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FDA Approved 88% Of Cancer Applications Since Oncology Office Opened In 2005

By Paul Goldberg

Conventional wisdom: Fixated on safety and guided by belief that cancer drugs must extend survival, FDA has erected insurmountable barriers to innovation in oncology, causing drug companies to abandon the field.

The agency's approval data in oncology points to a different picture: The FDA Office of Oncology Drug Products cancer division approved 53 new indications and declined to approve five. Another two applications were withdrawn by the sponsors.

Spanning the period between July 2005, when the office was created,

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In the Cancer Centers:

M.D. Anderson Wins 11th SPORE Grant, For Research On Brain Tumor Therapies

M. D. ANDERSON Cancer Center received a five-year, $12.5 million Specialized Program of Research Excellence grant from NCI to advance two new therapies for malignant brain tumors.

This is the 11th SPORE grant received by M. D. Anderson. The center holds SPORE grants in leukemia and melanoma as well as cancers of the breast, bladder, pancreas, ovaries, uterus, head and neck, prostate and lung, with the last shared with University of Texas Southwestern Medical Center in Dallas. The 11 grants out of 60-plus SPOREs awarded by the NCI are the most held by a single institution.

"This award marks a very significant event for M. D. Anderson and indicates the important role that the institution plays in the field of translational research," said Raymond DuBois, M. D. Anderson provost and executive vice president. "We are essentially leading the way in developing multidisciplinary research teams to accelerate the transition of basic knowledge into the clinic. I am extremely proud of our neuro-oncology team and all of the people involved who will use this brain tumor SPORE to ultimately make a difference for patients."

The co-principal investigators are **W. K. Alfred Yung**, chairman of the Department of Neuro-Oncology, and **Oliver Bogler**, associate professor in the Department of Neurosurgery.

The grant will support four projects:

—The engineered adenovirus Delta-24-RGD, developed at M. D. Anderson, will advance to clinical trial and a second-generation version will

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Oncology Drug Pipeline Running Strong, Pazdur Says

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through December 2007, this tabulation shows that the agency's approval rate in oncology stands at 88.3 percent.

"The public gets a skewed look of the oncology drug approval process," said Richard Pazdur, director of the agency's oncology office director. "Public discussion is centered on products we take to the Oncologic Drugs Advisory Committee."

Applications that require the input from the advisory committee of clinicians are usually problematic, and do not reflect the full picture of what goes on in oncology.

"People frequently don't hear about the many drug approvals that don't require consultation with ODAC," Pazdur said.

The slides from Pazdur's presentation at a workshop on cancer drug development are posted at http://www.cancerletter.com/publications/special-reports/Approvals.ppt.

The June 18-20 workshop was co-sponsored by the agency, NCI, Duke Comprehensive Cancer Center, the American Society of Clinical Oncology, and the American Association for Cancer Research.

"Oncology continues to be a very active area," Pazdur said in an interview. The numbers of Investigational New Drug issued by the office and meetings that precede the start of phase II testing have gone up dramatically, he said.

"The number of new INDs has risen from 925 in fiscal 2003 to what is expected to be over 1,400 in fiscal 2008," Pazdur said. "Industry requests for critical development milestones for products that are well past the initial IND phase have risen by 245 percent since 2003. The number of such meeting requests for oncology drugs is almost double that of the next highest therapeutic class, endocrinology."

"This level of activity would translate into applications—New Drug Applications and Biologic License Applications—coming into the Office of Oncology Drug Products," Pazdur said.

—Of the 53 approvals, 18 represented new molecular entities and 35 were supplemental indications. The data don't include cancer vaccines, cancer imaging devices, and test kits, which aren't reviewed by the oncology office.

—Altogether, the office gave out 38 regular approvals and 10 accelerated approvals. The total also includes five former accelerated approvals that were converted to full approvals during this period.

—The most frequently used endpoint was response rate, which figured in 17 indications, followed by progression free survival and time to progression, which together accounted for 12 approvals. Overall survival came third, with 10 indications, and disease-free survival followed with five indications.

—Also, the agency used several novel endpoints, including reduction in hepatic iron and depletion of asparagine.

—The trials of four of the five drugs that didn't get approved failed to meet their primary endpoints. Another cause of failure was the sponsors' decision to ignore the agency's advice on acceptable endpoints.

"Behind these numbers, we have noticed dramatic changes in some diseases, with not only one drug being approved, but multiple drugs being approved, and these multiple drugs have changed the treatment landscape," Pazdur said.

Oncologists now have more choices in treatment of even relatively rare cancers, approval data show. This includes three new agents for the treatment of advanced renal cell carcinoma, three agents for the multiple myeloma indication, three supportive care indications, and four pediatric indications.

The agency has been battling the misconception that it approves drugs based on survival only, and that it's reluctant to accept surrogate endpoints. In recent years, the agency has been increasingly willing to approve

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cancer drugs based on metrics of delay in progression.

Though a delay in progression is usually a poor surrogate for clinical benefit, the agency has started to recognize it as a benefit in its own right.

"I have heard people claiming that the number of accelerated approvals has decreased," Pazdur said. "However, one has to be cognizant that some of the endpoints that we had previously used for accelerated approval are now being used to regular approval."

In the past, an approval based on response rates would likely have indicated that the drug produced tumor shrinkage in solid tumors. This was usually shown with a single-arm trial.

By contrast, in this crop of approvals, response rates were used primarily in hematological malignancies.

"Many of the approvals based on response rates were in hematological diseases, such as CML and cutaneous T-cell lymphomas, where there had been a high degree of activity, we accepted response rate as a primary endpoint," Pazdur said, describing the 18 indications that were approved based on response rates.

Reliance on metrics of delay in progression has pushed the agency to require randomized trials. Not only does this provide more robust information on the drugs, but it is useful to sponsors who seek approval in the European Union, which has similarly adopted progression metrics.

"A randomized trial gives us much more information than single-arm trial that examines response rates," Pazdur said. "We've been on record saying that randomized trials give us more information about the drug. Not only do randomized trials provide information about the response rates, but they also give us information about time to progression and survival. Randomized trials also provide data on comparative toxicities, comparative safety profiles of the drugs."

Unlike other therapeutic areas at FDA, the oncology office doesn't always demand data from multiple trials.

"One of the reasons that we generally accept one trial is that randomized trials generally provide data on multiple endpoints," Pazdur said. "If the primary endpoint is survival, a secondary endpoint might be time to progression or response rates. These secondary endpoints provide us corroboration of the drug's effect."

Randomization is crucial for drugs that don't shrink tumors, but stabilize disease and delay progression.

"If you have a drug where you think the primary action is going to be delaying the progression of the disease rather than reducing tumor size, a randomized study may be the only way to evaluate the drug," Pazdur said. "A well-designed randomized trial may save the drug that may not have a meaningful response rate in a single-arm trial."

Pazdur said the FDA approval criteria are now largely consistent with those of the European Medicines Agency. However, one distinction is the value of a delay in progression in late-stage disease.

"The EMEA has accepted time to progression as a registration endpoint for first-line therapies. Our recent actions have brought us into harmony with them," Pazdur said. "However, the EMEA usually requires an improvement is survival as an endpoint in more refractory disease. In contrast, our view is that if TTP reflects clinical benefit in the first-line setting, it would also represent a clinical benefit in a more refractory setting."

Attempts at data-dredging of trials that failed to meet their primary endpoints haven't played well at FDA.

"In general, many of the drugs that were not approved failed their primary endpoints," Pazdur said. "These applications also came in with one trial which failed the primary endpoint, which is problematic. In addition, several sponsors didn't take the FDA advice at end of phase II meetings on primary endpoints, and the primary endpoints that were selected were problematic upon review."

The controversy over drug safety hasn't dampened the sponsors' interest in cancer treatment, Pazdur said.

"In oncology, we have a different safety profile that has evolved over the past 30 or 40 years," he said. "Unlike other therapeutic areas, our major hurdle is demonstration of sufficient efficacy."

The most recent FDA overview of approvals was published in the Journal of Clinical Oncology five years ago.

At that time, the agency summarized the endpoints for 71 cancer drug applications approved over 13 years. The paper showed that endpoints other than survival were the approval basis for 68% (39 of 57) of the applications that received regular approval and for all 14 applications that received accelerated approval.

Tumor response was the approval basis in 26 of 57 regular approvals, supported by relief of tumor-specific symptoms in nine of these 26 regular approvals. Relief of tumor-specific symptoms provided critical support for approval in 13 of 57 regular approvals.

The paper is posted at http://jco.ascopubs.org/cgi/content/full/21/7/1404.

NCI News:

Advisors Approve Concepts For Research Programs

The NCI Board of Scientific Advisors approved several concepts for Requests for Applications and Request for Proposals at it meeting June 23.

Following are edited portions of the concept statements:

Transdisciplinary Cancer Genomics Research: Translation of Genome-Wide Association Studies. Concept for a new RFA, cooperative agreement, first-year set-aside $24 million, five to eight awards, estimated total $96 million over four years. Program directors: Daniela Seminara and Elizabeth Gillanders, Division of Cancer Control and Population Sciences.

This RFA would solicit collaborative, transdisciplinary research projects pursued by multi-center teams of epidemiologists and basic scientists, which would thoroughly and efficiently investigate the significance of genomic regions reported to be associated with cancer susceptibility.

Applications should focus only on cancers of the colon, breast, prostate, lung, pancreas, bladder, and melanoma. Each application would be required to involve multiple centers with existing initial GWA datasets, which would be analyzed together using either pooled analysis or meta-analysis.

The overall goals are 1) to exploit the power of existing GWAS of cancer by combining previously generated "initial scan" GWAS data, and 2) to accelerate and coordinate integrative post-GWAS research in the T1 phase, to expedite clinical and public health translation.

To ensure that the maximal scientific benefit is derived, this RFA will require broad data sharing. It is expected that as soon as genotype, phenotype, and exposure data have passed appropriate date quality assessments that it will be made publicly available via NCI's cancer Biomedical Informatics Grid. Funding may be requested within the application to support local efforts for standardizing or harmonizing phenotypes and exposure data, registering the harmonized elements within caBIG, as well as coordination of genotype, phenotype and exposure data sharing within caBIG.

Cancer Care Outcomes Research and Surveillance Consortium. Concept for a re-issued RFA, first-year set-aside $3.7 million, seven awards, estimated total $11 million over three years. Program directors: Anita Ambs and Neeraj Arora, DCCPS.

The purpose of the CanCORS renewal is to provide continued support for CanCORS, which is the only NCI effort to conduct collaborative community-based cancer care delivery research across the entire spectrum of the health care delivery system, including NCI comprehensive cancer centers, community cancer centers, cancer registries, and healthcare provider organizations. These entities are committed to the science of obtaining the best possible evidence about what factors determine the quality of cancer care, have access to diverse patient populations, and are able to collect community-based patient and physician information relevant to research on quality cancer care in population based settings.

Support for this second phase of CanCORS will have the following specific research objectives:

1. Measurement of long term (defined as occurring beyond one year post-diagnosis) clinical and patient-reported health outcomes not collected during the first phase of CanCORS, and that are necessary to fully characterize the effects of the initial care in general clinical practice.

2. Assessment of variations in and outcomes of post-treatment surveillance, including the use of new imaging tests, therapies for recurrence/progression, and palliative care following the transition from the initial acute treatment phase to survivorship and end-of-life care.

3. Identification of the key barriers to adoption of newly emerging targeted therapies for the treatment of initial, metastatic and recurrent disease.

A secondary objective in this final phase of CanCORS will be maximizing the investment in CanCORS by expanding opportunities for conducting new ancillary studies funded through separate, competitive grant mechanisms and the application of existing CanCORS data to help answer important questions in care delivery and outcomes that CanCORS data is uniquely positioned to address. This will be accomplished primarily through the creation of a shared, open database resource accessible to investigators outside of CanCORS and by encouraging collaboration of CanCORS investigators with other outside investigators to increase the understanding and utility of the CanCORS data.

NIH Centers for Population Health and Health Disparities. Concept for an RFA reissue, first-year set-aside $10 million, five awards, estimated total $50 million over five years. Program director: Shobha

Srinivasan, DCCPS.

The purpose of this proposal is to continue support for the CPHHD initiative in 2009, with a competitive RFA yielding a second round of centers. The goal is to expand transdisciplinary research for addressing fundamental research questions concerning the multilevel determinants of cancer disparities. The centers will develop and implement novel and sophisticated strategies to understand the etiology, pathways, and novel mutli-factorial interventions for the reduction of cancer disparities. This transdisciplinary science would span all levels from individual cells to society as a whole—whereby research would be conducted, for example, simultaneously in the laboratory (e.g., in cell and tissue culture and in animal models), in individual patients (e.g., by determining their exposures, behaviors, etc) and in populations (e.g., by examining how geographic location relates to biological risk variables).

The new RFA will include a training component that was not included in the previous solicitation. Since the new RFA will be a P50 mechanism, it will allow for training the next generation of researchers in a multidisciplinary environment.

Comprehensive Minority Institution/Cancer Center Partnership. Concept for an RFA reissue, first-year set-aside $5 million, four U54 awards (two partnerships), estimated total $25 million over five years. Program director: H. Nelson Aguila, NCI Office of the Director.

Initiated in 2001, the MI/CCP aims to create stable, comprehensive, and long-term partnerships between minority serving institutions and NCI-designated cancer centers or groups of centers in the areas of research, training, career development and outreach. Through these collaborations, the institutions work together to train scientists from diverse backgrounds in cancer research, and enhance efforts to effectively reach racially and ethnically diverse communities with cancer advances.

Cancer Disparities Research Partnership Program. Concept for an RFA reissue, first-year set-aside $4.2 million, five awards, estimated total $14.5 million over five years. Program director: Rosemary Wong, Division of Cancer Treatment and Diagnosis.

This letter RFA is for the reissuance and recompetition of the CDRP program initiated in 2002. The program uses the U56 cooperative agreement structure developed and managed by the Radiation Research Program.

Due to lack of screening and the delay in accessing healthcare, disparity populations suffer disproportionately from locally advanced cancers such as cervix, breast, lung and head and neck for which radiation therapy is a mainstay of treatment. The primary challenges of this grant, using radiation oncology as the backbone but expanding into multi-disciplinary care are 1) to accelerate research treatment discoveries in disparities populations, 2) translate those advances into clinical delivery to those populations, 3) establish a sustainable culture of research within these communities and 4) have successful CDRP grantees re-compete and become sustainable participants in NCI research programs after the second funding cycle.

Pediatric Preclinical Testing Program. Concept for an RFP reissue, estimated cost $14.3 million, one award for five years. Project officer: Malcolm Smith, DCTD.

The primary objective of the program is to systematically develop robust preclinical datasets that pediatric oncologists can use in prioritizing novel agents for clinical evaluation in children with specific cancer types. The PPTP accomplishes this through using its panel of molecularly characterized pediatric preclinical models of childhood cancers to test 10 to 12 agents or combinations of agents each year. For agents tested, pharmacokinetic studies will be performed to determine the drug levels and systemic exposures associated with antitumor activity. Results from the preclinical testing program will continue to be correlated with the clinical activity and with the pharmacokinetic profile of the tested agents to assess the predictive capabilities of the program. The intended outcome of the project is to improve survival for children with cancer by identifying for clinical testing the most effective agents from among the universe of oncologic agents potentially available for evaluation in children with cancer.

The Pediatric Drug Development Group reviews proposals for agents to undergo evaluation through the PPTP.

Replication and Fine-Mapping Studies for the Genes Environment and Health Initiative. Concept for a new RFA, first-year set-aside $2 million, five awards, estimated total $2 million over one year. Program director: Elizabeth Gillanders, DCCPS.

The GEI is a four-year NIH-wide program designed to identify major genetic susceptibility factors for diseases of substantial public health impact and

to develop technologies for reliable and reproducible measurement of potentially causative environmental exposures. The purpose of this funding opportunity is to provide support for replication and fine-mapping studies of genetic regions putatively associated with common complex traits (primarily those identified by GWAS), with the aim of enhancing the identification of causal variants influencing complex diseases. Any phenotype may be considered: acceptable phenotypes need not be cancer or cancer-related.

In the Cancer Centers:

NCI Selects Duke To Lead CTMS Knowledge Center

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be developed as a single therapy and in combination with other drugs. Delta-24 will be injected directly into tumors during a phase I clinical trial under review at FDA. PIs are **Juan Fueyo**, associate professor of neuro-oncology, and **Frederick Lang**, professor of neurosurgery.

—Blocking a malignant pathway: Drugs that block a molecular signaling cascade known to fuel brain tumors, the PI3K pathway, will be developed and tested in phase I trials. One candidate inhibitor has been developed by **Garth Powis**, professor and chairman of M. D. Anderson's Department of Experimental Therapeutics, who is co-PI with Yung and Bogler on the project.

—Identifying treatment guideposts: Researchers are developing and validating a set of genes that predict survival and sensitivity to treatment for glioblastoma patients. PIs are Kenneth Aldape, professor in the Department of Pathology, and **Howard Colman**, assistant professor of neuro-oncology.

—Pinpointing genetic role in brain impairment: By analyzing the genetic makeup of glioblastoma patients and relating it to the type and degree of cognitive impairment they experience after radiation treatment, researchers aim to identify and understand genes that affect cognitive outcomes. PIs are **Melissa Bondy**, professor in the Department of Epidemiology, and **Christina Meyers**, professor of neuro-oncology.

DUKE COMPREHENSIVE CANCER CENTER was selected by NCI to lead the operation of the cancer Biomedical Informatics Grid's Clinical Trials Management Systems Knowledge Center, in collaboration with Robert H. Lurie Comprehensive Cancer Center at Northwestern University, and SemanticBits.

Administered by the NCI Center for Biomedical Informatics and Information Technology, the caBIG initiative has been developed to advance basic and clinical research in cancer and to improve clinical outcomes for patients. The initiative has successfully launched key tools and infrastructure based upon agreed upon common standards that enable individuals and organizations in the cancer community and other domains to share information and data and collaborate with one another on research studies and clinical initiatives.

"The CTMS Knowledge Center will become the cross-roads for those seeking support for the various clinical trials tools, culminating in a vast repository of experiences and solutions," said **Bob Annechiarico**, the Knowledge Center director and director of Duke Comprehensive Cancer Center's Information Systems.

Each of the caBIG Knowledge Centers provides a centralized, authoritative repository of knowledge and information, and web-based support to facilitate the adoption of caBIG tools, standards and infrastructure for that domain. Member institutions of the caBIG initiative have been responsible for the development of several of the core applications in the Clinical Trials Management Systems, such as the cancer Adverse Event Reporting System (caAERS), the Patient Study Calendar (PSC), and the Cancer Central Clinical Patient Registry (C3PR).

For more information about the cancer Biomedical Information Grid, see http://cabig.nci.nih.gov.

UNIVERSITY OF COLORADO Cancer Center and the Colorado State University Cancer Supercluster are celebrating a 20-year research collaboration that has lead to breakthroughs in cancer treatment for humans and companion animals.

"We are very distinct universities, located miles apart, who have decided that our cancer research collaboration is beneficial to the people of Colorado and all Americans," said **Paul Bunn Jr**., director of the University of Colorado Cancer Center.

The collaboration has led to characterizing cancers for better diagnostics, better treatments, and better monitoring of treatment effectiveness, said **Robert Ullrich**, director of the UCCC Carcinogenesis Program and chief research officer of the CSU Cancer Supercluster. The UC cancer research enterprise includes scientists and clinicians from UC Denver, University of Colorado Boulder, and University of Colorado Colorado

Springs.

The CSU Cancer Supercluster consists of cancer-research members from five colleges and 12 departments, including the Animal Cancer Center—the largest companion animal cancer research center in the U.S.

DANA-FARBER CANCER INSTITUTE has begun a national continuing medical education course to bring science and guidelines to community and sub-specialist oncologists. The first program, Master Class for Oncologists, is an 18-month program delivered on-line and in live programs. "The program is tailored to community oncologists needing education in a variety of subspecialty areas in oncology, and to sub-specialists needing great depth within their respective sub-specialty," said **Robert Mayer**, director of the Center for Gastroinstestinal Oncology at Dana-Farber and course chairman. He also is the Stephen B. Kay Family Professor of Medicine and associate dean of admissions at Harvard Medical School.

ROSWELL PARK CANCER INSTITUTE announced the appointment of **Anthony Billoni** as director of the Erie-Niagara Tobacco-Free Coalition, housed within the Department of Health Behavior. The coalition represents dozens of health and human service agencies in the Western New York region and is responsible for sponsoring activities to reduce the harm that tobacco causes. Billoni was director of admissions at The Park School of Buffalo. Also at RPCI, **Asoke Mal** was appointed assistant professor of oncology in the Department of Cell Stress Biology. Mal was a faculty member, Department of Molecular Genetics, at the Lerner Research Institute, Cleveland Clinic Foundation. His research includes rhabdomyosarcoma.

ERWIN VAN MEIR, professor of neurosurgery and hematology and medical oncology, Emory University Winship Cancer Institute, received a $600,000 research grant to study the role of the Galectin-3 protein in brain cancer. The three-year award is from the Goldhirsh Foundation.

ALAN LIST was named executive vice president, physician-in-chief at Moffitt Cancer Center. List was division chief of malignant hematology at MCC. He replaces **Clifford Schold Jr**., who retired. **Eduardo Sotomayor** takes over as chief of the malignant hematology division. He has been part of the malignant hematology faculty since 1999.

Philanthropy:

Foundation Begins Planning For Brain Tumor Banking

Children's Brain Tumor Foundation began the initial phase of a tissue bank consortium designed to jump-start meaningful analyses that could lead to treatments for pediatric brain tumors, where survival rates are low with current treatment options.

Under a planning grant from the Licensing Industry Merchandisers' Association, CBTF is conducting a feasibility study with participation by leading pediatric institutions.

Through the multi-institution research program, participating hospitals will agree to collect and analyze tissue samples and share data publicly.

A standardized database will be used to collect and centrally record clinical data. Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh and Children's Memorial Hospital in Chicago are participating in the planning study, led by Tom Curran, deputy scientific director, and Children's Hospital of Philadelphia.

"The need for this approach is nearly palpable among pediatric oncologists who specialize in brain and spinal cord tumors," said Robert Budlow, CBTF president. "As the advocate and voice for children and families fighting what can seem like insurmountable odds, the Children's Brain Tumor Foundation is committed to growing the tissue bank consortium to open the doors to speeding scientific progress on this horrible disease."

According to Curran, although pediatric brain tumors can be devastating, their low incidence has created a roadblock for researchers who need a large enough data set to conduct statistically significant analyses. "Everyone in this field believes that research is the key to better treatments, but this is very much a numbers game," Curran said. "We need the power of statistics with a large sample set to make a difference."

In the project's initial phase, Curran is planning the procedures to establish consistent tissue collection and analysis from participating hospitals. The second phase will establish the network to collect and analyze the samples.

"Once we have this avenue for collecting and characterizing a large enough sample set, then we can apply very sophisticated genomic research tools to understanding the origin and genetic mutations responsible for pediatric brain tumors, with the hope of uncovering new therapeutic avenues," Curran said.

"Collecting and characterizing the samples is just a beginning. We also would try to collect tumor materials to promulgate in model systems that we can make them available to any investigator who needs them for study."

CBTF is seeking co-funding support from foundations and organizations in addition to support from the LIMA.

"For pediatric brain and spinal cord tumors, tumor tissue banking is like a small pie cut into too many pieces," said Susan Weiner, chairman of the CBTF grant committee. "Many hospitals have tissue banks, but few if any have sufficient volume of different kinds of tumors to conduct comprehensive research. Without the new tissue bank consortium, meaningful analysis that might lead to treatment and cures is virtually impossible."

ACS Plans Fourth Relay In "Second Life" Online Game

American Cancer Society plans to hold its fourth annual Relay For Life event in the Second Life virtual world on July 19-20.

The society's real-world relay, first begun in 1985, is expected to include 3.5 million people in 20 countries. The virtual relay in Second Life is expected to attract 2,000 participants on about 80 teams to reaching a fundraising goal of $125,000. Last year, the Second Life event raised $118,000—more than double its total for the previous two years combined—and attracted more than 1,700 participants.

Relay For Life in Second Life began in 2005, when ACS volunteers in the Second Life community approached society staff about creating a Relay For Life event in the virtual world. The result of this collaboration is a cyberspace community gathering in which participants, represented by avatars, continuously navigate a custom-built track, encompassing a 480-acre virtual park, to raise money to fight cancer.

Last summer, the society created a virtual headquarters in the Second Life community to provide the same, round-the-clock cancer information and services that the organization delivers in the real world. Relay For Life in Second Life is piloting a corporate sponsorship program, with General Electric as the first sponsor.

In the non-virtual relay, teams of people gather at schools, fairgrounds and parks and take turns walking or running laps while aiming to keep at least one team member on the track at all times.

Further information on the Second Life Relay For Life event and the society virtual headquarters office is available at www.cancer.org/slrfl and www.slrfl.org.

Funding Opportunities:

RFA-AT-08-003: Mechanisms of Immune Modulation. R01. Application Due Date: Oct. 17. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-08-003.html. Inquiries: Young Kim, 301-496-0126; yk47s@nih.gov.

RFA-AT-08-004: Mechanisms of Immune Modulation. R21. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-08-004.html.

RFA-CA-08-024: Measures and Determinants of Smokeless Tobacco Use, Prevention, and Cessation. R01. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-024.html. Letters of Intent Receipt Date: Oct. 24. Application Due Date: Nov. 24. Inquiries: Mark Parascandola, 301-451-4587; paramark@mail.nih.gov.

RFA-CA-08-025: Measures and Determinants of Smokeless Tobacco Use, Prevention, and Cessation. R21. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-025.html.

PA-08-185: Exploratory/Developmental Grant for Complementary and Alternative MedicineStudies using Cells, Tissues, and Animal Models of Disease. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-185.html. Inquiries: Cindy Davis, 301-594-9692; davisci@mail.nih.gov.

PA-08-190: Research Supplements to Promote Diversity in Health-Related Research. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-190.html. Inquiries: Peter Ogunbiyi, 301-496-7344; po43t@nih.gov.

PA-08-191: Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-191.html. Inquiries: Peter Ogunbiyi, 301-496-7344; po43t@nih.gov.

RFP S08-224: CMO for IL-15 Production. Full text: http://www.fbodaily.com/archive/2008/06-June/13-Jun-2008/FBO-01591581.htm. Inquiries: Melissa Borucki, 301/228-4041; boruckim@mail.nih.gov.

SS-NCI-TSB-2008-1: Collection and Taxonomy of Shallow Water Marine Organisms. Response Due date: July 7. Full text: http://www.fbodaily.com/archive/2008/06-June/27-Jun-2008/FBO-01601201.htm. Inquiries: Robin Irving, 301-228-4220; irvingr@mail.nih.gov or Timothy Crilley, 301-228-4224; tcrilley@mail.nih.gov.

NOT-OD-08-083: NIH Extramural Loan Repayment Programs. Application period: Sept. 1 through Dec. 1, at 8:00 PM EST. Full text: http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-08-083.html. Inquiries: 866-849-4047; lrp@nih.gov.; http://www.lrp.nih.gov.

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Business & Regulatory Report

Clinical Trials:

Phase III Study Open Testing Combination Of Avastin, Herceptin For Breast Cancer

BETH, Bevacizumab and Trastuzumab Adjuvant Therapy in HER2-positive Breast Cancer, a pivotal international phase III study, is investigating the benefits of combining two monoclonal antibodies, the anti-angiogenic, bevacizumab (Avastin) and the targeted therapy trastuzumab (Herceptin), together with chemotherapy for early stage HER2-positive breast cancer.

BETH was developed through the collaboration of the National Surgical Adjuvant Breast and Bowel Project and Cancer International Research Group, which will both lead the 3,500-patient study. The primary outcome measure will be invasive disease-free survival. Secondary endpoints include disease-free survival, overall survival, safety, and tolerability, the groups said.

"Trastuzumab is already the standard of care across all stages of HER2-

(Continued to page 2)

Deals & Collaborations:

Collaboration For Early Trials Of Aegera Therapy For Lymphoma And Leukemia

Aegera Therapeutics Inc. of White Plains, N.Y., and **The Leukemia & Lymphoma Society** said they have executed an agreement for $3.3 million to support an international phase I/II trial for the Aegera AEG35156, a targeted therapy for follicular lymphoma, small lymphocytic lymphoma and chronic lymphocytic leukemia.

The trials will take place in Canada and the U.S., the groups said.

The agreement marks the first clinical trial under the LLS Therapy Acceleration Program, a program that advances therapies with high prospects of providing near-term benefit in blood cancers, the groups said.

In another development, the Leukemia & Lymphoma Society and **Memgen** of Dallas and San Diego said they are collaborating in a phase I trial of ISF35, the Memgen active immunotherapy for chronic lymphocytic leukemia.

Treatment in the 12-patient trial in 17p-, refractory or resistant CLL with limited therapeutic options, will consist of three infusions of ISF35, followed by up to three courses of FCR (fludarabine, cyclophosphamide and rituximab). Safety and efficacy of the regimen will be determined after one year, the collaborators said.

In the initial phase I CLL trial of ISF35, conducted by William Wierda, at M. D. Anderson Cancer Center, a single infusion of ISF35 resulted in

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Large International Trial Open Of Avastin-Herceptin Combo

(Continued from page 1)

positive breast cancer and has a proven survival benefit," said Dennis Slamon, director of clinical/translational research at the University of California, Los Angeles, Jonsson Comprehensive Cancer Center and principal investigator, Cancer International Research Group. "Bevacizumab has shown benefit in combination with chemotherapy for metastatic breast cancer. The design of the BETH trial is based on the preclinical and early clinical work from the Slamon/TRIO Laboratories at UCLA."

"Despite treatment advances, over 400,000 women worldwide still die from breast cancer every year, so striving to improve treatment outcomes remains critical," said Norman Wolmark, chairman of the Department of Human Oncology at the Allegheny General Hospital, and principal investigator, NSABP Foundation Inc., Pittsburgh.

In BETH, randomization will be to a regimen of chemotherapy (either six cycles of docetaxel/carboplatin or three cycles of docetaxel, followed by three cycles of FEC) plus trastuzumab with or without bevacizumab.

Bevacizumab is used in metastatic breast cancer and trastuzumab in both early and late HER2-positive breast cancer. This is the first phase III trial to evaluate combining the two therapies in treating early stage breast cancer, the groups said.

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Aegera Therapeutics Inc. of Montreal said it has begun a phase I trial of HGS1029 (formerly AEG40826), the Inhibitor of Apoptosis Protein inhibitor, as a monotherapy in advanced solid tumors.

The small molecule IAP inhibitor was developed by Aegera and licensed to **Human Genome Sciences Inc.** (NASDAQ:HGSI) for oncology development in 2007. Under the agreement, Aegera said it maintains full ownership of all rights to this class of molecules for the Japanese market and global rights for non-oncology indications.

Aegera also said it has received its first milestone payment of $5 million under the collaboration agreement, which was triggered by FDA clearance of the IND application for HGS1029.

AXL1717 is a targeted small-molecule IGF-1 receptor inhibitor with no effect on the almost identical insulin receptor, the company said. Pre-clinical data show anti-tumor efficacy, including tumor extermination, in animal models for a range of human cancers such as breast and prostate cancers, malignant melanoma, multiple myeloma, glioblastoma and sarcoma. The agent is given orally.

Bradmer Pharmaceuticals Inc. of Toronto said it has received notification from FDA that it can begin a phase III trial evaluating Neuradiab as a front-line therapy for glioblastoma multiforme.

The 760-patient randomized phase III trial, or the GLASS-ART Trial, would investigate Neuradiab as an adjuvant therapy to surgery, external beam radiation and temozolomide in newly diagnosed glioblastoma multiforme. The trial would be conducted at brain tumor treatment centers across the U.S.

Neuradiab is a monoclonal antibody, conjugated to radioactive iodine, used to treat glioblastoma multiforme. The drug delivers tumor-killing radiation specifically to residual brain tumor cells after surgery, with minimal impact on normal brain tissue. During the course of development at the Preston Robert Tisch Brain Tumor Center at Duke University, over $60 million in research grants and related support was invested to produce a series of phase I and phase II trials on Neuradiab and other closely related technologies. Two hundred brain cancer patients, including 160 with GBM, have been treated with the Neuradiab therapy regimen, and survival benefits have exceeded historical controls in each completed trial, the company said. Neuradiab has been referred to in literature as 131I anti-tenascin monoclonal antibody 81c6.

The GBM Locoregional Agent Survival Study-

Antitenascin Radiolabeled antibody Therapy Trial would determine the survival benefit derived from adding Neuradiab to the standard of care therapy, consisting of surgery, radiation and adjuvant chemotherapy (temozolomide), in primary glioblastoma mulitforme and whether the drug regimen is safe. The goal is to replicate the increase survival benefit reported by Duke University investigators in patients treated with Neuradiab.

CuraGen Corp. (NASDAQ: CRGN) of Branford, Conn., said its phase II trial evaluating CR011-vcMMAE for unresectable stage III or stage IV melanoma has met the efficacy criteria for advancement to the second stage of enrollment.

Of the first six, one patient has had a confirmed objective response, as measured by RECIST criteria, the company said. As part of the Simon 2-stage design, the trial will expand to a total of 32.

CR011-vcMMAE targets the GPNMB protein, which is overexpressed in melanoma, breast cancer and brain tumors, the company said.

Endocare Inc. (NASDAQ: ENDO) of Irvine, Calif., said a group of academic institutions are collaborating on Salvage Cryotherapy Registry Evaluation, or SCORE, an 800-patient, multi-center, prospective study on the effectiveness of cryoablation in prostate cancer that has recurred after radiation therapy.

The study is being led by E. David Crawford, and Al Barqawi, both of the University of Colorado Cancer Center, and physicians from 25 medical institutions, including M.D. Anderson Cancer Center, Loma Linda University, Washington University, the University of Tennessee and Maimonides Medical Center, the company said.

Endocare manufactures the Endocare Cryocare System, a cryoablation device. The SCORE Study is the largest prospective trial undertaken in cryoablation, the company said.

Exelixis Inc. (NASDAQ: EXEL) of South San Francisco said it has reached an agreement with FDA on the phase III registration trial of XL184, a small molecule anticancer compound targeting MET, RET, and VEGFR2, via the Special Protocol Assessment process.

The trial for medullary thyroid cancer would begin this summer. Exelixis said it also has discussed the trial design with European regulatory agencies.

The trial has been designed in collaboration with Steven Sherman, of M.D. Anderson Cancer Center, Douglas Ball and Barry Nelkin, of Johns Hopkins University, and Martin Schlumberger, of the Institut Gustave Roussy, Paris.

The 315-patient study will be a randomized, placebo-controlled, double-blinded trial of XL184 as single-agent therapy in unresectable, locally advanced, or metastatic MTC. Randomization will be in a 2:1 ratio to receive XL184 or placebo administered as a daily oral dose. The primary endpoint will be duration of progression-free survival. In a planned event-driven analysis, the study size provides 90% power to detect a 75% increase in progression-free survival in documented progressive disease prior to study entry. Secondary endpoints will include overall survival, objective tumor response rate, and changes in serum biomarkers (carcinoembryonic antigen and calcitonin). Additional secondary endpoints will be assessment of the relationship between germline and/or tumor DNA sequence alterations and the efficacy of XL184, as well as assessment of pharmacodynamics and pharmacokinetics of XL184, the company said.

Genmab A/S (OMX: GEN) said it has begun a phase I/II study of zalutumumab (HuMax-EGFr) in combination with irinotecan chemotherapy in refractory colorectal cancer.

The 97-patient study will examine standard chemotherapy that has failed and where disease has progressed during or within three months of stopping cetuximab-based therapy.

The open label study consists of two parts. In both parts of the study, treatment will consist of weekly doses until disease progression. Part I will include 3 to 15 patients treated with weekly doses of first 8mg/kg of zalutumumab in combination with bi-weekly irinotecan and if safe subsequently treated with 16 mg/kg zalutumumab in combination with irinotecan, the company said.

Part II will be an open label randomized parallel group enrolling 14 to 82 who will receive weekly doses of zalutumumab with or without bi-weekly irinotecan administration until disease progression. In total a maximum of 97 will be enrolled.

Human Genome Sciences Inc. (NASDAQ: HGSI) of Rockville, Md., said it has begun dosing in a phase I trial of its IAP inhibitor, HGS1029, as a monotherapy in advanced solid tumors. HGS1029 will be administered as a 15-minute infusion once weekly for three consecutive weeks followed by a week off.

Nektar Therapeutics (NASDAQ: NKTR) of San Carlos, Calif., said it has expanded the phase II development plan for NKTR-102 (PEG-irinotecan).

The company said it would target newly-characterized colorectal cancer with K-Ras mutated gene status in its phase II study in advanced colorectal cancer. Also, NKTR-102 will be evaluated in phase II trials in two new indications: platinum-refractory ovarian cancer and advanced breast cancer that is refractory to anthracycline and/or taxane-based therapies.

The studies would begin in the second half of 2008.

The data show that colorectal cancer with tumors that have K-Ras oncogene mutations (K-Ras mutant types) do not respond to EGFR-inhibitors, such as cetuximab. Up to 45% of colorectal cancer cases have the mutated K-Ras gene. To target the newly- characterized K-Ras mutant population, Nektar said it would begin a prospective study to evaluate the efficacy of the agent in this group. The primary endpoint would be a clinically meaningful improvement in progression-free survival as compared to standard irinotecan monotherapy, the company said.

"With the recent clinical studies on K-Ras, there is no longer a clear standard of care for the second-line treatment of advanced colorectal cancer with the K-Ras gene mutation," Daniel Haller, professor of medicine at the Abramson Cancer Center at the University of Pennsylvania, said in a statement. "The novel oncolytic, NKTR-102, could offer an alternative and promising approach for tumors in this patient population."

The company also announced new trials for NKTR-102 in breast and ovarian cancer. The studies for NKTR-102 in breast and ovarian cancer will be open-label, single-arm studies to evaluate the overall response rate of the NKTR-102 monotherapy in each tumor setting. The studies will implement a minimax design, known as the Simon design, which was first proposed by Richard Simon of NCI in 1989.

NKTR-102, a PEGylated form of irinotecan, was invented by Nektar using its small molecule PEGylation technology platform. By applying the small molecule PEGylation technology to irinotecan, NKTR-102 may be a more powerful and tolerable anti-tumor agent, the company said.

Oncolytics Biotech Inc. (TSX: ONC, NASDAQ: ONCY) of Calgary said enrollment has begun in a phase I/II trial in metastatic ovarian, peritoneal and fallopian tube cancers using concurrent intravenous and intraperitoneal administration of Reolysin, the Oncolytics proprietary formulation of the human reovirus.

NCI is sponsoring the trial under its Clinical Trials Agreement with Oncolytics, and Oncolytics will provide clinical supplies of the drug, the company said. The principal investigator is David Cohn, associate professor, Division of Gynecologic Oncology at The Ohio State University College of Medicine in Columbus.

In the phase I portion, treatment will consist of a constant dose of IV Reolysin on days 1-5 every 28 days, as well as an escalating dose of IP Reolysin on days 1-2 every 28 days, the company said. In the phase II portion, treatment will consist of a constant dose of IV Reolysin on days 1-5 every 28 days as well as the Maximum Tolerated Dose of IP Reolysin from the phase I portion.

The primary objective of the phase II trial is objective response rate of treatment with IV and IP Reolysin in recurrent, platinum-refractory ovarian, peritoneal and tubal carcinomas. The phase I/II would have an enrollment of 70.

In a related development, Oncolytics said it received an approval letter from the U.K. Medicines and Healthcare products Regulatory Agency to begin a phase II trial using intravenous administration of Reolysin in combination with paclitaxel and carboplatin in advanced head and neck cancers.

The principal investigator is Kevin Harrington of the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, the company said.

The 14-patient, single arm, open-label, dose-targeted, non-randomized, multi-centre trial of Reolysin given intravenously in combination with a standard dosage of paclitaxel and carboplatin will include advanced or metastatic head and neck cancer that are refractory to standard therapy or for which no curative standard therapy exists.

Oncothyreon Inc. (NASDAQ: ONTY) (TSX: ONY) of Bellevue, WA, said treatment has begun in phase Ib trial of PX-12 in advanced metastatic cancer.

PX-12 is a proprietary small molecule inhibitor of thioredoxin, a protein that regulates diverse molecular pathways that contribute to the growth, survival and drug resistance of cancers, the company said.

The primary objective of the dose-escalation 28-patient trial is the safety and tolerability of a 72-hour continuous infusion of PX-12 given on the first three days of a 21-day cycle, the company said. Other objectives include an evaluation of the pharmacokinetics and pharmacodynamics of the prolonged infusion,

together with identification of any anti-tumor activity.

A phase I 38-patient trial of the agent for advanced metastatic cancer showed it was well tolerated and produced a decrease in plasma concentrations of thioredoxin that was significantly correlated with increased survival, the company said. Fifteen of the 38 patients achieved stable disease of up to 322 days. Oncothyreon also said it is conducting a phase II trial of PX-12 given as a 3-hour infusion daily for five days of a 21-day cycle in advanced pancreatic cancer that has progressed on gemcitabine or a gemcitabine-containing regimen.

Wyeth Pharmaceuticals of Collegeville, Penn., said it has begun INTORACT, Investigation of Torisel and Avastin Combination Therapy study, a randomized, open-label, phase IIIb study comparing Torisel (temsirolimus) plus Avastin (bevacizumab) versus Avastin plus interferon-alfa for first-line treatment in advanced renal cell carcinoma.

Wyeth Research is conducting the study with the support and assistance of Roche and Genentech, the company said.

The primary end point is independently assessed progression-free survival in all risk groups. Secondary end points include safety, investigator-assessed PFS, independently assessed objective response rate, the company said.

A treatment regimen combining the mTOR inhibitor Torisel with the vascular endothelial growth factor inhibitor Avastin was shown in a phase I/II trial in stage IV renal cancer to have an acceptable safety profile and supported further investigation.

Deals & Collaborations:

First Immunotherapy Trial Funded by LLS Program

(Continued from page 1)

the rapid decline in circulating and lymph node bound leukemic cells, induced long-term immune based responses against these cells and sensitized them to standard chemotherapies, even in several patients with drug resistant disease," said Charles Prussak, a founder of Memgen.

The agreement marks the first immunotherapy clinical trial funded by the LLS Therapy Acceleration Program, which advances therapies with high prospects of providing near-term benefit in blood cancers, the collaborators said.

The ISF35 results are achieved through its ability to bind to a protein found on leukemic B lymphocytes, the groups said. This activates a natural immune process that causes malignant cells to become more sensitive to subsequent chemotherapy treatments.

Cell Therapeutics Inc. (NASDAQ: CTIC; MTA) of Seattle said it has entered into an agreement with **Bayer Schering Pharma** to gain access to the Bayer phase III Zevalin ([90Y]-ibritumomab tiuxetan) First-line Indolent Trial, or FIT, data.

CTI said it would review the data for a supplemental Biologics License Application for the agent. Based on the data the European Medicines Commission approved the drug as consolidation therapy after remission induction in untreated follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established, the company said.

The FIT study, which evaluated Zevalin as first-line consolidation therapy in follicular lymphoma, was sponsored by Bayer Schering Pharma AG, which has exclusive rights to the product in all countries except the U.S.

Under the agreement, CTI will make an initial payment to Bayer with an additional payment upon FDA approval of a sBLA for Zevalin based on the FIT trial results. CTI also will pay Bayer royalties on net product sales up to a specified aggregate amount.

CTI said it has requested a meeting with FDA to expand the label for Zevalin in the U.S. to include consolidation following first-line treatment of follicular lymphoma based on the FIT trial data.

The multinational, randomized phase III study evaluated the benefit and safety of a single infusion of Zevalin in CD20-positive follicular lymphoma that had achieved a partial remission or a complete remission after treatment with standard first-line chemotherapy regimens. The trial demonstrated that when used as a first-line consolidation therapy for follicular lymphoma, Zevalin improved the median progression-free survival time from 13.5 months (control arm) to 37 months ($p<0.0001$), the company said.

The primary investigators concluded that Zevalin consolidation of first remission in advanced stage follicular lymphoma is highly effective, resulting in a total complete response (CR + CRu) rate of 87% and prolongation of median progression-free survival (PFS) by two years, with a toxicity profile comparable to that seen with use of the drug in approved indications. Zevalin-treatment had reversible Grade 3 or 4 hematologic side effects including neutropenia in 67%, thrombocytopenia in 61%, and anemia in 3%. Nonhematologic toxicities

were 23.5% Grade 3, and Grade 3/4 infection was 7.9 percent, the company said.

Zevalin, a radioimmunotherapy, is indicated as part of the therapeutic regimen in relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, including rituximab refractory follicular NHL. The product also is indicated, under accelerated approval, for relapsed or refractory, rituximab-naive, low-grade and follicular NHL based on studies using a surrogate endpoint of overall response rate nonhematologic toxicities were 23.5% Grade 3, and Grade 3/4 infection was 7.9%.

Exiqon A/S of Vedbek, Denmark, said it has signed a collaborative research agreement with the Kleberg Center for Molecular Markers at **M. D. Anderson Cancer Center** to discover microRNA based biomarkers in breast cancer.

Under the agreement, Exiqon said it would use its miRCURY LNA products to discover microRNA biomarkers. The project would identify miRNA expression signatures associated with relapse and progression of breast cancer, and develop and validate diagnostic tools that would guide patient management.

LNAs are nucleotide analogues that bind to RNA and DNA targets, the company said.

Fox Chase Cancer Center and **VisEn Medical** said they are entering into a partnership to advance phase I trials of one of the VisEn Medical fluorescence activatable imaging agents to identify and characterize early stage cancer.

Olympus Medical Systems Corp. will provide paired fluorescence laparoscopic imaging systems for the detection and evaluation of ProSense highlighted tumors. The clinical trials will focus on ovarian cancer and would begin next year at Fox Chase Cancer Center.

Under the program, VisEn will develop and submit an IND application on a clinical analog of its proprietary fluorescence molecular imaging agent, ProSense, which highlights enzymatic processes associated with early stage cancer development in vivo. Fox Chase Cancer Center will invest in the ProSense clinical program through VisEn and will receive rights, equity and royalties on future sales.

The ProSense Activatable Imaging Agent platform provides in vivo readouts of protease activities known to underlie disease states in oncology, inflammation, and cardiovascular disease, the company said.

The H. Lee Moffitt Cancer Center of Tampa and **Xceed Molecular** of Wellesley, Mass., said Moffitt has joined the Xceed Strategic Collaborator Program and granted Xceed a worldwide, exclusive license to a gene signature for colon cancer.

The colon cancer-specific gene signature was discovered by Timothy Yeatman, Steven Eschrich, and Gregory Bloom, at Moffitt Cancer Center. The collaboration would develop a molecular test that is more predictive of prognosis than available assays, the groups said. Xceed will work with the Moffitt team, which also includes Steven Enkemann, to complete the clinical development and validation of the gene signature, which would predict the likelihood of disease-free survival in colon cancer using biopsy tissues from a colonoscopy.

The Strategic Collaborator Program is a mutually beneficial agreement with a high-profile institution or investigator that advances the clinical research of the partner, while providing Xceed with additional real-world clinical-laboratory experience and access to critical research results, the company said.

Orion Genomics of St. Louis said it has entered into a worldwide exclusive license agreement with **Johns Hopkins University** to commercialize products that identify risk for colorectal cancer.

The license is based on a suite of issued and pending JHU patents covering imprinting abnormalities of the insulin-like growth factor 2 gene, the company said. The Orion blood-based risk assessment test would identify who carries the IGF2 biomarker and may be at increased risk of developing sporadic colorectal cancer. The test would enable at-risk patients to undergo screening for colorectal cancer earlier, allowing removal of precancerous polyps, the company said.

Roche of Basel, Switzerland and **DxS Ltd.** said they have signed an exclusive distribution agreement for the DxS TheraScreen K-RAS Mutation Test and TheraScreen EGFR 29 Mutation Test.

The tests identify genetic mutations that can affect response to cancer drugs, the company said.

The TheraScreen K-RAS Mutation Test detects seven mutations in codons 12 and 13 of the K-RAS oncogene, the company said. The mutations are common in colorectal cancer, pancreatic cancer, lung adenocarcinoma, gall bladder cancer, bile duct cancer and thyroid cancer.

The TheraScreen EGFR 29 Test detects 29 of the most common somatic mutations in the EGFR gene

and detects mutations with greater sensitivity than sequencing, the company said.

ThromboGenics NV (Euronext Brussels: THR) of Leuven, Belgium, and **BioInvent International AB** (Nordic Exchange: BINV) of Lund, Sweden, said they have entered into a license agreement with **Roche** (SWX: ROG) of Basel, Switzerland, for the ThromboGenics anti-cancer agent TB-403.

TB-403, a monoclonal antibody, blocks Placental Growth Factor, one of the growth factors responsible for the development of new blood vessels, the companies said.

Under the agreement, Roche would pay ThromboGenics and BioInvent an upfront payment of EUR 50 million. ThromboGenics, which discovered TB-403, would receive 60% and BioInvent 40% of the revenue. Roche would have a worldwide, exclusive license to develop and commercialize the product. ThromboGenics and BioInvent would retain co-promotion rights in the Benelux, Baltic and Nordic regions, the companies said.

Product Approvals & Applications:

FDA Approves Eloxatin sNDA To Include Overall Survival

Sanofi-aventis U.S. of Bridgewater, N.J., said FDA approved the supplemental New Drug Application to include six-year overall survival analysis from the MOSAIC trial in the Eloxatin (oxaliplatin injection) prescribing information.

The trial also reports five-year disease free survival data in stage III colon cancer treated following surgery to remove the primary tumor, the company said.

The trial results showed that after a median follow-up of six years, stage III colon cancer treated with FOLFOX4 had a 20% reduction in the risk of dying compared to treatment with standard chemotherapy alone (hazard ratio of 0.80, confidence interval [0.65, 0.97] p=0.023). Stratified log-rank test was not adjusted for multiple comparisons.

Also, stage III was treated with the Eloxatin-based regimen at 5 years were 22% less likely to relapse or risk of disease recurrence (HR=0.78 [CI: 0.65, 0.93], p =0.005) after 77 month follow-up, the company said.

In the trial, neutropenia was the most frequently reported side effect, affecting 78.9%. The side effect was complicated by fever or infection in only 1.8% of cases. Peripheral sensory neuropathy occurred in 92.1% treated with FOLFOX4. Half (48.2%) of the episodes were grade 1, and 12% were severe (grades 3 and 4). Partial or total recovery was observed within 18 months following treatment in most experiencing grade 3 peripheral sensory neuropathy. Treatment with FOLFOX4 also resulted in nausea (73.7%), diarrhea (56.3%) and vomiting (47.2%), the company said.

Cancer International Research Group of Edmonton, Canada, said FDA has approved a treatment of the chemotherapeutic agents Taxotere (docetaxel) and carboplatin combined with Herceptin (trastuzumab) for the adjuvant treatment of HER2-positive early breast cancer.

The AC-TH regimen (doxorubicin and cyclophosphamide followed by Taxotere and Herceptin), also investigated in the BCIRG 006 study, received approval at the same time, the company said.

Results from the BCIRG 006 trial showed that the TCH regimen reduced the risk of disease recurrence by one third (HR=0.67, 95% CI [0.54-0.83], p=0.0003), compared to the AC-T control arm.

The experimental AC-TH treatment reduced the risk of disease recurrence by 39% (HR=0.61, 95% CI [0.49-0.77], p<0.0001), compared to the AC-T control arm, the group said.

The DFS benefit of TCH and AC-TH was present regardless of age, the tumor responsiveness to hormones, or whether or not the cancer had spread to lymph nodes. There was no statistically significant difference in DFS between the two experimental arms, the group said..

OS was also improved with the TCH regimen with 34% reduction in the risk of death (HR=0.66, 95% CI [0.47-0.93], p=0.0182) compared to the AC-T control arm. Similarly, AC-TH was associated with a 42% reduction in the risk of death (HR=0.58, 95% CI [0.40-0.83], p=0.0024) compared to the AC-T control arm. There was no statistically significant difference in OS between the two experimental arms.

With the TCH regimen, the risk of congestive heart failure was five-fold lower compared to that observed with AC-TH (0.4% vs 1.9% vs 0.3% in women treated with TCH, AC-TH, and AC-T respectively).

The primary endpoint was to compare disease-free survival of each of the experimental regimens with standard anthracycline-based chemotherapy. Secondary endpoints included evaluation of overall survival and cardiac toxicity.

The BCIRG 006 was conducted by the CIRG and sponsored by sanofi-aventis, of Paris with additional support from Genentech of South San Francisco.

Genta Inc. (BULLETIN BOARD: GNTA) of Berkeley Heights, N.J., said it has submitted an amendment to FDA of its New Drug Application for Genasense (oblimersen sodium) Injection plus chemotherapy for relapsed or refractory chronic lymphocytic leukemia.

The submission is based on new information from Genta phase III trial that showed an increase in overall survival for complete or partial response when treated with Genasense plus chemotherapy compared to treated with chemotherapy alone.

Genta said it was notified in March that its appeal of a non-approvable decision for the Genasense NDA had been denied by the FDA Center for Drug Evaluation and Research. However, that decision described a regulatory path forward that included but was not limited to determination of long-term survival in patients who entered the study. Genta said its submission comprises a complete response to the FDA decision.

GlaxoSmithKline of Philadelphia and London said it has submitted an NDA and data from two phase III trials for Rezonic/Zunrisa (casopitant) to FDA.

The data demonstrated a reduction in chemotherapy-induced nausea and vomiting. Adding a single oral dose of casopitant to the standard dual therapy of Zofran (ondansetron HCI) and dexamethasone achieved this effect in highly emetogenic and moderately emetogenic chemotherapy treatment regimens.

Data from the two phase III trials demonstrated complete response rates of 86% with a single oral dose of casopitant together with the standard dual therapy in the HEC trial, and 73% with either single oral or three-day oral doses of casopitant together with the standard dual therapy in the MEC trial.

The prophylactic treatment resulted in clinically meaningful and statistically significant improvements compared to controls. To achieve complete response, there had to be no vomiting or retching and no rescue medications for five days following chemotherapy.

An NDA for casopitant was submitted to FDA for the proposed indication of prevention of chemotherapy-induced nausea and vomiting as an add-on therapy to the standard dual therapy of a 5-HT3 receptor antagonist, such as Zofran, and dexamethasone, the company said. Applications have been submitted for both the IV and oral formulations. The submission also included the proposed indication of the prevention of postoperative nausea and vomiting.

The multi-national, double-blind, controlled phase III trial evaluated the tolerability and efficacy of a single oral dose and a three-day IV/oral dose regimen of casopitant or placebo added to standard dual therapy for reducing CINV in cisplatin-based HEC regimens, the company said.

The 180-patient phase III trial demonstrated that, when added to standard dual therapy of ondansetron and dexamethasone, a single oral dose (one 150mg tablet) or a three-day IV/oral dose regimen (90mg IV and OND on day one and 50mg tablets on days two and three) of casopitant provided a statistically significant reduction in CINV events over the first five days after receiving HEC versus the control group. The primary endpoint of overall complete response, defined as no vomiting, retching or rescue medication use in the first five days after chemotherapy, was achieved when receiving HEC (86% in the single oral dose, $p<0.0001$, and 80% in the three-day IV/oral dose, $p<0.0004$, vs. 66% in the control population), with the clinical benefit maintained through repeat cycles.

Significant improvements were also observed in the complete response for the acute (95% in the single oral dose, $p=0.0044$, and 94% in the three-day IV/oral dose, $p=0.0165$, vs. 88% for control population) and delayed phases (86% in the single oral dose, $p<0.0001$, and 80% in the three-day IV/oral dose, $p=0.0004$, vs. 66% in the control population), the company said.

The most commonly reported all-cause adverse events in the treatment arms were neutropenia, leukopenia and anemia, which occurred at a higher rate in the casopitant arms. The incidence of serious neutropenia adverse events was two percent in the active control arm, one percent in the single oral dose arm and four percent in the three-day IV/oral arm.

The second phase III trial demonstrated the tolerability and efficacy of a single oral dose, a three-day oral dose regimen, and a three-day IV/oral dose regimen of casopitant or placebo added to standard dual therapy for reducing CINV in breast cancer with standard MEC regimens, the company said.

The 1,933-patient trial showed that both oral casopitant doses (a single 150mg tablet on day one, or a 150mg tablet on day one followed by 50mg on days two and three) and IV/oral doses (90mg IV on day one followed by 50mg tablets on days two and three)—all in addition to standard OND and DEX doses—resulted in clinically meaningful and statistically significant improvements ($p<0.0001$) in the number achieving a complete response for their CINV over the first five days after receiving MEC versus the control group (73% in both oral doses and 74% in the IV/oral dose vs. 59% in the control group).