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New Approvals Point To Greater Role Of Randomization In Cancer Trials

By Paul Goldberg

Over the past year, critics from the right lambasted FDA for its role in development of two cancer drugs: Bayer Healthcare's Nexavar and Pfizer's Sutent.

Conservative editorialists, think tanks, politicians, and patient groups charged that the agency's insistence on randomized trials was outmoded and antiscientific. The Wall Street Journal editorialists claimed that an act of Congress would be required to "modernize" the agency.

Indeed, last November, Sen. Sam Brownback (R-Kan.) introduced the "Access, Compassion, Care and Ethics for Seriously-ill Patients Act," which would limit the use of placebo-controlled trials and allow companies to sell drugs after completion of phase I testing (The Cancer Letter, Aug. 5 and Dec. 2, 2005).

Political heat notwithstanding, FDA's recent approval of the drugs in question provided something critics could not have foreseen: two case studies that are likely to prompt drug companies to place greater reliance on randomized trials, expand randomization to phase II, and—in some

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In Brief:

White House Reappoints Kripke To Panel; Adamson Receives Toxicology Forum Award

MARGARET KRIPKE, executive vice president and chief academic officer at University of Texas M. D. Anderson Cancer Center, was appointed by President **George W. Bush** to a second three-year term on the President's Cancer Panel. Bush originally appointed Kripke to the panel in 2003, where she served with Chairman **LaSalle Leffall Jr**., professor of surgery at Howard University, and cycling champion and cancer survivor **Lance Armstrong**. Kripke oversees M. D. Anderson's research and educational programs, as well as faculty recruitment, and development. The panel was established as part of the National Cancer Act of 1971. Last year, the panel issued recommendations for improving cancer care. . . . **RICHARD ADAMSON** received the 2006 Philippe Shubik Distinguished Scientist Award from the Toxicology Forum, a nonprofit organization that Shubik helped found for the discussion of toxicology issues. Shubik was a member of the National Cancer Advisory Board and the President's Cancer Panel. The award recognizes Adamson's scientific administration, research, and service in toxicology during his 40-year career, including 33 years at NCI. He retired from NCI

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Randomized Phase II Trial Helped Drug Find Disease

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cases—use placebo controls.

Had it been tested in a garden variety single-arm trial designed to measure tumor shrinkage, Bayer's Nexavar (sorafenib) would surely have been discarded. It produced a meager objective response—just 2 percent of patients had tumor shrinkage.

Yet, since the drug was tested in randomized phase III trials, German-based Bayer was able to demonstrate that the median progression-free survival was 167 days for the treatment arm, compared to 84 days for placebo. The spectacular p value of less than 0.000001 led to the drug's full approval.

Sutent (sunitinib malate) produced the objective response rate of 6.8 percent in gastrointestinal stromal tumor, usually not enough to squeak through approval. However, the GIST study was randomized, and Pfizer was able to measure time to progression and progression-free survival, earning regular FDA approval for that indication. In two single-arm studies in kidney cancer, Sutent produced the tumor shrinkage of 25.5 percent and response duration of 27 weeks, enough for an accelerated approval.

"You gotta randomize. You gotta randomize. You gotta randomize," said Mark Ratain, associate director for clinical sciences at the University of Chicago Cancer Research Center, who designed an innovative randomized phase II program for Nexavar. "The companies that have been successful have done it this way. And the companies that are floundering, they go into phase III on a wing and a prayer."

"The moral of both of these stories is that as you understand biology, as you tailor agents to that structural biology, you are going to see more positive results in clinical trials," said Robert Figlin, professor of medicine and urology at the UCLA David Geffen School of Medicine and medical director of the UCLA Kidney Cancer Program, who was an investigator in one of Sutent trials.

"What's new is the recognition that benefits to patients are not always linked to the classical definitions of objective responses," Figlin said.

Nicholas Vogelzang, a renal cancer expert and director of Nevada Cancer Institute, said politicization hasn't helped to advance knowledge. "For political people and lay people who do not see and experience on a daily basis the nature of cancer to tell us how to figure out drug treatment for cancer is ludicrous," he said. "Basically, the message is, butt out."

The incentives to randomize are likely to become even stronger after London-based European Agency for the Evaluation of Medicinal Products institutes its counterpart to the FDA accelerated approval mechanism.

The European agency, which approves drugs for 25 European Union countries as well as Norway and Iceland, is developing accelerated approval criteria based on the risk-benefit ratio, which is measured in randomized trials (The Cancer Letter, Nov. 11, 2005).

Since many registration trials are conducted internationally, the more stringent European standard would likely conflict with the less stringent U.S. accelerated approval standards. At the moment, these standards are under attack, as conservative critics suggest that the cancer drug approval system of the future should be based on single-arm phase II trials that would be compared with historical data.

However, if the Europeans implement the approval system they envision, drug companies that seek to sell on the U.S. and European markets would have to default to Europe's more rigorous criteria. Under the European plan, conditional approval would be granted based on interim analysis of data from phase III randomized trials, followed by full approval based on proof of benefit to patients.

The impact of divergent standards was apparent in the case of Bayer's Nexavar. Sources said that European regulators and the drug's sponsor are still uneasy about the U.S. agency's decision to stop the trials and grant

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approval based on progression-free survival, hampering the company's efforts to continue the trials long enough to measure overall survival.

Go With Level One Evidence

Sutent and Nexavar have similar mechanisms of action—inhibition of receptor tyrosine kinases.

Sutent was studied in metastatic renal cell carcinoma after failure of cytokine-based therapy as well as for GIST after disease progression on or intolerance to Gleevec (imatinib mesylate). Nexavar was studied in advanced renal cancer in patients who had received one prior systemic therapy.

"Without the randomized trials with Nexavar, we would have been left wondering whether that was truly a drug effect," Figlin said. "Now, we don't have that question at all. We know that the drug is having a positive impact on patients. We see it every day in the clinic, and we can feel comfort that when we are treating a person with Nexavar, we are doing something for them."

Sutent seems to show activity that is beyond what has been reported historically for many other treatments for renal cell carcinoma, Figlin said. Even though Naxavar was the first drug to get approval, the agency decided to approve Sutent because it addressed the needs of patients who could benefit from tumor shrinkage, sources said.

"That was enough to get FDA approval for that unmet medical need, and now we have to wait for larger randomized trials to see the comparative impact," he said. "If Nexavar had taken the strategy that Sutent took, which was to do sequential phase II trials, they would have had a hard time convincing FDA that there was a sufficient drug effect to warrant approval, whereas with a randomized trial that's placebo-controlled, they had a clear and unequivocal result."

Clinicians say that it's significant that the labels on the two drugs don't require that renal cell carcinoma patients go through treatment with IL-2 or interferon before taking these less toxic oral drugs.

"These patients come in with lots of problems, and the healthiest patients should get IL-2, but only the healthiest," said Vogelzang. "Let's be realistic, this is a pill that causes some skin rash and diarrhea. This isn't an IV injection that requires you to be in the intensive care unit on pressors. It's that simple."

As it stands, physicians are likely to have difficulty deciding which of the two new drugs they might prescribe.

"The dilemma that doctors have is that they have two FDA-approved drugs; one from a randomized prospective trial, the other from two phase II trials in a similar but not exactly identical population that shows clinical benefit," said Figlin. "The treating physician doesn't yet have the tools to decide one versus the other. The doctor is left interpreting the data, making a decision for their own individual patient, recognizing that they now have two alternatives for the treatment of kidney cancer, the first such approval since in renal cell carcinoma since 1992."

Both drugs were approved based on debatable evidence of patient benefit. Progression-free survival, the endpoint met by Nexavar, is a surrogate endpoint for clinical benefit. Tumor shrinkage—the endpoint for the Sutent approval—is similarly a surrogate.

"I go with Level One evidence," said Vogelzang, who accrued patients to clinical trials of both drugs. "Level One evidence is a randomized phase III trial showing the primary endpoint of either survival or progression-free survival."

This makes Nexavar the first drug Vogelzang would prescribe in most cases.

However, when the goal is to reduce the size of tumors, Vogelzang will use Sutent. "For the patient who has rapidly progressive disease, symptomatic, having pain, I will probably use Sutent first," he said. "But for the patients whose disease isn't progressing very rapidly, I use Nexavar.

"Ultimately, I will probably use both drugs in all patients. If I put somebody on Nexavar and they progress, I'll say, 'There is another FDA-approved drug out there, why don't we try that?' In the absence of a protocol, that's what I'll do.

"After Nexavar and Sutent, I will go to Avastin, because Avastin has activity, and whether there is cross-reactivity there is unclear. Or else, I'll use interferon and Avastin."

Potential differences between Nexavar and Sutent are being sorted out in randomized trials. Figlin said he is interested in seeing how these drugs compare with IL-2, the approved standard of care for renal cell cancer, or interferon, a commonly used treatment.

"We are anxious to see the results of a large trial comparing Sutent to interferon," Figlin said, referring to Pfizer's registration trial in front-line renal cancer, which is expected to be completed later this year. "If that trial demonstrates a clear and unequivocal benefit for the newer agent, then that will become the new standard of care."

To sort out potential treatments, a randomized phase II study led by Eastern Cooperative Oncology

Group will compare doublets of Sutent, Nexavar, Avastin, and the Wyeth drug CCI 779.

Also in the works are two large, placebo-controlled adjuvant trials in high-risk resected non-metastatic renal cell carcinoma. The U.S. trial, led by ECOG, will compare placebo to Nexavar and Sutent. In Europe, the trial will compare placebo with one or three years of planned treatment with Nexavar.

It would be ethical to give placebo to these patients, said Robert Comis, chairman of ECOG.

"The patients who receive surgery plus the placebo will receive the standard of care, and that standard will be compared with surgery plus these very interesting and possibly effective drugs," Comis said. "The standard of care is the real comparator."

The adjuvant trials, which are yet to start, are controversial for other reasons. "We've never given these tyrosine kinase inhibitors to adjuvant patients," Figlin said. "We have to see how compliant the patients would be to take extended therapy with these agents, and we don't know whether these drugs will be equal or different in their ability to produce benefit in an adjuvant population of patients. I don't think that trial is going to be as much Sutent vs. Nexavar as it's going to be a VEGF TKI vs. standard of care, which is observation."

Sorting Through Targets in Phase II

The story of Nexavar illustrates the value of randomization in phase II trials.

Nexavar was a difficult drug to develop, in part, because even preclinical data suggested that it seemed to inhibit tumor growth without promoting significant tumor shrinkage. Originally, the company viewed Nexavar as a potential treatment for colorectal cancer.

Trying to design an innovative strategy, Rachel Humphrey, then a director of global clinical strategy in oncology at Bayer, approached Ratain for advice.

"I said to Rachel, 'I have the design for you,'" Ratain said, recalling the meeting in 2000. The design Ratain had in mind—a randomized discontinuation trial—was first proposed in 1975, and it has been used in other areas of medicine. In oncology, the design was first employed in a study of the renal cell carcinoma drug carboxyaminiomidazole.

"Not only did we convince the company to do a randomized discontinuation design, but I convinced them to let me do a multi-tumor randomized discontinuation design," Ratain said. "I said to them, 'Don't be so sure that you know what the target is and therefore where the drug is going to work.'"

Ratain and Humphrey designed a phase II trial that could show disease stabilization across many indications for the drug used as a single agent.

"When you are doing a placebo-controlled trial, you can have heterogeneity, because you have a control group," Ratain said. "We would stratify by disease type in the randomization, and so you have the control group. And that's the huge advantage of controlled trials. You don't have to worry about what's the right historical control. You compare two things that are the same, except one is getting the drug and one isn't. And it worked. It worked reliably and robustly."

Altogether, 484 patients with solid tumors were randomized, Ratain said. Patients weren't randomized up-front. Instead, everyone received the drug for the first 12 weeks.

At that point, responders—patients whose tumors shrunk by 25 percent or more—continued to get treatment open-label. Patients whose disease progressed—increasing by 25 percent or more—were taken off treatment. Everyone in-between—those whose tumors decreased by less than 25 percent—was randomized to Nexavar or placebo for another 12 weeks. This randomization answered the crucial question: were these "stable disease" patients truly benefiting?

Patients who progressed after randomization were unblinded, and those who received placebo were offered Nexavar.

The study's primary endpoint was progression-free survival at 24 weeks.

"The screening proved to be quite fruitful," Ratain said. "We had no signal in colorectal cancer, but we got some signals in a bunch of other diseases, and then it became clear that the signal was so strong in kidney cancer that we should focus on kidney cancer."

Changing focus, the trial accrued 202 patients with renal cell carcinoma.

"The key point here is that the randomized discontinuation study, with 202 renal cancer patients, came to the same conclusion as the large, randomized placebo-controlled phase III study using hundreds more patients," said Humphrey, vice president for immuno-oncology at Bristol-Myers Squibb.

Accrual in the solid tumor trial started in October 2002 and concluded in January 2004. The drug was approved 3.2 years following the start of phase II.

The moral of the story is clear, Ratain said. Randomization should be part of phase II designs. Indeed, one company, Genentech, now prefers to run similar phase II trials.

"Placebos, randomization, double-blind—these are key elements in drug development; these are the

fundamental principles of developing drugs," Ratain said. "And the reason we have failed in oncology is because every oncology fellow out there writes a protocol and thinks he is an expert in drug development, and nobody really learns the principles.

"And what is really scary to me is what the 'experts' think."

NCI Programs:

NCI Plans Expansion Of CTSU In Managing Clinical Trials

By Kirsten Boyd Goldberg

NCI is recompeting a contract for the Cancer Trials Support Unit, a pilot project begun six years ago to centralize administrative tasks for phase III trials.

Previously, many of these tasks were the responsibility of the institute-funded cooperative groups, a system involving 3,000 member sites that enroll about 25,000 patients a year on clinical trials. The CTSU was intended to facilitate access to clinical trials by physicians and patients across the cooperative groups and streamline the administrative burden.

The recompetition makes clear that NCI no longer considers CTSU a pilot project, but plans to continue its functions and significantly expand its role over the next three to seven years. Some of the expansion plans are likely to be controversial within the cooperative groups.

According to documents included the Request for Proposals, the institute might pursue the following "optional tasks" to "provide new challenges" for the CTSU:

—Increasing accrual through the inclusion of other NCI-supported clinical trials, such as those conducted through cancer centers and Specialized Programs of Research Excellence, including phase II trials.

—Holding and filing Investigational New Drug applications for certain trials.

—Developing a new financial payment system in which the CTSU would "negotiate contracts with all the cooperative group member sites to distribute the capitation funds directly, rather than having the groups transfer funds to their sites as is currently done. The CTSU would therefore replace the cooperative groups totally for the distribution of per capita payments (including, but not limited to, enrollment payments, follow-up payments, quality of life and other ancillary study payments, etc.)." This would be done through a "simplified, model contract" with all group members.

—Integrating regulatory support services for the Children's Oncology Group to facilitate collaboration with the adult groups on particular trials.

"The Central Resource" For Large Trials

"The CTSU will increasingly become the central resource for large, multi-center trials sponsored by NCI," according to the RFP Statement of Work. "While there will likely always be alternatives, the CTSU's centralized operations offer several advantages from the government's perspective.

"A centralized system can promote unification and consistency in standards, informatics interfaces and administrative tasks," the document states. "This has a significant advantage in terms of lowering training costs across the country and enabling the NCI to leverage hardware and software costs. But more importantly, common systems and procedures facilitate participation in more trials by more sites, allowing clinical trials to be completed more rapidly."

Under the new contract, NCI plans to eliminate "redundancy" in the activities of the CTSU and the operations and statistical offices of the cooperative groups, according to the RFP.

"Groups will be required to use the Regulatory Support System of the CTSU for all IRB and credentialing needs for all their studies (Phase 1-3), and to fully integrate this system with their in-house operations," the document states. "The development of a randomization hub with 24 hours a day, 7 days a week, on-line availability linked to each group will offer all sites a single method for assessing eligibility and assigning treatment arms for randomized group Phase 2 and 3 studies."

The final database for clinical trials will reside with the lead group, but the CTSU will offer a "menu" of data management services to the groups, called "basic," "basic plus," and "comprehensive."

"One critical point going forward is that there should no longer be duplicate databases set up in the Lead Group and the CTSU for a single trial," the document states.

Westat Inc. of Rockville, Md., holds the current $88 million contract to operate the CTSU. Contract proposals were due Feb. 23.

The CTSU has enrolled 11,866 patients to 64 phase III cooperative group trials as of Feb. 23. About 5,000 are enrolled on the NCI of Canada phase III trial of exemestane versus anastrozole for postmenopausal women with receptor positive primary breast cancer. The trial was temporarily closed Jan. 23.

* * *

NCI has awarded contracts worth a total of $43.6 million to nine institutions to conduct phase II trials of compounds for treatment of solid tumors, leukemias, and lymphomas. The institutions, principal investigators, and contract awards are as follows:

University of Chicago, Everett Vokes, $4,306,090.

University of Texas M.D. Anderson, David Stewart, $4,961,947.

University Health Network/Princess Margaret Hospital, Amit Oza, $4,485,000.

Montefiore Medical Center, Joseph Sparano, $4,808,204.

Mayo Foundation, Rochester, Charles Erlichman, $5,930,308.

Sloan-Kettering Institute, David Kelsen, $6,131,642.

Ohio State University, Miguel Villalona, $3,041,729.

H. Lee Moffitt Cancer Center, Daniel Sullivan, $4,794,750.

University of California, Davis, David Gandara, $5,170,500.

NIH News:

Companies Commit $25 Million To NIH For Genome Studies

NIH has entered into a public-private partnership with the Foundation for the National Institutes of Health, Pfizer Global Research & Development of New London, Conn., and Affymetrix Inc. of Santa Clara, Calif., to accelerate genome association studies to find the genetic roots of widespread diseases.

The partnership, called the Genetic Association Information Network (GAIN), will start with a $5 million donation from Pfizer to set up the management structure and $15 million worth of laboratory studies to determine the genetic contributions to five common diseases. Affymetrix will contribute laboratory resources to study two additional common diseases. On average, it costs about $3 million to carry out one study.

The initial GAIN genotyping supported by Pfizer will be carried out by Perlegen Sciences Inc., of Mountain View, Calif., and will start in late summer.

* * *

The President's budget proposal for fiscal 2007 includes $68 million for the NIH Genes and Environment Initiative to combine genetic analysis and environmental technology development to understand the causes of common diseases.

If approved by Congress, the funding will begin in FY 2007 and continue for multiple years. Of the first year's funding, $26 million will go to genetic analysis and $14 million for the development of new tools to measure environmental exposures that affect health.

The proposed funding will enable GEI to perform genotyping studies for several dozen common diseases, which will be determined by peer review.

* * *

The NIH Real Property Management group, which includes about 380 employees, was selected as the Most Efficient Organization to provide the institutes with services in Construction Management, Property Management and Operations, and Central Utilities.

The outcome is the conclusion of a competition that began in 2003, but was extended under a settlement agreement between NIH and an unsuccessful private offeror, in which the government and private sector proposals were re-evaluated.

* * *

The NIH Biomedical Research and Development Price Index for FY 2005 has been revised to 5.5 percent, up from 4 percent.

NIH estimates of the BRDPI for future years are: 4.1 percent for FY06; 3.8 percent for FY07 and FY08; 3.7 percent a year for FY09 to FY11; and 3.8 percent a year for FY12 to FY16.

In Brief:

ONS To Recognize Wilmoth, Degner, At Annual Congress

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in 1994 as director of the Division of Cancer Etiology and scientific director and joined the National Soft Drink Association (now the American Beverage Association) as vice president for scientific and technical affairs. At NCI, Adamson conducted long-term studies of toxicity and carcinogenic potential of rodent carcinogens, food additives, therapeutic agents, and N-nitroso compounds in newborn cynomolgus and rhesus monkeys, the largest and longest chemical carcinogenesis study in nonhuman primates ever undertaken. . . . **NANCY MENDENHALL** was named medical director of the new proton institute at the University of Florida in Jacksonville, said **C. Criag Tisher**, dean of the College of Medicine. She also will serve as associate chairman of the Department of Radiation Oncology in Jacksonville. She was chairman of the Department of Radiation Oncology in Gainesville. **Robert Amdur** was appointed interim chairman of the department in Gainesville. . . . **ONCOLOGY NURSING Society** will recognize two of its members at the 31st Annual Congress to be held May 4-7 in Boston. **Margaret Wilmoth** will present the 2006 ONS Foundation Mara Mogensen Flaherty Memorial Lectureship. She is professor in the College

of Health and Human Services at the University of North Carolina in Charlotte. **Lesley Degner**, distinguished research professor and chairman of cancer nursing at the University of Manitoba, will receive the 2006 Oncology Nursing Society Distinguished Researcher Award for the development of a program on patient participation in treatment decision making. . . . **NATIONAL INSTITUTE of Allergy and Infectious Diseases** appointed five individuals to senior management positions. **Hugh Auchincloss Jr.** was named principal deputy director to NIAID Director **Anthony Fauci**. Auchincloss was chief operating officer of the Immune Tolerance Network, an NIAID-directed clinical research consortium. In 1998, he founded the Juvenile Diabetes Research Foundation Center for Islet Transplantation and was its director until 2003. **H. Clifford Lane** was named deputy director for clinical research and special projects. He will continue as clinical director and director of the new Division of Clinical Research. Lane will also be the NIAID liaison with the Departments of Defense and Homeland Security. **John McGowan** was appointed to the new position of deputy director for science management. He will direct business and administrative requirements as well as its science planning, policy, and integration. He has been director of the Division of Extramural Activities since 1991 and acting NIAID associate director for management and operations since 2004. **Kathryn Zoon,** acting director of the Division of Intramural Research since 2005, was appointed its director. She was deputy director of the NCI Center for Cancer Research. **Gregory Folkers** was named chief of staff to Fauci, in the newly created Immediate Office of the Director. For the past decade, Folkers has worked directly with Fauci as a special assistant and senior public affairs advisor. . . . **CHRISTOPHER PORTIER** was named associate director for risk assessment at the National Institute of Environmental Health Sciences where he will apply the results of toxicological studies to national and international assessment of human health risks of chemical, drugs, and physical agents. The new position underscores a renewed interest by the institute in using environmental health sciences to understand human disease and improve human health, said NIEHS Director **David Schwartz**. Portier was associate director of the National Toxicology Program, director of the Environmental Toxicology Program, and head of Environmental Systems Biology, Laboratory of Molecular Toxicology at NIEHS. **Allen Dearry**, director of the Division of Research, Coordination, Planning and Translation, will be interim associate director of the NTP.

Funding Opportunities:

Armstrong Foundation Grants

Letters of Intent Receipt Date: March 1 to April 24.

The Lance Armstrong Foundation is accepting applications for research grants in issues of cancer survivorship and the basic and clinical science of testicular cancer. For each topic area, two types of grants are available:

—Young investigator research grants of up to $50,000 per year for a maximum of two years.

—Grants of up to $75,000 per year for three years to support projects by established investigators.

Applications: www.livestrong.org/research.

RFA Available

RFA-RM-06-007: Nanomedicine Development Centers. Application Receipt Date: June 23. The goal of the initiative is to characterize quantitatively the nanoscale components of the cell and to precisely control and manipulate the molecules and supramolecular assemblies in living cells to improve human health. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-007.html.

Inquiries: Richard Fisher , fisherr@mail.nih.gov.

RFPs Available

RFP N02-CM-67005-19: Manufacture of Bulk Chemical and Bulk Pharmaceutical Ingredients for Preclinical and Clinical Studies. Pharmaceutical Resources Branch, NCI Division of Cancer Treatment and Diagnosis, seeks contractor to procure bulk chemicals and drugs for the Drug Treatment Programs for preclinical and clinical use. The RFP is posted at http://rcb.cancer.gov/rcb-internet/appl/rfp/published_rfps.jsp**.** Inquiries: Diane Stalder; 301-435-3822; ds88b@nih.gov/.

RFP S06-143: Biospecimen and Biorepository Facility. Response Due Date: April 27. SAIC-Frederick, the Operations and Maintenance Contractor for the NCI Frederick Cancer Research Facility, will solicit for services on behalf of NCI and NHGRI. The RFP is intended to solicit responses from parties interested in providing centralized biorepository and biospecimen services to the joint NCI and NHGRI: The Cancer Genome Atlas.

NCI proposes to establish a centralized Biospecimen Resource Center that would acquire material from existing cancer tissue repositories. The centralized facility will have a role in evaluating for suitability to the TCGA other existing repositories for potential acquisition of their biospecimens. The facility will provide ongoing services for importing the materials from such repositories, processing those materials into molecular derivatives, and distributing those derivatives to the various analytical sites. The RFP is available at http://www.fbodaily.com/archive/2006/02-February/18-Feb-2006/FBO-00989551.htm. Inquiries: Jeanne Lewis, 301/228-4007 or Gregory Davis, 301/228-4011, jlewis@ncifcrf.gov, gdavis@ncifcrf.gov.

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Business & Regulatory Report

Clinical Trials:

Enrollment In Avastin Study Suspended For DSMB Review Of Adverse Events

Genentech Inc. (NYSE:DNA) of South San Francisco said enrollment in AVANT, a phase III study of Avastin (bevacizumab), Xelox, and Folox chemotherapy regimens in early-stage colon cancer, has been suspended to enable the Data Safety Monitoring Board to review 60-day safety data.

The DSMB recommendations are based on adverse events observed at a higher rate in the Xelox/Avastin arm of the study compared to the other two arms of the study in Folfox and Folfox/Avastin, the company said. Also, the rapid recruitment in the AVANT trial—more than 200 patients per month—could prevent an adequate and timely safety assessment. The Xelox regimen consists of capecitabine and oxaliplatin and the Folfox regimen consists of oxaliplatin, 5-FU, and leucovorin.

Excluding deaths due to recurrent colon cancer, all-cause mortality was

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Deals & Collaborations:

M.D. Anderson Licenses New Class Of Drugs To Callisto Pharmaceuticals

Callisto Pharmaceuticals Inc. (Amex: KAL; FWB:CA4) of New York said it signed an agreement with **M. D. Anderson Cancer Center** to license a new class of cancer drugs called Degrasyns as anti-cancer agents.

The anti-cancer activity of the analogs, developed by scientists at M. D. Anderson, can selectively degrade proteins in tumor cell proliferation and survival, the company said. The degradation appears to be specific for C-MYC, BCR-ABL and JAK2, all targets for tumors.

"What we are most excited about is this novel mechanism that causes the degradation of important cancer causing and cancer driving proteins in a way that appears to be specific for these few key targets," said Moshe Talpaz, one of the inventors and professor of experimental therapeutics at M. D. Anderson. "It is our priority to get one of these compounds into the clinic as soon as possible."

* * *

CytRx Corp. (NASDAQ:CYTR) of Los Angeles said it would transfer its ribonucleic acid interference therapeutics assets into a newly formed subsidiary to accelerate the development and commercialization of drugs based on RNAi technology.

CytRx said it would retain ownership in the new company.

"A thorough analysis of our corporate structure and current valuation

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Genentech's AVANT Study Suspended For DSMB Review

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0.6 percent (4 cases) for Folfox (Arm A), 0.4 percent (3 cases) for Folfox/Avastin (Arm B) and 1 percent (7 cases) for Xelox/Avastin (Arm C), the company said. An occurrence of cardiac (2 cases) and unknown (3 cases) deaths, some of which occurred in younger patients, was noted in Arm C. Since the AVANT trial began recruitment in December 2004, almost two-thirds of the target number of 3,450 patients has been enrolled, and in January 2006 alone more than 250 patients were recruited.

The DSMB will continue to monitor adverse events, including gastrointestinal perforations, an adverse event observed in previous studies of Avastin plus chemotherapy that also has been observed in Avastin-treated patients in the AVANT study at a rate of about 1 percent. This is less than what has been observed in the metastatic setting (up to 2 percent), the company said.

The study is evaluating whether the addition of Avastin to chemotherapy following surgery can reduce recurrence in stage II and III colorectal cancer. The study randomizes patients to the following regimens: Arm A: Oxaliplatin, leucovorin and 5-FU (control arm); Arm B: Avastin, oxaliplatin, leucovorin and 5-FU (experimental arm); Arm C: Avastin, capecitabine and oxaliplatin (experimental arm).

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Enrollment continues in the U.S. cooperative group C-08 Study, conducted by the National Surgical Adjuvant Breast and Bowel Project. The two-arm study is randomizing for either Folfox alone or Folfox/Avastin. Unlike the AVANT study, this trial does not include a Xelox/Avastin arm, the company said.

The NSABP study has enrolled more than 1,600 of a planned 2,714 patients since the trial opened in 2004, the company said. The C-08 trial has an independent DSMB that reviews safety data on a regular basis. NSABP has consulted with the DSMB to review current safety data from both the AVANT and C-08 trials. The DSMB found no disparities in non-disease-related deaths or gastrointestinal perforations between the treatment arms of C-08, and has recommended that no changes be made to the conduct of the trial.

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Abeille Pharmaceuticals Inc. of Princeton said it has begun a phase I pharmacokinetic study of AB-1001, a transdermal patch for chemotherapy induced nausea and vomiting.

AB-1001 delivers a commercially available 5HT3-anatgonist through the skin for up to five days, providing sustained relief for CINV, the company said.

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ADVENTRX Pharmaceuticals Inc. (AMEX: ANX) of San Diego said recruitment has surpassed the half-way point in the CoFactor multi-national phase IIb trial, begun in May 2005, for metastatic colorectal cancer.

CoFactor (ANX-510) is a folate-based biomodulator that enhances the activity and reduces the toxicity of 5-fluorouracil (5-FU), the company said.

The 300-patient parallel group study would detect a reduction in the frequency of grade 3 or grade 4 hematological or gastrointestinal toxicities, the company said. Randomization will be to one of two arms containing either CoFactor or leucovorin, each in combination with 5-FU. A biweekly infusional regimen of an initial dose of 400mg/m2 of 5-FU followed by 600 mg/m2 of 5-FU via a 22-hour infusion on days 1 and 2 will be administered to both arms.

The study is being conducted in Europe and India, the company said. James Cassidy, professor of oncology and head of the Department of Cancer Research in the U.K, Department of Medical Oncology at the University of Glasgow, is the chairman for the trial.

The company said it is planning a phase III study to evaluate the drug in the first-line treatment of metastatic colorectal cancer, and a phase III study to test it in a third-line setting for advanced breast cancer.

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Aegera Therapeutics Inc. of Montreal said it has begun a third clinical study for AEG35156, its proprietary therapeutic targeting the X-linked Inhibitor of Apoptosis Protein, a regulator of apoptosis.

The phase I trial is an open-label study of the agent in combination with ara-C and idarubicin in refractory or relapsed acute myeloid leukemia, the company said.

The study is being conducted at M. D. Anderson Cancer Center, led by Elihu Estey, and Princess Margaret Hospital, led by Aaron Schimmer.

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Affymax Inc. of Palo Alto said it has begun a phase II trial of Hematide for anemia associated with cancer and chemotherapy.

The open-label, dose-escalation trial is being conducted at multiple clinical sites in Europe and will evaluate the safety, pharmacodynamics, and pharmacokinetics of subcutaneously administered Hematide.

The drug has been evaluated in a phase I trial in healthy volunteers and in a phase II trial for anemia due to chronic kidney disease where dialysis has not occurred nor has treatment with erythropoietin.

To date, final results from the phase I study and interim results from the first cohort in the phase II CKD trial have demonstrated proof-of-concept erythropoietic activity, the company said. After 28 days of follow-up of CKD patients, results showed that a single IV dose of Hematide was well tolerated and resulted in a clinically significant increase in hemoglobin from baseline, which was sustained for more than one month. Six of seven patients (86 percent) who received Hematide had a hemoglobin increase >1 g/dL. Changes in other pharmacodynamic parameters were consistent with stimulation of erythropoiesis, the company said.

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Alfacell Corp. (NASDAQ:ACEL) of Bloomfield, N.J., said it has revised its international, confirmatory phase IIIb trial evaluating Onconase (ranpirnase), the investigational drug candidate, for unresectable malignant mesothelioma:

The company said it would reach full enrollment of 316 ahead of the previously announced timeframe of end of first quarter of the year. Also, as a result of the FDA Fast-Track designation granted for the UMM indication, the company said it would expedited regulatory review of the NDA upon filing.

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Bayer Pharmaceuticals Corp. (NYSE:BAY) of West Haven, and **Onyx Pharmaceuticals Inc**. (NASDAQ:ONXX) of Emeryville, Calif., have begun a randomized, double-blind, placebo-controlled phase III trial of Nexavar (sorafenib) tablets administered in combination with carboplatin and paclitaxel for non-small cell lung cancer.

The multicenter study, open to all types of NSCLC including those with squamous cell or adenocarcinomas, will compare Nexavar when co-administered with carboplatin and paclitaxel versus carboplatin and paclitaxel alone. The 900-patient study will assess overall survival as the primary endpoint. Secondary endpoints include progression-free survival, tumor response and safety. Patients may not have received prior systemic anticancer treatment.

Randomization will be to receive 400 mg of oral Nexavar twice daily or matching placebo, in addition to carboplatin and paclitaxel for six cycles. The study will be conducted at 130 sites in North America, South America, Europe, and the Asia Pacific region.

FDA has completed a Special Protocol Assessment for the phase III NSCLC trial.

In another development, **Bayer HealthCare**, Diagnostics Division, a member of the Bayer Group (NYSE:BAY) of Tarrytown, N.Y., said it has been granted licenses under patent rights relating to free PSA and tacrolimus tests from **Abbott Laboratories**.

Bayer said it would develop the two tests for its ADVIA Centaur and ADVIA Centaur CP immunoassay systems.

"By adding free PSA to the oncology portfolio, Bayer HealthCare Diagnostics will have a very comprehensive diagnostic menu for prostate cancer markers," said Samir Taneja, director of urologic oncology, NYU Cancer Institute and School of Medicine. "The flexibility will allow physicians to select the tests they feel most appropriate to differentiate malignant and benign prostate disease within the individual patient."

The tacrolimus test determines the amount of immunosuppressant drug in the system, the company said. The drug tacrolimus is used as an immunosuppressant for liver transplantion.

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Bioniche Life Sciences Inc. (TSX: BNC) of Belleville, Ontario, said FDA approved the IND application for the first of two phase III trials using its Mycobacterial Cell Wall-DNA Complex for bladder cancer.

The first phase III study will examine the efficacy of MCC as therapy in superficial bladder cancer refractory to Bacillus Calmette-Guerin, the company said.

FDA is reviewing the IND for the second part

of the phase III program, in which 600 patients will be randomized in a double-blind, multi-center study comparing MCC to BCG as first-line therapy in superficial bladder cancer at high risk of recurrence or progression.

MCC has been shown to have immune stimulatory and apoptosis activity against cancer cells, the company said. It is produced at the Bioniche manufacturing facility in Pointe-Claire, Quebec.

Alvaro Morales, professor of urology and oncology at Queen's University in Kingston, Ontario, will serve as principal investigator for the phase III program.

* * *

BioVex Inc. of Cambridge, Mass., said initial dosing had begun in its phase II trials of OncoVEXGMCSF for malignant melanoma and for head and neck cancer.

A 50-patient study will look at tumor response rate as a primary endpoint, with secondary endpoints including time to disease progression and median survival time. The principal investigator is John Nemuniatis of Mary Crowley Medical Research Center in Dallas.

A 16-patient open-label head and neck cancer trial is a combination with chemoradiotherapy and is taking place at the Royal Marsden Hospital in London. The principal investigator is Kevin Harrington.

OncoVEX GMCSF is an oncolytic virus that selectively kills tumor cells and induces tumor cells to secrete GMCSF.

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Chemokine Therapeutics Corp. (TSX: I; OTCBB: CHKT) of Vancouver said it has received approval from Health Canada to begin a phase Ib/II trial using CE-9908, a chemokine CXCR4 antagonist.

The 30-patient study for late stage cancers would evaluate safety as well as early efficacy, the company said. The trial would study a mixed group of tumors that will include ovarian, lung, and breast. Chemokine said it would expand its CE-9908 clinical program with the filing of an IND to FDA. FDA granted orphan-drug designation to CE-9908 for osteogenic sarcoma.

In another development, **Chemokine** said it has executed a Material Transfer Agreement with Dana-Farber Cancer Institute wherein it will supply Dana-Farber with CE-9908. Dana-Farber will perform preclinical studies with the agent to see if it can inhibit the growth of glioblastoma cells, the company said.

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CuraGen Corp. (NASDAQ:CRGN) of Branford, Conn., and **TopoTarget A/S** (Copenhagen Stock Exchange: TOPO) said the companies have begun dosing in a phase II trial evaluating the efficacy and safety of PXD101, a small molecule histone deacetylase inhibitor, for cutaneous T-cell, peripheral and other T-cell non-Hodgkin's lymphomas.

The study would establish the efficacy and safety of PXD101 as a single-agent, the company said.

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Favrille Inc. (NASDAQ:FVRL) of San Diego said it has completed enrollment in a phase III trial of FavId begun in July 2004.

The trial evaluates FavId following Rituxan therapy for follicular B-cell non-Hodgkin's lymphoma. The randomized, double-blind, placebo-controlled trial, conducted at 67 centers in the U.S., includes both treatment-naive and relapsed/refractory patients with stable or responding disease following treatment with Rituxan.

Favrille said it has been granted FDA Fast-Track designation for the agent.

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Gastrotech Pharma A/S of Copenhagen said it has begun a phase II study of GTP-200 in cancer cachexia.

The study is designed as a double-blind, randomized, controlled trial in 30 patients with end-stage cancer and significant weight loss. The principal investigator for the single-center trial is Kent Lundholm of Sahlgrenska University Hospital in Gothenburg, Sweden.

Treatment will consist of daily injections of two different dosages of GTP-200 for a total of 8 weeks, the company said. The primary goal is the effect of GTP-200 on key parameters such as body weight, body composition, appetite and quality of life.

GTP-200 is based on the peptide hormone, ghrelin, shown to be a stimulator of appetite.

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Isis Pharmaceuticals Inc. (NASDAQ:ISIS) of Carlsbad, Calif., said **Eli Lilly and Co.** (NYSE:LLY) has begun clinical trials of LY2275796 for cancer.

LY2275796, a second-generation antisense drug, targets eukaryotic initiation factor-4E (eIF-4E), a protein in the translation of growth and survival factors in tumor progression and the spread of cancers.

The product was discovered in the Isis-Lilly drug discovery collaboration, and is the second antisense drug candidate from the strategic alliance to advance into phase I development. Lilly said it would pay Isis $750,000 for the milestone. Lilly said it is funding the development of LY2275796.

"eIF-4E is a drug target that oncologists believe

may play a key role in initiating and maintaining various cancers, yet considered undruggable with traditional drug discovery technologies," said C. Frank Bennett, senior vice president, Antisense Research at Isis. "Our antisense drug could work against cancer, including breast, head and neck, colon, prostate, bladder, and lung cancer."

* * *

Peregrine Pharmaceuticals Inc. (NASDAQ: PPHM) of Tustin, Calif., said it has completed enrollment and dosing in a phase I trial for Tarvacin Anti-Viral in chronic hepatitis C virus infection.

The single dose ascending trial was conducted in chronic HCV where response to standard of care treatment either failed or where there is no longer a response, the company said.

Tarvacin Anti-Viral is a monoclonal antibody that also is in phase I trials for advanced refractory solid cancers, the company said.

Separately, Peregrine said John McHutchison is joining the Peregrine Scientific Resource Board. McHutchison, an HCV expert, is director of gastroenterology/hepatology research at the Duke Clinical Research Institute and professor of medicine at Duke University Medical Center.

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Sunesis Pharmaceuticals Inc. of South San Francisco said it has begun a phase I trial of SNS-032, a small molecule inhibitor of cyclin-dependent kinases 2, 7 and 9.

The trial is an open-label, multi-center study that would examine the safety and preliminary anti-tumor activity of SNS-032 advanced solid tumor cancers. Once a maximum-tolerated dose has been identified, enrollment will expand by 24 patients with lung cancer, breast cancer or melanoma, the company said.

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OXiGENE Inc. (NASDAQ: OXGN, XSSE: OXGN) of Waltham, Mass., said it would begin a phase II trial in the U.S. evaluating its lead clinical candidate, Combretastatin A4P, in combination with concurrent chemoradiotherapy for all histological types of unresectable stage IIIa/IIIb non-small cell lung cancer.

The study will initially enroll 12 patients to establish the dose and then proceed as a randomized, open label, multi-center trial comparing two cohorts: an investigational group and an active control group. Sixty-six patients without prior treatment for NSCLC will be randomized 2:1 into the two groups. The investigational group will be treated with radiotherapy and seven cycles of chemotherapy plus CA4P, followed by maintenance chemotherapy plus CA4P. The objective is to evaluate the survival benefit at one year. The response rate will be evaluated according to Response Evaluation Criteria in Solid Tumors, the company said.

OXiGENE said it also has received regulatory clearance from the Medicines and Healthcare Products Regulatory Agency to begin a phase III trial of the agent in the UK for inoperable stage IIIb/IV NSCLC, a subset not deemed suitable for curative treatment with concurrent radiotherapy.

"We expect the phase II trial in the U.S., combined with the phase III trial in Europe for stage IIIb/IV NSCLC, may provide a springboard for the company to maximize its registrational opportunities in an oncology indication, and with standards of therapy most often selected by oncologists for each subset of patients," said Frederick Driscoll, president and CEO of OXiGENE.

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Vion Pharmaceuticals Inc. (NASDAQ:VION) of New Haven said it would begin a phase II trial of Cloretazine for poor-risk acute myelogenous leukemia.

The company said it met with FDA to discuss data from Vion CLI-033, a phase II trial for AML and high-risk myelodysplastic syndromes. In Stratum A of the trial, patients over the age of 60 with previously untreated AML and high-risk MDS were treated with Cloretazine as a single agent. In that stratum, a response rate of 31 percent was achieved in 107 patients. Vion also reported a response rate of 49 percent in a subgroup of 45 with de novo AML.

In a related development, Vion Pharmaceuticals Inc. said Cloretazine, under the product name of of 1,2-bis (methylsulphonyl)-1-(2-chloroethyl)-2-[(methylamino)carbonyl] hydrazine, was granted orphan designation by the European Commission for acute myeloid leukemia.

Deals & Collaborations:

CytRx To Transfer RNAi Technology To Subsidiary

(Continued from page 1)

led us to conclude that repositioning our RNAi technology could accelerate the movement of high-value RNAi drug candidates into the clinic, thereby increasing the value of the technology for our shareholders," said Steven Kriegsman, president and CEO of CytRx. "We believe that this structure will enable us to capitalize on recent progress in the field of RNAi by promoting

research collaborations, other strategic alliances, and direct financing opportunities. Most significantly, this subsidiary will be a pure play RNAi company and can now more easily be compared with other RNAi companies, which could materially increase CytRx's overall valuation."

CytRx said it would move at least one RNAi-based drug through preclinical development this year and toward the filing of an IND application for a clinical trial.

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DrugMax Inc. (NASDAQ:DMAX) of Farmington, Conn., said it has acquired the assets of **Central Florida Pharmacy**, an oncology pharmacy, for less than $500,000.

The pharmacy, which had $6.7 million in revenue in 2005, provides oncology and pain related specialty pharmaceuticals.

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MDS Pharma Services of Philadelphia said it has been selected as the preferred contract research organization of the Multiple Myeloma Research Consortium.

MDS Pharma Services will manage multiple MMRC pre-clinical and clinical research, including data management for the MMRC tissue collection program, the company said.

MMRC is a non-profit organization comprised of seven member institutions involved in promoting myeloma research.

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Medarex Inc. (NASDAQ:MEDX) of Princeton and **Organon**, a unit of Akzo Nobel of the Netherlands, said they have entered into an agreement to develop therapeutic antibodies.

Organon said it would use the Medarex UltiMAb Human Antibody Development System to discover fully human antibodies in mice, to generate therapeutic antibodies against disease targets discovered by Organon and/or its alliance partners in discovery research.

In another development, Medarex said it received a milestone payment from its licensing partner **ImClone Systems Inc**. following acceptance of an IND application for a fully human IgG1 antibody for cancer.

The antibody was developed using the Medarex UltiMAb technology.

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Medicsight PLC, a majority owned subsidiary of **Medicsight Inc**. (AMEX:MGT) of London and **Viatronix Inc.** of Stony Brook, N.Y., said the Medicsight ColonCAD, integrated as part of the Viatronix V3D-Colon workstation, will be used in the SIGGAR1 clinical trial to interpret colonography studies.

Vertec Scientific, a Viatronix U.K. sales and service provider, will install the combined Viatronix/ Medicsight imaging systems into all 15 SIGGAR1 trial sites around the UK, the company said.

The 4,500-patient multi-center trial, conducted by the Special Interest Group for Gastrointestinal and Abdominal Radiology and sponsored by the National Health Service Health Technology Assessment program, would compare colonography with barium enema and optical colonoscopy for diagnosis of colonic cancer in older symptomatic patients in the UK.

* * *

Monogram Biosciences Inc. (NASDAQ: MGRM) of South San Francisco said it has entered into a collaboration agreement with **Dana-Farber Cancer Institute** for the Monogram eTag technology in preclinical and clinical oncology research studies.

The studies would identify and validate clinical biomarkers and predictive algorithms for disease prognosis and therapeutic response.

Under the agreement, Monogram and Dana-Farber will conduct experiments employing eTag assays to investigate the relationship between signaling pathway activation and clinical responsiveness to targeted anti cancer drugs.

Monogram said it would have rights to diagnostic and predictive medicine applications of all resulting inventions.

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Sequenom Inc. (NASDAQ:SQNM) of San Diego said the Kleberg Center for Molecular Markers at **M. D. Anderson** has purchased the Sequenom proprietary MassARRAY genetic analysis system and iPLEX assay molecular marker research and individualized cancer care initiatives.

The system will be used for genotyping and epigenomic studies to identify individuals at high risk for developing specific types of cancer, said Gordon Mills, chairman of the Department of Molecular Therapeutics and co-director of the Kleberg Center.

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Vaccinex Inc. of Rochester said it has entered into research collaboration with **Schering AG** to identify disease targets and develop therapeutic antibodies for cancer.

Vaccinex said it would receive a technology access fee and research funding and would be eligible for milestone payments and royalties.

Product Approvals & Applications:

FDA Approves Rituxan For NHL With CHOP Therapy

Genentech Inc. and **Biogen Idec Inc**. (NASDAQ: BIIB) of Cambridge, Mass., said FDA approved Rituxan (Rituximab) for first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens.

"Diffuse large B-cell lymphoma can be fatal within as little as six months to two years without aggressive treatment," said Sandra Horning, chairman of the lymphoma committee of the Eastern Cooperative Oncology Group. "With this approval, Rituxan in combination with chemotherapy becomes the first FDA-approved treatment to improve survival for this type of non- Hodgkin's lymphoma since the introduction of the CHOP chemotherapeutic regimen more than 25 years ago."

The approval was based on efficacy and safety data from three randomized, controlled, multicenter studies of Rituxan in combination with CHOP or other anthracycline-based chemotherapy induction regimens in 1,854 previously untreated patients. In each study, hazard ratios for the time-to-event comparison, as well as the overall survival benefit, favored the Rituxan-containing arms. Results were consistent across subgroups, including age, gender and disease prognostic variables. With two years of follow-up, more patients were alive in the Rituxan-containing versus control arms for each study.

In one of the studies with five years of follow-up, the GELA trial, R-CHOP improved overall survival by 47 percent compared to CHOP alone (a hazard ratio of 0.68, equivalent to a 32 percent decrease in the risk of death), the companies said.

The studies included in the submission to the FDA were GELA/LNH 98-5 (the Group d'Etude des Lymphome d'Adulte), E4494 (an NCI-sponsored Intergroup trial led by the Eastern Cooperative Oncology Group) and MInT (MabThera International Trial M39045), the companies said. Rituxan is known as MabThera in Europe.

The GELA trial evaluated the efficacy and safety of Rituxan in combination with induction CHOP chemotherapy in 399 patients 60 years of age or older with DLBCL, the companies said. Patients were randomized to receive chemotherapy or Rituxan plus chemotherapy. At five years, an estimated 58 percent of patients who received Rituxan plus chemotherapy were alive versus 46 percent of patients who received chemotherapy alone, the companies said.

In addition to GELA, the MInT and E4494 trials demonstrated an overall survival benefit with the addition of Rituxan to chemotherapy in a wide range of patients, the companies said. In the MInT trial, the addition of Rituxan increased survival in younger (<60 years) DLBCL patients. Ninety-five percent who received Rituxan in addition to chemotherapy survived two years versus 86 percent of patients who received chemotherapy alone.

In the E4494 study of older (greater than or equal to 60 years) DLBCL patients, 74 percent of patients who received Rituxan plus chemotherapy survived two years versus 63 percent who received chemotherapy alone.

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American Pharmaceutical Partners Inc. (NASDAQ:APPX) of Schaumburg, Ill., said it has received two FDA approvals of Abbreviated NDAs for Octreotide Acetate Injection, single-dose and multiple dose vials, the generic equivalent of the Novartis Pharmaceuticals Sandostatin Injection.

In another development, APP received FDA approval for its Abbreviated NDA for Carboplatin Injection (liquid form) in a 600 mg multi-dose vial.

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AstraZeneca (NYSE:AZN) of Wilmington, Del., said FDA has granted Zactima (ZD6474) Fast-Track designation for medullary thyroid carcinoma.

Zactima is in a phase II trial for medullary thyroid cancer, and AstraZeneca said it is enrolling patients in a single arm phase II study in locally advanced or metastatic hereditary medullary thyroid cancer.

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Cell Therapeutics Inc. (Nasdaq: IC; MTAX: IC) of Seattle said FDA has given Xyotax, a biologically-enhanced version of Taxol, Fast-Track designation for patients with poor performance status advanced non-small cell lung cancer.

The company's PIONEER trial exclusively targeting women with lung cancer is underway at 170 sites, about half in the U.S.

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GlaxoSmithKline (NYSE:GSK) of Philadelphia said FDA has accepted a supplemental NDA for Hycamtin (topotecan HCl) for Injection.

FDA also agreed to priority review, the company said. The sNDA seeks marketing approval for the new use of Hycamtin in combination with cisplatin for stage IVB recurrent or persistent carcinoma of the cervix not

amenable to curative treatment with surgery and/or radiation therapy.

The application is based on a randomized, multicenter phase III trial by the Gynecologic Oncology Group which enrolled women with measurable, histologically-proven stage IVB recurrent or persistent carcinoma of the cervix. The study demonstrated a survival advantage with Hycamtin in combination with cisplatin compared to cisplatin alone.

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Morphotek Inc. of Exton, Pa., said FDA has cleared its investigational NDA for MORAb-009 for mesothelin-expressing cancers.

Mesothelin is highly over-expressed in pancreatic adenocarcinoma tumors, non-small cell lung cancer, ovarian cancer, and mesotheliomas, the company said. Morphotek obtained rights to develop the antibody from NCI.

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NeoGuide Systems Inc.of Los Gatos, Calif., said it has received FDA clearance to market its Endoscopy System, a computer assisted colonoscopy system which gives physicians better control of the colonoscope and eliminates looping, the reason conventional colonoscopy procedures can be painful.

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Schering-Plough Corp. (NYSE:SGP) of Kenilworth, N.J., said Health Canada has granted approval for Temodal(temozolomide) capsules in combination with radiotherapy for adults with newly diagnosed glioblastoma multiforme.

Temodal is marketed in Canada for recurrent or progressive GBM or anaplastic astrocytoma.

The new indication was based on efficacy and safety data from a phase III study conducted by NCI of Canada and the European Organisation for Research and Treatment of Cancer. In the trial of 573 patients, significant improvements in overall survival were observed.

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Roche of Basel, Switzerland, submitted a Marketing Authorization application to the European Medicines Agency for Herceptin (trastuzumab) as adjuvant treatment for early-stage HER2-positive breast cancer.

The application is based on data from the international HERA study, which showed that Herceptin following standard chemotherapy reduces the risk of cancer recurrence by 46 percent.

Genentech similarly filed a supplemental BLA for Herceptin in early-stage HER2-positive breast cancer with FDA two days before the European filing, the company said.

The application is based on a combined interim analysis of two large U.S. trials.

* * *

YM BioSciences Inc. (AMEX:YMI) of Mississauga, Canada, said FDA has designated tesmilifene as a Fast-Track product in combination with an anthracycline chemotherapeutic for advanced breast cancer.

Tesmilifene is being studied in a 700-patient phase III trial for metastatic and recurrent breast cancer. The trial compares tesmilifene combined with epirubicin/cyclophosphamide against epirubicin/cyclophosphamide alone in rapidly progressing metastatic and recurrent breast cancer.

YM said it began a phase II trial in collaboration with Sanofi-Aventis combining tesmilifene with Taxotere for metastatic and recurrent breast cancer. Separately, YM has licensed tesmilifene to the Shin Poong Pharmaceutical Co. of Seoul, South Korea, under which Shin Poong would expand the development program into gastric cancer.

Oncology Management:

UPMC Backs Venture To Bring Radiation Therapy To Hospitals

Alliance Oncology has been formed by the University of Pittsburgh Medical Center and Alliance Imaging.

The new venture aims to bring the latest radiation therapies (IMRT and IGRT) to hospitals that lack the capital and expertise to do this on their own. Alliance Oncology, in which UPMC holds a 20 percent stake, opened two radiation therapy centers in November in California and has five under development in the Boston area, with plans to add five to seven centers annually in the coming years. The venture plans to partner with hospitals instead of competing with them through freestanding centers of its own.

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Oncology Therapeutics Network of South San Francisco has entered into an agreement with **One Equity Partners** to acquire ivpcare, the largest privately-held national specialty pharmacy offering clinical services and distribution of pharmaceuticals for chronic conditions.

OTN has partnered with ivpcare to provide home delivery services of oral chemotherapy directly to patients. Ivpcare will become a subsidiary of OTN.