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Avastin Vote Puts Focus On FDA Criteria In First-Line Metastatic Breast Cancer

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee last week split 5-4 to recommend against approval of Avastin (bevacizumab) for first-line treatment of breast cancer.

Though technically a setback for the Avastin application, the one-vote margin at the meeting Dec. 5 doesn't constitute a mandate in either direction. The agency has been known to disregard even unanimous votes.

And while FDA's challenge of the application was vigorous, that, too, doesn't predict a negative outcome. The agency frequently uses ODAC to stimulate public discussion of regulatory issues and air out information it can't release otherwise.

The Avastin case urgently needed sunshine. Though the data at the heart of the application received a standing ovation at the 2005 meeting of the

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In the Cooperative Groups:

Coltman Retires After 44 Years With SWOG; Two Fellowship Programs Named For Him

CHARLES COLTMAN JR. announced his retirement from the Southwest Oncology Group. He served as the group's associate chairman of cancer control and prevention since 2005, when he turned over the chairmanship of the group to **Laurence Baker**. He was named chairman emeritus at the group's fall meeting.

SWOG established two fellowship programs in Coltman's honor. Each program will span both cancer therapeutics and cancer control and prevention, the areas that Coltman emphasized in his career.

The Dr. Charles A. Coltman Jr. Fellowship, supported by Novartis Pharmaceuticals, will provide $50,000 per year for two years to three researchers in the areas of oncology: breast, GI, GU, gynecologic, leukemia, lung, melanoma, and myeloma. The Coltman Fellowship in Translational Medicine, supported by Genentech BioOncology, will fund three fellows at $50,000 per year for two years within any of SWOG's major disease areas.

Further information about application requirements will be made available on the SWOG website in early 2008 at http://www.swog.org.

Coltman, professor of medicine at the University of Texas Health Science Center at San Antonio, joined SWOG in 1964 and served as chairman of the Lymphoma Committee (1966-1977) and the Leukemia Committee (1977-1981) prior to his election as chairman of the group 1981. He served as group chairman for 24 years.

The Cancer Letter Takes Winter Publication Break

This is the final issue of The Cancer Letter for 2007. The next issue is scheduled for Jan. 11, 2008.

ODAC No Longer Unanimous On Survival In First-Line BC

(Continued from page 1)

American Society of Clinical Oncology, FDA bounced the application back to Avastin's sponsor, Genentech Inc., seeking additional documentation.

What went wrong? Genentech declined to release the agency's "approvable" letter, and FDA was precluded by law from discussing the controversy at any venue other than ODAC. On Dec. 5, it did.

To approve Avastin for first-line metastatic breast cancer, the agency would have to abandon its long-time reliance on survival and accept time to progression as a metric for drug approval for this indication.

Over the past year, FDA accepted the extension of time to progression as a basis for approval of two drugs—GlaxoSmithKline's Tykerb (lapatinib) and Bristol-Myers Squibb's Ixempra (ixabepilone)—for second and third-line metastatic breast cancer.

In the adjuvant setting, where the stakes are particularly high, treatments are routinely approved based on a related metric, disease-free survival. Last year, Genentech's biologic Herceptin (trastuzumab) was approved for the adjuvant treatment of HER2-positive node-positive breast cancer based on DFS.

In the past, FDA accepted PFS in the front-line setting, approving two combination therapies, Herceptin and paclitaxel in 1998 and the Eli Lilly's Gemzar (gemcitabine) and paclitaxel in 2004. However, in both cases, survival data were added to the label later.

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In June 1999, FDA asked ODAC's opinion on acceptability of PFS in front-line metastatic breast cancer. The committee voted unanimously 12-0 that a delay in progression wasn't acceptable for full approval in that setting (The Cancer Letter, June 18, 1999).

By contrast, at the Dec. 5 meeting, FDA asked the advisory committee to return to this question before getting into the specifics of the Avastin application. Though no vote was taken, committee members made it clear that the uncomplicated unanimity exhibited eight years earlier has been lost:

—"From the patient perspective, I think PFS is a very meaningful endpoint in first, second, and third-line therapy," said committee member Joanne Mortimer, vice chairman Medical Oncology and professor at the Division of Medical Oncology & Experimental Therapeutics at the City of Hope Comprehensive Cancer Center. "If you talk about first-line therapy today, most of these women are heavily pretreated, and so very few truly are first-line therapy, making it harder to expect an overall survival advantage. Outside of trastuzumab, I don't believe that any chemotherapy alters overall survival. This just reflects that we don't know who the subsets are who truly benefit from each of these different therapies."

—"There is no question among my colleagues and myself that PFS is clinically meaningful," said ODAC member Gary Lyman, director of the Health Services and Outcomes Research Program-Oncology at Duke University Medical Center. "The differences between managing first-line metastatic disease and subsequent second- and third line therapies in the last few years have become very cloudy.

"And that has to do with the fact that the vast majority of patients who come to me have had an anthracycline, have had an alkylating agent, they've had a taxane. If they are Her-2 positive, they've had Herceptin, and are already fairly extensively treated in the adjuvant setting before I see them for first-line metastatic disease. I don't think that compilation overall is any different than a patient who comes back with a recurrence after their first-line of metastatic disease."

Subsequent therapies may affect survival, too. "Many of my patients, after the first line approach, go through five, six, seven additional regimens, and that just adds enormous noise and can cloud the survival differences of a first-line regimen," Lyman said.

—"I do think it's a clinical benefit parameter," said Gail Eckhardt, director of the Division of Medical Oncology GI Malignancies Program at the University of Colorado Health Sciences Center.

The boundaries between front-line and subsequent therapies are a problem, too. "The measurement bothers me, and I think overall survival just in terms of what happened in the past 10 years, even on the control arm, to me, signifies the variability of second-and third-line therapy, which really has implications going forward in front-line metastatic breast cancer," she said.

PFS can be a poor predictor for overall survival, said Maha Hussain, ODAC chairman and professor of medicine and urology at the University of Michigan.

"I come from a field where there have been one or two examples where early positive indications didn't translate into a survival advantage," Hussain said. "If anything, early therapy with drugs resulted in worse survival. Therefore, if you ignore the survival, and you just go by response or progression-free survival, you would have actually put harmful drugs on the market."

Responding to this comment, Richard Pazdur, director of the FDA Office of Oncology Drug Products, said that whenever the agency chooses to accept PFS, it will mandate sponsors to conduct trials to produce proof of more tangible clinical benefit. "Let me guarantee you that we would demand that the sponsors provide survival data as a follow-up," he said. "That is not even a question here."

Had the Avastin trials shown a deficit in survival, the case wouldn't have gone to ODAC, Pazdur said. "If we saw an inferior survival, we wouldn't even be here," he said.

HUSSAIN: "My concern is, if you are going to begin to say PFS now is the primary endpoint for everything, then studies would not be powered for survival, sample sizes go down, follow-up go down."

PAZDUR: "Let me assure you that in our discussions with sponsors on this—when we are negotiating PFS—and these conversations are usually in more refractory disease settings—we ask them to power the trials to ensure that we could take a look at overall survival."

Biostatistician Ralph D'Agostino said he was having difficulty recommending approval of a drug based on a statistical construct like PFS.

"I would like to know what the clinical benefit is in this setting, outside of the fact that it's progression-free survival," said D'Agostino, chairman of the Mathematics and Statistics Department at Boston University and a temporary voting member of ODAC. "I haven't heard anything about clinical benefit outside of the measurement of PFS."

HUSSAIN: "They pay me as the chair, so I am going to take a stab at it. I think part of the problem is that we have no way of measuring some subtle issues that are of benefit. So those of us who sit in the clinic in front of patients, I will guarantee you that there is not a tool out there that captures the nightmares, the sleepless nights, the worry about scans, and so if one wants to be removed about it and just think of things we can measure, I agree with you that there is no clinical benefit. But for those of us who are clinicians—and assuming that the drug is safe—patients are a nervous wreck when their disease is progressing. And that you have no tool to measure."

Filling in the Blanks

In September 2006, FDA stunned observers by demanding that Genentech provide additional documentation on the Avastin supplemental Biologic License Application.

Until the Avastin trial—E2100, conducted by Eastern Oncology Cooperative Group—the agency didn't require cooperative groups to conduct central radiology review of scans in registration trials, relying instead on the investigators' determination.

Now, suddenly, the agency was saying that while the investigator's determination was good enough in trials that measured survival, it was no longer sufficient for trials that measured the delay in disease progression (The Cancer Letter, Sept. 15, 2006).

FDA-watchers yearned for a blow-by-blow regulatory history, pointing out that Genentech had benefited from NCI funding in conducting the trial, and was now treating the agency's "approvable letter" as proprietary information.

"Has the year-plus delay made any difference, has it provided benefit in the overall process?" Robert Erwin, president of the Marti Nelson Foundation, reflected at the public hearing session during the ODAC meeting Dec. 5. "Although the complete response letter was never made public, the briefing documents have been. And I would say that the delay has been valuable if the following was achieved: and that is reconfirmation and reestablishment of the FDA's high bar for new drug approval."

Erwin had pressured FDA, NCI, and Genentech to clarify the mystery (The Cancer Letter, Sept. 29, 2006). His questions were answered in the documents made public before the ODAC meeting.

"Apparently, NCI ignored input from the FDA in May 2002, regarding the clinical trial design," Erwin said at the meeting. "Genentech ignored FDA's request for independent radiology review back in September

2005. I would like to see as much cooperation as possible, cooperation with disclosure, cooperation with transparency.

"There are some additional questions: Should NCI essentially be a [contract research organization] for industry? I would argue No."

Erwin, as well as another speaker, Carolina Hinestrosa, executive vice president of the National Breast Cancer Coalition, made no approval recommendation, urging instead that the committee refrain from approving the agent if that requires lowering the bar for approval.

The patient advocate who voted with the committee was overtly negative about the drug. "It's very painful reality that metastatic breast cancer is not curable, and I don't think we should just say, 'Well dear, try this,' if there isn't meaningful data to support it," said Natalie Portis, of Breast Cancer Action, an author of multiple postings on the group's website. "And in this study, there is missing data, there are inconsistencies, and I feel very uncomfortable about this."

Portis's vote in opposition to Avastin could have been easily predicted.

On Nov. 29, a week before the meeting, her group sent a letter to FDA, urging the agency to deny approval for breast cancer drugs that aren't shown to extend survival or improve quality of life. Then, on Dec. 3, two days before the meeting, the group followed up with a statement urging the agency to deny the Avastin application.

The day after the negative recommendation, the group sent out an e-mail blast titled "Victory on Avastin."

E2100 Not Designed as Registration Trial

Since E2100 wasn't originally designed as a registration trial, it had a 15 percent to 25 percent power to detect a two to three-month improvement in overall survival. By contrast, the trial had 85 percent power to detect a 33 percent improvement in PFS. Anything short of a massive shift in survival was likely to remain undetected.

The front-line study was attempted by ECOG at the time when Genentech was conducting a study of capecitabine with and without bevacizumab in the second- and third-line therapy of metastatic breast cancer.

The ECOG study opened for accrual in December 2001. In September 2002, the company-sponsored trial AVF2119 failed to meet its primary endpoint, which was also PFS.

According to the FDA presentation, the protocol for E2100 was first submitted to the agency in October 2001 with no indication that the trial was intended to support approval. In May 2002, when Genentech first noted that the study would be presented for approval, FDA told NCI that the study was deficient.

In its presentation Dec. 5, the agency said that in 2002, it sent two letters to NCI, pointing out the problems with the trial's endpoints and its statistical analysis plan. "NCI did not request a meeting to discuss adequacy of the trial design and analysis plan," the agency said to ODAC.

The issue of endpoints resurfaced in October 2004, when FDA told Genentech that E2100 may not be adequate to support label extension because of its non-blinded structure and the lack of pre-specified, detailed, and objective radiological and clinical parameters for determining disease progression.

Also, the agency said that some survival data would be required. "Genentech asked if PFS would be an adequate endpoint for full approval [and] FDA replied [that] it depends on the overall robustness and magnitude of PFS and results of survival data at the time of PFS analysis," the agency said.

After the trial was stopped based on the PFS results in April 2005, FDA agreed to accept E2100 as a basis of an sBLA. At that time, the agency said that PFS could support an accelerated approval, but final overall survival would be required for full approval.

A Moving Target?

The agency said it had three reasons for not approving the application last year:

—There was no cut-off date for safety and efficacy analysis. For example, during the first interim analysis, there were 260 PFS events. The data presented at ASCO was based on 355 events. The first sBLA submission was based on 395 events, and the second on 445 events.

—An independent radiology review of at least a subset of patients was necessary, because of the subjective nature of the endpoint and the open-label design of the trial.

—The submission was judged incomplete, because of missing documentation of eligibility, study violations, and treatment delays and discontinuations due to toxicity.

After Genentech completed a review of the data, not everything could be verified. In the 722-patient study, there were 16 percent of patients who started a non-protocol therapy before documentation of progressive disease, 7 percent were incorrectly stratified

based on their estrogen receptor status or prior treatment, and 6 percent were treated beyond progression, the agency said.

In the retrospective analysis, Genentech was unable to obtain scans for 10 percent of patients, and 34 percent of patients were not followed until the PFS event or the end of the study.

These problems didn't alter the PFS outcome. The patients who got paclitaxel and Avastin had the PFS of 11.3 months, while patients who got paclitaxel alone had the PFS of 5.8 months. The p-value was 0.0001.

According to the FDA analysis, there were 5 deaths due to treatment on the Avastin and paclitaxel arm, and no treatment deaths on paclitaxel alone. Grade 3 and 4 hypertension was reported by 20.1 percent of patients receiving Avastin and paclitaxel, compared to 0.5 percent for those receiving paclitaxel alone. Materials presented at the meeting are posted at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4332b1-00-index.htm.

Contacted after ODAC, Kathy Miller, associate professor of medical oncology at the Indiana University School of Medicine and the study's principal investigator, disagreed with the agency's evaluation of E2100.

"Even though scans were collected retrospectively for independent review, the rates of missing scans and discordant assessments in E2100 are very similar to recent studies that collected scans prospectively (compare to the lapatinib, ixabepilone and oxaliplatin approvals)," Miller wrote in an e-mail.

"The FDA lumped discordant assessment with a discordant date of disease progression," she wrote. "In many cases, the discordance in the date was no more than a few days.

"For example, a patient comes in on Monday with a new palpable lymph node and worsening symptoms.

"Scans performed on Wednesday confirm progression. The investigator lists Monday as the date of progression, because that is when it was first detected, but the IRF [Genentech's independent review panel convened in response to FDA's demand] lists Wednesday, since all they have to review are the scans. Lumping these very separate issues, not providing any leeway for dates to be considered concordant, and merely reporting a combined rate is very misleading.

"Many of the patients that were listed as not followed to progression are an artifact of the independent review process—namely patients in whom investigator-determined progression could not be determined centrally. In some cases progression was based on lesions only assessed by physical exam, in some cases it is a difference in interpretation of scans. Regardless of the reason, the investigator believed they had progressed and were off-study, therefore no additional scans were available for IRF review.

"Perhaps more importantly, the entire rationale for conducting an independent review is to identify and eliminate any systematic bias that might influence the results.

"There is simply no evidence of systematic bias in E2100," Miller wrote. "The IRF review of E2100 strongly supports the results we first reported."

Living Better?

"A patient is not living better, which you have shown us that they are not, and they are not living longer," said ODAC chairman Hussain at the committee meeting. "How does this translate into clinical benefit? I'd argue that these patients' quality of life went down, not up. You didn't show that they are feeling better, and you didn't show that they are living longer. And so when you put all of that together—and the fact that in your study the five-month difference in PFS eclipses anything that is shown in terms of other trials—yet that didn't make it into survival in an era where there are all kinds of second- and third-line treatments, which I don't buy as the reason we didn't see a survival differences."

Responding to this comment, Eric Winer, director of the Breast Oncology Center at Dana-Farber Cancer Institute, who took part in the Genentech presentation, said an improvement in PFS translates into an improvement in quality of life.

"First, in terms of why there was no difference in terms of overall survival, there was a small narrow difference," Winer said at the ODAC meeting. "It is reasonably likely that it didn't arise by chance alone. And much of that may relate to what is some intrinsic behavior of cancer in women with metastatic disease, and we could argue that particularly in women with ER-positive metastatic breast cancer therapies may do very little ultimately to change survival, and it's all about maintaining disease control.

"What we have demonstrated in this trial is not a quality of life improvement associated with paclitaxel and bevacizumab, but the fact that it declined less than in women who received paclitaxel alone and there was a significant difference. But the real issue is, does PFS in this setting translate into an improvement in quality of life? And I actually believe it does, because in a substantial number of patients, one is avoiding moving to a new therapy, with both a physical and psychological trauma."

Hypertension, one of the most common toxicities reported on the Avastin arm of E2100 isn't among the more debilitating toxicities that afflict cancer patients, said Miller, the study's PI.

"I think what is lost in lumping the toxicities together is what these toxicities mean to women with metastatic disease," Miller said to the committee. "When my patients tell me about toxicities that are troubling to them, they tell me about nausea, fatigue, diarrhea, hair loss, neuropathy and myalgia. Nobody mentions hypertension as something that limits them in their day-to-day lives. It certainly is an important toxicity that women and their physicians need to know about, that needs to be monitored, and in 15 to 16 percent of the patients we need a medical intervention, which means taking an oral antihypertensive."

Is PFS Good Enough?

The measurement of PFS falls short of demonstrating Avastin's efficacy in this setting, said Aman Buzdar, professor of medicine at the Department of Breast Medical Oncology at M.D. Anderson Cancer Center.

"There is no study which is perfect; there are going to be shortcomings, but there are major shortcomings in this study," said Buzdar, a temporary voting member on the committee. "So we have to keep that in mind, that a single study which shows one endpoint which is positive, there are other studies which do not support that. The thing is, are we enhancing the patients' choices, or are looking at something, which is not established, really? It may be effective, but the data we have to look at it critically, is the data which is available today, does it meet the standard to put the drug on the market?"

D'Agostino agreed. "There is no improvement in overall survival," he said. "If the survival went the other way, we wouldn't have the presentation before us, if the survival were over the p-value of .98 or something. We have it before us, because it looks like there may be a signal, and all of us have lived through chasing after signals. So I don't think there is a trend here. There might be, but the data isn't here to convince us. The toxicity is a real problem.

"Our approval would rest completely on buying into progression-free survival as an appropriate measure of efficacy, and I don't think we have capability at the moment, given the data that's before us."

The distinction between the first-line setting and the subsequent settings is artificial, countered Lyman.

"To me, this is a more difficult question, because of the nature of the data, and this was [a study] designed initially without the anticipation of the label extension," he said. "I do think that in this context a 5.5 month difference in PFS is clinically meaningful, and certainly statistically significant. It seems to hold up to a variety of both FDA and the sponsor sensitivity analyses.

"It is true that there is not a significant difference in overall survival, and there certainly is a trend. Statisticians don't like trends, but at least it assures me to a large extent that subsequent studies designed a little bit better would [not] show any worsening of survival. I think the probability with random numbers would be extremely low that this is such an extreme false signal.

"Do we really need to make the distinction in terms of products that are acceptable in the first-line setting, but not in the second- and third-line setting? Keeping in mind, these are metastatic patients. It's very unlikely any of these patients will not die of breast cancer or some other co-morbidity. It is a fatal disease."

Mortimer, too, said she supported approval, in part because other drugs have been approved based on PFS for second- and third-line metastatic settings despite having greater toxicity.

"Ixabepilone was approved for second and third-line therapy with 70 percent incidence of neurotoxicity and 65 percent incidence of myelosuppression, I think we are being inconsistent here," Mortimer said.

Describing her rationale for voting against approval, Hussain pointed to flaws in the E2100 data.

"If this were not perfect, but semi-perfect, I would be willing to vote Yes," she said. "I am moving to a No vote because I think there are too many uncertainties in the way the data was collected, the discordance as far as imaging, the fact that things were not set up from the beginning for registration so that you would have everything done in a way that makes the case.

"So I think the vote of a Yes today on something like that to me lowers the bar. I think there are other agents out there that are available for this patient population. I fully recognize that it's imperfect, but I don't think we can sanction suboptimal conduct of trials this early, and I have utmost respect for ECOG—I work with SWOG—and I know the limitations and the strengths of the cooperative groups, but I think that what we saw today in terms of deficiencies is concerning enough for me that it takes away from the positive results otherwise."

Despite the negative recommendation, it is unclear how FDA would decide on the Avastin application. The agency is expected to make a decision by Feb. 23, 2008.

In Europe, where PFS is a preferred endpoint, Avastin was approved for first-line metastatic breast cancer last March. The approval was based on the results of E2100. Now, ECOG, Genentech, and the European sponsor Roche are planning trials of Avastin in adjuvant breast cancer.

The phase III HER2 negative adjuvant breast cancer program is already recruiting patients and consists of two trials:

—The E5103 study is set to include 4,950 patients and will compare Avastin with the addition of an anthracycline-containing chemotherapy course versus anthracycline-containing chemotherapy alone. Additional information on the trial is posted at http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=528955&versio

—The BEATRICE study, sponsored by Roche, will investigate Avastin in combination with standard chemotherapies compared to chemotherapies alone in 2,530 patients who are not candidates for hormonal therapy.

—Avastin is being investigated in HER-2-positive breast cancer patients post surgery via the BETH trial. This study will investigate the addition of Avastin to Herceptin in combination with established chemotherapy regimen.

NCI Programs:

NCI Plans To Restructure Mouse Models Consortium

By Kirsten Boyd Goldberg

Advisors to NCI approved the institute's proposal to restructure the Mouse Models of Human Cancers Consortium, which provides about $19 million a year in grants to investigators.

The NCI Board of Scientific Advisors voted unanimously to approve the reissuance of a Request for Applications for the consortium.

The mission of the program would change from deriving new cancer models to exploring how to apply cancer models, NCI officials said to the board at its Nov. 15 meeting.

The consortium currently consists of 24 projects. Under the new structure, the consortium will be organized into four "grant clusters," each lead by a single multi-project U19 grant in one of four thematic areas, and up to 20 individual U01 grants, each aligned with one or more of the four clusters. The program is led by the NCI Division of Cancer Biology.

The board also unanimously approved the reissuance of RFAs for the Community Clinical Oncology Program and the Minority-Based CCOPs.

Excerpts of the MMHCC concept statement follow:

NCI Mouse Models of Human Cancers Consortium. Concept for a reissued RFA, first year set-aside $19 million, four U19 awards and 20 U01 awards, five years, estimated total $104 million. Program director: Cheryl Marks, Division of Cancer Biology.

The purpose of this proposed RFA is to change significantly the goals of the NCI-Mouse Models of Human Cancers Consortium beyond the original ones of generating and disseminating new genetically engineered mouse cancer models to goals that stress integration of cancer models into translational and clinical research.

The new mission will center the Consortium preclinical models research on elaborating innovative applications of models to the basic discovery, translational, and clinical needs of human cancer research. It will also support continued enhancement of the informatics infrastructure that assimilates, aggregates, and deploys information about preclinical model science and its merger with data stores from translational, clinical, and genetic epidemiology research.

In particular, the RFA intends to:

—Promote the application of existing mouse models to cancer research in one of four major areas: basic discovery, experimental therapeutics, early interventions, and susceptibility.

—Continue the Consortium's original vision to be a nexus for innovation in the comparative use of mouse and other animal models for: New insights about human cancer biology; appropriate, judicious use of in vivo models for experimental therapeutics; deciphering the genetic and environmental underpinnings of human cancer susceptibility; and, identifying at-risk populations and devising and testing suitable early interventions.

—Support systematic collaborations among Consortium groups that cluster within one of the four major areas.

—Provide structured collaborations across the Consortium groups that cluster into these four research areas of emphasis.

—Enhance the NCI's capacity for rapid communication of research outcomes on preclinical models and integration with translational and clinical research.

—Connect the Consortium to other NCI extramural and intramural programs and research communities.

Background: The initial phase of the Consortium and its infrastructure featured a strong focus on generation of new cancer models by germ line alteration and cross-species validation by pathology. To foster and facilitate internal collaborations, Division of Cancer Biology staff relied upon the disease-site specific emphasis of the Consortium groups, and used that emphasis for outreach to other NCI programs and the cancer research community.

The NCI investment yielded:

—Many refined GEM cancer models; a number of novel modeling techniques; many GEM cancer models for

malignancies previously not available.

—A database of models descriptions, a database of annotated histology images of mouse and corresponding human cancers an informational website, and a public mouse repository.

—Regular communication with the translational and clinical communities, and the pharmaceutical and biotechnology sectors.

—Protocols for model evaluation and characterization, histology standards, and vocabularies, that enable cross-species comparison.

—New approaches to stimulate collaborative research with the cancer community.

During the current phase of the Consortium, the NCI emphasized research on validation of the models and their translational applications, and development of an advanced informatics infrastructure for cross-species comparisons. DCB encouraged internal collaborations in both disease-site-specific research and in cross-cutting Consortium interests in cancer biology, interventions, susceptibility genetics, and phenotyping. Since program re-competition in 2003, the Consortium derived several hundred mouse strains to discover how particular altered genes factor into the etiology, natural history, and clinical course of cancer. In addition, they derived scores of significantly improved GEM models of cancer for many disease sites and for disease sites for which no models existed in 2000. They applied these models and inbred mice to cancer research to: Demonstrate their utility for discoveries about human cancer biology; employ them for experimental therapy and prevention; image response to therapy and recurrence; discover candidate biomarkers; identify human susceptibility and modifier genes; understand model and laboratory variability through cross-institutional experimental therapy and prevention trials.

Using previously established criteria for evaluating the competing renewal of an NCI program, DCB invited three external reviewers to evaluate the NCI-MMHCC. The external reviewers judged the Consortium to be highly successful in accomplishing its goals.

New NCI-MMHCC Structure: To reflect the change in the mission of the NCI-MMHCC from a program to derive new cancer models to one designed to explore how to apply cancer models and to integrate research across the cancer research continuum, the present RFA will implement an organizational structure that is consonant with those goals. The new configuration provides greater clarity for the research focus, integral use of the present information infrastructure, and structured collaborations within the program. The NCI-MMHCC program will emphasize the innovative use of mouse models to inform human cancer biology, experimental therapy, early interventions, and cancer susceptibility, which are the major areas of research that have emerged over the past four years, both within the NCI-MMHCC and the broader cancer research community. These areas will serve as the primary organizing principle for the Consortium.

At the present time, the Consortium consists of 24 projects; the proposed re-structured Consortium will redistribute the present level of resources to support up to 24 grants. The program will be organized into four grant clusters, each lead by a single multi-project (U19) grant whose research focus represents one of the four thematic areas, and up to 20 individual (U01) grants, each aligned with one or more of the 4 clusters. Grant applications will be solicited to form the two organizational components of the new structure:

—The multi-project (U19) grants will: Consist of up to 5 sub-projects, led by senior-level researchers who propose mouse model science that significantly advances one of the four areas above; enable regular communications intended to stimulate collaborations among the U01 grants that fit into that research cluster; develop with the cluster members potential pilot projects for the NCI to solicit from the research community; furnish two representatives to the Steering Committee; maintain regular communications with the other three U19 clusters and with the NCI; convene focused workshops with participants who augment the cluster's research expertise; continue to develop the specific informatics resources for the cluster's research focus in collaboration with the caBIGTM program and the other clusters; provide a communications and outreach locus for the cancer research community.

—The individual (U01) grants will: Pursue objectives that significantly advance the use of animal models for any aspect of human cancer research; affiliate with one primary multi-project (U19) cluster, and with any others based on scientific interests; attend biannual Steering Committee meetings; maintain communications with other U01s and the U19 in the cluster; organize workshops, and participate in development of pilot projects and resources.

The estimated budget for the final (FY2008) budget period of these U01 projects is about $21 million. DCB requests total costs for the program of $19 million in FY2009 to fund no more than four U19 multi-project grants and up to 20 U01 grants in response to this RFA. For U19 grants, applicants may request a project period of up to five years and an annual budget of no more than $1.8 million total costs. For U01 grants, applicants may request a project period of up to five years and an annual budget of no more than $600,000 total costs. The anticipated award date is April 1, 2009.

Funding Opportunities:

PA-08-037: Thyroid in Aging. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-037.html. Inquiries: Nancy Emenaker, 301-496-0116; emenaken@mail.nih.gov.

PA-08-038: Thyroid in Aging. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-038.html.

PA-08-039: Thyroid in Aging. R03. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-039.html.

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THE CANCER LETTER

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Business & Regulatory Report

Clinical Trials:

Genzyme To Conduct Mutation Analysis For CALGB Trial In Lymphocytic Leukemia

Genzyme Genetics, a business unit of Genzyme Corp. (NASDAQ: GENZ), said it is participating in a Cancer and Leukemia Group B study sponsored by NCI for chronic lymphocytic leukemia.

The multi-center 1,700-patient study would test the hypothesis that early treatment of patients with negative risk factors leads to longer survival. Genzyme will perform the IgVH mutation analysis for the study.

"This study is critical in helping us to understand the natural history of CLL with respect to early versus delayed progression," said John Byrd, director of hematologic malignancies and co-director, Division of Hematology-Oncology, Department of Medicine, Ohio State University

(Continued to page 2)

Deals & Collaborations:

Bristol-Myers Squibb Plans Review To Increase Productivity, Profitability

Bristol-Myers Squibb Co. (NYSE:BMY) of New York said it would conduct a comprehensive review of its business and research and development operations, and outline its strategy to improve shareholder value, increase profitability, and improve top-line growth.

The overview would provide investors with insight into how the company intends to transform itself through its productivity initiative into a next-generation biopharma company. The plan would focus the commercial and scientific units on specialty and biologic medicines, while enhancing productivity and rewarding entrepreneurship, the company said.

BMS said it plans to reallocate resources to make acquisitions, such as the recent acquisition of Adnexus Therapeutics, as well as pursue partnerships and other collaborative arrangements. The alliances would add to the company portfolio and pipeline to on growth areas, such as specialty medicines and biologics.

Senior management will examine the scope and details of its Productivity Transformation Initiative, which was begun earlier this year, the company said. Over 300 initiatives have been identified that will enhance efficiency, effectiveness and competitiveness, and cost base.

Productivity initiatives include reducing general and administrative operations by simplifying, standardizing and outsourcing, where appropriate, processes and services, rationalizing the company's mature brands portfolio, consolidating its global manufacturing network while eliminating complexity and enhancing profitability, simplifying its geographic footprint and

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Study Designed To Help Individualize CLL Treatment

(Continued from page 1)

and a primary investigator. "We chose Genzyme to perform the IgVH analysis because of its expertise in molecular testing."

IgVH is an independent prognostic marker, which can segregate all stages of CLL, the company said. Data show that CLL patients with mutations in their IgVH gene have a longer median survival—293 months, than CLL patients without the mutations—117 months. Fifty to 70 percent of CLL patients have evidence of mutations. NCCN recommends IgVH Mutation Analysis for CLL. The assay can be performed on either peripheral blood or bone marrow aspirate. Genzyme said it launched its IgVH mutation analysis test in February.

"CALGB is pleased to partner with Genzyme in this important study that will help to individualize the treatment of CLL," said Richard Schilsky, professor of medicine at the University of Chicago and chairman of the CALGB.

The CALGB study will be open to its affiliate centers in the U.S. as well as the Eastern Cooperative Oncology Group and Southwest Oncology Group.

In another development, **Genzyme Corp**. (NASDAQ:GENZ) of Cambridge, Mass., said it has completed enrollment in a phase II trial of the safety and effectiveness of Clolar (clofarabine) in untreated, older adults with acute myelogenous leukemia who are unlikely to benefit from standard induction therapy.

Treatment consists of an induction cycle of intravenous clofarabine administered as 30mg/m2 per day for five consecutive days then, based on response, receive up to five additional cycles of treatment at a dose of 20 mg/m2 per day for five consecutive days, the company said.

The first stage of the trial required at least 11 responses in the first 59 patients to continue to the second stage of the study. In September, Genzyme said the number of responding patients had exceeded the requirement.

AstraZeneca (NYSE:AZN) of Wilmimgton, Del., said it has completed enrollment in the ZEST (Zactima Efficacy Study versus Tarceva) study, the first of four phase III trials for the oral anti-cancer drug vandetanib.

ZEST is a randomized, double-blind, multi-center 1,150 patient-study to assess the efficacy of vandetanib versus erlotinib in overall survival and progression-free survival with locally-advanced or metastatic non-small cell lung cancer after failure of first-line anti-cancer therapy, the company said.

The other studies, which are recruiting patients, are ZODIAC (vandetanib + docetaxel versus docetaxel alone); ZEAL (vandetanib + pemetrexed versus placebo + pemetrexed); and, ZEPHYR (vandetanib + best supportive care (BSC) versus placebo + BSC), the company said.

The phase III program in NSCLC follows results from two phase II trials where vandetanib was studied either alone or in combination with standard chemotherapy (docetaxel), the company said.

Vandetanib is also being evaluated as a treatment option in medullary thyroid cancer and has been awarded FDA Orphan Drug status and Fast-Track designation for the indication, the company said.

EntreMed Inc. (NASDAQ:ENMD) of Rockville, Md., said it has begun a multi-center phase II trial of MKC-1 in advanced pancreatic cancer.

The primary objectives are to determine the antitumor activity of orally-administered MKC-1 in unresectable or metastatic pancreatic cancer with at least one prior chemotherapy regimen failure, the company said.

The study will also assess the safety, tolerability and overall median survival. Massachusetts General Hospital Cancer Center is the lead institution for the study and Eunice Kwak, assistant in medicine, Tucker

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Gosnell Center for Gastrointestinal Cancers, is principal investigator, the company said.

MKC-1 is an orally-active cell cycle inhibitor with in vitro and in vivo efficacy against solid tumor cell lines, including multi-drug resistant cell lines, the company said.

Genmab A/S (OMX: GEN) of Copenhagen said it has initiated a phase I/II safety and dose finding study of HuMax-CD38 for multiple myeloma.

The 122-patient study will treat multiple myeloma that has relapsed or been refractory to at least two different treatments and has no further established treatment options, the company said.

HuMax-CD38 is a fully human antibody that targets the CD38 molecule expressed on the surface of multiple myeloma tumor cells, the company said.

Nventa Biopharmaceuticals Corp. (TSX: NVN) of San Diego said it has completed enrollment and initiated dosing of the second cohort in its phase I dose escalation trial of HspE7 for cervical dysplasia.

HspE7 is vaccine for human papillomavirus-related diseases, the company said. The cohort has received the first of three immunizations of 500 mcg of the agent with 500 mcg of adjuvant.

United Therapeutics Corp. (NASDAQ:UTHR) of Silver Spring, Md., and its wholly-owned subsidiary, Unither Pharmaceuticals Inc. said they have completed two trials of OvaRex MAb for advanced ovarian cancer.

Preliminary analysis demonstrates that the studies failed to reach statistical significance, the companies said.

The randomized, double-blind, placebo-controlled identical studies, known as IMPACT I and II, Munotherapy Pivotal ovArian Cancer Trial, enrolled 367 patients. The objective was efficacy of the mono-immunotherapy during the period following front-line carboplatin-paclitaxel based chemotherapy, the companies said. The studies demonstrated no difference between active and control populations.

The results of IMPACT I and II were consistent with each other. There were no statistically significant differences in safety profiles and the quality of life between the active and control groups, the companies said.

OvaRex MAb-B43.13 (oregovomab) is one of five investigational immunotherapeutic monoclonal antibodies, which Unither Pharmaceuticals licensed from AltaRex Medical Corp., a wholly-owned subsidiary of ViRexx Medical Corp. Based on preliminary results from the IMPACT trials, Unither Pharmaceuticals said it would terminate the license agreement and intends to cease further development of the entire platform of antibodies.

VION Pharmaceuticals Inc. (Nasdaq Capital Market: VION) said it has begun an investigator-sponsored phase I trial of Cloretazine (VNP40101M) in combination with hematopoietic cell transplant in advanced hematologic malignancies.

The trial is being conducted by Roy Jones, professor, Department of Stem Cell Transplantation, University of Texas M.D. Anderson Cancer Center, the company said.

Trial objective is the maximum tolerated dose of Cloretazine (VNP40101M) when given to 18 to 65 year olds with poor-prognosis leukemia, lymphoma, and Hodgkin's disease who are undergoing either an allogeneic or autologous HCT, the company said.

Deals & Collaborations:

BMS Plans Overhaul To Focus On Productivity

(Continued from page 1)

implementing a more efficient go-to-market model, the company said.

Specific productivity goals include: reducing the number of brands in the company's mature products portfolio by 60 percent between 2007 and 2011; reducing the number of manufacturing facilities by more than 50 percent by the end of 2010; and reducing total headcount by approximately 10 percent between 2007 and 2010, the company said.

Some positions have been eliminated in 2007 and the substantial majority of positions will be eliminated in 2008 and 2009, the company said.

While reducing headcount in certain functions, BMS will continue to invest in R&D, biologics and commercialization talent, the company said.

The company announced that the Board of Directors declared an 11 percent dividend increase, the first increase since 2002. The dividend increase will result in a quarterly dividend of 31 cents per share on the company's Common Stock for an indicative dividend for the full year of 2008 of $1.24 per share, subject to the normal quarterly review by the board. The next quarterly dividend on the $.10 par value Common Stock of the company will be payable on Feb. 1 to stockholders of

record at the close of business on Jan. 4.

The board also declared a quarterly dividend of 50 cents per share on the $2 Convertible Preferred Stock of the corporation, payable March 3 to stockholders of record at the close of business on Feb. 8.

AEterna Zentaris Inc. (NASDAQ: AEZS; TSX: AEZ;) of Quebec City it has completed the sale of all issued and outstanding shares of its wholly-owned Salt Lake City, Utah-based subsidiary, **Echelon Biosciences Inc**., to **Frontier Scientific Inc**.

The transaction represents $3.2 million, including $2.6 million upfront and payable immediately with a $0.6 million in contingent consideration, the company said.

The companies said they address a common life sciences research customer base, which includes pharmaceutical companies and research universities. The companies said they would maintain their facilities in Logan and Salt Lake City and work toward a common senior management structure.

Abeome Corp. of Athens, Ga., and said it has entered into an agreement with **Millipore Corp**. (NYSE: MIL) for Millipore to distribute a monoclonal antibody for stem cell research.

Under the agreement, Millipore is granted an exclusive worldwide license to market and distribute the antibody for research use, the companies said. Abeome received an upfront payment and will also receive royalties on sales by Millipore.

The antibody was developed by Abeome in collaboration with Novocell Inc.

ARIUS Research Inc. (TSX: ARI) of Toronto said it has entered into a manufacturing supply and technology transfer agreement with **Avid Bioservices** for its CD44 Cancer Stem Cell antibody a cGMP manufacturing services for the biotechnology and biopharmaceutical industries provider.

Avid manufactures a supply of the drug for clinical trials, which it plans to initiate next year. ARIUS said it has scheduled a pre-IND meeting with FDA.

ARIUS said it is advancing the formal pre-clinical toxicology program for CD44 Cancer Stem Cell program, an anti-cancer antibody targeting an epitope of CD44 found in breast, colon, and prostate cancers. Pre-clinical data from a dose-ranging pilot toxicology study in non-human primate models demonstrated no dose-limiting toxic effects at doses up to 95 mg/kg and significant tumor growth inhibitory activity in in vivo animal models of breast, prostate, liver, and AML cancers. The CD44 Cancer Stem Cell program was generated using the ARIUS proprietary FunctionFIRST technology, which selects antibodies based on their ability to kill cancer cells, the company said.

Compendia Bioscience Inc. of Ann Arbor, Mich., said it has licensed Oncomine, its compendium of oncology gene expression profiles and analysis tools, to **AstraZeneca** for cancer research programs.

The agreement gives AstraZeneca access to Oncomine Concepts Edition, a value-added product extension of Oncomine that combines 7,000 proprietary cancer gene signatures with 11,000 gene, protein, drug, and pathway signatures collected from public sources, the company said. The Concepts Map application uses gene sets as a common language to compare and link disparate biological concepts.

A study published in Nature Genetics (2007 Jan; 39(1): 41-51) used Oncomine Concepts Map to analyze prostate cancer gene expression in the context of the other gene signatures available in OCM, the company said. The result was an important new model describing the progression of prostate cancer, the company said.

Oncomine combines a compendium of 20,000+ cancer transcriptome profiles with an analysis engine and a Web application for data mining and visualization, the company said.

Exelixis Inc. (NASDAQ:EXEL) of South San Francisco said it would receive a $5 million milestone payment from **Bristol-Myers Squibb** (NYSE:BMY) triggered by an IND application, or foreign equivalent, for a compound discovered and developed under their Liver X Receptor collaboration.

Exelixis and BMS established the collaboration in January 2006 for two years. Under the collaboration, the companies would identify drug candidates that are ready for IND-enabling studies, with BMS then undertaking further preclinical development. BMS also has responsibility for clinical development, regulatory, manufacturing and sales/marketing activities for such compounds. At time of signing, Exelixis said it received a $17.5 million upfront payment and a commitment from BMS to provide R&D funding of $10 million per year for the two year period.

In September, Exelixis said the collaboration had been extended through January 2009. Terms of the extension include additional research funding paid to Exelixis in the amount of $7.5 million.

Fate Therapeutics of Seattle, announced its formation by a group of stem cell scientists from Harvard University, Stanford University, University of Washington, the Scripps Research Institute, and Massachusetts General Hospital, in partnership with investor groups.

The company plans to develop drugs to modulate adult stem cells.

"We are proving that adult stem cell proliferation and differentiation can be modulated in the human body, and we now have the ability to induce pluripotent stem cells from adult human tissue rather than relying on the use of stem cells derived from embryos," said Ben Shapiro, retired executive vice president of Worldwide Basic Research, Merck Research Labs., and a member of the Fate Therapeutics science advisory board.

The company said it expects to have a lead adult stem cell modulating drug, in a cancer-related indication, enter the clinic in 2008.

The Fate Therapeutic platform is two-fold, the company said. It focuses on both regenerative and reprogramming medicine, the company said. The regenerative medicine platform involves developing drugs that awaken adult stem cells to repair damaged cells and tissues. The reprogramming medicine platform involves developing drugs to reprogram mature adult cells into stem cells which when differentiated can become healthy heart, bone, brain or other tissues.

Applications of the two approaches include treating the effects of neurological diseases such as Down syndrome, Alzheimer's and Parkinson's; healing damaged heart tissue after heart attacks; increasing bone and muscle strength in the severely frail; and protecting organs after infection or transplantation, the company said. Fate said it will also tackle cancers, such as pancreatic and colorectal cancer, by developing drugs to prevent the expansion and maturation of cancer stem cells.

Fate said it has a different approach from others working with stem cells. The company said it focuses exclusively on traditional therapeutics, namely small molecules and protein therapeutics, to direct cell fate. In addition, the work has application across all degenerative diseases, developmental disorders and cancers, and in enabling the creation of healthy patient-identical cells for transplantation.

Fate founders include researchers from multiple scientific disciplines, including basic biology, biological chemistry and translational medicine: Philip Beachy, Stanford University Institute for Stem Cell Biology and Regenerative Medicine and HHMI; Sheng Ding, Scripps Research Institute; Randall Moon, University of Washington, director, Institute for Stem Cell and Regenerative Medicine, HHMI, and UW Department of Pharmacology; David Scadden, Harvard University, co-director and co-founder, Harvard Stem Cell Institute, director Massachusetts General Hospital Center for Regenerative Medicine, Leonard Zon, Harvard University, director, Stem Cell Program, Children's Hospital of Boston, and HHMI.

Fate Therapeutics has additional stem cell scientists, research leaders, and drug development experts on its scientific advisory board: Robert Langer, Institute Professor of Chemical and Biomedical Engineering, Massachusetts Institute of Technology; Ram Sasisekharan, professor of biological engineering and health sciences and technology, Massachusetts Institute of Technology; Ben Shapiro, retired executive vice president of worldwide basic research, Merck Research Laboratories.

The investment team includes venture capital firms ARCH Venture Partners, Polaris Venture Partners, Venrock and OVP. The syndicate group has a combined $7 billion under management, the company said.

Fate Therapeutics was co-founded by Alex Rives, of ARCH Venture Partners. The board of directors includes Amir Nashat, general partner, Polaris Venture Partners; Robert Nelsen, co-founder and managing director, ARCH Venture Partners; and Bryan Roberts, managing general partner, Venrock.

GlaxoSmithKline of Redwood City, Calif., and **OncoMed Pharmaceuticals** of London said they have entered into a worldwide strategic alliance to discover, develop and market antibody therapeutics to target cancer stem cells.

The alliance with GSK will be conducted through its Center of Excellence for External Drug Discovery, the companies said.

The alliance leverages the OncoMed knowledge of cancer stem cell antibody therapeutics and provides GSK with an option to license four product candidates directed at multiple cancer stem cell targets from the OncoMed library of monoclonal antibodies, the companies said. OncoMed will receive an undisclosed initial payment comprised of cash as well as an equity investment. OncoMed is eligible to earn milestone payments up to $1.4 billion from GSK based on the achievement of specified discovery, development, regulatory and commercial milestones. OncoMed will also receive double-digit royalties on all collaboration product sales. GSK will have an option to invest in a

future initial public offering by OncoMed.

OncoMed would use its in vivo xenograft cancer stem cell models to identify monoclonal antibodies in a cancer stem cell pathway. Upon the OncoMed achievement of clinical proof of concept in an agreed indication, GSK will have an exclusive option to license such monoclonal antibody. GSK would then assume responsibility for funding of further clinical development and commercialization on a worldwide basis.

Caris Diagnostics of Irving, Tx, said it has entered into a definitive agreement to combine with **Molecular Profiling Institute Inc**. of Phoenix and its subsidiary, the Tissue Banking and Analysis Center Inc., to develop and commercialize molecular diagnostic tests based for genomic and proteomic profiling.

MPI is a specialty reference laboratory that applies the discoveries of the Human Genome Project to personalized medicine. The company provides testing facilities, prognostic testing services, and resources for genomic and proteomic profiling for cancer treatment.

Through its Tissue Banking and Analysis Center, MPI also has biospecimen procurement, storage, tracking, analysis, and reporting for research institutes, pharmaceutical and diagnostic companies, and medical centers, the company said.

Panacea Pharmaceuticals Inc. of Gaithersburg, Md., said it has developed PAN-622, a fully human sequence monoclonal antibody against HAAH, in collaboration with Massachusetts Institute of Technology.

PAN-622 would have fewer adverse effects compared to chimeric or humanized monoclonal antibodies, the company said. Clinical trials with the agent should begin in early 2009.

Human Aspartyl (Asparaginyl) Beta-Hydroxylase is an enzyme that modulates signaling factors such as Notch, and is over-expressed in malignant cells, the company said. When HAAH expression is silenced or its enzymatic activity is neutralized on the cell surface, the cancer cells revert to a normal phenotype.

Raven Biotechnologies Inc., of South San Francisco said **Wyeth Pharmaceuticals**, a division of Wyeth (NYSE:WYE), has exercised an option to extend its evaluation of selected Raven MAb antibodies.

As a result of the option, Raven said it would receive an undisclosed milestone payment.

The antibodies included in the agreement were discovered using Raven proprietary immunization technology and tumor-derived stem-cell lines and were screened to select antibodies that are active alone or in a conjugated form, the company said.

Starpharma Holdings Ltd. (ASX: SPL; Pink Sheets: SPHRY) of Melbourne, Australia, said it has signed a collaborative research agreement with **Stiefel Laboratories Inc**., to apply the Starpharma dendrimer nanotechnology to drugs used dermally.

Translational Genomics Research Institute of Sunnyvale, Calif., said it is using technology from SGI (NASDAQ:SGIC) to analyze molecular profile data sets for cancer research.

Purchased through an NIH grant, the SGI Altix 4700 assists TGen in genomic variation—a process that requires comparison searches of enormous data sets—used to individualize diagnosis and treatment.

The system will be housed at Arizona State University in Tempe with operational support provided by the ASU Fulton High Performance Computing Initiative, the company said.

Wellness Community and **Lance Armstrong Foundation** are collaborating in Live Well! Life Beyond Cancer Program that facilitates the transition for cancer survivors from active treatment to post-treatment care.

"The program provides information, skills and tools to address exercise, nutrition, emotional health, quality of life and medical management after treatment ends," said Mitch Golant, senior vice president of The Wellness Community. "Together with the Lance Armstrong Foundation, we are poised to develop a state-of-the-art, evidence-based survivorship program that helps fill the gap between cancer treatment and life beyond cancer."

The free program will be offered in 10 cities and will be held for two and one-half hours once a week for six weeks. For more information: http://www.thewellnesscommunity.org/.

In another development, the Lance Armstrong Foundation awarded $1.5 million to community-based cancer survivorship initiatives across the country.

The grant funding includes $1.4 million to 15 community-based non-profit organizations for cancer survivorship programs and $162,000 to six cancer survivorship community-based participatory research projects.

ICx Technologies (NASDAQ:ICXT) of

Washington and La Jolla, Calif., a developer of advanced technology solutions for homeland security and force protection, said it is working on a research study with **Merck & Co. Inc**. and **Fred Hutchinson Cancer Research Center**.

The study would test and refine a set of protocols for detecting and recovering circulating nucleic acids from blood to support the development of an investigational cancer therapy. The study is being conducted by its La Jolla, Calif.-based Biosystems unit with participation by the Hutchinson Center, the company said.

Innovex of Bracknell, U.K., said it has entered into a services agreement with **PharmaMar**, a subsidiary of Zeltia SA, to create an oncology sales team in Western Europe to promote Yondelis, the PharmaMar treatment for soft tissue sarcoma.

PharmaMar, which holds the marketing authorization, will be responsible for marketing the drug, the company said.

Biocept of San Diego said it is initiating a collaborative study with the **University of Texas M.D. Anderson Cancer Center** to investigate the ability to isolate circulating tumor cells in blood.

The study will use the Biocept proprietary Cell Enrichment and Extraction technology, designed to capture rare cells from a larger heterogeneous cell population for treatment of ovarian cancer, the company said.

Product Approvals & Applications:

Cephalon's Treanda Granted Priority Review By FDA

Cephalon Inc. (Nasdaq: CEPH) of Frazer, Pa., said FDA accepted and granted priority review designation to the New Drug Application for Treanda (bendamustine HCl) in chronic lymphocytic leukemia.

Cephalon said an FDA review decision would occur by the end March.

FDA granted Orphan Drug status for the drug in CLL in August 2007, which would entitle the company to a seven-year period of marketing exclusivity in the U.S, if approval is granted.

Treanda is a rationally designed purine analog/ alkylator hybrid, the company said. Preclinical data demonstrate the hybrid acts in two ways to kill cancer cells: by damaging the DNA which leads to apoptosis and stops cancer cells from dividing to create new cancer cells.

The Treanda NDA for CLL is based on a large, international multi-center phase III trial that evaluated the safety and efficacy of bendamustine HCl, the active ingredient in Treanda, compared to chlorambucil in an untreated group, the company said. Chlorambucil, a chemotherapy drug, is FDA-approved as a first-line therapy for CLL. In the trial, bendamustine HCl met both primary endpoints—overall response rate and progression-free survival--and demonstrated a manageable tolerability profile. The company anticipates that results from this study will be released at the upcoming American Society of Hematology annual meeting in December 2007.

Celldex Therapeutics of Phillipsburg, N.J., said FDA has granted Orphan Drug designation to CDX-110 for EGFRvIII expressing glioblastoma multiforme.

CDX-110 is an immunotherapy that targets the tumor-specific growth promoter EGFRvIII, the company said.

Celldex also said it reached a definitive merger agreement with AVANT Immunotherapeutics Inc. (NASDAQ:AVAN) in October.

Cephalon Inc. (NASDAQ:CEPH) of Frazer, Pa., said FDA has accepted and granted priority review designation to the Treanda (bendamustine HCl) New Drug Application for the first-line treatment of chronic lymphocytic leukemia.

Treanda is a rationally designed purine analog/ alkylator hybrid. The Treanda NDA is based on a multi-center phase III trial that evaluated the safety and efficacy of bendamustine HCl, the active ingredient in Treanda, compared to chlorambucil where no treatment had taken place, the company said. Bendamustine HCl met both primary endpoints—overall response rate and progression-free survival—and demonstrated a manageable tolerability profile.

Medarex Inc. (NASDAQ:MEDX) of Princeton, N.J., said it has filed the allowance of two separate investigational new drug applications with FDA for MDX-1342, one for chronic lymphocytic leukemia and the other for rheumatoid arthritis.

MDX-1342 is a fully human antibody that targets CD19, a molecule expressed on normal B-cells and malignant B-cells in diseases such as CLL, acute lymphoblastic leukemia, follicular non-Hodgkins lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma, the company said.

Oncology Management:

Health Plans To Reward Participation In QOPI

American Society of Clinical Oncology said it is collaborating with participating health benefits companies and associations, including Aetna, Blue Cross Blue Shield Association, UnitedHealthcare, WellPoint, Wellmark Blue Cross and Blue Shield of Iowa and Wellmark Blue Cross and Blue Shield of South Dakota, to recognize physicians who participate in the ASCO Quality Oncology Practice Initiative, an oncologist-led, practice-based quality improvement program.

"It's important for ASCO members to see that health plans across the country value their ongoing efforts to improve the care they deliver to their patients daily," said Nancy Davidson, president of ASCO and director of the Breast Cancer Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. "The QOPI Health Plan Program is an important step in promoting oncologists' commitment to quality."

The program adds to the benefits of QOPI participation. "The QOPI primary programmatic goal is to provide a defined methodology, measures and system for quality improvement within the oncology practice," said Joseph Simone, chairman of the ASCO QOPI Subcommittee. "Through the program, ASCO offers its members a way to self-assess and continually improve."

Practices that devote the time and resources to abstract medical records and submit de-identified data to the central QOPI database are rewarded with detailed reports that compare their own practice with the QOPI aggregate. The reports provide the basis for data-driven improvement efforts, the group said.

For this reason, ASCO said it has promoted the use of QOPI participation and data for multiple purposes since the program's open enrollment began in 2006, including for continuing medical education credit and the practice performance requirement for maintenance of certification by the American Board of Internal Medicine. The QOPI Health Plan Program adds value for QOPI participants by allowing recognition by health plans and seeks to reduce competing data collection programs initiated by plans.

Health plans have acknowledged the QOPI quality improvement and additional plans are expected to join the program in 2008, said ASCO. The health plans will recognize physicians that participate in the QOPI program through a method or initiative that each deems appropriate, such as including a special designation for QOPI participants in physician directories or providing financial incentives for participating.

"Blue Cross Blue Shield Association supports collaboration with medical specialty societies that have established meaningful quality measures, and our organization believes it is important to recognize physicians who are committed to quality improvement and who participate in the QOPI program," said Carole Redding Flamm, executive medical director for Blue Cross Blue Shield Association.

"The establishment of QOPI illustrates the important commitment that ASCO and its members have made to promote quality care for patients with cancer," said Sam Nussbaum, executive vice president and chief medical officer of WellPoint. "Collaborations between health benefits companies and specialty societies on initiatives such as QOPI will encourage an environment that brings to patient care continuous scientific advancement in the practice of clinical oncology."

Ultimately, "engaging physician leadership is a crucial step in improving quality of care for patients," Simone said. "QOPI enables oncologists to set meaningful standards of quality cancer care, learn from one another, and build improvement resources. Health plan recognition of these activities will be an important force in the QOPI ongoing growth and development."

Oncology practices seeking more information about the QOPI Health Plan Program can phone 703-519-2943 or email qopi@asco.org.

US Oncology of Houston said it has named Glen Laschober executive vice president and CEO effective Jan. 2.

"Glen's Fortune 500 operating experience, combined with his work in large diversified healthcare organizations, greatly strengthens our existing operating team," said Bruce Broussard, president of US Oncology. "His proven success in working with physicians and healthcare professionals, in areas such as care management programs, process efficiency and leadership development, will accelerate the implementation of our initiatives, such as Practice and Quality Efficiency and Comprehensive Disease Management, including Cancer Care Pathways."

Laschober was CEO for Omnicare, a Fortune 500 healthcare company with revenues of $6.5 billion, the company said. He has also been executive operating officer at CVS, Provantage, and Caremark. Laschober will be based at headquarters in Houston.