THE CANCER LETTER

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FDA Clears Avastin-Interferon Combination In Renal Cancer; Interferon Role Undefined

By Paul Goldberg

FDA earlier this week approved Avastin (bevacizumab) in combination with interferon-alfa for metastatic renal cell carcinoma.

The approval Aug. 2 triggered considerable surprise among agency-watchers, who point out that interferon-alfa is not approved for kidney cancer.

"Since they approved Avastin for use with interferon, but interferon is not approved in this indication, following the Avastin label would lead to off-label use of interferon," said Richard Schilsky, professor of medicine at the University of Chicago and chairman of Cancer and Leukemia Group B, a cooperative group that conducted one of the trials that led to the approval.

"Also, it's unclear what interferon adds to Avastin in this setting, as

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In the Cancer Centers:

Rowley, Brinker Win Presidental Medals Of Freedom As "Agents Of Change"

JANET DAVIDSON ROWLEY, a pioneer in demonstrating that cancer is a genetic disease, will receive the 2009 Presidential Medal of Freedom, the White House said. **President Barack Obama** will award the Medals of Freedom, the nation's highest civilian honor, to Rowley and 15 others at a ceremony Aug. 12.

Rowley, the Blum Riese Distinguished Service Professor of Medicine, Molecular Genetics & Cell Biology and Human Genetics at the University of Chicago, will receive the award for her discovery of recurring chromosomal abnormalities in leukemias and lymphomas—findings that have revolutionized how cancer is understood and treated.

Nancy Goodman Brinker, founder of Susan G. Komen for the Cure, also will receive a medal for her work.

Among the other honorees are: **Sen. Ted Kennedy** (D-Mass.); British physicist **Stephen Hawking**; tennis star and promoter of gender equity **Billie Jean King**, civil rights leader **Rev. Joseph Lowery**, former Supreme Court Justice **Sandra Day O'Connor**, actor **Sidney Poitier**, **Archbishop Desmond Tutu**, microfinance pioneer **Muhammad Yunus**, as well as **Pedro José Greer Jr.**, founder of Camillus Health Concern; **Joseph Medicine Crow**, the last living Plains Indian war chief; performer **Chita Rivera**; and former

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The Cancer Letter On Summer Break

The Cancer Letter will not be published over the next three weeks while the staff takes its annual summer break. The next issue will be published Sept. 4.

FDA Says Avastin-Interferon Combo Improved Efficacy

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the trial did not have an Avastin-alone arm," Schilsky said.

Schilsky is not the only cancer drug development expert surprised by the decision. "I don't understand why this isn't a de facto combination product," said Mark Ratain, Leon O. Jacobson Professor of Medicine and chairman of the Committee on Clinical Pharmacology and Pharmacogenomics at the University of Chicago.

"Shouldn't FDA require the company to show how each component contributes to safety and efficacy of the combination?" said Ratain, who has consulted for Avastin's sponsor Genentech its parent company Hoffman LaRoche, which also makes an interferon-alfa. "Is there a reason to think Avastin with interferon is better than Avastin alone? Why wasn't there a randomized trial showing that you need interferon?"

FDA officials say that interferon's role in the regimen has a precedent in oncology, citing the 2004 approval of the Eli Lilly drug Alimta (pemetrexed) as a precedent.

"A previous example of a using drug in an unapproved indication as a comparator in an 'add one' design is the use of cisplatin in the registration trial of pemetrexed (Alimta) for advanced mesothelioma," Richard Pazdur, director of the FDA Office of Oncology Drug Products, said in an email. "Cisplatin is not approved in this indication. The trial design—Alimta plus cisplatin vs. single-agent cisplatin—allowed for the isolation of Altima's effect. The product label for Alimta contains the clinical trial information and the indication statement specifies the combination of the two drugs. The cisplatin label contains neither the indication nor information on the clinical trial." Pazdur responded to questions from The Cancer Letter.

The agency is not alone in approving the Avastin-interferon combination for advanced renal cancer. The European Commission approved the therapy in December 2007. The European label specifies interferon-alfa-2a, a Hoffman LaRoche agent. The FDA label cites "interferon alfa," which would cover at least one more agent sold in the U.S., Schering's interferon alfa 2b.

The approval reflects an unusually rapid development of therapies in kidney cancer, where a generation of agents was approved within a short period of time, largely based on comparison with the accepted community standard of treatment—interferon. One of the drugs, Bayer's Nexavar (sorafenib), was approved based on a comparison with placebo, though in one of the supporting trials it failed to beat interferon.

FDA officials note that they approved the Avastin-interferon combination simply because it met the endpoints, improving efficacy over the previous standard of care—interferon-alfa, and it will be up to doctors to determine how the drugs will be used. The agency doesn't regulate the practice of medicine and addressing issues of cost and comparative effectiveness, officials said.

Data That Led To U.S., European Approval

According to Genentech, the FDA approval was based on data from a randomized, double-blind, placebo-controlled phase III study (AVOREN) of 649 patients with previously untreated metastatic renal cell carcinoma.

The CALGB study, which was not intended to support registration, randomized 732 patients and produced similar results.

In the AVOREN study, patients who received Avastin plus interferon-alfa had a 67 percent increase in progression-free survival, compared to those who received interferon-alfa alone (hazard ratio=0.60, 95 percent CI=0.49, 0.72).

In AVOREN, median PFS was 10.2 months for patients who received Avastin plus interferon-alfa compared to 5.4 months for patients who received interferon-alfa alone, corresponding to an 89 percent improvement in median PFS.

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In AVOREN, secondary analysis endpoints included objective response and overall survival.

In the study, tumor size decreased in 30 percent of patients in the Avastin plus interferon-alfa group, compared to 12 percent of patients who received interferon-alfa alone.

There was no improvement in overall survival based on the final analysis after 444 deaths, with a median OS of 23 months in the Avastin plus interferon-alfa arm and 21 months in the interferon-alfa plus placebo arm (hazard ratio=0.86, 95 percent CI=0.72, 1.04).

Adverse events were consistent with those previously reported for Avastin or interferon-alfa, the company said.

Grade 3 to 5 adverse events that occurred at a rate of at least 2 percent more often in patients who received Avastin plus interferon-alfa versus interferon-alfa plus placebo included fatigue (13 percent vs. 8 percent), weakness (10 percent vs. 7 percent), protein in the urine (7 percent vs. 0 percent), hypertension (6 percent vs. 1 percent) and bleeding (3 percent vs. 0.3 percent).

Both the AVOREN study and the CALGB study were powered for overall survival. However, in consultations with the FDA and European regulatory authorities, the primary analysis endpoint was revised to assess improvement in PFS, Genentech said.

This shift of endpoints coincided with the evolution of the regulators' thought on metrics of delay of disease progression. Such metrics were acceptable as surrogate endpoints when these trials began. While the drugs were being tested in the clinic, regulators started to accept delay in progression as a tangible patient benefit sufficient to support full approval.

In fact, the approvals of Nexavar and Pfizer's Sutent (sunitinib malate) were landmark cases in this shift in regulatory philosophy. They showed how delay in progression measured in rigorous randomized trials can result in global registration for products that don't demonstrate the survival advantage (The Cancer Letter, Feb. 24, 2006).

"We have been using PFS in the recent approvals for renal cell cancer," Pazdur said in an email. "Since 2005, PFS has been used as regulatory endpoint in this disease. From a historical perspective, IL-2 (Proleukin) was approved in 1992 based on an overall response rate (particularly the complete response rate and duration) in a single arm trial."

Pazdur cited the following chronology of approvals of RCC drugs:

• December 2005: Nexavar receives regular approval on the basis of an improvement in PFS. The median PFS was 167 days in the sorafenib group vs. 84 days in the placebo-controlled group (HR 0.44, 95% CI for HR: 0.35 -0.55, log rank $p < 0.000001$).

• January 2006: Sutent receives accelerated approval based on partial response rates and response duration. In February, 2007 this accelerated approval was converted to regular approval based on an improvement in PFS in a trial comparing the new drug to interferon-alfa. Median PFS was 47.3 weeks for the Sutent-treated patients was 22.0 weeks for patients with interferon (HR 0.415, 95% CI .320- 0.59, $p<0.000001$).

• May 2007: Torisel (temsirolimus), a Wyeth drug, is approved both on improvement in overall survival and PFS. The trial leading to the approval of Torisel compared single-agent temsirolimus to interferon-alfa.

• March 2009: Afinitor (everolimus), a Novartis drug, is approved based on an improvement in PFS with a median PFS of 4.9 and 1.9 months (HR 0.33, $p < 0.0001$) in the everolimus and placebo arms, respectively.

"Accepted Community Standard"

Brian Rini, the principal investigator on the CALGB trial and staff oncologist at the Department of Solid Tumor Oncology at the Cleveland Clinic Taussig Cancer Institute, describes interferon-alfa as a former "default standard of care."

Though interleukin-2 was the only FDA approved drug at the time, many patients didn't qualify to receive it, and many doctors lacked expertise to use it. "Unless you used high-dose interleukin-2, you used low-dose interferon," Rini said.

Hence, the unapproved therapy became a benchmark for a generation of treatments. In the case of Avastin, interferon is also being combined with the new-generation therapy.

"At the time the [CALGB] trial was designed, it wasn't thought that Avastin was the more active agent," Rini said. "We didn't know. Avastin clearly has activity as monotherapy in kidney cancer and clearly has activity in combination with interferon. The million-dollar question is what does interferon add? My personal belief is that it does add clinical activity, but at a cost of toxicity. Then it becomes a question, how do you best use interferon in this regimen? Do all patients get it? There has never been data that says that dose of interferon matters. Maybe you can get away with less. Those are unanswered questions."

FDA's Pazdur said the use of interferon as a

comparator presented no methodological or regulatory problems.

"The trial design used for the approval of Avastin in the renal cell carcinoma application is referred to as a 'add-on' design—A + B versus B," he said. "The design allows for the isolation of the effect of drug A. This design has been used many times in oncology and in other therapeutic areas for drug registration. The consistent policy in the oncology divisions is that the indication and product labeling will only be changed for the drug where the effect has been isolated."

The acceptance of an unapproved treatment in a combination is not a problem either, Pazdur said "In part, this is due to the extensive off-label use of products in oncology," he said. "Also, in oncology, placebo-controlled randomized trials are frequently considered impractical or unethical to conduct. Allowing an 'add-on' design facilitates accrual. Cognizant of these issues, FDA guidance on available therapies specifically has stated that drugs 'supported by compelling literature evidence (e.g. certain established oncologic treatment) be considered available therapy.'"

With a new generation of therapies hitting the market, oncologists who treat kidney cancer haven't had the time to compare and optimize treatments.

"What's unique in kidney cancer is that these drugs got registered over a short interval," said Rini, who has consulted for Genentech and Roche and conducted sponsored research for Roche. "Unlike other solid tumors, where you get regimen A as the standard—and you add something to it, and then you add something to that—these have emerged simultaneously, so there is some confusion. What I usually tell patients is that I don't know which therapy is going to be the best for them. We have absolutely no predictive markers. It's an empirical decision, an educated guess."

Since kidney cancer patients are living longer, most of them receiving a succession of therapies, Rini said.

It's unclear how the Avastin-interferon combination would be used. "U.S. physicians have never embraced interferon for RCC, so they may either not use it at all or use a reduced dose initially or with any toxicity," Rini said. "Practically, this is what's going to happen. It's not exactly what the data supports, but I think it's a very reasonable approach."

These dilemmas fall outside FDA's mandate, Pazdur said.

"Frequently, we hear that the FDA approves new 'standards of care,'" he said. "People may want to give us authorities that we do not have. We approve marketing applications that provide evidence that the drug for a given indication is 'safe and effective.'

"FDA does not have a comparative efficacy standard. With the approval of multiple new drugs in the treatment of advanced renal cell carcinoma since 2005, the role of interferons in the treatment of advanced renal cell cancer has obviously changed.

"Does the design and results of the registration trial allow us to determine if Avastin is safe and effective as a treatment for renal cell carcinoma? Yes.

"However, the ultimate determination of the acceptance, priority, and relative role of Avastin plus interferon-alfa to other approved drugs will be determined by the practice of medicine," Pazdur said.

NCI News:

NCI Plans Preclinical Testing Of Tamoxifen Metabolite Endoxifen For Breast Cancer

By Kirsten Boyd Goldberg

NCI plans to begin preclinical toxicology and pharmacology studies of endoxifen, a metabolite of tamoxifen that is thought to be able to bypass the pharmacogenetic limitations of tamoxifen and potentially be more effective in treatment or prevention of breast cancer than tamoxifen.

Studies conducted at the Mayo Clinic, University of Michigan, and Indiana University, as well as NCI, have demonstrated that patients with variant forms of the gene CYP2D6 may not receive the full benefit from tamoxifen because of difficulty metabolizing tamoxifen to endoxifen. Patients who are poor metabolizers of tamoxifen have lower levels of endoxifen and poorer clinical outcomes, compared to patients who metabolize tamoxifen more extensively.

Also, recent studies suggest that taking selective serotonin reuptake inhibitor antidepressants such as Paxil, Prozac, and Zoloft can decrease the effectiveness of tamoxifen, because these drugs compete for the CYP2D6 enzyme. A study presented in June at the American Society of Clinical Oncology annual meeting found that after two years, 7.5 percent of women who took only tamoxifen had a recurrence, compared with 16 percent who took Paxil, Prozac, or Zoloft. Patients taking weaker antidepressants such as Celexa, Lexapro, and Luvox did not have an increased risk of recurrence.

In theory, giving patients endoxifen rather than tamoxifen could increase the effectiveness of treatment by 15 to 20 percent, said James Doroshow, director of

the NCI Division of Cancer Treatment and Diagnosis.

"The idea, which has yet to be tested, is that if you were to administer the metabolite—endoxifen—rather than the parent drug tamoxifen, you might get around genetic variations in drug metabolism," Doroshow said in an interview with The Cancer Letter.

Tamoxifen has been used for 30 years in treatment of breast cancer, and for the past 10 years to reduce the risk of breast cancer in women who are at increased risk of developing the disease.

The endoxifen project was proposed by two scientists at the Mayo Clinic in Rochester, Minn., Matthew Ames, chairman of the Department of Molecular Pharmacology and Experimental Therapeutics, and Matthew Goetz, associate professor of oncology and assistant professor of pharmacology.

The two presented their data to NCI about six months ago, Doroshow said. Because the chemical structure of endoxifen has been known for 20 or more years, the Mayo Clinic can't patent the chemical structure. Without a patentable molecule, it would be "difficult, if not impossible" to get a commercial sponsor to develop it as a new drug, he said.

"So they came and presented their data and asked if we could help them," Doroshow said. "We exist to help academic investigators, especially when, either because of intellectual property issues or because of risk, there really isn't any other avenue—if the potential benefit is great enough, and I think the potential benefit is, but who knows?

"Because this metabolite has never itself been given directly to patients, we don't know, for example, if it is absorbed if you take it by mouth. What is its direct toxicity if you give it alone?" Doroshow said. "You have to do all of the preclinical studies in animals to understand its further metabolism and toxicity, and it's got to be produced in a fashion that can be administered to people, and under GMP conditions.

"The toxicological studies and the pharmacology studies are really quite expensive to support the filing of an IND for a phase I study," Doroshow said. "Most academic centers, no matter how well positioned, don't have the resources to do that."

NCI will produce the molecule and work with Ames and Goetz over the next six months to a year to conduct the preclinical studies, Doroshow said.

"The molecule is not new, but needs to be treated as new," Doroshow said. "Still, we know something about it, so the process will be faster than it would be if it was something completely novel. Then we will come to a point where we either do or don't have information that would make a reasonable package to file an IND application with the FDA."

NCI's preclinical drug development programs focus on these kinds of projects that wouldn't be picked up by pharmaceutical and biotech companies, or that need help getting over certain barriers before they can be licensed to commercial sponsors, Doroshow said. "We now have the ability to expand where we can provide assistance to people," he said.

For example, NCI's Chemical Biology Consortium is looking for projects at an earlier stage than the endoxifen project, Doroshow said. The consortium is designed to assist biochemists who have found a new target or pathway who need assistance finding molecules that might inhibit the target or pathway, as well as chemists who have developed a new class of drugs and need help studying the targets and pathways.

The institute plans to issue a request for projects that would be open to academic investigators. "We will be looking for projects that academic investigators need help with," Doroshow said. "The whole idea is to make those resources available to the investigational community."

caBIG, Love/Army Of Women Partner For Online Cohort

NCI's cancer Biomedical Informatics Grid (caBIG) and the Love/Avon Army of Women said they plan to work together to build the largest online cohort to study women to improve prevention, diagnosis, and treatment of breast cancer.

"This collaboration is a real-world example of how caBIG leverages biomedical informatics to connect consumers and researchers," said Ken Buetow, director of the NCI Center for Biomedical Informatics and Information Technology. "This effort will enable an unprecedented level of participation on the part of patients and consumers. And, in so doing, will also drive faster and more productive research based on access to huge amounts of clinical and molecular data."

Through the use of tools that are often applied in social networks, women of all ages and backgrounds across the U.S. can sign up and respond to secure online questionnaires concerning their health history. This population of women is then "connected" to the research community via the web, and researchers who are partners in this initiative can design study protocols that reflect the clinical profiles of potential research participants housed in the database. The benefits of such an enterprise are already being realized through faster

patient accrual and richer study populations.

The collaboration was announced at the caBIG annual meeting July 20 in Washington, D.C.

"One of the problems we've had with the Army of Women is that we don't have enough projects for all the women who have signed up," said Susan Love, president of the Dr. Susan Love Research Foundation and the Love/Avon Army of Women. "We have over 300,000 women. So, in talking to Ken Buetow, we came up with the idea that this was the perfect resource to launch the first cohort that was totally done online."

The collaboration will recruit from the Army of Women the women who are willing to be part of a longitudinal cohort, Love said in a podcast available at http://cabig.cancer.gov/resources/podcasts/. "All of it will be done online," Love said. "Women will sign up, they'll receive their questions online and fill them out, and we'll have immediate access to the cross-sectional data, and we will also be following them longitudinally over time to help us pick out what the causes of breast cancer are.

"Our goal is to have a million women, and because we're doing it online, we should be able to be fairly nimble about what we can do and what questions we can ask," Love said.

This effort builds upon caBIG capabilities to advance clinical research, including software tools that enable researchers to collect, store, query and share a massive amount of data, Buetow said.

"We believe that advances in health will be driven in the future by the velocity of information—that is, the ability to broadly connect members of the healthcare community in a seamless, secure network that facilitates rapid data sharing, collaboration, and continuous enhancement of knowledge to inform the bench-to-bedside-to-bench continuum," said Buetow.

William Klein Named Director, Behavioral Research Program

WILLIAM KLEIN was named associate director in the NCI Division of Cancer Control and Population Sciences.

He will direct the Behavioral Research Program, which includes the Office of the Associate Director and five branches (Applied Cancer Screening Research, Basic and Biobehavioral Research, Health Communication and Informatics Research, Health Promotion Research, and Tobacco Control Research).

This position plays a central and highly visible leadership role in the NCI's efforts in the social and behavioral sciences and their application to cancer prevention and control.

Since 2002, Klein has been a member of the graduate faculty at the University of Pittsburgh in the Social Psychology and Biological and Health Psychology programs. Most recently, he was director of undergraduate studies. Klein has also held secondary appointments in the School of Nursing, Clinical and Translational Science Institute, and the University of Pittsburgh Cancer Institute. Prior to 2002, Klein was on the faculty at Colby College where he served as chairman of the Psychology Department.

Klein's research interests fall under the areas of self-judgment, risk perception, and risk communication.

NIH News:

NIH Awards Seven Clinical, Translational Science Awards

Clinical and Translational Science Awards will be made to seven more academic health centers, bringing the consortium to 46 member institutions, the National Center for Research Resources said.

The NCRR also released the first progress report outlining the impact of the CTSA program in its first two years. Begun in 2006, this network now includes awardees in 26 states. When the program is fully implemented, it will support about 60 CTSAs. The report is available at www.ncrr.nih.gov/ctsa/progress_report_2009.

The institutions receiving new CTSA funding include: Medical University of South Carolina, Mount Sinai School of Medicine, New York University School of Medicine, University of Arkansas for Medical Sciences, University of Florida, University of Illinois at Chicago, and University of Texas Medical Branch.

These seven institutions join the University of Cincinnati, announced earlier this year, as the 2009 CTSA recipients.

"Now in its third year, the momentum behind the CTSA consortium continues to build as membership expands across the nation," said NCRR Director Barbara Alving. "The CTSA institutions provide opportunities for clinical and basic researchers to train and work as interdisciplinary teams which are now essential for developing and delivering new treatments and prevention strategies."

A fifth funding announcement for CTSAs is available, calling for the next round of applications to be submitted by Oct. 14, with the awards expected in July 2010: www.ncrr.nih.gov/crfunding.

In the Cancer Centers:

Presidential Medals Honor "Breaking Down Barriers"

(Continued from page 1)

Irish President and UN High Commissioner for Human Rights **Mary Robinson**.

Medals also will be awarded posthumously to **Harvey Milk**, the first openly gay elected official from a major city in the U.S., elected to the San Francisco Board of Supervisors in 1977; and **Jack Kemp**, a U.S. Congressman, Secretary of Housing and Urban Development, and Republican nominee for vice president in 1996.

"These outstanding men and women represent an incredible diversity of backgrounds," Obama said in a press release. "Their tremendous accomplishments span fields from science to sports, from fine arts to foreign affairs. Yet they share one overarching trait: Each has been an agent of change. Each saw an imperfect world and set about improving it, often overcoming great obstacles along the way. Their relentless devotion to breaking down barriers and lifting up their fellow citizens sets a standard to which we all should strive."

FOX CHASE CANCER CENTER appointed **Mary Daly** as chairman of the center's newly created Department of Clinical Genetics. The department is built on the success of Fox Chase's Margaret Dyson Family Risk Assessment Program, which Daly began in 1991 for individuals with a family history of breast and/or ovarian cancer, women who have had breast or ovarian cancer, or a biopsy showing benign breast disease. Since 1991, Fox Chase has developed additional risk assessment programs in melanoma, gastrointestinal and prostate cancers.

The new department will consolidate all of the clinical aspects of the existing risk assessment programs into a comprehensive service designed to provide risk assessment, testing, genetic counseling, and clinical intervention in the prevention of cancers among high-risk individuals and families.

"Dr. Daly, our genetic counselors, oncologists and researchers at Fox Chase have worked together to create risk assessment programs that have served as national models for both research and patient care," said **Michael Seiden**, president and CEO of Fox Chase.

The department will be closely aligned with research initiatives in Fox Chase's Cancer Prevention and Control Program, as well as its Keystone Program in Personalized Risk and Prevention, a collaborative translational science program co-led by Daly and funded through philanthropic donations to Fox Chase.

"We have gotten to the point as an institution where our risk assessment programs warrant a full-fledged clinical department, allowing us to expand the services we can offer and incorporating other gene disorders, as well as provide new opportunities for the researchers with whom we collaborate," Daly said.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY selected neurosurgeon **Philip Gutin** as its Honorary Member for 2009. Gutin will be honored during ASTRO's annual meeting in Chicago in November. Gutin is the chairman of the Department of Neurosurgery and the Fred Lebow Chair in Neuro-Oncology at Memorial Sloan-Kettering Cancer Center and professor of Neurological Surgery at Cornell University's Weill Medical College in New York. He devoted his career to scientific and clinical investigations of the treatment of brain tumors and has collaborated with many of the world's leading radiation oncologists and radiation biologists in advancing this practice. Gutin has also had leadership roles in several organizations, including the Radiation Therapy Oncology Group, the American College of Surgeons, and the Neurosurgical Society of America. . . . **JAMES MOHLER**, a prostate cancer translational scientist who has led the development of minimally invasive surgery for urologic cancers at Roswell Park Cancer Institute, was appointed senior vice president for translational research. He joined RPCI in 2003 as chairman of the Department of Urologic Oncology and as the leader of RPCI's Prostate Program. He also serves as professor of urology at the University at Buffalo School of Medicine and Biomedical Sciences. His laboratory focuses upon the role of the androgen receptor and androgen metabolism in prostate cancer and his clinical practice focuses upon robotic prostatectomy. Mohler is chairman of the National Comprehensive Cancer Network Prostate Cancer Guidelines Committee, past president of the Society for Basic Urologic Research and vice-chairman of the Urology Committee of the Cancer and Leukemia Group B. . . . **MEMORIAL SLOAN-KETTERING CANCER CENTER** made the following appointments: **Beatriz Korc-Grodzicki** has been appointed chief of the newly established Geriatrics Service in the Department of Medicine. The service will serve as the focal point for geriatric patient care, educational programs, and clinical research and provide leadership for a broadly based geriatric effort at MSKCC. Korc-Grodzicki comes to MSKCC from Mount Sinai School of Medicine, where she was director

of Clinical Services in the Brookdale Department of Geriatrics and Adult Development. **William Breitbart** was named vice chairman of the Department of Psychiatry and Behavioral Sciences. He remains chief of the Psychiatry Service, a position he has held since 1996. Also, he is a psychiatrist on the Pain and Palliative Care Service in the Department of Medicine. . . . **EMORY UNIVERSITY'S** Department of Radiation Oncology has recruited **Cynthia Anderson** as assistant professor. Anderson joins Emory from an independent practice group in Jacksonville, Fla. Anderson has conducted research testing radiosurgery, and she evaluates new therapies for patients with brain and spinal tumors and gastrointestinal cancers. While in training at Emory, she published several peer-reviewed research papers on prostate and rectal cancer patient outcomes as well as on tumor imaging. . . . **FRED HUTCHINSON CANCER RESEARCH CENTER** basic scientist **Wenying Shou** was named among the W.M. Keck Foundation's 2009 class of Distinguished Young Scholars in Medical Research. Shou is among five U.S. scientists tapped to receive the five-year, $1 million award. Shou, an assistant member of the center's Basic Sciences Division, studies social interactions between cells. . . . . **TRANSLATIONAL GENOMICS RESEARCH INSTITUTE** said an international scientific team led by **Jeffrey Trent**, TGen's president and research director, received a $1 million grant to study skin cancer from the Melanoma Research Alliance. Trent is the Team Lead among the principal investigators in the two-year study: Identification of Novel Melanoma Risk Genes Using High-throughput Genomics. The study is part of a collaboration with the International Melanoma Genetics Consortium (GenoMEL), which has identified families worldwide that are predisposed to getting skin cancer. The other principal investigators are **Nicolas Hayward** of the Queensland (Australia) Institute of Medical Research; **Goran Jonsson** of Lund (Sweden) University; and **Graham Mann** of the University of Sydney (Australia). Arizona's non-Hispanic Caucasian population has among the nation's highest incidence rate of skin cancer. Australia has the highest incidence rate of the disease in the world.

In Brief:

Former Rep. Pryce, Walker Elected To CureSearch Board

Former **Rep. Deborah Pryce** (R-Ohio) and Columbus, Ohio, businessman **Randy Walker** have been elected to the CureSearch National Childhood Cancer Foundation Board.

Hope Street Kids, a program founded by Pryce and Walker, and CureSearch National Childhood Cancer Foundation and the Children's Oncology Group joined forces under the umbrella of CureSearch in June. Pryce and Walker founded Hope Street Kids in 1999 in honor of their daughter, Caroline Pryce Walker, who died from to neuroblastoma that same year. Since its inception, the program has raised over $9 million and awarded 90 research grants to 34 leading pediatric cancer institutions.

Pryce represented Ohio's 15th District in the U.S. House of Representatives from 1993 to 2009. After leaving Congress, Pryce joined the law firm of Womble Carlyle Sandridge & Rice, in Washington, D.C.

Funding Opportunities:

Recovery Act of 2009: Information on Quarterly Reporting Requirements for NIH Award Recipients (NOT-OD-09-129) http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-129.html

Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (R01) (RFA-DA-10-001) http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-10-001.html

Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (R21) (RFA-DA-10-002) http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-10-002.html

AHRQ Announces Intent to Publish Grant and Contract Solicitations for Comparative Effectiveness Research (CER) Projects with Funds from the American Recovery and Reinvestment Act (ARRA) (NOT-HS-09-009) http://grants.nih.gov/grants/guide/notice-files/NOT-HS-09-009.html

Innovations in Biomedical Computational Science and Technology (R01) (PAR-09-218) http://grants.nih.gov/grants/guide/pa-files/PAR-09-218.html

Innovations in Biomedical Computational Science and Technology Initiative (SBIR [R43/R44]) (PAR-09-220) http://grants.nih.gov/grants/guide/pa-files/PAR-09-220.html

Innovations in Biomedical Computational Science and Technology Initiative (STTR [R41/R42]) (PAR-09-221) http://grants.nih.gov/grants/guide/pa-files/PAR-09-221.html

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Business & Regulatory Report

Regulatory Approvals & Applications:

Alimta Approved In Europe For Advanced Or Metastatic Non-Small Cell Lung Cancer

Eli Lilly and Co. (NYSE: LLY) of Indianapolis said the European Commission has granted approval for the use of Alimta (pemetrexed for injection) as monotherapy for maintenance treatment of patients with other than predominantly squamous cell histology in locally-advanced or metastatic non-small cell lung cancer whose disease has not progressed immediately following platinum-based chemotherapy.

The approval is based on data that showed pemetrexed improved overall

(Continued to page 2)

Clinical Trials:

Boehringer Ingelheim Begins Phase III Trial Of Oral EGFR Inhibitor For NSCLC

Boehringer Ingelheim of Ridgefield, Conn., announced the initiation of a phase III trial of BIBW 2992 as first-line treatment in non-small cell lung cancer patients with epidermal growth factor receptor mutations. BIBW 2992 is the first orally-administered irreversible dual inhibitor of EGFR and HER2, to reach phase III development in NSCLC.

The LUX-Lung 3 trial will compare the efficacy and safety of the single-agent BIBW 2992 to that of standard chemotherapy (cisplatin/pemetrexed) as a potential first-line treatment for NSCLC patients with EGFR mutations. Boehringer Ingelheim's LUX-Lung trial program currently includes two phase III trials assessing the efficacy and safety of BIBW 2992 in various NSCLC patient populations across the globe.

"The Boehringer Ingelheim LUX-Lung 3 trial studying BIBW 2992 in patients with EGFR mutations will be important as we continue to work towards providing personalized medicine for patients with lung cancer," said James Yang, professor at the Graduate Institute of Clinical Medicine and the Graduate Institute of Clinical Pharmacy at the College of Medicine at the National Taiwan University. "BIBW 2992 is an irreversible tyrosine kinase inhibitor whose clinical benefit we are hoping to confirm in the first-line setting for patients with EGFR mutations."

On May 29, Boehringer Ingelheim announced that it entered into an agreement with the Manchester, UK, based company DxS to provide a companion diagnostic test kit for BIBW 2992 to identify mutations of the EGFR in patients with NSCLC. Under the agreement, DxS and Boehringer Ingelheim will work jointly to make a suitable companion diagnostic test

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Alimta Approved In Europe As Maintenance Therapy

(Continued from page 1)

survival in other than predominantly squamous NSCLC patients in the maintenance setting.

Pemetrexed is a chemotherapy agent currently approved for first-line treatment of advanced, other than predominantly squamous NSCLC in combination with a platinum-based chemotherapy, and as a single agent in the second-line setting for advanced, other than predominantly squamous NSCLC patients with recurrent disease.

The concept of maintenance therapy represents a paradigm shift in the treatment of advanced, other than predominantly squamous NSCLC, the company said. Traditionally, patients who respond to first-line chemotherapy are monitored until the disease recurs and are then treated with a second-line regimen. In maintenance therapy, rather than halting further treatment until disease progression, patients who respond to a first-line therapy are treated immediately with a maintenance regimen.

"The idea behind Alimta as maintenance therapy for nonsquamous, non-small cell lung cancer is to treat patients immediately following their initial course of therapy, in an effort to prolong survival," Richard Gaynor, vice president, cancer research and global oncology platform leader at Lilly, said in a statement. "The study that led to this approval was the first that showed improved overall survival in the maintenance setting for NSCLC. This was also the third trial to show the benefit of tailoring Alimta treatment to the nonsquamous NSCLC patient population."

Overall survival data for pemetrexed as a maintenance therapy for NSCLC was presented at this year's annual meeting of the American Society of Clinical Oncology.

The trial compared efficacy with respect to overall survival of pemetrexed plus best supportive care versus placebo plus best supportive care in 663 patients with stage IIIB/IV NSCLC whose disease had not progressed after four cycles of platinum-based induction chemotherapy.

Pemetrexed was not included among the induction regimens studied in the maintenance trial. The trial supported two previous studies looking at the use of histology to tailor treatment for patients with advanced, other than predominantly squamous NSCLC.

Patients in the trial were treated with pemetrexed (500 mg/m2 on day one of each 21-day cycle) plus best supportive care or placebo plus best supportive care. All patients were supplemented with vitamin B12, folic acid and dexamethasone.

The approval—the fourth in Europe—follows an initial positive opinion issued by the European Medicines Agency's Committee for Medicinal Products for Human Use on May 29 and the recent approval by FDA of pemetrexed for maintenance therapy in advanced, nonsquamous NSCLC patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

Apart from the existing approvals in the E.U. and U.S. for the use of pemetrexed in the treatment of patients with locally-advanced or metastatic other than predominantly squamous NSCLC, pemetrexed is also approved, in combination with cisplatin, in both the E.U. and U.S. for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

AstraZeneca (NYSE: AZN) said it has submitted a New Drug Application to FDA and a Marketing Authorisation Application to the European Medicines Agency for an investigational drug, vandetanib 100 mg for use in combination with chemotherapy for the treatment of advanced non-small cell lung cancer in patients previously treated with one prior anti-cancer therapy.

The U.S. and European submissions are supported by data from phase III clinical studies evaluating the

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safety and efficacy of vandetanib 100 mg in combination with chemotherapy. Pending approval, the treatment will be marketed as Zactima.

Evaluation of vandetanib is ongoing, as monotherapy or in combination with other anti-cancer therapies in a range of tumour types, including thyroid cancer. Results from the ZEPHYR (300mg monotherapy study in EGFR failures in advanced NSCLC, phase III) and ZETA (300 mg monotherapy in advanced medullary thyroid cancer, phase III) studies will be presented in the first half of 2010.

Vandetanib has a unique profile that fights cancer through two clinically proven mechanisms -- by blocking the development of tumour blood supply (anti-angiogenesis or anti-VEGFR), and by blocking the growth and survival of the tumour itself (anti-EGFR). Vandetanib also inhibits RET-tyrosine kinase activity, an important growth driver in certain types of thyroid cance, the company saidr.

ZODIAC (ZACTIMA in cOmbination with Docetaxel In non-smAll cell lung Cancer) is a phase III randomised, double-blind, placebo-controlled study evaluating the combination of vandetanib 100mg once daily plus docetaxel versus docetaxel alone in patients with locally advanced or metastatic NSCLC, treated with one prior anti-cancer therapy. It enrolled 1391 patients at 250 centres throughout Europe, North America, South America and Asia Pacific.

ZEAL (ZACTIMA Efficacy with Alimta in Lung cancer) is a randomised, double-blind, placebo-controlled phase III study evaluating the combination of vandetanib 100mg with pemetrexed versus pemetrexed alone in patients with locally advanced or metastatic NSCLC, treated with one prior anti-cancer therapy. It enrolled 534 patients at 160 centres across 23 countries.

ZEST (ZACTIMA Efficacy Study versus Tarceva) is a phase III randomised, double-blind, multi-centre study to assess the efficacy of vandetanib 300mg versus erlotinib in patients with locally advanced or metastatic NSCLC after failure of at least one prior anti-cancer therapy. It enrolled 1240 patients at 171 centers across 22 countries.

ZEPHYR (ZACTIMA Efficacy trial for NSCLC Patients with HistorY of EGFR-TKI and chemo-Resistance) is a phase III, randomised, double-blind, parallel-group, multi-centre study evaluating the efficacy of ZACTIMA 300mg plus best supportive care versus best supportive care in patients with locally advanced or metastatic (stage IIIB-IV) NSCLC after prior therapy with an EGFR inhibitor. The study is running in approximately 170 centres across 23 countries.

ZETA (Zactima Efficacy in Thyroid Cancer Assessment) is a phase III, randomized, double-blind, placebo-controlled, multi-centre study, evaluating once-daily ZACTIMA 300mg as a monotherapy in advanced medullary thyroid cancer.

Cell Therapeutics Inc. (NASDAQ and MTA: CTIC) of Seattle announced today that it had requested and the EMEA has agreed to an oral explanation in support of the OPAXIO Marketing Authorization Application in September, 2009, extending the review for the Committee for Medicinal Products for Human Use opinion on approval until Q4-2009.

In April, 2008 the EMEA accepted for review the MAA for OPAXIO for first-line treatment of patients with advanced non-small cell lung cancer who are performance status 2, based on a non-inferior survival and improved side effect profile. The previously scheduled June, 2009, meeting with the EMEA on OPAXIO did not occur due to conflicts in regulatory schedule as CTI focused on completing the pixantrone New Drug Application submission in June, 2009.

Opaxio (paclitaxel poliglumex, CT-2103), which was formerly known as Xyotax, is an investigational, biologically enhanced, chemotherapeutic that links paclitaxel, the active ingredient in Taxol, to a biodegradable polyglutamate polymer, which results in a new chemical entity. When bound to the polymer, the chemotherapy is rendered inactive, potentially sparing normal tissue's exposure to high levels of unbound, active chemotherapy and its associated toxicities.

Blood vessels in tumor tissue, unlike blood vessels in normal tissue, are porous to molecules like polyglutamate. Based on preclinical studies, it appears that OPAXIO is preferentially distributed to tumors due to their leaky blood vessels and trapped in the tumor bed allowing significantly more of the dose of chemotherapy to localize in the tumor than with standard paclitaxel.

Once inside the tumor cell, enzymes metabolize the protein polymer, releasing the paclitaxel chemotherapy. Preclinical and clinical studies support that Opaxio metabolism by lung cancer cells may be influenced by estrogen, which could lead to enhanced release of paclitaxel and efficacy in women with lung cancer compared to standard therapies.

Cell Therapeutics Inc. (NASDAQ and MTA: CTIC) of Seattle said it was notified by EMEA that pixantrone is eligible to be submitted for a Marketing Authorization Application through the EMEA's

centralized procedure.

The centralized review process provides for a single coordinated review for approval of pharmaceutical products that is conducted by the EMEA on behalf of all European Union.

The EMEA also designated pixantrone as a New Active Substance; if approved, compounds designated as an NAS receive a 10-year market exclusivity period in E.U. member states. CTI will request a meeting with the EMEA to discuss the submission of the MAA for pixantrone to treat aggressive non-Hodgkin's lymphoma in the E.U. member states.

CTI completed the submission of the New Drug Application to FDA for pixantrone to treat relapsed or refractory, aggressive NHL in June 2009 and requested priority review, which if granted could lead to an approval decision from the FDA in the fourth quarter of 2009. Pixantrone is currently available in Europe on a named-patient basis.

The SME program is an initiative by the EMEA that is dedicated to addressing the needs of small and medium size companies developing medicinal products in Europe. Companies granted SME status are able to seek assistance, information and training from dedicated EMEA personnel, particularly in support of MAA.

In addition, SME status may result in reduced or deferred fees associated with marketing authorization applications, scientific advice and inspections. The EMEA also provides for translation of certain required documents. Restricted to companies based in the European Union, SME status has been granted to CTI Life Sciences Limited, a wholly-owned subsidiary of CTI, based in London.

Keryx Biopharmaceuticals Inc. (NASDAQ: KERX) of New York announced that it has reached agreement with the FDA regarding a Special Protocol Assessment on the design of a phase III trial for its PI3K/Akt pathway inhibitor, KRX-0401 (perifosine), in relapsed or relapsed / refractory multiple myeloma patients previously treated with bortezomib (Velcade). The SPA provides agreement that the Phase 3 study design adequately addresses objectives in support of a regulatory submission.

The trial, "A Phase III Randomized Study to Assess the Efficacy and Safety of Perifosine Added to the Combination of Bortezomib and Dexamethasone in Multiple Myeloma Patients Previously Treated with Bortezomib" will be a double-blind, placebo-controlled trial comparing the efficacy and safety of KRX-0401 vs. placebo when combined with bortezomib and dexamethasone.

The trial, powered at 90%, will enroll approximately 400 patients with relapsed or relapsed / refractory multiple myeloma. The primary endpoint is progression-free survival and secondary endpoints include overall response rate, overall survival and safety.

The phase III trial is a randomized (1:1), double-blind trial comparing the efficacy and safety of KRX-0401 to placebo when combined with bortezomib and dexamethasone in approximately 400 patients with relapsed or relapsed / refractory multiple myeloma. Patients must have been previously treated with both bortezomib (VELCADE) and an immunomodulatory agent (REVLIMID or THALIDOMID), and been previously treated with one to four prior lines of therapy. The primary endpoint is progression-free survival and secondary endpoints include overall response rate, overall survival and safety.

Micromet Inc. (NASDAQ: MITI), of Bethesda, Md., received Orphan Drug Designation from EMEA for BiTE antibody blinatumomab (MT103) for acute lymphoblastic leukemia.

Blinatumomab is a novel therapeutic antibody that activates a patient's T cells to seek out and destroy cancer cells.

In June, Micromet announced that the company had achieved its primary endpoint in an ongoing phase II study of ALL patients. The company presented data at the the 14th Congress of the European Hematology Association in Berlin, showing an 81% response rate in acute lymphoblastic leukemia patients with minimal residua l disease.

The patients included in this phase II clinical trial were in complete hematological remission following intense chemotherapy regimens, but retained a detectable level of ALL cancer cells in their bone marrow--so called minimal residual disease.

Various studies have confirmed that ALL patients with MRD following chemotherapy have a significantly worse prognosis than patients without MRD.

Mylan Inc. (NASDAQ: MYL) of Pittsburgh, Pa., said its subsidiary Mylan Pharmaceuticals Inc. has received approval from FDA for its Abbreviated New Drug Application for Bicalutamide Tablets, 50 mg.

Bicalutamide Tablets are the generic version of AstraZeneca's prostate cancer treatment Casodex, which had total U.S. sales of about $322 million for the 12 months ending March 31 for the same strength, according to IMS Health. Mylan has begun to ship

this product. Mylan has 118 ANDAs pending FDA approval representing $82.8 billion in annual brand sales, according to IMS Health. Thirty-five of these pending ANDAs are potential first-to-file opportunities, representing $16.7 billion in annual brand sales, according to IMS Health.

Peregrine Pharmaceuticals Inc. (NASDAQ: PPHM) of Tustin, Calif., and **Affitech A/S** (NASDAQ OMX: AFFI) of Horsholm, Denmark, announced that they have entered into a licensing agreement for antibody therapeutic rights under Peregrine's preclinical anti-VEGF antibody program.

Under the agreement, Affitech will license exclusive worldwide rights to develop and commercialize products under Peregrine's selective anti-VEGF intellectual property portfolio, including the fully human antibody r84, which was discovered by Affitech and jointly developed by the companies under an ongoing collaboration.

Affitech will be responsible for future preclinical and clinical development and potential product commercialization. Peregrine will receive an upfront payment, research fees and future milestone payments. Peregrine will also receive royalties on any future sales and a share of sublicensing revenues. Additional financial terms were not disclosed.

The fully human and selective anti-VEGF monoclonal antibody, r84, which is the most advanced candidate in Peregrine's anti-VEGF antibody program, targets the cancer-promoting growth factor VEGF. Data presented at IBC's 5th Annual International Anti-Angiogenesis Conference in 2007 showed that r84 was as effective as Avastin (bevacizumab) in inhibiting tumor growth in a number of models of human cancers, including a mouse model of human breast cancer.

r84 is distinctive because it selectively blocks VEGF from binding to VEGF receptor 2, while non-selective agents such as Avastin block binding to both VEGFR2 and VEGF receptor 1, the company said.

Watson Pharmaceuticals Inc. (NYSE: WPI) of Morristown, N.J., announced that it received a Complete Response Letter from FDA on its New Drug Application for Trelstar 22.5 mg (triptorelin pamoate for injectable suspension), a 24-week formulation of Trelstar for the palliative treatment of advanced prostate cancer. The Trelstar NDA was prepared in cooperation with Debiopharm Group.

According to the letter, the FDA has requested clarifications related to the clinical testing of the product, additional information regarding the chemistry, manufacturing and controls of the product and other components, and information related to third party manufacturing. Watson is working to ensure the requested information is provided to the FDA expeditiously.

Trelstar 22.5 mg builds on Watson's long-standing track record in prostate cancer and expanding urology franchise. The new, longer-acting formulation of Trelstar is designed to be conveniently administered and to continuously suppress the production of testosterone in men with advanced prostate cancer for 24 weeks.

Trelstar is a therapy with established efficacy and safety in two formulations—a four-week formulation (TRELSTAR DEPOT) and a 12-week formulation, the company said.

Trelsar, developed by Debiopharm Group and marketed by Watson, administers a synthetic luteinizing hormone releasing hormone agonist, triptorelin, which suppresses the production of testosterone in the testicles.

In clinical trials, the most common adverse events occurring in patients were hot flushes, skeletal pain, impotence and headache. As with all LHRH agonists, triptorelin causes an initial transient increase in testosterone levels and may initiate or worsen symptoms during this transient period. Rare post-marketing reports of anaphylactic shock and angioedema have been reported.

Clinical Trials:

Keryx Begins Phase I Trial Of Agent For Solid Tumors

(Continued from page 1)

kit globally available.

The global LUME-Lung Phase III clinical trial program is investigating BIBF 1120 in combination with standard second-line chemotherapy in patients with advanced NSCLC. The studies are ongoing with a recruitment target of 2,600 patients worldwide. This is one of the largest phase III study programs in an advanced NSCLC patient population to date.

Keryx Biopharmaceuticals Inc. (NASDAQ: KERX) of New York announced the initiation of a phase I clinical study to evaluate KRX-0401 (perifosine) as a single agent treatment for recurrent solid tumors in pediatric patients.

This phase I study is now open for enrollment at Memorial Sloan-Kettering Cancer Center in New York

City. Oren Becher, instructor, Department of Pediatrics, in coordination with Eric Holland, director of the Brain Tumor group at Memorial Sloan-Kettering Cancer Center, will act as the study's Principal Investigator. The study is being fully funded by an external grant provided by a private organization.

KRX-0401 is a novel, oral, anticancer agent that modulates Akt and several other important signal transduction pathways. Keryx is in the process of finalizing late-stage protocols for Perifosine in the treatment of Multiple Myeloma and Metastatic Colon Cancer.

Activation of the PI3K/AKT pathway has been associated with poor prognosis, or proliferation, in several pediatric tumors such as neuroblastoma, glioblastoma, rhabdomyosarcoma, and medulloblastoma. Perifosine's inhibition of this and other pathways, as well as its ability to cross the blood-brain barrier has generated much interest in exploring its potential activity in the treatment of patients with advanced brain tumors.

In vitro and in vivo data presented at AACR 2009 by investigators from the National Cancer Institute demonstrated that single agent perifosine not only induced tumor regression and delayed tumor growth, but that perifosine also improved the survival of mice bearing neuroblastoma tumors. Moreover, in a Phase II study conducted at Memorial Sloan-Kettering Cancer Center, perifosine induced responses and delayed disease progression in adult patients with advanced brain tumors.

Additionally, combination studies of perifosine with novel agents in patients with advanced brain tumors are expected to commence later this year. Such studies also to be funded by external grants.

Ron Bentsur, CEO of Keryx Biopharmaceuticals, commented, "We're very excited that Memorial-Sloan Kettering has taken on a leadership role in the first pediatric study of perifosine." Mr. Bentsur continued, "We are extremely grateful for the external financial support which we have received, and we look forward to working with Drs. Becher and Holland, and their team of renowned oncologists on this study."

The single-center, open-label, Phase I study is entitled "Study of Single Agent Perifosine for Recurrent Pediatric Solid Tumors." In this study, perifosine is being evaluated as a single-agent in pediatric patients with any solid tumor that has failed standard therapy. Patients up to 18 years of age with a performance status of greater than 40% are eligible for this study.

The study has been designed as a dose escalation study to determine the maximum tolerated dose of perifosine alone in recurrent/progressive pediatric tumors. A standard 3+3 dose escalation design will be employed with 3 to 6 patients at each dose level. All patients will receive perifosine at a loading dose on the first day, followed by a maintenance dose to start on day two until progression of disease. A minimum of 4 and a maximum of 24 patients will be required to complete the study.

KRX-0401 (perifosine) is in-licensed by Keryx from Aeterna Zentaris, Inc. in the United States, Canada and Mexico.

Lexicon Pharmaceuticals Inc. (NASDAQ: LXRX) of The Woodlands, Tex., announced today that it has initiated a phase II clinical trial of LX1032, the company's oral drug candidate for managing gastrointestinal symptoms associated with carcinoid syndrome.

LX1032 is designed to reduce serotonin production in patients with metastatic carcinoid tumors. Elevated levels of serotonin contribute to the gastrointestinal and possibly other symptoms experienced by these patients.

In addition to LX1032, Lexicon has three other drug candidates progressing through various stages of clinical development, including LX1031 for irritable bowel syndrome, LX2931 for rheumatoid arthritis, and LX4211 for diabetes.

The phase II clinical trial is designed as a four-week, randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability of LX1032 and its effects on symptoms associated with carcinoid syndrome. The study will include up to 28 patients with carcinoid syndrome who are symptomatic despite treatment with currently available therapy. Up to four dose levels may be evaluated in a serial ascending fashion. Once an optimal or maximal dose is identified, additional patients will be added to confirm clinical observations.

The clinical trial sites will include The University of Texas M.D. Anderson Cancer Center in Houston, Texas; the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida; and Hematology Oncology Services of Little Rock, Arkansas, the company said.

LX1032 is being developed in a product development collaboration with Symphony Capital Partners, L.P. and its co-investors.

LX1032 was discovered and developed at Lexicon to reduce serotonin production by inhibiting tryptophan hydroxylase (TPH), a key enzyme in the synthesis of serotonin. Excessive levels of serotonin have been

implicated in symptoms associated with carcinoid syndrome. Serotonin's breakdown product, 5-HIAA, is a biomarker used in the diagnosis of the condition.

Quantum Immunologics Inc. of Tampa, Fla., announced that the first patient in its breast cancer trial has begun to receive its dendritic cell therapy.

QI is currently sponsoring and conducting an FDA-authorized phase I/II clinical trial testing the safety and efficacy of its immunotherapy on 27 Stage IV breast cancer patients who have failed conventional therapy. The clinical trials involve the use of dendritic cell therapy using the oncofetal antigen, or iLRP -- immature Laminin Receptor Protein, as a cancer antigen (a protein found on cancer cells that can be targeted by the body's own immune system) found in many tumor cell lines or fetal tissue, but absent on normal, healthy tissue. QI believes that the OFA antigen can serve as a unique, valuable and promising antigen for individualized breast cancer immunotherapy.

Centered in Mobile, Ala., QI's clinical trial is designed around the use of QI's proprietary dendritic cell therapy, which employs OFA to recruit the patient's own immune system to target and attack the cancer cells with the intent to improve patient survivability and quality of life.

Each patient will receive three monthly injections of the patient's own dendritic cells that have been sensitized to OFA. It is anticipated that once the sensitized cells are injected back into the patient, the patient's T-cells will locate the OFA found on the patient's cancer cells, thereby generating an immune response with the goal of killing the cancer cells and preventing further spread of the disease.

US Oncology, Inc. of The Woodlands, Tex., said US Oncology Research will participate in the **BiPar Sciences** phase III, Multi-center, Open-Label, Randomized Trial of Gemcitabine/Carboplatin (G/C), with or without BSI-201, in patients with Estrogen Receptor, Progesterone Receptor, and HER2-negative metastatic breast cancer.

Joyce O'Shaughnessy, co-chair of the US Oncology Breast Cancer Research Committee, associate director for clinical research for US Oncology and co-director of the Breast Cancer Research Program at Baylor-Charles Sammons Cancer Center and Texas Oncology, a US Oncology affiliate in Dallas, Texas, will lead the study as a follow-up to the phase II study presented in a plenary session at the 45th Annual Meeting of the American Society of Clinical Oncology.

BSI-201 targets PARP, or poly (ADP-ribose) polymerase, a key enzyme involved in DNA repair and cell proliferation. By inhibiting the enzymatic activity of PARP, BSI-201 significantly enhances the anti-tumor effects of chemotherapy and has shown promising safety and efficacy results in patients with solid tumors.

Physicians within the US Oncology network are expected to enroll more than 100 participants in this 420-patient study. Enrollment in the study opened July 17 in centers nationwide.

Patients targeted for the study include adults with histologically documented metastatic breast cancer with measurable disease that is ER-negative, PR-negative, and HER2- non-overexpressing. They will receive the chemotherapy combination of gemcitabine/carboplatin with or without BSI-201.

Patients must have measurable metastatic breast cancer with zero to two prior chemotherapy regimens for metastatic disease; adjuvant chemotherapy is allowed. Primary objectives of the study are to evaluate: overall survival, progression-free survival, the objective response rate, and to further evaluate the safety and tolerability of BSI-201 in combination with gemcitabine and carboplatin.

Phase II of the study in triple negative breast cancer patients found that BSI-201 + G/C resulted in a statistically and clinically significant improvement in clinical benefit rate (CBR), median progression-free survival and OS, compared with G/C alone. BSI-201 + G/C was well tolerated with adverse events (AEs) consistent with known safety profiles of G/C regimens.

Deals & Collaborations:

Merck Licenses BioWa Platform For Antibodies

BioWa, Inc. of Princeton, N.J., said it has entered into a license agreement with **Merck KGaA**, Darmstadt, Germany, providing the global healthcare and chemicals company with access to BioWa's Potelligent Technology platform for the research, development and commercialization of their antibody therapies with enhanced antibody-dependent cellular cytotoxicity.

Under the terms of the license agreement, BioWa grants Merck KGaA non-exclusive rights to research, develop and commercialize therapeutic antibodies generated through Potelligtent Technology for an undisclosed number of targets. In return, BioWa will receive upfront payments, and may receive development milestone payments and royalties on products. Other

details of the agreement are not disclosed.

Potelligent Technology improves potency and efficacy of antibody therapeutics, by enhancing ADCC, one of the major mechanisms of action for antibody therapeutics.

BioWa is a wholly owned subsidiary of Kyowa Hakko Kirin Co., Ltd., and is the exclusive worldwide licensor of AccretaMab platform. AccretaMab platform consists of Potelligent and Complegent Technologies, creating a superior antibody molecule with enhanced ADCC and CDC activities.

Debiopharm Group, a Swiss-based global biopharmaceutical group of, and **MSM Protein Technologies**, a human antibody drug discovery company based in Medford, Mass., announce the signing of an exclusive agreement for the development and commercialisation of Debio 0929, an antibody targeting a G protein-coupled receptor, to be developed into a new oncology therapeutic drug.

Under the agreement, Debiopharm and MSM have formed a partnership to select antibodies against the GPCR. Upon completion of the discovery phase, MSM will grant Debiopharm a worldwide exclusive licence for the development and commercialisation of the antibody. MSM will retain marketing rights for Russia, Ukraine and several other countries in Eastern Europe and Asia. MSM will receive milestone payments from Debiopharm during the development of the product, as well as a share of royalties on net sales.

MSM is a closely held drug discovery company based in Boston, MA. The company applies its proprietary SIMPL platform and magnetic proteoliposome particles to display multispanners such as GPCRs in highly concentrated and purified form while retaining their native conformation and orientation thereby maximizing the probability of raising functional antibodies.

FORMA Therapeutics of Cambridge, Mass., entered into a collaboration agreement with **Novartis.**

Under the agreement, FORMA will utilize its cell-based screening platform to discover inhibitors for undisclosed protein-protein interaction targets in the field of oncology.

FORMA is integrating transformative chemistry and biology to unlock the best targets and pathways that genomic medicine has revealed. Capitalizing on the targets and pathways validated by the Cancer Genome Atlas Project and other related efforts, FORMA is developing a new generation of cancer therapies aimed at previously elusive drug targets. The company is achieving this by applying its proprietary cell-based screening, structure-guided drug discovery and Diversity Oriented Synthesis technologies, which FORMA also uses to discover novel compounds for its partners in indications beyond oncology.

Morphotek Inc. of Eston, Pa., and **Cancer Innovations Inc.**, a privately held biotechnology company specializing in the development of oncology products, have entered into an evaluation and option agreement in which Morphotek will evaluate monoclonal antibodies targeting certain tumor-associated proteins.

Morphotek is a subsidiary of **Eisai Corp. of North America.**

The agreement with CII provides Morphotek access to several of CII's monoclonal antibodies. Morphotek will evaluate one or more of the antibodies and have the right to exercise an option for a license during the evaluation period. Should Morphotek choose to exercise its option, the parties will enter negotiations for a license under which Morphotek would receive an exclusive worldwide license to develop the antibodies for potential therapeutic, diagnostic and prophylactic use, and would retain the responsibility for the commercialization of the antibodies.

Nuevolution of Copenhagen announced the execution of a worldwide technology cross-licensing agreement with **GlaxoSmithKline.**

The agreement relates to a number of patented technologies for rapid synthesis and DNA-tagging of hundreds of millions of chemically diverse drug-like small molecule compounds and the efficient screening of these, facilitating the identification of potent drug leads. These technologies were developed by Nuevolution and Praecis Pharmaceuticals, a wholly owned subsidiary of GlaxoSmithKline.

Under the cross-licensing agreement, GlaxoSmithKline will obtain a non-exclusive license under technology patents of Nuevolution, and Nuevolution will obtain a one time license fee and a non-exclusive license under technology patents of GlaxoSmithKline.

Nuevolution has developed Chemetics, a hybrid of proven wet chemistry and molecular biology which represents the ultimate fragment based lead discovery technology. Chemetics enables rapid synthesis and DNA-tagging of hundreds of millions of chemically diverse drug-like small molecule compounds and the efficient screening of these, facilitating the identification of potent drug leads.