THE CANCER LETTER

Vol. 35 No. 36
Oct. 2, 2009

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A Biostatistic Paper Alleges Potential Harm To Patients In Two Duke Clinical Studies

By Paul Goldberg

Biostatistics journals aren't usually the place to go for sensational allegations. The most recent issue of the Annals of Applied Statistics is an exception.

A paper published on this journal's website alleges that cancer patients may be harmed by being placed on two Duke University clinical trials that rely on biomarkers to select therapies.

The paper is the culmination of efforts by Keith Baggerly and Kevin Coombes, biostatisticians at M.D. Anderson Cancer Center, to verify the work by a group of Duke researchers led by Anil Potti and Joseph Nevins.

In multiple publications, the Duke team has claimed that microarray

(Continued to page 2)

NIH News:

President Obama Visits NIH To Announce 12,000 Recovery Act Grants Worth $5 Billion

By Kirsten Boyd Goldberg

President Barack Obama visited the NIH campus in Bethesda, Md., on Sept. 30 to announce that the institutes have awarded more than 12,000 grants totaling $5 billion, about half of the $10.4 billion allocated to NIH in the American Recovery and Reinvestment Act.

Obama toured the campus with NIH Director Francis Collins, who took office just six weeks ago, and Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases. He then made brief remarks to NIH leaders in Masur Auditorium.

"We know that these investments in research will improve and save countless lives for generations to come," Obama said. "And as I was taking a tour with Dr. Collins and Dr. Fauci and others, just listening to the possibility of a HIV/AIDS vaccine, or hearing the latest treatments of cancer that allow people who previously only had resort to the most violent types of radiation or chemotherapy, now being able to take pills and seeing extraordinary progress, it is something that is entirely inspiring.

"But we also know that these investments will save jobs, they'll create new jobs—tens of thousands of jobs—conducting research, and manufacturing and supplying medical equipment, and building and modernizing laboratories and research facilities all across America," Obama said. "And that's also what the Recovery Act is all about. It's not just about creating make-work

(Continued to page 5)

Duke Team Acknowledges "Clerical Errors" In Research

(Continued from page 1)

analysis of patients' tumors can be used to predict their response to chemotherapy.

Baggerly and Coombes started their efforts to check these claims after oncologists at M.D. Anderson asked whether the approach was ready for use in the clinic.

Practicing a subspecialty they call "forensic bioinformatics," Baggerly and Coombes found that the Duke team has made multiple errors. Over the past three years, they have been documenting these errors and presenting critiques to journals that have published papers by the Duke team.

One example was an "off-by-one" error, where gene probe identifications were mismatched with the names of genes. Columns were literally off by one space, which rendered a table meaningless. The Duke group acknowledged this mistake and others in a letter published in the November 2007 issue of Nature Medicine.

Last week, Baggerly and Coombes published a paper that delivered their strongest allegation thus far. "Unfortunately, poor documentation can shift from an inconvenience to an active danger when it obscures not just methods but errors," Baggerly and Coombes wrote in the Annals of Applied Statistics. "Patients in clinical trials are currently being allocated to treatment arms based on these results. However, we show in five case studies that the results incorporate several simple errors that may be putting patients at risk."

The paper is posted at http://www.imstat.org/aoas/next_issue.html.

Duke researchers say that their errors were minor and had no bearing on their findings. "We stand by our work," said Potti, a medical oncologist and an assistant professor at Duke. "Yes, we have made mistakes, and, actually, we've learned from those mistakes. Because we recognized that the mistakes were manual mistakes—mistakes of cut-and-paste—we have automated the entire process."

In the Duke clinical studies, "there is no manual error possibility," Potti said in an interview.

The trials in question are:

• A 270-patient randomized phase II study that uses genomic expression profiling to assign preoperative systemic therapy with doxorubicin/cyclophosphamide or docetaxel/cyclophosphamide for HER2 negative early stage breast cancer to compare responses in genomically guided versus random assignment and validate chemosensitivity prediction signatures. A description of this study, which is co-sponsored by Duke and the Department of Defense, is posted at http://clinicaltrials.gov/ct2/show/NCT00636441?term=Potti&rank=3.

• A 100-patient randomized phase II study that uses a genomic predictor of platinum resistance to guide therapy in stage IIIB/IV non-small cell lung cancer. The study is co-sponsored by Duke and Eli Lilly, the sponsor of Alimta (pemetrexed), a drug that would be given to patients shown to be resistant to platinum. A description of the study appears at http://clinicaltrials.gov/ct2/show/NCT00509366.

Reliance on biomarker tests to determine the course of treatment has emerged as a principal challenge in "personalized medicine." Though oncology experts universally acknowledge that an unreliable test can be as harmful as a bad drug, validation of claims in this area is exceedingly difficult. Baggerly estimates that over the past three years, he and collaborators have devoted over 1,500 hours to the project. Much of this time was uncompensated, he said.

Fact-checking was feasible only because Duke researchers relied on a collection of publicly available cell lines maintained by NCI, and because Potti and Nevins posted their in-house software on their website. Had proprietary cell lines or proprietary software been used, verification would have been impossible.

"This has focused my attention on the need for reproducibility in high-throughput biology," Baggerly said. "The thing that has been scary to me is the amount

THE CANCER LETTER

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Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial: 202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Subscriptions/Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
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of effort required to reconstruct what must have been done. That's forensic bioinformatics."

Duke Team Stands By Results

The Annals of Applied Statistics invited the Duke researchers to respond to the Baggerly and Coombes paper in writing, but they declined.

"Our intent is to respond in the form of another publication of our own, in which we lay out the process we are using in the trials—because it does involve a certain refinement of methodology—and in the context of that, a demonstration of the performance of the predictors in that context," said Nevins, the Barbara Levine University Professor of Breast Cancer Genomics at Duke.

"Rather than continuing a back-and-forth with these investigators, the scientific community is better served by an ability of us to lay it out in a much more detailed way," Nevins said. "Doing this in the context of the trial in a sense forces you to really address the standardization methods."

Nevins said he accepts responsibility for what he describes as "confusion" about the methods used by the team.

"I think there is confusion based on some of those errors in how the data was presented and how the methodology was described," Nevins said. He characterized the off-by-one error as "an unfortunate mistake."

"I am not saying that it's trivial, but it's a clerical error," Nevins said. "It doesn't affect how that group of probe sets from the microarray actually performs."

Potti and Nevins argue that reliance on their technology to allocate patients to treatment in the two Duke trials is appropriate because in all cases these patients would be receiving standard treatment.

"We are not assigning patients to some novel therapy," Potti said. "Within standards of care, it's reasonable to test biomarkers, and that should be the initial starting point for biomarkers."

Recently, NCI took a different view, nixing the proposal by a cooperative group—Cancer and Leukemia Group B—to use the Duke technology to stratify patients for therapies in a different trial. A proposal for another CALGB trial relying on Duke technology is under review by that group and NCI, CALGB officials said.

Nevins said the Duke results have been confirmed by researchers at the European Organization for Research and Treatment of Cancer and were published by Lancet Oncology in December 2007.

"Data was made available to us, blinded," Nevins said. "All we got was the gene expression data. We ran the predictions and sent it back to the EORTC investigators, including the statisticians in the EORTC group.

"They took the results, analyzed it in the context of the clinical responses in that study, and did further analyses with respect to evaluating developing combined probability measures. Even if you just look at the predictions for single agents in that study that came from our predictions—that was completely blinded to us—there is a clear ability to predict in the two arms of the trial with the individual predictors."

The EORTC publication falls short of validation of the Duke result, Baggerly objects. "We have tried to reproduce the results of the EORTC paper as well, and we can't do it," he said.

Duke officials said they are looking into the allegations in the Baggerly and Coombes paper.

"The information from the recent online publication by Baggerly et al. was communicated to the Duke Cancer Center Protocol Review Committee, the Deans Office, the Duke IRB, and the Duke investigators who will use the information to review and consider the appropriate next steps for the trials cited," said H. Kim Lyerly, director of Duke Comprehensive Cancer Center.

Central Question In "Personalized Medicine"

"The systematic errors highlighted by Baggerly reflect inattention to detail by the authors," said David Beer, professor of surgery and radiation oncology at the University of Michigan, who had also tried unsuccessfully to replicate the Duke group's data on prognostic signatures of lung cancer.

"While some could be excused, the extent of these errors is truly disturbing," Beer said. "I have to agree that the methods this group used are in question, given that Baggerly's analyses found them to predict at levels no better than chance. Basing a clinical trial and treating patients using this data, and given the concerns they raise, is extremely risky. The authors and funding agencies must be held accountable."

Joe Gray, professor of laboratory medicine and radiation oncology at the University of California, San Francisco, and director of the Division of Life Sciences at Lawrence Berkeley National Laboratory, said the Baggerly and Coombes paper raises the important issue of the weight of evidence needed to justify selecting patients based on markers developed from preclinical data.

"The potential advantages of patient selection based on preclinical data are reduced trials cost and time,

increased probability of finding drugs that are effective against small subpopulations and avoidance of treating patients with potentially toxic therapies that will not benefit the patient," Gray said. "However, the utility of markers based on preclinical studies model systems are always determined by the accuracy with which the models reflect the biology of the tumor and patient and the accuracy of the analytical methods used to support marker selection.

"The Baggerly and Coombes analysis raises the important issue of how a regulatory process should be developed to evaluate the weight of preclinical data before initiating marker guided clinical trials," Gray said. "This important issue should be debated and resolved by the basic and clinical scientists and patient communities in the near future to provide a basis for proper and ethical execution of the growing number of marker guided trials that are now planned. I think the community will welcome continued discussions of the processes required to overcome the challenges in delivering on the promise of personalized medicine."

NCI has funded much of the Duke team's work. An NIH database shows that group investigators have at least three ongoing R01 grants. Also, the institute has been involved in reviewing proposed clinical trials of the technology.

Recently, CALGB and Duke proposed launching a study in which stage I non-small-cell lung cancer patients would receive adjuvant chemotherapy if the Duke test, called Metagene, showed them to be at high risk of recurrence.

However, the institute decided against that design, mandating instead that all patients be randomized to chemo versus observation regardless of test result. With this design, the patient's biomarker score doesn't determine the treatment decision. The trial's description is posted at http://clinicaltrials.gov/ct2/results?term=CALGB+30506.

"We are not using it to make any clinical decision, and since we are not making any clinical decision, we are not telling the patient what the score shows, because we don't know if it's accurate," said Richard Schilsky, CALGB chairman. "They are getting randomized to standard adjuvant vs. observation. Neither patient nor physician is informed about the score."

In stage I lung cancer, observation is the standard of care. "Now we are testing to see whether giving adjuvant chemotherapy is beneficial, just as it seems to be beneficial with patients with stages Ib and II non-small-cell," Schilsky said.

Schilsky said NCI and CALGB are reviewing a proposal for a randomized phase II trial in which patients would be randomized to standard chemotherapy or having their therapy selected using the Duke technology.

In principle, Schilsky agrees with the idea that biomarkers can be used in studies to assign patients to established therapies. In lung cancer, "there are at least four or five accepted standard combination chemotherapy regimens, four of which were compared head-to-head in an Eastern Cooperative Oncology Group trial that showed no difference between them," Schilsky said. "One could reasonably argue that any one of those regimens could be an appropriate treatment for patients with non-small-cell lung cancer."

However, the test has to be scientifically valid, said Schilsky, who hasn't read the Baggerly and Coombes paper.

"Obviously—for any kind of a test—if the test is not performed properly, it's potentially dangerous to patients," he said. "And if there were any problems with these results as they originally reported them, I can only assume that as they go forward that they will correct whatever problems existed.

"In the CALGB study, we will not go forward unless we and NCI together have concluded that the methods of the test they are proposing to use are valid," Schilsky said.

"That's part of what the ongoing review is about."

Baggerly Warns of Patient Harm

The Baggerly and Coombes paper relies on "case studies" to present a critique of the Duke data. The Cancer Letter asked Baggerly to summarize these concerns as they relate to the two Duke trials.

His comments follow:

• Breast cancer trial in which patients are being allocated to either docetaxel or doxorubicin in one arm based on genomic signatures:

In assembling and testing a predictive model, some of the most important things to keep straight are the labels indicating whether the samples are really sensitive or resistant.

In the training data, these labels determine which direction the prediction will go, and in the test data, these labels determine the accuracy that will be assessed and reported.

Changing labels in the training set could potentially put patients at risk, because that could lead the model to predict that a resistant patient will be responsive and vice versa. In the only numeric data ever posted for docetaxel

and doxorubicin (posted in November 2007, removed in August 2008), all of the training data labels were reversed, so the predictions should be actively wrong.

But they reported good predictive accuracy. One reason that may explain part of why the predictions look good is that the labels of samples used to test the models were not reversed but rather "scrambled."

Some test samples were included more than once (giving them inappropriate weights), in some replicated cases the same sample was labeled both sensitive and resistant, and in other cases the labels were simply wrong.

This is not just a few samples; our best estimates suggest that slightly less than half of the data labels are wrong. Such scrambling (which was also present in new test data posted in Aug 08) can easily alter assessments of predictive accuracy from poor to good.

• Cisplatin/pemetrexed lung cancer study in which all patients are being allocated to treatments based on the genomic signature for cisplatin:

In building a predictive model, we also need to select the right genes. If we incorrectly include "noise" genes, this will bring our performance closer to simply flipping a coin. If we incorrectly include "important" genes, however, this will affect the predictions and could potentially harm patients either now or later.

If they are included with the wrong sign, we'll allocate more of our current patients to the actively wrong treatment, putting them at risk. If they are included with the right sign, this will incorrectly make the method look better than it is, causing us to trust it more with later patients and putting them at risk.

In the trial involving pemetrexed and cisplatin, the training data labels (i.e., which samples are sensitive or resistant) are reversed for pemetrexed, which could potentially put patients at risk as in the breast cancer trial described above. However, treatment allocation is apparently being made solely on the basis of the signature for cisplatin, where the training labels are not reversed and where they note that the signature includes ERCC1 and ERCC4, which are known to be important.

Unfortunately, all of the genes they have reported for the cisplatin signature are wrong. For all but four genes, the names are "off by one" from those that should have been used, meaning in essence that they're looking at the wrong row of the data. The other four aren't produced by their software because they don't significantly predict the training data; these four include ERCC1, ERCC4, ERCC1 (a second measurement), and FANCM. The last two of these aren't even measured by the type of arrays used. Thus, the genes are wholly incorrect, mostly noise, but a few important (where we don't know the sign).

NIH News:

Collins: NIH "Grateful For A President Who Values Science"

(Continued from page 1)

jobs; it's about creating jobs that will make a lasting difference for our future."

Obama said the funds will expand the Cancer Genome Atlas project and explore environmental factors that cause cancer.

"This represents the single largest boost to biomedical research in history," Obama said. "One of the most exciting areas of research to move forward as a result of this investment will be in applying what scientists have learned through the Human Genome Project to help us understand, prevent, and treat various forms of cancer, heart disease, and autism.

"In cancer, we're beginning to see treatments based on our knowledge of genetic changes that cause the disease and the genetic predispositions that many of us carry that make us more susceptible to the disease," Obama said. "But we've only scratched the surface of these kinds of treatments, because we've only begun to understand the relationship between our environment and genetics in causing and promoting cancer."

Of the 12,000 grants, more than 1,800 were awarded to investigators who have never previously held a "major NIH grant," Collins said. "We are very grateful at NIH to have a president who values science, who respects its independence, and who understands its huge potential for improving American lives."

Tyler Jacks, president of the American Association for Cancer Research, said the stimulus funding is important, but without sustained funding for NIH, the full potential of this investment will not be realized.

"In today's speech, the president emphatically reiterated his commitment to supporting science and technology for biomedical research in general and for cancer in particular," said Jacks, director of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. "President Obama is correct in saying that our leaders have not supported science adequately in the recent past. The overwhelming number of grant applications submitted in response to the stimulus funding is a clear indication that there is no shortage of good ideas in America and that with proper funding, powerful new approaches to

understanding and controlling cancer can be brought to bear.

"The stimulus funding is indeed a windfall for the research community and it is very much appreciated, but we look to the administration to deliver on its promise to provide increased investment in biomedical research over the long term," Jacks said. "Only in this way can we ensure that the United States remains the world's leader in scientific breakthroughs and discovery."

Video of Obama's visit to NIH is available at http://videocast.nih.gov/.

The full text of Obama's speech is available at http://www.whitehouse.gov/the_press_office/Remarks-by-the-President-on-the-American-Recovery-and-Reinvestment-Act-at-the-National-Institutes-of-Health/.

In the Cancer Centers:

USC Wins $10M NCI Grant To Collect Epigenomic Data

UNIVERSITY OF SOUTHERN CALIFORNIA Epigenome Center was awarded a $10.4 million NCI grant to fund a collaborative effort with Johns Hopkins University to collect epigenomic data from all major types of cancer over the next five years. The funds come from the the $787 billion economic stimulus package. The epigenomic data collected will contribute to The Cancer Genome Atlas, a long-term genome characterization and sequencing project funded by NCI and National Human Genome Research Institute. The project is designed to provide a comprehensive "map" of molecular changes in cancer. Principal investigators are **Peter Laird**, USC Epigenome Center director, and **Stephen Baylin**, of Johns Hopkins. "The Cancer Genome Atlas will look at as many as 500 different samples of tumors and tissues from each cancer type to map the diversity of molecular changes within and between the different types of cancer," said **Peter Jones**, director, USC Norris Comprehensive Cancer Center and co-investigator on the grant. "It's a huge operation and a wonderful boost to our cancer research program." . . . **UNIVERSITY OF COLORADO CANCER CENTER** researchers received a $900,000, two-year NIH Challenge Grant to create new validated thyroid cancer cell lines and validate that currently used cell lines are thyroid cancer. **Bryan Haugen**, head of the Division of Endocrinology and professor of medicine and pathology at the University of Colorado Denver School of Medicine, is the grant's principal investigator. He will collaborate with **Rebecca Schweppe**, assistant professor of medicine at UCD SOM, and two thyroid cancer researchers from Memorial Sloan-Kettering Cancer Center in New York: **Jim Fagin** and **Jeff Knauf**. Haugen and Schweppe in December published a paper that described a rampant problem with contamination in thyroid cancer cell lines used in research labs around the world. This grant comes as a solution to that problem: make new validated thyroid cancer cell lines and validate existing cell lines. . . . **OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER** received a five-year, $11.5 million NCI Specialized Program of Research Excellence (SPORE) grant to study and treat leukemia. The SPORE grant represents a milestone for the leukemia program at OSUCCC-James, which is only the second recipient of such an NCI grant directed at leukemia research. Principal investigator **John Byrd** and co-principal investigators **Clara Bloomfield** and **Guido Marcucci** will lead a team of senior investigators who have worked together for years to improve prognostic factors and treatments for acute and chronic leukemias. "This prestigious award will help an extraordinary team of accomplished cancer researchers at Ohio State's Comprehensive Cancer Center engage in bedside and laboratory translational research of adult leukemia with the ultimate goal of improving clinical outcomes for patients," said **Michael Caligiuri**, director of the cancer center. The SPORE grant supports five research projects, each led by Ohio State cancer center researchers including Byrd, Bloomfield, Caligiuri, Marcucci, Albert de la Chapelle, William Blum, Michael Grever, and Robert Lee. Also, the grant will support five cores that will provide a SPORE leukemia tissue bank and services for biostatistics, biomedical informatics, medicinal chemistry and administration and operations. The SPORE grant also supports a career development program geared toward young women and minority researchers, and a developmental research program to recruit innovative pilot projects that, if successful, may later become part of the SPORE. In other news at the center, the Ohio State University Board of Trustees approved architecture and construction plans for an expansion project that will add almost 100 beds to the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. The $1 billion investment will transform Ohio State University Medical Center's central campus and will include a centralized single tower design that will house a new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (The James), along with a new critical care building and integrated spaces for research, education and patient care. . . . **FADLO KHURI** was named deputy director of the Emory

Winship Cancer Institute. Khuri, a Georgia Cancer Coalition Distinguished Scholar, is chairman of Emory's Department of Hematology and Medical Oncology and will retain those duties. "Dr. Khuri is internationally respected for his groundbreaking research into lung and head and neck cancers," said **Walter Curran**, executive director of Emory Winship. "He is a tremendously dedicated physician investigator who believes deeply in working with his patients and their loved ones to ensure they are receiving the very best care." Khuri also holds the Roberto C. Goizueta Distinguished Chair for Cancer Research and is professor of otolaryngology, medicine, and pharmacology and serves as director of the Emory Winship Cancer Institute's scientific program known as Discovery and Developmental Therapeutics. Khuri's research interests include development of molecular, prognostic, therapeutic and chemopreventive approaches to improve the standard of care for patients with tobacco-related cancers. His research team is investigating how to inhibit cellular signal transduction in lung and head and neck cancers. . . . **EMORY WINSHIP CANCER INSTITUTE** received a $1 million grant from the Centers for Disease Control and Prevention to study health disparities and informed decision-making among prostate cancer patients. **Theresa Gillespie**, associate professor, Department of Surgery and the Emory Winship Cancer Institute, is principal investigator of the multi-site, national study based at Emory. Other members of the study team include: **Joseph Lipscomb**, Health Policy and Management, Rollins School of Public Health; **Michael Goodman**, Epidemiology, Rollins School of Public Health; **John Petros**, Department of Urology, Emory School of Medicine; and **Katharina Echt**, Department of Geriatrics & Gerontology, Emory School of Medicine. **Kevin Ward**, will direct the Emory Winship shared core resource support in data management. In other new at Emory University Hospital, the Department of Radiation Oncology has earned provisional full membership in the Radiation Therapy Oncology Group, an NCI-supported cooperative group conducting large multi-center clinical trials. RTOG has been continuously funded by the NCI for over 40 years, and Emory joins 28 American and seven Canadian institutions who constitute the group's full member roster. Emory is the first institution in the U.S. in more than in three years to be granted this designation. The provisional full membership enables the Emory Winship Cancer Institute to establish affiliate members across the U.S. and Canada. Affiliate members play an important role because clinical researchers are able to accrue patients from a wide geographic and demographic spectrum and more patients have an opportunity to participate in clinical trials. "The benefit to patients is increased access to new investigational therapies and the absolute highest standard of care, which are established by the NCI and other federal agencies," said Walter Curran, who has served as RTOG group chairman for the past 12 years. "We will work with the Georgia Cancer Coalition and the Georgia Center for Oncology Research and Education to expand the availability of RTOG trials throughout the state of Georgia." . . . **UMDNJ-NEW JERSEY** Medical School associate professor of medicine **Robert Wieder** received two state and federal grants to enhance the clinical trials program at the New Jersey Medical School/University Hospital Cancer Center. An NCI grant provides $1.85 million in funding to the Cancer Center's Clinical Research Office and establishes it as an NCI-designated Minority-Based Community Clinical Oncology Program, one of 14 in the nation and the only such program in New Jersey. A grant by the NJCCR, in collaboration with the New Jersey Department of Health and Senior Services, provides $476,000 in support to the Cancer Center's Clinical Research Office and is the only clinical research grant funded by the NJCCR geared toward combating health disparities. The goal of the grant is to support the Cancer Center's efforts to provide minority and medically underserved patients with access to cancer clinical trials.

Professional Societies:

ASCO, ONS Issue Standards For Safe Chemo Administration

Two major oncology professional associations released the first national standards for safe administration of chemotherapy drugs. These policies seek to serve as a benchmark for providers of adult cancer care and encourage them to evaluate their current standards.

The American Society of Clinical Oncology and the Oncology Nursing Society developed the standards to reduce the risk of errors and provide a framework for best practices in cancer care.

"Administration of chemotherapy is a complex process, and safety challenges will only grow as the number and complexity of chemotherapeutic regimens increases and oral chemotherapy drugs become more commonplace," said Joseph Jacobson, lead author of the Journal of Clinical Oncology article on the standards. "Adhering to standards for safe chemotherapy administration should be a goal of all cancer care providers."

The 31 standards issued by ASCO and ONS cover a range of processes related to chemotherapy, including staff education and training; chemotherapy ordering, preparation and administration; patient education and informed consent; assessing how patients respond to treatment; and monitoring toxicity of the treatment to the patient.

In order to avoid chemotherapy administration errors, ASCO and ONS state that practitioners must follow standardized approaches for chemotherapy delivery, develop and follow policies and procedures for system improvement, and undertake a multi-disciplined review of errors when needed.

ASCO and ONS also recommend increased use of electronic medical record systems, which may lead to improvement in the safety and quality of outpatient chemotherapy administration. E-prescribing, for example, may prove to be a tool for reducing errors in chemotherapy ordering, as automated systems can reduce errors in regimen selection in a busy clinical setting.

ASCO also has developed a guide, available online at www.asco.org/safety, to help oncology practices review and develop policies and procedures needed to adhere to these chemotherapy safety standards.

NCI News:

NCI Signs Letters Of Intent With Latin American Countries

NCI formalized bilateral partnerships this week with the governments of Argentina, Brazil, Mexico, and Uruguay, to accelerate progress against cancer in Hispanic populations in the United States and Latin America and improve cancer research.

NCI Director John Niederhuber signed formal letters of intent to collaborate in cancer research efforts. These countries, along with Chile (which signed a letter of intent in June) and the U.S., comprise the United States-Latin America Cancer Research Network (US-LA CRN), which is committed to developing a comprehensive understanding of the cancer burden among Hispanic populations in Latin America and the U.S. and to enhance the cancer research and care infrastructures in both regions of the hemisphere.

"The coming together of nations today is certainly symbolic of our common commitment to advance cancer research, but it is much more," Niederhuber said. "Understanding why certain cancers are more prevalent in certain countries and why immigration patterns may affect cancer's burden will be crucial. By electronically linking cancer research data, cancer researchers in Latin America and the United States will be able develop new knowledge of cancer trends—from individual communities to large populations."

Spearheaded by NCI's Office of Latin American Cancer Program Development, this partnership will support the co-development of programs in three broad scientific areas: cancer research and clinical trials; multinational and multidisciplinary training programs; technology and capacity building. The Latin American countries will link their research efforts through the cancer Biomedical Informatics Grid, an information network enabling the US-LACRN members to share data and knowledge. The network participants will also initiate pilot projects to expand research efforts and improve the delivery of cutting-edge cancer treatments to patients in the United States and Latin America.

For the first pilot project of this collaboration, the countries identified research concepts that are intended to improve breast cancer management in Latin America. At the same time, they will provide an opportunity to enhance research training, capacity building, and establishment of a sustainable clinical research infrastructure for future projects. The effort builds on collaborative resources among the countries as well as co-sponsorships of workshops and conferences with domestic and international foundations and organizations to support cancer research in Latin America.

Funding Opportunities:

RFAs Available

Developing Research Capacity in Africa for Studies on HIV-Associated Malignancies (D43) (RFA-CA-09-016) Application Receipt Date: Dec. 17 http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-016.html

Recovery Act 2009 Limited Competition: AHRQ Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE) Grants (R01) (RFA-HS-10-003)Agency for Healthcare Research and Quality American Reinvestment and Recovery Act of 2009 Application Receipt Date: Dec. 16 http://grants.nih.gov/grants/guide/rfa-files/RFA-HS-10-003.html

Recovery Act 2009 Limited Competition: Innovative Adaptation and Dissemination of AHRQ Comparative Effectiveness Research Products (iADAPT) (R18) (RFA-HS-10-004) Agency for Healthcare Research and Quality American Reinvestment and Recovery Act of 2009 Application Receipt Date: Dec. 16 http://grants.nih.gov/grants/guide/rfa-files/RFA-HS-10-004.html

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THE CANCER LETTER

Vol. 24 No. 8
September 2009

Business & Regulatory Report

Regulatory Approvals & Applications:

Folotyn Wins Accelerated Approval For Peripheral T-Cell Lymphoma

FDA has approved Folotyn (pralatrexate), the first treatment for peripheral T-cell lymphoma.

The drug was approved under the accelerated approval process for patients who have progressed or were resistant to other forms of chemotherapy.

Folotyn is sponsored by Allos Therapeutics Inc. of Westminster, Colo.

(Continued to page 2)

Clinical Trials:

Poniard To Begin Data Analysis In Study Of Picoplatin For Small Cell Lung Cancer

Poniard Pharmaceuticals Inc. (NASDAQ: PARD) of South San Francisco announced that 320 evaluable events (patient deaths) have occurred in its pivotal phase III SPEAR (Study of Picoplatin Efficacy After Relapse) trial in the treatment of small cell lung cancer.

The study is being conducted in accordance with a Special Protocol Assessment with FDA.

"The 320th event in our pivotal registration SPEAR trial was defined in our SPA with the FDA to enable the company to begin final analysis of data," Jerry McMahon, chairman and CEO of Poniard, said in a statement. "Our goal is to complete and report the results of our preliminary analysis in the fourth quarter of 2009 and, if positive, initiate the rolling New Drug Application filing process for picoplatin by year-end under the Fast Track designation previously granted by the FDA."

SPEAR is evaluating the efficacy and safety of picoplatin as second-line therapy in 401 cancer patients with SCLC who have not responded to or who relapsed following first-line platinum-based therapy. The primary endpoint of the trial is overall survival.

The Statistical Analysis Plan of the trial, as agreed to in the SPA, is 90 percent powered to show a 33 percent reduction in risk in overall survival for picoplatin treatment with best supportive care compared with BSC alone (hazard ratio of 0.67; $p<0.05$). The trial completed enrollment in March 2009.

The SPEAR trial randomized patients with SCLC who were refractory

(Continued to page 4)

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Folotyn Approved By FDA On Objective Response Data

(Continued from page 1)

As a condition of accelerated approval, Allos will conduct studies to confirm that tumor shrinkage actually does an increase in survival, the agency said.

It is a relatively rare disease, occurring in less than 9,500 patients each year in the U.S.

"Folotyn's approval demonstrates FDA's commitment to the rapid approval of drugs for rare and uncommon diseases," Richard Pazdur, director of the FDA Office of Oncology Drug Products said in a statement.

FDA approved Folotyn based on evidence that it produces objective response, taking this for a surrogate endpoint for a clinical benefit, such as extending the survival. Tumor shrinkage was seen on imaging scans in one study. Of 109 patients with PTCL in the trial, 27% had reduction in tumor size.

Folotyn was granted priority review, ensuring a review within six months rather than 10 months for a standard review, the agency said. The drug was also designated as an orphan drug.

The most common adverse reactions were irritation or sores of the mucous membranes such as the lips, the mouth, and the digestive tract, low platelet cell counts, low white blood cell counts, fever, nausea, and fatigue.

Research on drugs of this class began in the 1950s at SRI International. A subsequent scientific collaboration among SRI International, Memorial Sloan-Kettering Cancer Center, and Southern Research Institute led to clinical trials on related compounds conducted by Memorial Sloan-Kettering Cancer Center starting in the 1980s. Pralatrexate was identified as a viable clinical candidate and was licensed to Allos Therapeutics for further development in 2002.

The drug is a selective antifolate designed to accumulate preferentially in cancer cells and is a relative of an older chemotherapy drug called methotrexate, which was found to be effective only in limited forms of leukemia and lymphomas.

Pralatrexate was first prepared at SRI International by Joseph DeGraw and William Colwell, two of the scientists in the tripartite agreement among SRI International in Menlo Park, Calif., Southern Research Institute in Birmingham, Ala. and Memorial Sloan-Kettering Cancer Center.

In the 1950s, scientists at SRI International focused on developing related drugs that would be more effective against tumor cells. Their first major discovery in this search was a modification of methotrexate that was a powerful enzyme inhibitor, but more easily absorbed through the walls of tumor cells.

In the late 1970s, Francis Sirotnak at MSKCC began to investigate improvements to methotrexate. He and his colleagues initially did research to understand what makes methotrexate effective against certain cancers.

Robert Piper at Southern Research Institute synthesized the key starting material (a bromomethyl compound) used to prepare the pralatrexate intermediates and later synthesized the multigram quantities of high-purity pralatrexate used in preclinical investigations and described in a patent application.

BioVex Inc. of Woburn, Mass., said FDA has signed off on the design of a single, pivotal, phase III clinical trial evaluating its lead product, OncoVEX (GM-CSF), for the first-line treatment of patients with squamous cell cancer of the head and neck.

The study is the second the company has agreed with the FDA under the Special Protocol Assessment procedure and highlights the broad potential utility of BioVex's first-in-class cancer destroying virus technology. The first SPA was in melanoma under which BioVex is currently conducting a pivotal phase III trial.

Patients with head and neck cancer often present with locally advanced, bulky disease that is too large,

THE CANCER LETTER

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Business & Regulatory Report
Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial: 202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724

Business & Regulatory Report is a supplement to The Cancer Letter. ISSN 1053-9611.

or too close, to vital organs to remove surgically. These patients typically undergo combination radiation and chemotherapy treatment, in some cases with additional surgery.

Patients who present with tumor-containing lymph nodes are particularly difficult to treat and approximately half of these patients relapse within two years.

The phase III study design agreed with the FDA follows directly from the design of the previous study. The study will also enroll previously untreated patients with locally advanced disease. The primary objective will be to demonstrate a statistically significant increase in 2-year event free survival (i.e. relapse, progression, or death) for patients treated with chemoradiation together with OncoVEX (GM-CSF) as compared to patients treated with chemoradiation alone. The study will involve approximately 400 patients with approximately 200 in each arm.

Cytopia Limited of Melbourne, Australia, said FDA has signed off on an Investigational New Drug Application for CYT387, a small-molecule oral JAK1/JAK2 kinase inhibitor designed to treat myeloproliferative disorders.

The company said it is finalizing preparations for a phase I/II study of CYT387 in patients with myelofibrosis. The study will be undertaken at the Mayo Clinic in Rochester, Minn.

Delcath Systems Inc. (NASDAQ: DCTH), said FDA has granted orphan drug designation for doxorubicin for the treatment of hepatocellular carcinoma.

Delcath Systems performed early clinical studies of doxorubicin with its Percutaneous Hepatic Perfusion technology, which allows physicians to deliver significantly higher doses of anti-cancer drugs to the liver without exposing the patient's entire body to those same potent levels of drug, with very encouraging results. The company plans to perform the clinical work necessary for a submission to the FDA of PHP with doxorubicin for treatment of HCC.

Endo Pharmaceuticals (NASDAQ: ENDP) of Chadds Ford, Penn., said Valstar (valrubicin), a treatment for a form of bladder cancer, has become available after years of absence from the market.

Valsar is the only FDA-approved intravesical therapy for patients with Bacille Calmette-Guerin-refractory carcinoma in situ of the urinary bladder for whom immediate removal of the bladder would be associated with unacceptable medical risks. Valsar represents a new treatment option for these patients who may otherwise have exhausted all other FDA-approved treatment alternatives, including BCG.

Valsar, a sterile solution for intravesical instillation of valrubicin, is placed directly into the bladder through a catheter and is administered once a week for six weeks under the supervision of a physician experienced in the use of intravesical cancer chemotherapeutic agents.

In the pivotal clinical trial, Valsar was shown to induce a complete response in about one in five patients at six months following initiation of therapy, and 29 percent of patients derived a clinical benefit from Valsar treatment, the company said. It is important to note that if after Valsar treatment a patient does not have a complete response of CIS after three months, or if CIS recurs, surgical bladder removal must be reconsidered.

Valsar was approved by the FDA for this indication in 1998 and marketed by Anthra Pharmaceuticals Inc. In 2002, Anthra voluntarily withdrew Valsar from the U.S. market because of a formulation issue with an inactive component.

Since market removal, Valsar has been on the FDA Drug Shortages List, which was established to address and alleviate shortages primarily of medically necessary drug products, since these can have significant public health consequences. On Feb. 27, 2009, Indevus Pharmaceuticals Inc., the previous owner of Valsar, received FDA approval to re-introduce Valsar after modifying the formulation. On March 23, 2009, Endo acquired Indevus Pharmaceuticals and began preparing to re-launch Valsar. Valsar represents the first product launch by Endo Pharmaceuticals in the urology and oncology therapy markets.

Wyeth Europa Ltd., a division of Wyeth (NYSE: WYE), said the European Commission has approved the mTOR (mammalian target of rapamycin) inhibitor Torisel (temsirolimus) for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.

In the European Union, Torisel is also indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors.

Torisel received Orphan Medicinal Product designation for the treatment of MCL in the EU in November 2006.

The approval was based on results of a phase III clinical study that showed patients with relapsed and/or refractory MCL treated with Torisel experienced a statistically significant improvement in median

progression-free survival, compared with single-agent therapy selected by the investigator (4.8 months vs. 1.9 months, P=0.0009).

The most frequently occurring severe or life-threatening (Grade 3 or 4) adverse events in patients with relapsed MCL treated with Torisel included thrombocytopenia, anemia, neutropenia and asthenia.

Torisel was approved in the EU in November 2007 for the first-line treatment for patients with advanced RCC who have at least three of six prognostic risk factors. These risk factors include less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase >1.5 times the upper limit of normal and more than one metastatic organ site. In the U.S., Torisel is indicated for the treatment of patients with advanced RCC.

Hospira Inc. (NYSE: HSP) of Lake Forest, Ill., said FDA has approved oxaliplatin injection in the U.S. The drug is a generic version of Sanofi-Aventis' Eloxatin. Hospira's oxaliplatin injection is one of the first generic versions of this drug to come in solution form.

Oxaliplatin injection, used in combination with infusional 5-fluorouracil/leucovorin, is indicated for adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor, and in the treatment of advanced colorectal cancer.

YM BioSciences USA Inc. (YM-USA) has received a license from the US Department of the Treasury's Office of Foreign Assets Control to further develop its lead product, nimotuzumab, for patients with solid tumor cancers in the U.S.

"This license from OFAC to develop nimotuzumab in any cancer indication is a major step forward in our US development program and will allow us to immediately discuss our IND submissions with the FDA to include U.S. patients in our randomized, double-blinded lung cancer and brain metastases trials," said David Allan, chairman and CEO of YM BioSciences. "Our development plans may also include extending some of the phase III trials being conducted worldwide into the U.S."

YM USA previously received a license from OFAC to import nimotuzumab into the U.S. to conduct a study in children suffering from recurrent diffuse intrinsic pontine glioma. This trial is ongoing at 10 hospitals in the U.S. and data is expected in 2010, the company said. Nimotuzumab is designated an orphan drug for adult and pediatric glioma by the FDA, as well as the EMEA for Europe.

Clinical Trials:

Poniard To Begin Data Analysis Of Picoplatin SPEAR Trial

(Continued from page 1)

to prior platinum-containing, first-line chemotherapy regimens or who had progressed within six months of first-line therapy. Picoplatin administered as an intravenous infusion once every three weeks plus BSC was compared to BSC alone.

Picoplatin is a platinum-based chemotherapeutic in clinical development for multiple cancer indications, treatment combinations and by two routes of administration. It is designed to overcome platinum resistance associated with chemotherapy in solid tumors.

Study data suggest that picoplatin has an improved safety profile relative to existing platinum-based cancer therapies. More than 1,100 patients have received picoplatin, the company said. Results obtained to date suggest that hematologic events are common but mana geable. Nephrotoxicity neurotoxicity are less frequent and less severe than is commonly observed with other platinum chemotherapy drugs.

In addition to SPEAR trial, Poniard is also evaluating intravenous picoplatin in a phase II study in colorectal cancer, in a phase II study in castration-resistant prostate cancer. Oral picoplatin is being evaluated in a phase I study in solid tumors. Poniard has received both Orphan Drug designation and Fast Track designation for picoplatin for the second-line treatment of refractory or resistant SCLC from the FDA and orphan medicinal product designation for the treatment of SCLC by the European Commission.

Bellicum Pharmaceuticals Inc. of Houston announced dosing of the first patient in a phase I/II clinical trial of BP-GMAX-CD1, a pharmacologically regulated dendritic cell vaccine for the treatment of prostate cancer.

The disease-specific trial is being conducted under a Bellicum Investigational New Drug application allowed by the FDA in 2008. The company anticipates reporting initial results of the study in 2010.

BP-GMAX-CD1 is a cancer vaccine that can be precisely activated at an optimal time and location

in the body. It is produced by genetically modifying autologous antigen-loaded dendritic cells to express an inducible costimulatory CD40 (iCD40) receptor. Twenty-four hours after intradermal administration, these genetically modified dendritic cells are activated in draining lymph nodes by intravenous administration of AP1903, a small-molecule dimerizer agent developed by ARIAD Pharmaceuticals, Inc. (NASDAQ:ARIA). In this way, the immune system's innate homeostasis is overridden and a potent and durable antigen-specific T cell response may be generated.

The dose-escalation trial will evaluate the safety of BP-GMAX-CD1 and AP1903 in a minimum of 24 patients with androgen independent prostate cancer (also known as castrate resistant prostate cancer or CRPC). Six doses will be administered on a weekly or every other week schedule, with responses assessed at week 13.

Patients whose disease has not progressed at the end of this acute phase will be eligible to receive booster vaccinations every eight weeks for up to one year. Exploratory efficacy endpoints include prostate-specific antigen dynamics, circulating tumor cell count, antigen-specific immune response, and clinical response.

The small-molecule dimerizer, AP1903, and the ARGENT(TM) cell-signaling regulation technology underlying BP-GMAX-CD1 were licensed from ARIAD Pharmaceuticals, Inc. AP1903 is designed to bring together two proteins and activate them. In the case of BP-GMAX-CD1, administration of AP1903 to patients leads to controlled activation of the ARGENT-regulated protein iCD40.

AP1903 was previously shown by ARIAD to be well-tolerated with defined pharmacokinetics in a Phase 1 clinical trial.

Onyx Pharmaceuticals Inc. (NASDAQ:ONXX) announced it has begun enrolling patients in a phase 1 study of ONX 0801, a novel alpha-folate receptor-mediated thymidylate synthase (TS) inhibitor, as a potential treatment for advanced solid tumors. This open-label, dose-finding study will evaluate the safety and pharmacokinetics of ONX 0801 in patients with advanced solid tumors.

"We are pleased to advance this product candidate so quickly into the clinic, following our acquisition of the compound late last year. ONX 0801 has a high selectivity for cancer cells that we believe will distinguish it from other agents in this proven class of drugs," said Tony Coles, president and chief executive officer of Onyx. "We expect this forward momentum in building our portfolio to continue, as we strategically maximize opportunities that will drive long-term sustainable growth."

The open-label, dose-finding phase I study is evaluating the safety and pharmacokinetics of ONX 0801 in approximately 60 cancer patients with advanced solid tumors. Cohorts of 3 to 6 patients will receive ONX 0801 at escalating doses until a maximum tolerated dose is determined. Each patient will receive a 3-hour intravenous infusion of ONX 0801 weekly (i.e., on days 1, 8, and 15) of repeated 21-day treatment cycles.

ONX 0801 is designed to work by combining two proven approaches to improving outcomes for cancer patients. These include receptor-mediated targeting of tumor cells and inhibition of thymidylate synthase (TS), a key enzyme involved in cell growth and division. In pre-clinical studies, ONX 0801 targeted malignant cells that overexpress the alpha-folate receptor, which is located on the cell's surface.

ONX 0801 is distinct from currently marketed TS inhibitors due to its selective tumor cell-specific uptake by the alpha-folate receptor, which is overexpressed in a number of tumor types with significant unmet needs, including ovarian cancer, lung cancer, breast cancer, and colorectal cancer.

ONX 0801 was discovered at the Institute for Cancer Research in the UK and is licensed to Onyx by BTG International.

PCI Biotech Holding ASA, a Norwegian drug delivery company, said the first patient has received treatment in the phase I/II trial with the drug Amphinex, which uses a new approach called photochemical internalisation.

The patient was treated at the University College Hospital in London. PCI's proprietary photosensitiser Amphinex is in this study combined with the therapeutic agent bleomycin.

When activated by light, Amphinex promotes effective delivery of large therapeutic molecules such as bleomycin through triggered endosomal release. The trial will investigate a broadly representative spectrum of cancers including head and neck cancer and breast cancer, to demonstrate the safety and potential of this new approach.

The primary objective of this study is to assess the maximum tolerated dose of Amphinex, in PCI treatment with bleomycin. Secondary objectives include determination of the antitumor activity of Amphinex when used in combination with bleomycin, as well as its pharmacokinetics.

Deals and Collaborations:

Abbott, Pfizer In Agreement To Develop NSCLC Test

Abbott and **Pfizer Inc**. said they entered into an agreement with to develop a molecular diagnostic test intended to screen non-small cell lung cancer tumors for the presence of gene rearrangements.

Pfizer has developed a novel investigational agent that selectively targets cancer-causing genes implicated in the progress of many cancers. To be eligible to receive Pfizer's oral therapy, a particular genetic translocation known to be found in NSCLC tumors and a wide variety of other cancers, but not in normal cells, must be present.

Under the agreement, Abbott will develop a companion diagnostic test that will determine a patient's genetic status and will be used in patient selection for future clinical trials of PF-02341066.

"This test will allow us to focus on the patient population most likely to benefit from our NSCLC candidate. Working in close partnership with the experienced Abbott team, we are confident that we will deliver yet another application of personalized medicine to address a currently unmet medical need in NSCLC," Garry Nicholson, General Manager, Pfizer Oncology Business Unit, said in a statement.

Cell Biosciences Inc. and **Alpha Innotech Corp**. (BULLETIN BOARD: APNO) said they have entered into an agreement for the acquisition of Alpha Innotech by Cell Biosciences for $1.50 per share, approximately $17.9 million in cash.

Alpha Innotech specializes in the use of high-sensitivity digital imaging systems for genomic and proteomic research. The company offers a broad range of best-in-class products, from entry-level gel documentation systems to premier systems for multiplexed fluorescence and proteomics applications. The company has sold over 10,000 systems worldwide. In 2008, Alpha Innotech achieved revenues of $17.6 million and was profitable on both an operating and a net income basis.

Cell Biosciences is focused on protein and biomarker research. The company's lead product is the CB1000, a nanofluidic immunoassay platform designed for ultrasensitive detection and characterization of oncoproteins and other signaling proteins in ultra-small biological samples, such as small tumor biopsies and stem cells.

Cephalon Inc. (NASDAQ: CEPH) of Frazer, Pa., said it has completed acquisition of all of the outstanding ordinary shares of Australian biotechnology company, **Arana Therapeutics Limited**.

Cephalon acquires an established protein engineering technology platform to transform proteins, including antibodies, into potent drug candidates. The lead biologic in the portfolio (ART621) is the first domain antibody to enter the clinic targeting TNF alpha, and is in a phase 2 clinical program for rheumatoid arthritis.

Additional biologics acquired include: a RANKL inhibitor for bone metastases; one targeting a novel epitope for colorectal cancer in collaboration with **Kyowa Hakko-Kirin**; one targeting gangliosides for small cell lung cancer and melanoma; one targeting IL 12 /23 for psoriasis and Crohn's disease as well as other earlier stage opportunities.

EMD Serono Inc. of Rockland, Mass., and **M. D. Anderson Cancer Center** announced a strategic alliance.

The agreement is set for three years with the potential to renew the alliance. This non-exclusive strategic alliance will collaboratively draw on the expertise and resources of M. D. Anderson and EMD Serono to help design and conduct clinical trials for EMD Serono's oncology product candidates.

EMD Serono is an affiliate of Merck KGaA, Darmstadt, Germany.

Oncology Management:

Firm To Develop Online Tools For NCCN Clinical Guidelines

Clinical Care Options of Reston, Va., a developer of medical education materials, formed a collaboration with the **National Comprehensive Cancer Network**.

Under the deal, CCO was granted permission by NCCN to develop Internet-based educational tools that will automate the NCCN Clinical Practice Guidelines in Oncology and provide an interface for their applicability of them in clinical practice.

The current version of the NCCN Guidelines for specific disease areas or supportive care will be adapted to a CCO automated tool that allows clinicians to enter specific clinical scenarios and rapidly obtain recommendations and references that support the NCCN Guideline, the company said. Accompanying each automated NCCN Guideline will be an interactive

CME-certified educational module that will provide clinicians an in-depth analysis of the evidence-based science that underpins the NCCN Guidelines and their application.

Chindex International Inc. (NASDAQ:CHDX), an independent American provider of Western healthcare products and services in the People's Republic of China, announced that the company's Western-style hospital network, United Family Healthcare, plans to launch a comprehensive, international-standard oncology program, called "New Hope," at a stand-alone outpatient facility near its Beijing United Family Hospital.

The New Hope Center will provide international expertise to diagnose and treat cancer and will offer an array of treatment modalities, including chemotherapy, radiation therapy and other oncology-related support services. The oncology program also will utilize established resources, such as medical and surgical cancer treatment from BJU, a leading institution in Beijing's medical community.

"While Beijing United Family Hospital is an established leader in a variety of cancer treatments, our New Hope Center will expand the spectrum of our patient care and provide an unparalleled, new-to-market approach in China," Roberta Lipson, president and CEO of Chindex, said in a statement. "This will include the highest quality medical expertise, multi-language support, proactive administration and psychological and nutritional services, delivered at Joint Commission International standards. Currently, Chinese patients have to travel abroad for this patient-centered approach to cancer care. When we first opened Beijing United Family Hospital, our approach to obstetrics and patient-centered primary care quickly became a model for emulation, attracting much attention and many patients. I fully expect that our comprehensive cancer program will have a similar following."

Chindex appointed Philip Brooks to lead the program and serve as vice president, medical affairs and director of oncology at BJU. Brooks is currently the only American medical oncologist in China to be certified by the American Board of Internal Medicine, the company said.

NIH Clinical Center's Department of Transfusion Medicine is using a prototype of the **CardianBCT** Quantum Cell Expansion System to reproduce human bone marrow stromal cells in an automated, sealed environment.

The collaboration is part of the trans-NIH Bone Marrow Stromal Cell Transplantation Center, created in 2008 to facilitate the use of clinical-grade bone marrow stromal cells prepared using procedures known to maintain their biological activities and to assist investigators in the preparation of protocols that utilize such cells. The trans-NIH group is co-coordinated by Pamela Robey of the National Institute of Dental and Craniofacial Research and Harvey G. Klein, chief of transfusion medicine at the Clinical Center.

Current methods used to expand cells are manual, labor intensive, and complex, which can limit the ability to provide stem cell therapy to a large number of patients. Cell processing laboratory staff take a piece of bone or bone marrow aspirate, a sample of the liquid bone marrow portion, and replicate the stromal cells by growing them in flasks and transferring to larger flasks as they grow in number. Staff must monitor the cells' development and move them by hand.

As an integrated, closed system, the cell expansion system improves efficiency of the stem cell growth process-allowing for larger scale manufacturing of cells with less risk of contamination and better control of the process. The new system produces cells in a sealed container using bioreactor technology, which circulates fluid through cartridges and automatically loads the cells into the cartridge, feeds the cells, and harvests the cells.

Until the machine's output is verified as comparable to the expanded stromal cells created through traditional methods, the Department of Transfusion Medicine will continue to make cells for patients using the traditional flask method. Within six to nine months, cells produced using the prototype should be ready for treatments, Klein said.

Quest PharmaTech Inc. (TSX-V: QPT) of Endmonton said it has acquired a pipeline of late-stage immunotherapy product candidates from **Paladin Labs Inc**. (TSX:PLB).

The pipeline of product candidates consists of five monoclonal antibodies targeting certain tumor antigens that are presented in a variety of cancers. The first and most advanced of these product candidates is Oregovomab, an anti-CA125 antibody for the treatment of ovarian cancer patients that Quest will evaluate in combination with front-line chemotherapy.

Quest also acquired anti-MUC1, anti-TAG72, anti-PSA and anti-CA19.9 antibodies that could potentially be used for the treatment of breast, lung, stomach, colorectal, pancreas and prostate cancer.

"We believe that these newly acquired

immunotherapeutic antibody products have the opportunity to become significantly more effective when combined with chemotherapy, radioimmuno therapy or photodynamic therapy," said Madi Madiyalakan, CEO for Quest.

"As one of the original inventors of this technology, I have a deep understanding of the potential of these compounds to become more efficacious treatments for cancer when used as an adjunct in combination with these established therapies," Madiyalakan said. "We intend to expeditiously evaluate the potential of the acquired products for conducting a registration trial for one or more combination therapies, which, if successful, could lead directly to one or more applications for regulatory approval."

As part of the transaction, Paladin receives an upfront payment of $37,500 and 1.5 million common shares of Quest, with an additional 1.5 million common shares to be issued to Paladin on or before Dec. 31, 2010.

Paladin may also receive an additional 2 million common shares of Quest if the company is successful in its future financing initiatives. The agreement also provides single-digit royalty payments to Paladin on future revenues. In addition to more than 50 issued patents (including eight issued U.S. patents), Quest will also receive associated Oregovomab documents that could be used as the basis for an ovarian cancer clinical trial application, and other product-related assets that could enable clinical trial conduct.

The immunotherapeutic approach to cancer treatment involves modulating the immune system to achieve a therapeutic goal. This approach has advantages in comparison to current conventional treatment practices, which are often radical in nature and associated with severe toxicities, thereby compromising the patient's quality of life. To date though, attempts to use monoimmunotherapies to elicit a therapeutic benefit have met with mixed results as evidenced recently by the data derived from a Phase III trial evaluating Oregovomab as a treatment for ovarian cancer patients.

However, based on the safety, immunology and efficacy data available from more than 1,000 cancer patients and its in-house expertise, Quest believes that it can make treatment modifications to its new portfolio of oncology product candidates to prolong, amplify and shape anti-tumor immune responses to increase the clinical benefits of these antibodies for the treatment of human cancer.

Hospira Inc. (NYSE: HSP) of Lake Forest, Ill., announced the acquisition of worldwide rights to a biogeneric version of filgrastim and an affiliated European manufacturing facility from **PLIVA Hrvatska** d.o.o. of Zagreb, Croatia.

The purchase will help extend Hospira's reach and vertical integration in biogenerics, the company said. Financial terms of the agreement were not disclosed.

As a result of the acquisition, Hospira will have full global rights to the biogeneric filgrastim that had previously been part of a strategic collaboration between Hospira and PLIVA/Barr, the latter two companies now owned by **Teva Pharmaceutical Industries Ltd**.

As part of the agreement, Hospira has also acquired process development capabilities and a manufacturing plant in Croatia. The site has capacity sufficient to meet Hospira's worldwide filgrastim and pegfilgrastim requirements, along with expansion possibility for additional biogenerics manufacturing.

"With this agreement, Hospira expands its reach to new markets for filgrastim, and its global manufacturing capacity for pegfilgrastim," said Ron Squarer, senior vice president, Global Marketing and Corporate Development, Hospira. "Hospira is already well-positioned in the biogenerics marketplace, given our internal capabilities, our strategic collaborations and our commercialization experience in Europe. The additional vertical integration this deal brings, as well as the access to broader markets for our products, further demonstrates Hospira's robust commitment to the biogenerics space."

Applications for product approval of filgrastim were filed with the European Medicines Agency (EMEA) and Australia's Therapeutic Goods Administration (TGA) in the first quarter of 2009.

Filgrastim is a granulocyte colony-stimulating factor (G-CSF) used to treat neutropenia, a condition in which the body makes too few infection-fighting white blood cells. The condition is often caused by drugs prescribed for cancer treatment.

Hospira's pegfilgrastim would be a biogeneric version of Amgen's Neulasta, a second-generation G-CSF also used to treat neutropenia. Hospira intends to launch its biogeneric pegfilgrastim in Europe, Asia and the United States prior to the expiry of patents relating to Neulasta, and is conducting the requisite clinical work to support these regulatory submissions. Hospira also intends to register the Croatian plant and an existing Hospira facility in Australia as global sites of manufacture for pegfilgrastim.