZDUR: As noted above, the E2100 trial was statistically robust. We are confident in an effect on the primary endpoint.

Many drugs that have had trouble at ODAC or in FDA review have failed to meet their primary endpoints. Attempts have been made to salvage these failed trials by exploratory analyses—either examining secondary endpoints or subsets of patients for efficacy claims or post-hoc analyses that were not pre-specified or planned. In most cases, we lack any degree of certainty of these effects. These analyses are exploratory or hypothesis-generating.

The "uncertainty" conveyed by accelerated approval is not whether there is a drug effect on the primary endpoint or its robustness, but on relationship of the endpoint to a clinical endpoint. Drugs approved under accelerated approval should have substantial evidence of their effect.

TCL: This trial raised questions about the need for central radiology review in trials run by cooperative groups. Should there be different standards for cooperative groups versus drug companies? Are there situations where you might consider not requiring central radiology or find another method for reducing the need for repeated radiology review?

PAZDUR: The purpose of the independent review is to verify that bias has not been introduced in the measurement and interpretation of subjective endpoints. In general, if a trial is blinded, we have not requested a review of radiographs. In contrast to E2100, the AVADO trial was blinded and did not have a central review.

After the E2100 trial was submitted, the FDA and NCI met to discuss procedures for registration trials to be conducted by cooperative groups. We agreed to meetings prior to the initiation of the future trials to discuss the trial's endpoints, need for radiographic review, safety data to be collected, and statistical plans. All parties-FDA, NCI CTEP, the cooperative group and the commercial sponsor should be present. These protocols are requested to be submitted as special protocol assessments.

We do not have separate standards for cooperative groups versus commercial sponsors.

ESA Controversy:

Study Finds Significant Increases In VTE, Deaths

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trials with 13,611 patients, and the VTE findings are based on 38 trials with 8,172 patients.

In the pooled studies, there were 334 VTE events among 4610 patients treated with ESAs, compared to 173 events among 3,562 control patients, which

translates into a 7.5% vs. 4.9% relative risk, 1.57; 95% CI, 1.31-1.87. The hazard ratio for mortality risk was 1.10; 95% CI, 1.01-1.20).

"We cannot identify any particular subset of patients where this drug is particularly safe or unsafe," Bennett said. The study doesn't provide empirical data related to tumor promotion. "What needs to be done is a correlation between what we found and the basic science," he said.

The findings, which were widely reported in the press, represent the first meta-analysis to show significantly increased mortality risks associated with ESAs. Also, the findings are consistent with eight separate studies pointing to toxicity and tumor promotion potential of these widely used agents (The Cancer Letter, Dec. 7, 2007).

The FDA Oncologic Drugs Advisory Committee is scheduled to review the new negative data at a meeting March 13. The label for these agents has been changed twice last year, the Centers for Medicare and Medicaid Services has tightened its coverage criteria, and according to industry figures, utilization of ESAs in oncology has dropped by about half in a year (The Cancer Letter, Jan 25).

Amgen Inc. and Johnson & Johnson, the companies that market ESAs, said the meta-analysis is inconclusive.

"This meta-analysis, which was previously presented last year, does not define any new risks associated with ESAs, and the risk of VTEs is included in current labeling and has been for some time," Ashley Koss, an Amgen spokesman, said in an email. "It's important that physicians and patients fully understand the benefit (transfusion avoidance) and risks and that these drugs be used appropriately according to the FDA approved labeling."

Ortho Biotech, a unit of J&J, said in a statement that the paper doesn't provide "an accurate reflection of the safety profile of erythropoiesis-stimulating agents when used for the treatment of chemotherapy-induced anemia in patients with cancer."

J&J said that "when used according to product labeling, ESAs remain safe and effective, and are the only proven treatment alternative to blood transfusions for patients with CIA." Amgen, J&J and Roche are providing data from their studies to the Cochrane Collaboration of meta-analysts to pool the studies on the patient level, creating a database of more than 15,000 patients.

The companies note that the studies that sparked concerns about safety of ESAs had the hemoglobin targets above 12 g/dL, the highest acceptable level noted on the label.

However, skeptics point out that the rationale for the label is thin since ESAs were approved based on their ability to prevent blood transfusions, and harder endpoints, including survival and disease progression weren't addressed. Toxicity and tumor promotion data were found in recent, more rigorous studies undertaken by the companies to justify pushing up the targets.

Michael Henke, one of the authors of the JAMA paper, said the results should influence the practice of medicine. "It's the first meta-analysis that confirms studies showing negative effects of ESAs," said Henke, a radiation oncologist at Freiburg University Clinic and author of a study that found negative effects of ESAs in head and neck cancer patients. "Changes in registration and treatment guidelines should be expected."

The American Cancer Society said the study raises questions about criteria for drug approval as well as control over marketing programs.

"The question we now need to ask ourselves is this: Why did this happen, and how do we prevent this from happening again?" said Len Lichtenfeld, ACS deputy chief medical officer. "These drugs were heavily promoted to doctors and even directly to patients. They became a widely used treatment before we truly understood their benefits and risks. If we fail to scrutinize how this happened, we are destined to repeat the same mistakes again and again."

Amgen stock lost about $1.50 per share over two days following the release of the JAMA paper, trading at $45.53 when the market closed Feb. 28. J&J stock dropped by about $1.90, trading at $61.71.

In the Courts:

Ohio Court Fines Group That Sought Newsletter's Confidential Sources

By Kirsten Boyd Goldberg

An Ohio judge ordered a prostate cancer organization to reimburse The Cancer Letter for legal expenses the newsletter incurred to defend itself from subpoenas seeking confidential source materials.

In the Feb. 26 ruling, Judge Gregory Frost of the United States District Court for the Southern District of Ohio, ordered the Ohio-based CareToLive to pay The Cancer Letter $6,000, about half of the expenses the newsletter incurred to respond to the subpoenas, which were found invalid by a court in Washington, D.C.

CareToLive's attorney, Kerry Donahue, engaged

in "unreasonable conduct" in the matter, Frost wrote. "Donahue was informed on several occasions as to the invalidity of the subpoenas, but failed to correct them," Frost wrote. "Moreover, it is clear that at least some of Donahue's behavior was meant to harass."

Donahue sought The Cancer Letter's confidential source materials in reporting on FDA's consideration of a Biological License Application for Provenge, a prostate cancer treatment by Dendreon Corp. Donahue also sought a physical inspection of The Cancer Letter's office in Washington, D.C.

CareToLive claimed The Cancer Letter's source material was relevant to the group's lawsuit against the federal government. The suit, filed last July, charged that FDA acted improperly in not approving Provenge last spring, and instead requesting more data from the sponsor.

Named in the suit were FDA Commissioner Andrew von Eschenbach, HHS Secretary Michael Leavitt, and FDA Office of Oncology Drug Products Director Richard Pazdur. Also named was Howard Scher, chairman of urologic oncology at Memorial Sloan-Kettering Cancer Center, in his capacity as a special government employee serving on the FDA advisory committee that reviewed Provenge.

Frost dismissed the suit, *CareToLive v. Andrew von Eschenbach*, on Nov. 21. CareToLive has filed an appeal.

Last November, Judge Royce Lamberth of the District of Columbia District Court denied CareToLive's petition to enforce the subpoenas against The Cancer Letter because the subpoenas were "facially invalid." Lamberth ruled that CareToLive's conduct was sanctionable, but sanctions would have to be sought in Ohio, where the suit was filed.

Frost's and Lamberth's opinions are posted at www.cancerletter.com.

In Brief:

NCAB Members Finish Terms; Emory Names Nursing Director

NCI RECOGNIZED five members of the National Cancer Advisory Board who completed their terms on the board: **Moon Chen**, of UC Davis Cancer Center; **Kenneth Cowan**, director of the Eppley Institute for Research in Cancer at University of Nebraska Medical Center; **Jean De Kernion**, professor and chairman of urology at David Geffen School of Medicine at UCLA; **Franklyn Prendergast**, director of the Mayo Clinic Comprehensive Cancer Center; and **Lydia Ryan**, of Children's Healthcare of Atlanta, AFLAC Cancer Center. . . . **DEENA GILLAND** was appointed director of nursing for Emory University Winship Cancer Institute, according to **Brian Leyland-Jones**, director Emory Winship. Gilland previously served as oncology services department director for Emory University Hospital. She joined the hospital in 1988 as a staff nurse in oncology and served as nurse manager in the Hematology/Leukemia Unit from 1996 to 2005. Gilland earned an M.S. in leadership and healthcare administration through Emory's Nell Hodgson Woodruff School of Nursing. She is a member of the Oncology Nursing Society and serves as a faculty member in Emory Healthcare's Oncology Residency Program. Gilland also is a member of the American Nurses Association and the Georgia Organization of Nurse Executives. . . . **SARAH CANNON RESEARCH** Institute announced two appointments. **Johanna Bendell** was named director of GI cancer research and will assume a leadership role in the SCRI Phase I Unit. Bendell was assistant professor of medicine at Duke University. **Daniel Couriel**, director of allogeneic transplantation for The Sarah Cannon Bone Marrow Transplant Program in Nashville, was named director of transplantation research at Sarah Cannon Research Institute. He will hold both positions. Prior to SCRI, Couriel was associate professor of medicine in the Department of Stem Cell Transplantation and Cellular Therapy at M.D. Anderson Cancer Center, where he led the acute and chronic graft-versus-host disease clinical and research programs. Bendell and Couriel practice at Tennessee Oncology. SCRI is a research program formed in 2004 as a joint venture between HCA and Tennessee Oncology. SCRI conducts community-based clinical trials in oncology and other therapeutic areas through affiliations with a network of nearly 500 physicians in 23 states.

Professional Societies:

Levine, Mendelsohn Win Landon-AACR Awards

Scientists whose discoveries have led to fundamental advances in the science and treatment of cancer are the recipients of two prizes offered by the Kirk A. and Dorothy P. Landon Foundation and the American Association for Cancer Research.

Arnold Levine, professor at the Institute for Advanced Study, School of Natural Sciences, and professor of pediatrics and biochemistry at UMDNJ-Robert Wood Johnson Medical School and the Cancer Institute of New Jersey, will receive the Kirk A. Landon-

AACR Prize for Basic Cancer Research. Levine is recognized for his work in establishing p53 as a tumor suppressor and for his contributions to understanding of the molecular basis of cancer.

John Mendelsohn, president and professor of cancer medicine at The University of Texas M. D. Anderson Cancer Center, will receive the Dorothy P. Landon-AACR Prize for Translational Cancer Research, for his pioneering translational research that led to the discovery of a new class of agents to treat cancer.

Honorees for each prize receive an unrestricted cash award of $100,000 and present a scientific lecture at the AACR annual meeting, scheduled for April 12-16 in San Diego, Calif.

Best known for his co-discovery of the p53 tumor suppressor protein, Levine has led the way in uncovering the actions of p53, its biological significance and its mode of regulation in normal and cancer cells. Based on the findings of Levine and his colleagues, the study of p53 has become a promising focus of basic cancer research. This work and the collaboration of many researchers has led to the realization that p53 is a pivotal tumor suppressor gene which is mutated or otherwise inactivated in a majority of human cancer cases, a fact that underscores its critical importance in preventing the development of cancer.

Levine discovered another piece of the puzzle with the identification of the Mdm2 oncoprotein as a potent inhibitor of p53. The Mdm2-p53 interaction has become a target for drug development studies, yielding several promising small molecule candidate drugs that activate p53 in tumor cells through disruption of the Mdm2-p53 interaction.

"The work of Dr. Arnold Levine has proven to be a cornerstone in our understanding of cancer on the molecular level," said Lewis Cantley, professor in the department of systems biology, Harvard Medical School and chairman of the Kirk A. Landon-AACR Prize for Basic Cancer Research selection committee. "With the discovery of the p53 tumor suppressor came a heightened interest and renewed fervor in building upon this area of basic cancer research. Decades later, researchers are still uncovering new pieces to the p53 puzzle, and Dr. Levine's influential thinking and trail-blazing work remain highly relevant to continued progress in molecular cancer research."

Mendelsohn has dedicated his research efforts to understanding how growth factors regulate the proliferation of cancer cells by activating receptors on the surface of the cells. Mendelsohn and his colleagues were the first to propose a new approach to cancer therapy by suggesting that blocking the epidermal growth factor receptor (EGFR) could prevent cancer cell growth and reproduction.

Mendelsohn and his colleagues proved their hypothesis by producing an anti-EGF receptor monoclonal antibody that blocked receptor kinase activation and inhibited cancer cell growth. Continued research on EGF receptors, carried out by Mendelsohn and numerous collaborators for almost two decades, proved the original demonstration that both inhibition of a growth factor receptor and inhibition of a tyrosine kinase could be useful approaches to creating new categories of anti-cancer agents.

The development of C225, the human chimeric version of the anti-EGF receptor monoclonal antibody, has changed the way some advanced cancers, including advanced head and neck and pancreatic cancers, are treated and it led to the 2004 FDA approval of cetuximab for treatment of advanced colorectal cancer. There are more than 130 active clinical trials using C225 to treat 15 cancer subtypes and two non-cancer diseases.

"Dr. John Mendelsohn had a hunch that paid off. When he identified an antibody against the EGF receptor in the early 1980s, he immediately forged ahead on the path to evaluate and develop this antibody as a treatment for tumors that expressed high levels of the receptor and relied on it for growth," said Stanton Gerson, director of the Case Comprehensive Cancer Center and chairman of the Dorothy P. Landon-AACR Prize for Translational Cancer Research selection committee.

"While the path was arduous, as it often is for pioneers in cancer therapy, Dr. Mendelsohn's hypothesis turned out to be spectacular, resulting in a new and effective treatment for many patients with non-small cell lung cancer and head and neck cancer," Gerson said. "His work, perhaps the most important new development in cancer therapeutics in the past 20 years, has helped define the field of targeted and personalized therapy for cancer. Rarely does a single discovery have such impact in the field of cancer."

Ullrich Wins Pezcoller-AACR Award

Axel Ullrich is the recipient of the 2008 Pezcoller Foundation-AACR International Award for Cancer Research for his pioneering work in the translation of genomics-based discoveries into novel approaches for cancer therapy. Ullrich is the director of molecular biology at the Max Planck Institute of Biochemistry in Martinsried, Germany, and is an expert in gene technology and one of the most frequently cited cancer scientists in the area of signal transduction research.

The award recognizes an individual who has made a major scientific discovery in basic or translational cancer research. The Pezcoller Foundation will hold an award ceremony in early May in Trento, Italy, where Ullrich will receive a cash award of €75,000.

Lauded for his contributions to the discovery of the HER2/neu oncogene, Ullrich has led the cancer research field in gene technology, studying gene expression and translating basic science discoveries into clinical applications and therapies. In the gene technology field's early days, Ullrich and his colleagues were the first to clone the genes of medically important proteins including the precursor to insulin, which led to the development of Humulin, the first therapeutic agent to be developed through gene-based technology. This research led to further study of the molecular genetic characterization of cell surface receptors through which Ullrich ushered in a new field of study, signal transduction. Ullrich's work in signal transduction research has uncovered fundamental molecular mechanisms that determine the physiology of normal cells and has provided insights into similar mechanisms in other major human diseases.

Ullrich's recent work led to the development of the first multi-targeted kinase inhibitor, SU1128/Sutent, approved by FDA in 2006 for the treatment of kidney carcinoma and gastrointestinal stromal tumors. He is currently investigating the impact of SNPs on cancer progression, susceptibility, resistance, and therapy response.

Funding Opportunities:

RFA Available

RFA-CA-08-017: Comparative Systems Genetics of Cancer. R01. Letters of Intent Receipt Date: April 14. Application Due Date: May 14. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-017.html. Inquiries: Cheryl Marks, 301-594-8778; marksc@amil.nih.gov.

Requests for Proposals

RFP No. N01-RC-81009-16: NCI Center for Cancer Research, Metabolism Branch, is soliciting proposals for a contractor that would identify and recruit between 20 and 80 new patients with HTLV-1 Associated Adult T-Cell Leukemia/Lymphoma for inclusion in phase I/II trials at NCI. The offeror would identify patients who meet the criteria specified by the Clinical Trials Protocols that will be provided to them by the MB, NCI. Contractor must demonstrate the ability to identify and provide follow up medical treatment and monitoring of patients diagnosed with HTLV-1 ATL. In addition, any contractor must be able to assume follow-up monitoring of current patients being monitored in Jamaica.

The contractor would provide the following: 1. identify members of this specific patient population; 2. interact with the staff at NCI, assist staff and patients with compliance of the clinical protocols for treatment of the patients at the NIH Clinical Center, in Bethesda, and then follow-up when the patients have returned to their home country; 3. perform patient diagnoses, pre-referral evaluations including laboratory data, post-referral evaluations, and provide blocks and slides of tissues to NCI; 4. assist patients in obtaining VISAs, passports and other documentation required for travel to the Washington, D.C. area airports, and to NCI from their hoc country; 5. interact with NCI staff electronically concerning patient issues; 6. comply with U.S. Food and Drug Administration regulations concerning Investigational New Drugs, adhere to all required Institutional Review Board regulations of NCI, and comply with the ethical regulations of the NIH Clinical Center in Bethesda; and 7. adhere to regulatory agency requirements in the contractor's geographic location.

The etiology of HTLV-1 ATL is such that the human populations who carry this disease exist in the Caribbean basin, areas of Japan, and sub-Saharan Africa, thus limiting participants for NCI studies to these locations. Inquiries: Annmarie Keane, 301-435-3814; keanea@mail.nih.gov.

RFP S08-080: CMO for Production of IL-15. Response Due date: Feb. 22. Full text: http://www.fbodaily.com/archive/2008/02-February/08-Feb-2008/FBO-01501603.htm. Inquiries: Melissa Borucki, 301-228-4041, mborucki@ncifcrf.gov. or gene Anderson, 301-228-4008, eanderson@ncifcrf.gov.

RFP S08-119: Cancer Biomarker Assays for Evaluation of In Vitro Nanoscale Diagnostic Devices. Response Due date: March 14. Full text: http://www.fbodaily.com/archive/2008/02-February/21-Feb-2008/FBO-01511461.htm. Inquiries: Matt Desantis, 301-228-4002, mdesantis@ncifcrf.gov. or Gene Anderson, 301-228-4008, eanderson@ncifcrf.gov.

RFP S07-103: caBIG Knowledge Centers. Response Due Date: March 19. Jennifer Thomas, 301-228-4004, thomasj@ncifcrf.gov. or Shannon Jackson, 301-228-4022, sjackson@mail.ncifcrf.gov. Full text: http://www.fbodaily.com/archive/2008/02-February/21-Feb-2008/FBO-01511466.htm.

RFP N02-CM-81010-48: Central Institutional Review Board Initiative. Response Due date: April 4. Full text: http://www.fbodaily.com/archive/2008/02-February/21-Feb-2008/FBO-01511468.htm. Inquiries: John Manouelian, 301-435-3813, jm486p@nih.gov. or Richard Hartmann, 301-496-8620, rh75f@nih.gov.

RFP N02-CP-81015-49: Multi-disciplinary Investigations of Environmental Causes of Cancer. Full text: http://www.fbodaily.com/archive/2008/02-February/16-Feb-2008. Inquiries: Sharon Miller, 301-435-3783, sm103r@nih.gov. or George Kennedy, 301-435-3779, kennedyg@mail.nih.gov.

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THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

Sanofi-aventis Seeks sNDA For Eloxatin To Include Survival and DFS Data

Sanofi-aventis of Bridgewater, N.J., said FDA has accepted for filing and assigned priority review status to a supplemental new drug application for changes to the Eloxatin (oxaliplatin injection) prescribing information to include a six-year analysis from the MOSAIC trial.

In the changes, sanofi-aventis said it seeks the inclusion of six-year overall survival and five-year disease free survival data in stage III colon cancer treated with either FOLFOX4 (Eloxatin-based chemotherapy regimen) or standard infusional 5-FU/LV-based chemotherapy alone, following surgery to remove the primary tumor.

In the randomized-controlled 2,246-patient trial, treatment after

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Deals & Collaborations:

Mass. General Developing 3D Imaging Technology With Help From NUCAR, NSF

Northeastern University Computer Architecture Research Lab of Waltham, Mass., and **Center for Subsurface Sensing and Imaging Systems**, **National Science Foundation,** said they are working with **Massachusetts General Hospital** on Digital Breast Tomosynthesis, a breast cancer detection technology.

The system creates a 3D breast image using a series of x-ray projections collected during a 20- second, 40-degree sweep, the groups said. The technology makes cancer lesions easier to detect among dense breast tissue by creating a stack of 1mm spaced high-resolution slices that can be displayed individually, or assembled into a 3D view.

NUCAR said it created a DBT reconstruction application on their desktop PCs using MATLAB, and then running the code on a Linux parallel cluster using Star-P software from Interactive Supercomputing Inc. With the Star-P approach, imaging reconstruction can be completed in minutes. The parallel programming task has been simplified using Star-P, reducing development time from months to days.

The Northeastern team said it was supported by a NSF Small Business Technology Transfer project with ISC, the NSF CenSSIS, and by Massachussetts General Hospital, the groups said.

"The support from Northeastern has radically shifted this paradigm," said Richard Moore, program director for Breast Imaging Research and CenSSIS at MGH. "With this kind of performance, we can realistically rely

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

Eloxatin sNDA Seeks To Add Data In Stage III Colon Cancer

(Continued from page 1)

complete surgical resection of the tumor with Eloxatin in combination with infusional 5-FU/LV had a 20 percent reduction in the risk of dying after a median of six years compared to standard 5FU/LV-based chemotherapy alone (hazard ratio of 0.80, confidence interval [0.65, 0.97], p=0.023), the company said. Also, disease-free survival (risk of disease recurrence) was improved by 22 percent in stage III (HR=0.78 [CI: 0.65, 0.93], p=0.005).

The most frequently reported side effect was neutropenia, with 78.9 percent affected, the company said. Neutropenia was complicated by fever or infection in only 1.8 percent of cases, the company said. 92.1 percent treated with Folfox4 had peripheral sensory neuropathy. Of the events, 12 percent were severe (grades 3 and 4), and half (48.2 percent) of the episodes were grade 1. Among those experiencing grade 3 peripheral sensory neuropathy, partial or total recovery was observed in most cases within 18 months following treatment. Patients receiving FOLFOX4 also reported nausea (73.7 percent), diarrhea (56.3 percent) and vomiting (47.2 percent).

The primary endpoint of MOSAIC evaluated how the addition of Eloxatin affected disease-free survival at three years. Secondary endpoints included overall survival and safety, including long-term adverse effects. Based on the data, Eloxatin in combination with infusional 5-FU/LV was granted U.S. approval in 2004 for stage III colon cancer with primary tumors surgically removed. At the time of the original analysis, there was no demonstrated benefit in overall survival after a median follow-up of four years, the company said.

Pharmion Corp. (NASDAQ:PHRM) of Boulder, Colo, said the European Medicines Agency has issued a positive opinion to recommend approval of the Marketing Authorization Application for Thalidomide Pharmion in combination with melphalan and prednisone untreated multiple myeloma, for those aged 65 years or older or ineligible for high dose chemotherapy.

Once ratified by the EC, a single marketing authorization would be granted to Pharmion to market its product for first line multiple myeloma in the 27 member states of the E.U. as well as Norway and Iceland, the company said.

The EMA positive opinion was based on data from studies of 1,400 patients, including the Intergroupe Francophone du Myelome 99-06 survival study. The three-arm study demonstrated the superiority of melphalan/prednisone plus Thalidomide over standard therapy of melphalan/prednisone or a combination of chemotherapies (vincristine, adriamycin, and dexamethasone) followed by melphalan and transplantation in newly diagnosed multiple myeloma, age 65 to 75 who were ineligible for intensive bone marrow transplantation. The study randomized 447 patients to one of the three treatment arms.

At final analysis, the overall median survival in the MPT arm was 51.6 months, compared to 33.2 and 38.3 months, respectively, for the MP and MEL 100 arms. The hazard ratios were 0.59 and 0.69, respectively. Thalidomide treatment was generally well-tolerated by the majority. Frequently reported adverse events associated with MPT included neutropenia, somnolence and constipation. The Thalidomide combination was also associated with a 5-10 percent greater risk of Grade 3 and 4 venous thromboembolism and peripheral neuropathy, the company said.

"Our study results demonstrate the profound impact on overall survival that the addition of Thalidomide to the standard of care can provide in untreated multiple myeloma," said Philippe Moreau, professor of clinical hematology at Nantes Faculty of Medicine and chairman of the Intergroupe Francophone du Myelome. "The recommendation recognizes the importance of the study results, opens drug access to all physicians and patients in Europe and provides great hope."

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Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

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In another development, Pharmion said the European Medicines Agency has accepted for review its Marketing Authorization Application for Vidaza (azacitidine for injection) in higher-risk myelodysplastic syndromes.

The phase III multi-center, international, randomized study demonstrated superiority in overall survival of Vidaza versus conventional care regimens, the company said.

Vidaza was designated as an Orphan Medicinal Product in the EU for MDS and for acute myeloid leukemia, the company said.

The agent exerts its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow, the company said.

Veridex LLC of Raritan, N.J., said FDA granted an expanded clearance for the CellSearch System to be used as an aid in the monitoring of metastatic prostate cancer patients. The system currently is cleared for monitoring metastatic breast and metastatic colorectal cancer patients.

CellSearch identifies and counts circulating tumor cells (CTCs) in a blood sample to predict progression-free survival and overall survival in patients with metastatic breast, colorectal, or prostate cancer, and can do so earlier than the current standard of care, the company said.

ActivBiotics of Wellesley Hill, Mass., said The Committee for Orphan Drug Products of the European Medicines Agency has granted orphan drug designation for M40403 to prevent oral mucositis in head and neck cancer patients receiving radiotherapy.

Algeta ASA (OSE: ALGETA) of Oslo said it would begin clinical development of Alpharadin in hormone-refractory prostate cancer in the U.S.

FDA has cleared the IND without objections to the application, the company said. Alpharadin has been studied in phase II trials in Europe and has demonstrated a significant survival benefit in HRPC with skeletal metastases, the company said.

BC1-08, an initial phase I pharmacokinetics, biodistribution, and dosimetry study with Alpharadin in HRPC with skeletal metastases will be conducted at the Memorial Sloan-Kettering Cancer Center. The trial will further expand the information in a similar phase I study, BC1-05, conducted at the Royal Marsden Hospital in London, for which enrolment has been completed.

Kiadis Pharma of Amsterdam said FDA approved its IND application to begin a phase III study for Reviroc in the U.S.

Revirocis is under development for the elimination of cancer cells from an autologous graft in bone marrow transplantations for end-stage blood cancer.

The completed phase II study demonstrated an elimination of cancer cells from the autologous bone marrow graft prior to the transplantation and showed an overall survival after autologous bone marrow transplantations in Non-Hodgkin's lymphoma, the company said.

Cephalon Inc. (Nasdaq: CEPH) of Frazer, PA., said FDA has accepted its NDA for Treanda (bendamustine HCl) for Injection for indolent B-cell non-Hodgkin's lymphoma that has progressed during or following treatment with rituximab or a rituximab-containing regimen.

The NDA is supported by three studies in NHL, including two single-agent studies and one in combination with rituximab, the company said. Treatment with Treanda had a high rate of response and a manageable and tolerable side effect profile, with adverse events similar to other chemotherapy agents such as myelosuppression, nausea, and vomiting.

Treanda is a hybrid of a purine analog and an alkylator, the company said.

Infinity Pharmaceuticals Inc. (Nasdaq:INFI) of Cambridge, Mass., and **MedImmune** of Gaithersburg, Md., said the U. S. Adopted Names Council, in consultation with the World Health Organization International Nonproprietary Names Expert Committee, has approved the nonproprietary or generic name retaspimycin for IPI-504, their heat shock protein 90 inhibitor.

Retaspimycin hydrochloride is in clinical trials for solid tumor cancers, including gastrointestinal stromal tumors, non-small cell lung cancer, and hormone resistant prostate cancer, the companies said.

In preclinical studies, retaspimycin killed cancer cells by inhibiting Hsp90, the companies said.

MedImmune is wholly owned by AstraZeneca plc (LSE:AZN) (NYSE:AZN).

VioQuest Pharmaceuticals (OTCBB: VQPH) of Basking Ridge, N.J., said FDA has granted orphan drug designation to VQD-002 (triciribine phosphate monohydrate or TCN-P) for multiple myeloma.

VQD-002, a tricyclic nucleoside that inhibits the

phosphorylation of Akt, has demonstrated anti-tumor activity against cancers in preclinical and clinical studies, the company said.

Deals & Collaborations:

Alfacell, BL&H, In Agreement On Distribution For Onconase

(Continued from page 1)
on 3D methods that were out of the question previously. It's not just the speed, it's the exploratory freedom."

Alfacell Corp. (NASDAQ:ACEL) of Somerset, N.J., said it has entered into a distribution agreement with **BL&H Co. Ltd**. of Southeast Asia to commercialize Onconase (ranpirnase) in South Korea, Taiwan and Hong Kong.

The drug candidate is in a confirmatory phase IIIb for unresectable malignant mesothelioma.

Under the agreement, Alfacell said it has granted BL&H exclusive rights in the defined territory for the marketing, sales and distribution of the product. Alfacell said it has received an up-front fee of $100,000. The company said it also will receive 50 percent of all net sales in the territory. In addition, Alfacell will manufacture and supply the product to BL&H, while BL&H will be responsible for all activities and costs related to regulatory filings and commercial activities in the territory.

Onconase, a natural protein isolated from the leopard frog, triggers apoptosis via multiple molecular mechanisms of action, the company said.

Caliper Life Sciences (NASDAQ:CALP) of Hopkinton, Mass., and **AntiCancer Inc.** of San Diego said they have entered into an agreement to establish a cross-licensing relationship and end patent litigation.

Under the arrangement, Caliper acquires the right to sublicense the AntiCancer fluorescent protein optical imaging patents to third parties, alongside the Caliper portfolio of in vivo fluorescent and bioluminescent optical imaging patents. AntiCancer acquires the right to sublicense the Caliper optical imaging patents, in the field of fluorescent protein imaging, to a specified annual number of third parties throughout the life of the agreement, alongside the AntiCancer fluorescent protein optical imaging patents. In addition, each company receives a royalty free license from the other for internal and contract research operations.

Cepheid (NASDAQ:CPHD) of Sunnyvale, Calif., and **Instrumentation Lab.** of Lexington, Mass., said they have released the Xpert HemosILFII & FV assay as a European CE IVD Mark product under the European Directive on In Vitro Diagnostic Medical Devices.

The assay delivers results in just over thirty minutes with a single GeneXpertcartridge, and detects Factor II and Factor V Leiden genetic variations associated with thrombophilia, the companies said. Developed and manufactured by Cepheid, the test should be ready for sale early next month.

Egenix Inc. of Millbrook, N.Y., said it has obtained a field-exclusive license under patent rights that cover technologies related to cancer therapy and prognostic testing from **Harvard University**.

The licensed technologies were developed jointly at Harvard Medical School by the Laboratory for Translational Research and the Department of Biological Chemistry and Molecular Pharmacology. They comprise small molecule inhibitors of translation initiation, a paradigm in target- specific, non-cytotoxic anti-cancer therapy, and the use of translation initiation-specific biomarkers to assess tumor sensitivity to anti-cancer therapy with the anti-cancer drugs. Specifically, the inhibitors of translation initiation licensed by Egenix from Harvard Medical School target the eIF4F and ternary complexes, the two regulators of messenger RNA translation into protein.

Exelixis Inc. (NASDAQ:EXEL) of South San Francisco said **Bristol-Myers Squibb Co.** (NYSE: BMY) has exercised its option to develop and commercialize the Exelixis compound XL139 in solid tumors.

Under the collaboration agreement, the selection of the compound entitles Exelixis to a milestone payment of $20 million, the company said. In addition, Exelixis said it would exercise its option to co-develop and co-commercialize XL139 in the U.S.

XL139 is a small molecule inhibitor of the hedgehog pathway, the company said.

Under the agreement, Exelixis deploys its drug discovery platform and is responsible for the identification and preclinical development of small molecule drug candidates against mutually selected targets, the company said. BMS has the right to select up to three IND candidates against three different targets for which it will pay $20 million per candidate. Following the selection, BMS will lead global activities, although the parties will co-develop and co- commercializes the programs in the U.S.

The parties said they will share equally

development costs, commercial profits and co-promotion responsibilities in the U.S., and Exelixis will receive royalties on product sales outside of the U.S.

Genmab A/S (OMX: GEN) of Copenhagen and **PDL BioPharma Inc.** (Nasdaq: PDLI) of Redwood City, Calif., said they have entered into an agreement under which Genmab would acquire the PDL antibody manufacturing facility of Brooklyn Park, Minn., for $240 million in cash.

The transaction also includes land, equipment, and access to a leased space housing a development lab, the companies said.

Genmab said the Minnesota facility will provide a sustainable source of both clinical and commercial scale material for its pipeline; it features two 1,000 liter and two 10,000 liter bioreactors, which support the simultaneous manufacture of multiple antibody products and will enable Genmab to transition three antibodies from research to manufacturing per year.

"Over the past few years Genmab has been preparing for the market launch of our late stage antibodies and we continue to build a broad pipeline of antibody products, which includes 10 products in clinical development. Consequently, the need to secure significant manufacturing capacity has become an increasing priority," said Lisa Drakeman, CEO of Genmab. "The new PDL manufacturing facility, with its complete antibody process development platform, represents our best option to secure manufacturing capacity."

In the transaction, Genmab said it would produce clinical material to supply the PDL investigational studies for its pipeline products under a clinical supply agreement.

Torben Lund-Hansen, vice president, head of manufacturing at Genmab since 2002, will be president of the manufacturing facility, the companies said. Lund-Hansen established manufacturing facilities for Novo Nordisk.

Lixte Biotechnology Holdings Inc. (BULLETIN BOARD: LIXT:OB) of East Setauket, N.Y., and its collaborator, **Surgical Neurology Branch** of the **National Institute of Neurological Disorders and Stroke, NIH,** said its compound LB-1, a patent-pending proprietary agent, has anti-cancer activity against medulloblastoma cells growing in culture and in a mouse model of cancer.

"In other studies done by Lixte independently of NIH, LB-1 and other lead compounds also have been found to have anti-cancer activity against a common human cancers growing in cell culture," said John Kovach, president and CEO of Lixte. "The effectiveness of the compounds will now be determined in mouse models of human cancer, starting with lung and pancreatic cancer."

Also, some of the Lixte compounds have been shown to have anti-fungal activity, the company said. LB-2.1 and other drugs in a second series of patent-pending proprietary compounds inhibit the growth of several types of fungi that cause life-threatening infections in the immuno-compromised, such as HIV-AIDS or bone marrow transplantation.

M. D. Anderson Cancer Center of Houston and **AstraZeneca** (NYSE:AZN) of Wilmington, Del., said they will collaborate on neuropathic pain caused by cancer chemotherapy.

The alliance would identify neurobiological differences between cancer chemotherapy-induced pain and little or no pain, the collaborators said.

"Our collaboration with AstraZeneca addresses a critical need in cancer care, which is improving the quality of life of cancer patients," said Charles Cleeland, chairman of the Department of Symptom Research at M. D. Anderson.

Northern Illinois University of Chicago said it has named **Northwestern Medical Faculty Foundation** as its expected provider of clinical services for the Northern Illinois Proton Treatment and Research Center LLC, a $160 million proton therapy cancer treatment and research center to be built in the DuPage National Technology Park, 35 miles west of Chicago.

Under the agreement between NIU and Northwestern Medical Faculty Foundation, physicians who are full-time faculty members or researchers at the Feinberg School of Medicine and are on the attending physician staff at Northwestern Memorial Hospital will deliver clinical and related services at the cancer treatment center. The agreement will be finalized within three months, officials said.

NIU said it has also negotiated a payment schedule with the Illinois Department of Public Aid for treating Medicaid patients and expects to offer its services to a full spectrum of applicants.

Sunesis Pharmaceuticals Inc. (NASDAQ:SNSS) of South San Francisco said it has earned a preclinical milestone payment from **Johnson & Johnson Pharmaceutical Research & Development L.L.C.**

under their drug discovery collaboration agreement for oral small molecule enzyme inhibitors for major chronic inflammatory and autoimmune diseases.

The payment was triggered by the J&JPRD selection of a compound targeting the Cathepsin S enzyme as a development candidate, the companies said. Under the collaboration agreement, Sunesis said it could receive additional development milestone payments from J&JPRD, as well as royalty payments based on future product sales.

Cathepsin S is an enzyme involved in the activation of immune system T-cells, the company said.

Vermillion Inc. (NASDAQ:VRML) of Fremont, Calif., said it has renewed a long-standing collaboration with **Johns Hopkins University** to develop biomarkers that can be applied toward disease detection, classification and monitoring of cancers, including ovarian, breast and prostate.

Vermillion said it would have access to exclusive commercial rights to the discoveries made through the partnership.

"For more than seven years we have had a highly productive relationship with Daniel Chan, professor of pathology, urology, oncology, radiology, director of the Clinical Chemistry Division in the Department of Pathology and director for the Center for Biomarker Discovery, and his team at Johns Hopkins University," said Eric Fung, chief scientific officer of Vermillion. "This dynamic collaboration has led to the development of our ovarian tumor triage test that could improve outcomes."

As part of the collaboration, Vermillion said it would continue to provide financial support, technical assistance and access to its advanced technology platforms, while Johns Hopkins will continue to contribute cancer serum samples and the clinical and scientific expertise of its physicians and scientists.

Clinical Trials:

ACORN Begins Phase IIb Trial Of Nexavar In Breast Cancer

Accelerated Community Oncology Research Network Inc. of Memphis said it has begun a phase IIb trial evaluating the efficacy of Nexavar (sorafenib) tablets in combination with gemcitabine (Gemzar) in metastatic breast cancer that has progressed during or after treatment with bevacizumab (Avastin).

The double-blind, randomized 220-patient trial will be conducted at 45 sites in 20 states and will assess efficacy, safety and quality of life as endpoints. Treatment with either Nexavar and gemcitabine, or placebo and gemcitabine, will be randomly assigned.

"The trial will establish the value of tyrosine kinase inhibition of the VEGF receptor after tumors have progressed on bevacizumab, an increasingly likely clinical scenario in metastatic breast cancer," said Clifford Hudis, lead investigator and chief of the Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center.

ACORN said it would enroll research sites, provide contract and budgeting services, foster the accrual of patients at the site level, collect data and monitor its accuracy, and provide overall project management.

Nexavar targets both the tumor cell and tumor vasculature and, in preclinical studies, has targeted two classes of kinases involved in both cell proliferation and angiogenesis, ACORN said. The kinases included Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, KIT, FLT-3 and RET.

Bionomics Ltd. of Melbourne, Australia, said it has begun treatment in a phase I trial of its anti-cancer drug, BNC105, for advanced cancer.

Treatment will consist of BNC105 on days 1 and 8 of a 21-day cycle, over two cycles, the company said. The trial will be conducted at sites within the Cancer Trials Australia network at the Royal Melbourne Hospital, the Peter MaCallum Cancer Centre and the Western Hospital in Melbourne, the company said.

The primary objective is the evaluation of the safety and tolerability of the product, as well as an appropriate dose or subsequent trials. Further objectives include, the evaluation of BNC105 pharmacokinetics and its activity against tumor vasculature and tumor growth, the company said.

BNC105 is a vascular disruption agent, which blocks the blood supply to a solid tumor, the company said. The agent has a dual mechanism of action with the ability to not only block the supply of nutrients to the tumor but also to directly destroy cancer cells.

Bionovo Inc. (NASDAQ:BNVI) of Emeryville, Calif., said the higher doses of its breast cancer drug candidate, BZL101, were well tolerated and therefore the dose escalation portion of its study will be extended.

BZL101, an oral drug for advanced breast cancer and pancreatic cancer, targets cancer cells while leaving normal cells healthy and intact, the company said.

Results of a phase I trial conducted at the University of California, San Francisco, and the Cancer

Research Network indicate that the drug has a favorable tolerability profile and demonstrates encouraging clinical activity in a heavily pretreated population, the company said. The product is in phase I/II clinical testing for late stage metastatic breast cancer.

EntreMed Inc. (NASDAQ:ENMD) of Rockville, Md., said it has begun a phase II study of MKC-1 in recurrent or resistant epithelial ovarian cancer and advanced endometrial cancer.

The study will be conducted at sites in Canada with Amit Oza, senior staff physician and associate professor of medicine, Princess Margaret Hospital, University of Toronto, as principal investigator, the company said.

The primary study objective is antitumor activity of the drug administered orally as a single agent in platinum or taxane refractory ovarian and endometrial cancer, the company said. The study will be a two arm parallel group design with each group having two stages.

MKC-1 is an orally-active cell cycle inhibitor with in vitro and in vivo efficacy against solid tumor cell lines, including multi-drug resistant cell lines, the company said. Data demonstrate broad-acting antitumor effects, showing tumor growth inhibition or regression in multiple preclinical models, including paclitaxel-resistant models.

MKC-1 has been shown to inhibit mitotic spindle formation, prevent chromosome segregation in the M-phase of the cell cycle, and induce apoptosis, the company said. MKC-1 inhibits the Akt-mTOR signaling pathways through inhibition of the mTOR/rictor pathway.

Hologic Inc. (NASDAQ:HOLX) of Bedford, Mass., said it has published a study evaluating the Hologic MammoSite Radiation Therapy System, one, two, and three years after treatment.

The study determined efficacy, cosmetic results and toxicities of enrollees in the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial.

The American Society of Breast Surgeons MammoSite Registry includes 1,440 patients with early stage breast cancer, who were undergoing breast-conserving therapy and were treated with MammoSite RTS between May 2002 and July 2004. Eighty-seven percent had invasive breast cancer and 13 percent had been diagnosed with ductal carcinoma in situ.

In the first 400 cases with a median follow-up of 37.5 months, the three-year actuarial rate of local or regional recurrence was less than 2 percent, the company said. The percentage of breasts with good and/or excellent cosmetic results was 93 percent at 36 months. A three-year actuarial local control rate of 100 percent in the first 48 patients enrolled with DCIS was demonstrated.

An analysis of the overall registry population with a median follow-up of 30.1 months, showed a two-year actuarial rate of local or regional recurrence of 1.0 percent; good and/or excellent cosmetic results of 94 percent at 24 months and a 10.6 percent rate of symptomatic seromas.

The MammoSite device is a balloon catheter that is inserted into the cavity created by a lumpectomy and delivers radiation from inside the lumpectomy cavity over a course of five days, the company said.

NexGenix Pharmaceuticals of New York said it has data on its Hsp90 inhibitor program.

NXD30001, one of several radicicol-based Hsp90 inhibitors the compound series, demonstrated efficacy in breast cancer tumor xenograft models without evidence of liver and kidney toxicity, the company said. The potency, tolerability, pharmacokinetic and pharmacodynamic properties of the product and its derivatives indicate that it, or an analog, may be useful in breast and other forms of cancer with an improved dosing and therapeutic window compared to 17AAG, the first-in-class Hsp90 inhibitor in phase II trials for cancer.

The compound series binds Hsp90 in a different mode than 17AAG or radicicol and exhibits higher affinity to Hsp90 than radicicol, the company said. NXD30001 and its analogs inhibit cell proliferation and deplete multiple Hsp90 client proteins such as Her2, Akt, c-Raf, Cdk4, and Cyclin D1 in Her2- overexpressing breast and other cancer cell lines at low nanomolar concentrations. Pharmacokinetic studies demonstrate that NXD30001 can achieve therapeutic levels via intraperitoneal dosing and that the compound accumulates in tumors at above micromolar concentrations, the company said.

Tumor pharmacodynamic analysis demonstrated depletion of multiple Hsp90 client proteins, including Her2, after a single dose; the client proteins remained undetectable for more than two days, consistent with the pharmacokinetic tumor data, the company said.

Poniard Pharmaceuticals Inc. (NASDAQ: PARD) of South San Francisco said it has data on safety and efficacy data from the phase I dose-escalating study of picoplatin in combination with full-dose docetaxel (75

mg/m squared) with prednisone in metastatic hormone refractory prostate cancer.

"The data we have generated with picoplatin in prostate cancer indicate a PSA response of 65 percent which suggests an improvement compared to docetaxel therapy alone," said Jerry McMahon, chairman and CEO of Poniard.

In the 33-patient study, treatment consisted of one of four doses (60, 80, 100 or 120 mg/m squared) of picoplatin, as well as either 60 mg/m squared or 75 mg/m squared (full-dose) docetaxel plus 5 mg prednisone twice daily, the company said. Nine patients received 120 mg/m squared picoplatin and 75 mg/m squared docetaxel every 21 days plus 5 mg prednisone twice daily. The dose, which is also the dose under study in the phase II trial, was well tolerated.

Hematological toxicity, including neutropenia, anemia and thrombocytopenia, was dose-dependent and reversible, the company said. Neutropenia was the dose-limiting toxicity. Mild neuropathy (grade 1) was observed in 3 of 33 patients (9 percent) and was unrelated to cumulative picoplatin dose. Neuropathy was infrequent, and no neuropathy of grade 2 or greater was observed. PSA response rate was 65 percent (20 of 31 evaluable patients). Survival data are not yet available. Withdrawal from study treatment occurred from death in four patients, progressive disease in eight, and withdrawal of consent in one patient. Treatment consisted of a median number of 7 cycles, and 13 of 33 patients completed the maximum of 10 cycles of treatment according to the study protocol.

Poniard also is evaluating intravenous picoplatin in a phase III trial, Study of Picoplatin Efficacy After Relapse, or SPEAR, in small cell lung cancer. The registrational trial is being conducted under a Special Protocol Assessment from FDA and is evaluating overall survival as the primary endpoint.

Raven Biotechnologies Inc. of South San Francisco said enrollment was completed in the maximum tolerated dose cohort expansion segment of its phase I/IIa trial of RAV12, an anti-cancer monoclonal antibody in RAAG12 antigen expressing cancers.

Based on radiographic re-evaluation, two patients remain on study drug beyond the original treatment period, the company said. Four received extended therapy in both the original cohort and the expanded cohort of the trial.

RAAG12 is a chimeric monoclonal antibody directed against a primate-specific glycotope that is displayed on the surfaces of tumor cells, particularly those of gastrointestinal origin, the company said.

The appropriate dose and schedule of RAV12 in a dose-escalation segment of the 33-patient trial revealed that a fractionated dosing regimen improved the side effect profile for the antibody, the company said. The MTD Cohort Expansion segment involved 20 additional patients.

Sosei Group Corp. (Sosei; TSE Mothers Index: 4565) of Tokyo said it has begun phase III studies for its fentanyl sublingual spray, AD 923, an opioid analgesic for cancer breakthrough pain.

The trial is a multi-center, randomized, double-blind, double-dummy, crossover study to evaluate the safety and efficacy of the opioid against an active comparator (morphine sulphate immediate release) for breakthrough pain in malignancies. The primary endpoint is the summary of pain intensity difference measure over the first 30 minutes from initial dosing, the company said.

Two studies will enroll 300 patients in 10 European countries. These will be followed by a single combined open label study to assess the long term effectiveness, safety and tolerability of the analgesic.

Tigris Pharmaceuticals Inc. of Bonita Springs, Fla., said it has begun a multi-center phase I ascending dose study of AFP-464, an aminoflavone pro-drug for cancer.

The primary objectives are dose limiting toxicity and maximum tolerated dose of the agent in advanced solid tumors. The 35-patient trial will take place at Institut Gustave-Roussy, Villejuif, France, and Jules Bordet Institute, Brussels.

The pro-drug is in two phase I trials sponsored by NCI.

Oncology Management:

Broussard Named CEO, President, Of US Oncology

US Oncology said Bruce Broussard was named president and CEO. He succeeds Dale Ross, who continues as executive chairman of the company.

The transition is a planned succession that follows the promotion of Broussard to president in November 2005, the company said. Broussard was elected to the Board of Directors, effective Feb. 1.

Also, **Advanced Medical Specialties** of Miami said it has entered into an agreement to join the US Oncology. AMS is a 47-physician oncology practice.