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Niederhuber Says Resignation "Pro Forma," Hopes To Stay As Director Or Lab Chief

By Kirsten Boyd Goldberg

NCI Director John Niederhuber said he hopes to stay in his job, or, failing that, to continue running his laboratory in the institute's intramural program.

In an interview with The Cancer Letter, Niederhuber said the resignation letter he is required to submit before the end of the Bush administration will state that he would be willing to continue in the job in the Obama administration.

The position of NCI director "has generally not been viewed as political position, and certainly, I have never viewed it as political position," Niederhuber said in a Dec. 18 interview. "I came into it somewhat by accident, I guess you might say."

Niederhuber acknowledged that he has met with the Obama transition

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FDA News:

Von Eschenbach To Leave FDA Jan. 20, Says He Was "In Love" With The Agency

By Paul Goldberg

On the way out, FDA Commissioner Andrew von Eschenbach spoke of "falling in love" with the agency he headed.

"I have said it is hard to fall in love with FDA from outside the agency because so few can fully appreciate who you are and what you mean to this country, but it is impossible not to fall in love with the agency and its mission once you are inside—that's why so many of you are here," the commissioner wrote in an email announcing his resignation to FDA staff.

Von Eschenbach, 67, said he would leave the agency on Jan. 20, 2009. "I will return to my home in Texas to be with my family, including my grandchildren," von Eschenbach wrote in the mass email dated Dec. 16. The email was signed simply as "Andy."

Before coming to the agency in 2005, von Eschenbach, a Texas urologist and a Bush family friend, headed NCI. He attempted to reorganize the institute around his favorite alliteration—Discovery, Development and Delivery—and vowed to eliminate "suffering and death due to cancer" by 2015.

The text of von Eschenbach's email follows:

From the first day I arrived at the agency, serving as your Commissioner has been an honor, and the past several weeks have been especially gratifying. In mid-November I had the special privilege of participating with Secretary

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This is the final issue of The Cancer Letter for 2008. The next issue will be published on Jan. 9.

"It's A Big Place. I Can Easily Hide," NCI Director Says

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team, but denied widely circulated reports that he has been told that he would be expected to vacate the director's office. "If the new administration, President-elect Obama and his team, desire that I continue to serve in the position as director of the NCI, I certainly would be honored to do so," Niederhuber said.

If he stays on as an intramural scientist or a lower-level administrator, Niederhuber would be the first NCI director make use of the practice called "burrowing" into the bureaucracy. All five of his predecessors who headed the institute since the National Cancer Act of 1971 made the job a presidential appointment left the Bethesda campus.

The term burrowing doesn't apply in his case, Niederhuber said. "I'm not burrowing into the federal government, because I came here not as an appointee, but as a Title 42, and as a deputy," Niederhuber said.

Before joining NCI, Niederhuber was a professor of surgery and oncology at the University of Wisconsin, where he had served as director of the comprehensive cancer center since 1997. He was asked to step down as center director in 2002 as a consequence of a dispute over fundraising strategies (The Cancer Letter, Sept. 22, 2006, and Oct. 7, 2005).

He was appointed by President Bush as chairman of the National Cancer Advisory Board in 2002, and began to interact more closely with institute director Andrew von Eschenbach. In 2005, von Eschenbach recruited Niederhuber to NCI to serve as deputy director for clinical and translational sciences. It that job, he was given Title 42 status, which confers a higher salary than regular civil service.

Niederhuber took over management of the institute in October 2005, just two days after he arrived to work as a deputy director of the institute, when von Eschenbach replaced the abruptly dismissed FDA Commissioner Lester Crawford. Bush formally appointed Niederhuber as NCI director in August 2006.

Niederhuber leads the Tumor and Stem Cell Biology Section, part of the Cell and Cancer Biology Branch of NCI's Center for Cancer Research. The lab is studying tissue stem cells, work that Niederhuber called "exciting" and "productive." Also, he holds a clinical appointment on the NIH Clinical Center medical staff.

Following is the text of the interview:

NIEDERHUBER: I sense that there have been at least a few rumors that have been floating around. I wanted to be as open and transparent as I could be. I have been really quite honored to have been given this opportunity to serve as the director of the NCI, and I very much have enjoyed it. It's a perfect time in my career to have this opportunity to serve.

I have always throughout my life have had lots of different responsibilities, many of them at the same time, administrative, teaching, and research. I've always had a research laboratory, as I do now. Because of those multiple responsibilities and the responsibility of taking care of patients, patients have always been the number one priority for me. It had to be, and I wanted it to be that way in my surgery part of my career. I kind of look at this job the same way. There are a lot of responsibilities with the job, a lot of things I do, both at NCI and across NIH, but in the end, the number-one priority, the number-one thing that I get up in the morning coming to work for is really to try to keep the cancer patient and the cancer patient's family the focus. I look at this period of transition in the government in much the same way. I will continue to try to do whatever I can to keep the stability and continuity of the National Cancer Institute in place and in a priority as we go through the transition, because I think it's so important to the people with cancer, the people that we serve. That's a certain personal bias or feeling that I have about it.

As you know, the position of director of the NCI is the one institute at the NIH that is a presidential appointment. Not a presidential appointment with senatorial approval, as are other offices in the department. The institute was founded in 1937. I'm the 13th director.

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I would say it has generally not been viewed as political position and certainly I have never viewed it as political position or appointment. I came into it somewhat by accident, I guess you might say.

As the process of transition goes, I will turn in the pro forma letter, as the other previous directors have in the past. That letter indicating, in my case, that I have appreciated the opportunity to serve, and as required by the transition, I'm submitting my resignation, but also indicating an interest and willingness to continue to serve, either in an interim capacity or if a new administration desires, in a permanent position.

I'm following the instructions that come to all government appointees and I'm fulfilling those instructions. I will continue to do my best to maintain the day to day operations and keep the NCI moving forward as normally as I can make it work. I don't think it will be difficult or an issue if the new administration, President-elect Obama and his team, desire that I continue to serve in the position as director of the NCI, I certainly would be honored to do so.

TCL: Have you met with the transition team?

NIEDERHUBER: The transition team was on campus for about two weeks, roughly. I met one-on-one with the transition team, as did other key directors, and then as part of a group of directors.

TCL: Were you told anything about your status in the new administration?

NIEDERHUBER: No, that was not part of the discussion. The discussion was focused on the issues that we face as institute directors, in terms of budget, personnel, those kinds of general issues that affect all of us at NIH. Also, a good deal of brainstorming about the future and what issues the new administration both at the department level and the White House should be aware of so that they aren't surprised by events. Trying to brainstorm for them what are the issues on the horizon they would need to face in the early days of the new administration.

TCL: If you were not selected to stay on as NCI director, would you stay in your lab? What would you want to happen?

NIEDERHUBER: That's a good question, and I can only honestly answer it by saying I will deal with that when the time comes. I have a very good lab right now, I'm very fortunate. We have some very exciting work related to the connective tissue cells of the microenvironment. We're excited about that. It's been a very productive past 12 months, when we began this particular project. We've had several projects in the lab, and this is one right now that is one that is really quite novel, and I think we are going to be publishing some of that soon, which I'm very excited about. Right now, I have great young people in the lab and it's a very exciting time in the lab, so I would certainly have to think long and hard about walking away from that. One never knows what other opportunities might come forward, but when I've been approached in recent months, I've said I'm not interested in looking at other options at present time. I want to stay focused on the job that I have and I won't make other decisions until that becomes more clear.

TCL: So it would it be an option for you to be a lab chief?

NIEDERHUBER: It certainly is an option for me to stay here at the NCI as a clinician-scientist.

TCL: Is that a tenured position?

NIEDERHUBER: At my age, it's probably irrelevant. I can stay, and even though I have only had the lab open three years, I did participate in the recent review of our big lab, as we call it, with the Board of Scientific Counselors.

TCL: Do you have Title 42 status?

NIEDERHUBER: I do.

TCL: Does that make a difference in your being able to stay as an employee?

NIEDERHUBER: Yes. Correct. I'm not burrowing into the federal government, because I came here not as an appointee, but as a Title 42, and as a deputy.

TCL: It would be unprecedented for an NCI director to do that.

NIEDERHUBER: It's a big place. I can easily hide.

TCL: Have you been able to publish your work in the past three years?

NIEDERHUBER: We have had a couple of papers come out already. One is in press, and one is out.

TCL: There have been a lot of rumors about investigations of the SAIC contract for Frederick. We know there is a Congressional investigation, but is there an Office of the Inspector General investigation? Can you confirm that?

NIEDERHUBER: The OIG investigation was not specifically of SAIC. There have been a couple of routine investigations. One was more of a review of the [Federally Funded Research and Development Centers in the federal government. That went extremely well. We helped inform the review committee considerably about how these work and how one differs from the other across the federal government. I think we got high marks on that. The other investigation that we were part of, we were one of several institutes that were reviewed because

of issues around the National Institutes of Environmental Health Sciences. That spawned a review around the processes that involved how grants are awarded, how we sometimes skip over a grant, the justifications, how that's documented, how we do exceptions funding. The review committee wanted to know more of a process review, what are the processes we use, how those are documented, how many sets of eyes review the process. Again, I believe we at the NCI kind of set the standard for this review committee. I believe we have done quite well in showing all the mechanisms that we have in place and the ways we document that all the way up through our National Cancer Advisory Board.

TCL: What would you say you have been most proud of in your time as director?

NIEDERHUBER: I started running [NCI] in the fall of 2005, though I didn't have a formal appointment [until 2006]. I've been managing it as you know through some difficult budget times. I think keeping the momentum and finding ways to begin new programs, despite a flat budget, probably has been the most difficult challenge. To manage expectations, to try to identify the most significant opportunities for the institute, in order to keep everybody's morale up and keep us moving forward and not simply idling. It has required a great team of supporters. I have wonderful division and center heads within the institute. They are great leaders and companions. They are fun to work with. I think they are willing to work with me to make hard decisions, and we've trimmed a lot of areas to redirect resources to our highest priorities.

FDA News:

"I Will Return To My Home In Texas," von Eschenbach Says

(Continued from page 1)

Leavitt in the opening of three new FDA locations in China as the first step in establishing FDA's presence beyond our borders. Then this month, my immediate office moved into the newly-renovated and historic Building One at FDA's White Oak campus, the site of modern state of the art facilities for the FDA.

I arrived at FDA as we prepared to celebrate the Agency's centennial, and now these events are some of the new chapters in the FDA of the 21st century. I am both proud and humbled to have played a part in this transformation that builds on the past and eagerly embraces the future. This critical time of opportunity has not been without its significant challenges, but I am firmly convinced that the transformation is under way.

With that knowledge I share with you, my FDA family, that as a public official appointed by President Bush and confirmed by the Senate, I serve you but at the pleasure of the President. I will do so until January 20, 2009, when a new President takes office and a new administration begins. That has always been my plan and the expectation of my family from the time of my confirmation as your Commissioner. I will return to my home in Texas to be with my family, including my grandchildren. I am thrilled to do so but also sad that I will no longer be among people I admire, respect, and have come to cherish.

I have said it is hard to fall in love with FDA from outside the agency because so few can fully appreciate who you are and what you mean to this country, but it is impossible not to fall in love with the agency and its mission once you are inside -- that's why so many of you are here. Like other alumni, I will certainly always have a special affection for FDA.

The incoming administration is responsible for appointing an Acting Commissioner until the new President nominates, and the Senate confirms, a permanent FDA Commissioner.

Until my final farewell on January 20, I will be working together with you to prepare the FDA for the change of political leadership. Our management team has developed extensive briefing materials for the incoming administration, and we are working closely with its transition team to ensure a seamless change in political leadership at the agency. As with any transition, there will likely be changes for other senior managers as well, although all current Deputy Commissioners and the Chief of Staff are career civil servants who have served me and FDA well.

I could not submit my letter of resignation today (to be effective January 20) without first informing you of my intention and telling you that I am very grateful for all your efforts and support. I am extremely proud of the progress we have made together. Resources are on a dramatic upward trajectory, and the gleaming new buildings and laboratories at our White Oak campus will make possible synergies and collaboration that were long beyond our reach. I look forward to this week's dedication ceremony for the headquarters building at White Oak.

During this time of political transition, as always, I know each and every one of you will keep the agency focused on the public health tasks at hand. You are the primary mainspring of our public health mission, and I know that you will continue your exemplary work in protecting and promoting the public health of the citizens we all serve.

Groups Propose Six Virtues Of Next FDA Commissioner

By Paul Goldberg

In a letter to HHS Secretary Designate Thomas Daschle, several key cancer patient groups and professional societies said that candidates for FDA commissioner's job shouldn't be excluded on the basis of past ties to the pharmaceutical industry.

The letter, which lists six "paramount characteristics" of the next FDA chief, appears to suggest that individuals with public health backgrounds shouldn't be seriously considered for the job.

Currently, Joshua Sharfstein, health commissioner of Baltimore and head of the Obama transition team at FDA, is widely viewed as a contender for the job.

"The commissioner must be capable of rising above politics to elevate the science of FDA by taking an impartial approach to complex issues, despite pressure from elected and appointed officials and from the news media," states the letter, which was circulated by Friends of Cancer Research, a Washington group headed by Ellen Sigal.

While politicians and the press have been known to inflict misery on FDA commissioners, so has regulated industry, which for some reason escaped mention in the letter.

"Candidates for commissioner should not be excluded due to relationships with industry during the course of his/her career," the letter continues. "In fact, diverse experience, including that with an FDA-regulated industry, should be viewed as a positive qualification."

Further, "the commissioner should have excellent scientific credentials," the letter states. "This individual should be science driven and have experience managing projects that are translational in nature."

Not all of the 34 organizations that signed the letter were pleased with its text after taking a closer look. "I should have read it more carefully," said Robert Erwin, president of the Marti Nelson Cancer Foundation, who signed the letter. "That sentence, which I read quickly, should include industry as one of the pressure groups that a commissioner should rise above."

Of course, the next commissioner should be able to resist pressure from the industry, Erwin said. However, management of translational research—work that moves between laboratory bench and the clinic—shouldn't be viewed as a job requirement, Erwin said.

"When I signed that letter, I should have been looking for what was missing—like the mentioning of the industry," Erwin said. "Also, I should have been thinking of potentially highly qualified candidates who might be excluded by this specific wording. To me, an individual who serves as a health commissioner of a major American city is highly qualified for the job."

Sigal and FOCR are on record promoting the candidacy of Janet Woodcock, head of the FDA Center for Drug Evaluation and Research.

According to the letter, the next FDA commissioner should also have these virtues:

—The commissioner must have proven managerial and administrative experience with the ability to execute effectively a forward-looking vision for the agency.

—The commissioner should have the capacity to build consensus around key issues related to the evaluation of products under review by engaging various stakeholder groups, including patients and their representatives.

—The commissioner must also have a vision for the advancement of evidence-based science in the drug development arena as well as the regulation of new and existing therapies.

The letter was signed by the American Society of Clinical Oncology, the American Association for Cancer Research, the American Cancer Society-Cancer Action Network, the American Association of Cancer Institutes, National Coalition for Cancer Research, Susan G. Komen for the Cure, C3: Colorectal Cancer Coalition, FasterCures, Friends of Cancer Research, Intercultural Cancer Council Caucus, Kidney Cancer Association, Leukemia & Lymphoma Society, Lung Cancer Alliance, Marti Nelson Cancer Foundation, Men's Health Network, National Health Council, National Patient Advocate Foundation, Ovarian Cancer National Alliance, Prevent Cancer Foundation, Research!America, Sarcoma Foundation of America, Society for Women's Health Research, and Society of Gynecologic Oncologists.

NCCS Urges FDA To Finalize Expanded Access Regulations

The Bush administration should finalize the FDA regulations on expanded access to investigational drugs, a Washington-based advocacy group urged in a letter to the Office of management and Budget.

"It has now been more than two years since the proposed regulations were published, and more than a year and a half since the comment period was completed," wrote Ellen Stovall, senior health policy advisor at the National Coalition for Cancer Survivorship.

"The regulations are practically non-controversial,

yet hold tremendous promise for cancer patients, providers and researchers," the Dec. 16 letter states. "Please take whatever action is required to ensure that these regulations are finalized before the conclusion of this administration in order to avoid further delay."

The White House has limited adoption of new regulations except in "extraordinary circumstances."

The agency's pending regulations, which cover expanding access to investigational drugs and describe procedures for charging for investigational drugs, meet this bar, Stovall wrote.

"Every day cancer patients who have exhausted their treatment options seek to consider the opportunity of access to investigational new therapies that might improve their chances of survival," Stovall wrote.

In October 2007, NCCS and the American Society of Clinical Oncology urged the administration to immediately finalize the regulations, which still remain in proposed form.

NCI Programs:

Advisors Approve Renewal Of Cancer Genome Atlas

By Kirsten Boyd Goldberg

An NCI advisory group approved the institute's plans to set aside up to $100 million over the next five years to continue The Cancer Genome Atlas Network.

TCGA, currently in the second year of a three-year pilot phase, is designed to identify genetic aberrations associated with cancer.

The NCI Board of Scientific Advisors voted 24-0 with two abstentions, in favor of continuing the network.

NCI program staff said the data generated to date on the pilot project validates the feasibility and benefits of the systematic effort to identify, quantify, and characterize molecular alterations for specific tumor types and subtypes.

"TCGA promises to be one of the defining efforts in cancer research over the next decade and beyond," according to the NCI concept statement. "The reissuance of this RFA will allow the NCI to capitalize on its investment and lessons learned to complete the genome characterization of a large number of tumors in the five-year period proposed."

The board also voted 16-0, with four abstentions, to approve reissuance of an RFA for the Integrative Cancer Biology program, and 22-0, with two abstentions, to approve reissuance of an RFA for the NCI Alliance for Nanotechnology in Cancer.

NCI staff withdrew a proposed new RFA concept for grants in stress regulation of tumor biology after board reviewers unanimously criticized the idea.

Excerpts of the concept statements follow:

The Cancer Genome Atlas Network: TCGA Genome Characterization and TCGA Genome Data Analysis Centers. Concept for a reissued RFA, first year set aside $18 million, 10 to 12 awards for five years, estimated total $90 million to $100 million. Program director: Daniela Gerhard, Office of the Director.

Acting on the recommendation from the February 2005 National Cancer Advisory Board's Biomedical Technology Subgroup Report, the directors of NCI and NHGRI agreed to pursue a pilot project, The Cancer Genome Atlas Pilot Project to determine the ultimate feasibility of identifying all of the genetic aberrations associated with cancer. The aim of the three-year pilot phase was to demonstrate that complete genomic characterization and resequencing of cancer and control biospecimens fromm well characterized patinets of a small number of tumors could be achieved within the projected time and cost for the pilot. A major goal from NCI's perspective was also to determine the value of identifying genomic regions of interest through genome characterizations that reflected biological parameters of interest. The vision for the pilot project was to establish a central data base where all data and analysis results would be readily accessible by individual investigators to drive informed discovery of new cancer interventions.

The RFA for the pilot project was released and awards made in late 2006. Development of the "pipeline" approach for TCGA was organized around key principles that emphasized the acquisition of quality biospecimens, the production of high fidelity nucleic acids to produce the highest quality data to date in cancer genomics. The pilot program focused on three cancers: glioblastoma, squamous carcinoma of the lung, and serous cystadenocarcinoma of the ovary.

The pilot project is composed of four components: a Biospecimen Core Resource (BCR), Cancer Genome Characterization Centers (CGCCs), Genome Sequencing Centers (GSCs) and a Data Coordination Center (DCC). The BCR collects and provides the CGCCs and GSCs with high quality DNAs and RNAs. The BCR accrues clinical data from the Tissue Sources Sites (TSS) which contribute samples to TCGA. The CGCCs apply a variety of advanced technologies to analyze copy number, loss of heterozygosity, gene expression profiles (including miRNA), chromosomal aberrations and DNA methylation changes. The CGCCs provide quality-controlled, raw and analyzed data to the DCC. The creation of the DCC was significantly enabled by the work of the Cancer Bioinformatics Grid (caBIG) and the NCI's Center for Bioinformatics is a working member of the TCGA Management Group. The GSCs deposit sequence data to NCBI trace archive database, and provide analyzed data to the DCC and perform verification and validation on putative mutations. TCGA data are classified by dat type (for

example, clinical, mutations, gene expression) and data level (raw, processed, integrated and segmented). All TCGA data are deposited to the DCC for public or ore limited access that insures patient privacy protection. The web site is http://cancergenome.nih.gov/.

The first cancer studied by TCGA, GBM, the most common primary brain tumor in adults and is nearly uniformly fatal in 12 to 14 months of diagnosis. The integrated analysis of multidimensional genomic data from complementary technology platforms have proved very informative. In addition to the discovery of two new genes that have not been previously closely associated with GBM, findings from TCGA are also finaly confirming deregulation of RB, p53 and RTK/RAS/PI(3)K pathways as obligatory events in most, and perhaps all, GBMs, the patterns of mutations are likely to inform future therapeutic decisions for GBM. Patients with deletions or inactivating mutations in CDKN2A or CDKN2C or patients with amplifications of CDK4/CDK6 would be candidates for treatment with CDK inhibitors, an approach not likely to be effective in patients with RB1 mutation. Similarly, patients with PTEN deletions or activating mutations in PIK3CA or PIK3R1 might be expected to benefit from a PI (3) K or PDK1 inhibitor, whereas tumors in which the PI(3)K pathway is altered by AKT3 amplification might prove refractory to those modalities. The data also suggest a finite number of discrete subtypes of GBM based on genomic alterations in discrete pathways.

The data generated to date on the pilot project validates the feasibility and benefits of a systematic effort to rigorously, comprehensively, and reproducibly identify, quantify, and characterize these molecular alterations for specific tumor types and subtypes.

The major goals of this reissuance are to increase the throughput of the discovery pipeline to include the thorough genome characterization of four to six tumors per year by the GCCs and to directly link TCGA data integration and defined value-added analysis to tumor-specific cancer biology through the GDACs. The project will increase throughput by taking advantage of newer technologies, reducing the redundancy in technologies/platforms, streamlining the data analysis process, and by taking advantage of the improved tissue acquisition process developed in the course of the pilot project. Concentration of disease-level analysis in tumor-specific Genome Data Analysis Centers (GDACs) will ensure that analysis is informed by current knowledge in cancer biology.

TCGA will produce data at the individual sample and disease levels. At the sample level, TCGA will produce genomic characterization data (copy number, LOH, translocation detection, gene expression, epigenomic and mutation) and provide clinical data for each of the cases for each tumor type evaluated. For each disease, TCGA wil identify recurrent genomic abnormalities, recurrent combinations of abnormalities (within a data type and across data types), pathway networks, and correlations between clinical variables and recurrent genomic abnormalities and pathway networks. GCCs will produce sample-level data; GDACs will produce the disease level data. All data will be deposited rapidly to the DCC by the BCR, the GCCs, and the GDACs. The DCC will provide access to TCGA data in bulk download and through database queries.

Each GCC will be required to have in-depth, demonstrated expertise in the use of the particular technology/platform in in a production pipeline, as well as expertise in data normalization methods appropriate to the technology/platform. Each GCC will be responsible for implementing quality control assurance for the data produced by the center. Each GDAC will be required to have significant expertise in bioinformatics and data analysis, experience with caBIG, and in depth capabilities and expertise in cancer biology. Each GDAC will be required to document its analysis process and make them available through the DCC so that the community can replicate all analysis processes and reproduce results as needed.

The BCR is a production center that focuses on obtaining and processing TCGA biospecimens to obtain the highest quality analytes for the project. This aspect of the project is being funded through the contract mechanism and will continue to function as the tissue and clinical data collection center for TCGA; ensuring that standards are developed and implemented for all aspects of cancer and cancer-related biospecimen collection and management to support genomic characterization and sequencing.

The DCC, currently funded through a contract overseen by NCI's Center for Bioinformatics, will continue to function as a coalescing center for all data generated by TCGA.

The total budget for the genome characterization (minimum 10) and genome analysis centers (minimum two) is anticipated to range from $1.5 million to $3 million per year for five years.

The Integrative Cancer Biology Program: Centers for Cancer Systems Biology. Concept for a reissued RFA, first year set aside $22.5 million, eight to 10 awards for five years, estimated total $112.5 million. Program director: Daniel Gallahan, Division of Cancer Biology.

Through this proposed RFA, NCI intends to enhance the application of computational models and systems approaches to questions of human cancer across various sectors of the cancer research spectrum, specifically in the areas of cancer biology, experimental therapeutics, early interventions and susceptibility. There will be an explicit focus on the development and application of predictive, computational models by the interdisciplinary research teams. The centers within the ICBP will be called Centers for Cancer Systems Biology. As a cooperative agreement with NCI, the ICBP will create an overarching infrastructure for cancer systems biology research that establishes resources and tools and serves as a focal point for cancer systems biology activities and integrates them with other NCI efforts.

The CCSBs will:

—Assemble interdisciplinary research teams focused

on integrating cancer biology with the fields of engineering, mathematics, computational modeling, physics, and information sciences. Each center will be required to have as co-PIs cancer/clinician biologist and a mathematician/engineer/physical scientist.

—Develop and experimentally validate predictive computational models that will generate experimentally testable hypothosis about cancer biology and that will be applicable to in silico assessment of novel preventive and therapeutic strategies.

—Develop and promulgate educational, training, and outreach programs at all levels from college through post-doctoral training, to encourage the further growth and expansion of this field.

NCI will support the centers in any research area that has the potential to enhance understanding of human cancer.

The NCI Alliance for Nanotechnology in Cancer. Concept for an RFA reissue, first year set aside $35 million. Five to eight U54 awards, eight to 12 U01 awards, four to five K99/00 awards, and four to six R25 awards. Estimated total $145 million to $170 million over five years. Program director: Piotr Grodzinski, CSSI.

The goal of reissuing these RFAs is the continuation of the ANC as a coordinated program to further explore nanotechnology tools, devices, and formulations in applications relevant to cancer prevention, diagnosis, and treatment. New RFAs will be issued as an open competition. The Alliance structure will involve Centers of Excellence, platform projects, and training mechanisms. Each center will consist of three to five research projects focused on developing a complete solution in one of the following areas: 1. Early diagnosis using in vitro assays and devices or in vivo imaging techniques. 2. Multifunctional therapeutic solutions. 3. Devices and techniques for cancer prevention and control. 4. Tools for preventing, detecting, and eradicating metastasis.

Each of the centers will need to demonstrate the translational potential of the entire technological solution in at least two different organ systems. The investigators will be encouraged to develop at least one application for cancer of those organs, where the disease is characterized by low survival rates: brain, lung, ovary, and pancreas.

The satellite, smaller programs in the form of U01s (instead of R01s from the first issuance) will be maintained to promote further innovation in single project, multi-investigator environment. The training program based on K99/00 and R25 awards will be established in place of F32s/F33s. Nanotechnology Characterization Laboratory will continue its function of performing nanomaterials characterization towards translational efforts.

The proposed budget includes: $15 million to $32 million per year for five to eight U54 centers; $5 million to $7 million a year for eight to 12 U01 projects; —$4 million to $5 million for four to five K99/00 awards and four to six R25 awards.

Funding Opportunities:

RFA-CA-09-004: Innovative and Applied Emerging Technologies in Biospecimen Science. R21. Letters of Intent Receipt Date: Jan. 23; April 27; Aug. 30. Application Due: Feb. 23; May 27; Sept. 30. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-004.html. Inquiries: Richard Aragon, 301-496-1550; raragon@mail.nih.gov.

RFA-CA-09-005: Innovative and Applied Emerging Technologies in Biospecimen Science. R33. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-005.html.

RFA-CA-09-006: Application and Use of Transformative Emerging Technologies in Cancer Research. R21. Letters of Intent Receipt Date: Jan. 23; April 27; Aug. 30. Application Due: Feb. 23; May 27; Sept. 30. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-006.html. Inquiries: Richard Aragon, 301-496-1550; raragon@mail.nih.gov.

RFA-CA-09-007: Application and Use of Transformative Emerging Technologies in Cancer Research. R33. http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-007.html.

RFA-CA-09-008: Innovative Technology Development for Cancer Research. R21. Letters of Intent Receipt Date: Jan. 23, April 27, Aug. 30. Application Due: Feb. 23, May 27, Sept. 30. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-008.html. Inquiries: Richard Aragon, 301-496-1550; raragon@mail.nih.gov.

PA-09-036: PA-09-036: NIH Pathway to Independence Award. K99/R00. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-09-036.html. Inquiries: Nancy Lohrey, 301-496-8580; lohreyn@mail.nih.gov.

PA-09-039: Mentored Quantitative Research Development Award. K25. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-09-039.html. Inquiries: Sonia Jakowlew, 301-496-8580; jakowles@mail.nih.gov.

PA-09-040: Mentored Research Scientist Development Award. K01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-09-040.html. Inquiries: LeeAnn Bailey, 301-496-7344; baileyl@mail.nih.gov.

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PAR-09-051: NCI Mentored Clinical Scientist Research Career Development Award to Promote Diversity. K23. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-09-051.html.

PAR-09-052: NCI Mentored Clinical Scientist Research Career Development Award to Promote Diversity. K01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-09-052.html.

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Business & Regulatory Report

Product Approvals & Applications:

FDA Approves Mozobil With G-CSF For Autologous Stem Cell Transplantation

FDA granted marketing approval for Mozobil (plerixafor injection), used in combination with granulocyte-colony stimulating factor to mobilize hematopoietic stem cells for autologous transplantation in non-Hodgkin's lymphoma and multiple myeloma.

Mozobil is sponsored by **Genzyme Corp**. (NASDAQ: GENZ) of Cambridge, Mass. The product has also been granted orphan drug designation.

"Mozobil is an important advancement in the treatment of patients with certain types of cancer who require a stem cell transplant," said John DiPersio, professor, Washington University, St. Louis. "This product should

(Continued to page 2)

Oncology Management:

Co-Payments To Rise As Access To Drugs Tightens For Patients On Medicare Part D

Cancer patients enrolled in Medicare Part D plans will spend more on co-payments and face increased restrictions on access to these drugs in 2009, a study by **Avalere Health** and the **American Cancer Society** Cancer Action Network shows.

The research found that over the past four years Medicare stand-alone prescription drug plans have been shifting name-brand oral cancer drugs to higher formulary tiers.

In 2009, the large majority of PDPs placed name-brand oral oncology products—including Gleevec, Sutent, Tarceva, Thalomid, and Tykerb—on specialty tiers that require cost sharing of 26 percent to 35 percent for each prescription. For example, 84 percent of PDP enrollees are in plans that put Gleevec on their most expensive tiers (fourth or higher) in 2009, up from 39 percent in 2006.

"This pattern of shifting the costs of branded medications to patients needs to be scrutinized, especially in light of the economic difficulty being experienced by so many seniors," said Valerie Barton, vice president at Avalere Health.

"Shifts in drug coverage can limit access to treatment for people with cancer, significantly reducing their treatment options or even requiring a stoppage of treatment," said Daniel Smith, president of ACS CAN. "We urge policymakers to pay close attention to how these changes impact people with

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Mozobil Approved For NHL, Multiple Myeloma Transplants

(Continued from page 1)

become an integral part of the treatment regimen for transplantation because of the benefits it offers to patients, physicians and transplant centers."

Mozobil mobilizes hematopoietic stem cells from the bone marrow into the bloodstream where they can be collected, making it more likely for cancers to proceed to transplant, the company said.

In pivotal studies of the agent, 59 percent with NHL who received Mozobil and G-CSF collected the target number of 5 million stems cells/kg of body weight in four or fewer apheresis sessions compared with 20 percent with placebo. The median number of days to reach the target cell count was three days for the Mozobil group and not evaluable in the placebo group. Seventy-two percent with MM who received the drug and G-CSF collected the target number of at least 6 million stem cells/kg of body weight in two or fewer apheresis sessions compared to 34 percent with placebo. The median number of days to reach the target cell count was one day for the Mozobil group and four days for the placebo group. The target numbers of stem cells in the pivotal studies were chosen based on literature that suggests that reaching the targets can help to facilitate engraftment.

Updated 12-month follow-up findings showed that graft durability rates for the Mozobil plus G-CSF and placebo plus G-CSF arms were comparable, the company said.

In addition to its expected benefits in NHL and MM, Mozobil may offer economic benefits for transplant centers. The product could decrease the number of apheresis days and provide transplant centers with predictable and efficient use of the apheresis center, the company said. The treatment also could reduce the number who require a second mobilization procedure due to a failure to mobilize sufficient numbers of cells with current therapy of G-CSF alone.

Genzyme said it will commercialize Mozobil in the U.S. through a blood and marrow transplant sales force, part of the Transplant and Oncology business unit.

The company said it has submitted an application in Europe for approval of Mozobil and expects approval of the product in the second half of 2009.

Mozobil, a small molecule CXCR4 chemokine receptor antagonist, increases the number of stem cells in circulation in the blood in non-Hodgkin's lymphoma and multiple myeloma.

ImClone Systems Inc. (NASDAQ: IMCL) and **Bristol-Myers Squibb Co**. (NYSE: BMY) said they submitted an application to FDA to broaden the use of Erbitux (cetuximab) to include first-line treatment of advanced non-small cell lung cancer in combination with platinum-based chemotherapy(cisplatin/vinorelbine).

BMS and ImClone, co-owners of Erbitux in North America, said ImClone would be notified in February whether the submission would be accepted.

The submission is based on data from the pivotal, multinational FLEX (First-line in Lung cancer with Erbitux) phase III study which demonstrated that the addition of Erbitux to cisplatin/vinorelbine significantly increased overall survival in the first-line treatment in advanced NSCLC when compared with cisplatin/vinorelbine alone, the companies said. The improvement in overall survival, the primary endpoint, was observed across all histological subtypes, performance status, age, previous smoking history, and gender groups, the companies said.

The FLEX study, conducted by Merck KGaA, of Darmstadt, Germany, enrolled 1,100 Stage IIIB with malignant pleural effusion or stage IV NSCLC with no prior chemotherapy. Treatment with Erbitux in combination with cisplatin/vinorelbine, prolonged median overall survival by 1.2 months when compared to cisplatin/vinorelbine treatment alone (11.3 months vs. 10.1 months) with a hazard ratio of 0.871 [95 percent Confidence Interval (CI) = 0.762-0.996], p=0.044.

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Grade 3/4 adverse events were reported in 91 percent in the Erbitux plus cisplatin/vinorelbine arm compared with 86 percent in the cisplatin/vinorelbine alone arm, the companies said. Grade 3/4 adverse events reported in the Erbitux plus cisplatin/vinorelbine versus cisplatin/vinorelbine alone arms included: neutropenia (53 percent vs 51 percent), febrile neutropenia (22 percent vs 15 percent), anemia (14 percent vs 17 percent), grade 3 acne-like rash (10 percent vs <1 percent), diarrhea (5 percent vs 2 percent), and infusion-related reactions (4 percent vs <1 percent).

ImClone also said it has received FDA approval for multi-product biologics production in its BB50 manufacturing facility.

"The multi-product FDA approval of BB50 significantly enhances ImClone's operational flexibility as we scale up production of our pipeline of proprietary antibodies for the growing number of phase II and phase III trials that will be commencing in the next year," said Richard Crowley, senior vice president, biopharmaceutical operations at ImClone.

The 250,000-square-foot multi-suite BB50 facility received FDA approval to manufacture Ebitux (cetuximab) in 2007, the company said. Together with the BB36 manufacturing facility, ImClone said it has a total production volume capacity of up to 140,000 liters at its Branchburg, N.J., campus. This is among the largest antibody manufacturing capacities in the biotechnology industry and is a component of the ImClone fully integrated operations supporting the development and commercialization of antibodies, the company said.

Three antibodies in the ImClone pipeline are now entering late stage clinical development, with the first beginning a phase III trial earlier this year. IMC-1121B, which targets the vascular endothelial growth factor receptor-2, is in phase II studies for metastatic melanoma, liver, non-small cell lung, ovarian, prostate and renal cancers. A phase III study of the antibody in metastatic breast cancer is beginning enrollment, and phase III testing in gastric cancer may begin in 2009. IMC-A12 targets the insulin-like growth factor-1 receptor is in phase II studies in breast, prostate, pancreatic, colorectal, liver and head and neck cancers, as well as sarcoma. And IMC-11F8, a fully human IgG1 monoclonal antibody targets the epidermal growth factor receptor. IMC-11F8 is in phase II testing for metastatic colorectal cancer, the company said.

Kiadis Pharma of Amsterdam said FDA has granted Orphan Drug Designations to Reviroc for two types of Non-Hodgkin Lymphoma: One ODD is for diffuse large B-cell lymphoma and the other one is for follicular lymphoma.

The agent is under development to eliminate blood cancer cells in autologous transplants for end stage blood cancer, the company said.

The Committee for Medicinal Products for Human Use, a unit of the European Medicines Agency has adopted a positive opinion and is recommending to grant a marketing authorization for Firmagon (degarelix), a GnRH receptor antagonist for advanced, hormone-dependent prostate cancer.

The agent is sponsored by **Ferring Pharmaceuticals**, a Swiss biotherapeutics company.

In phase III studies degarelix produced a significant reduction in levels of testosterone, within three days in more than 96% of study patients. Testosterone plays a major role in the growth and spread of prostate cancer cells.

The data show that degarelix provided an extremely fast effect on testosterone levels, close to the immediate effect achieved with orchidectomy, the company said.

The phase III study compared monthly administration of degarelix with monthly luteneising hormone releasing-hormone agonist leuprorelin's 7.5 mg in a 12-month randomised, open-label, parallel-group study in prostate cancer patients. In comparison to leuprorelin, degarelix suppressed serum testosterone and Prostate Specific Antigen significantly faster. In addition, degarelix was able to sustain these low levels during the entire 12-month study, the company said.

By day three of the study, testosterone levels were suppressed to 0.5ng/mL in 96.1% of patients in the degarelix arms of the study compared to 0% in the leuprorelin arm. By day 14, 100% of patients in the degarelix arms achieved suppression of testosterone levels at =0.5ng/mL compared to 18.2% in the leuprorelin arm.

After 14 days of treatment, PSA levels had declined in the degarelix treated patients by a median of 64%, while patients who were administered leuprorelin saw an 18% decline. Both treatments were well tolerated and showed similar side effect profiles. The most common side effects are hot flushes, injection site pain, injection site erythema,

increased weight, nasopharyngitis, fatigue and back pain.

Ferring said it plans to launch the agent in Europe in the first quarter of 2009 and is also

awaiting an imminent FDA decision on approval for commercialisation in the US. It is expected that commercialisation in other key global markets will follow during 2009 and 2010 once approval is received from the relevant local regulatory authorities.

Oncology Management:

Medicare Shifting Drug Costs To Patients, Analysis Finds

(Continued from page 1)

cancer. At the same time, it is critical that people with cancer understand their health coverage and the potential hurdles that may impact their treatment."

In addition to changing tier placement, PDPs in 2009 are increasing their use of prior authorization to control access to branded cancer drugs. The Avalere-ACS CAN research found that Gleevec had the largest increase in the number of PDPs requiring prior authorization, with 70 percent of plans requiring it, up from 35 percent in 2006. Tarceva had the next highest increase, with 62 percent of plans requiring prior authorization in 2009, up from 35 percent in 2006. Thalomid was next, with 68 percent of plans requiring prior authorization in 2009, up from 43 percent in 2006.

Geography and plan choice influence how much a patient spends out-of-pocket in Medicare Part D. Avalere and ACS CAN modeled hypothetical drug regimens for women with breast cancer and found that total out-of-pocket costs for a woman enrolled in AARP MedicareRx Saver in Florida will be $1,985, while total out-of-pocket costs for beneficiaries enrolled in Humana PDP Standard in California will average about $2,551.

Avalere said it continues to analyze Medicare drug benefit data. Since the inception of the Medicare drug program, Avalere has used its proprietary DataFrame database to track trends in drug pricing, plan strategy and structure, and the beneficiary experience.

ACS CAN is an advocacy affiliate of the American Cancer Society.

Clinical Trials:

Merck Gives $1M To NCCN For Clinical Trials Of Zolinza

National Comprehensive Cancer Network of Fort Washington, Penn., said it received a $1 million research grant from Merck & Co. Inc. to conduct clinical trials on combinations of its cancer agent Zolinza (vorinostat), with radiation/chemoradiation in selected locally advanced non-metastatic cancers and areas of unmet medical need.

Vorinostat, a histone deacetylase inhibitor, is used for cutaneous T-cell lymphoma when the disease persists, worsens, or returns during or after treatment with other systemic therapies, the company said. In preclinical studies, the drug has shown activity in a range of cancers and shows promise when used in combination with chemotherapy and other targeted anti-cancer agents.

The research will focus on combinations of vorinostat in selected locally advanced non-metastatic cancers including non-small cell lung cancer, head and neck cancer, pancreatic adenocarcinoma, and brain metastases from a solid tumor with an emphasis on lung cancer, the company said.

"Vorinostat preferentially enhances the killing of tumor cells induced by radiation therapy," said Jose Garcia-Vargas, senior medical director, oncology clinical research, Merck Research Labs.

The NCCN Oncology Research Program facilitates all phases of clinical research by identifying clinical investigators and initiating trials at NCCN member institutions.

Aposense Ltd. of Petach-Tikva, Israel, said it has begun a phase II, multi-center study of its [18F]-ML-10 compound for molecular imaging of apoptosis at Memorial Sloan-Kettering Cancer Center, following approval by its Institutional Review Board.

The study would evaluate the safety and efficacy of the compound in early assessment of response of metastatic brain tumors to high-dose, single-fraction radiotherapy, the company said.

"Functional imaging tools can identify biological changes that occur in a tumor as a result of treatment. said Kathryn Beal, radiation oncologist at Memorial Sloan-Kettering Cancer Center and principal investigator. "The changes may act as early surrogate markers, which can significantly improve the way we treat patients."

The 30-to-60-patient study would detect response to treatment of brain metastases, within several days after treatment, the company said. Apoptosis will be observed by mapping the uptake of [18F]-ML-10 within the tumor by using a PET scan, to be performed prior to treatment and at two other points within one week after treatment. Changes in the [18F]-ML-10 uptake will be compared with changes in tumor size two months after treatment according to MRI. The study end-points include assessment of apoptotic changes occurring

within days after treatment, and the accuracy of these changes in predicting treatment results, the company said.

Cylene Pharmaceuticals of San Diego announced the initiation of a phase II trial of quarfloxin (CX-3543) in patients with carcinoid/neuroendocrine tumors (C/NET), which are malignant cancers arising from neural crest cells.

In the open-label study, quarfloxin will be administered to patients with low or intermediate grade C/NET, including those receiving concomitant treatment with a stable dose of octreotide. This multi-centered study will include an assessment of improvements in patients' symptoms and biochemical markers, in addition to RECIST tumor response measurements, the company said. The study is expected to enroll up to 25 patients at several leading cancer centers.

"Quarfloxin has demonstrated potent in vivo efficacy against a broad range of tumors and a considerable therapeutic window in preclinical antitumor models, and has a unique profile of concentrating in neural crest tissues," said Daniel Von Hoff, Cylene co-founder and vice president, medical affairs.

Quarfloxin is a small-molecule targeted cancer therapeutic derived from the validated fluoroquinolone class of drugs. Rationally designed to selectively inhibit ribosomal RNA biogenesis in cancer cells, quarfloxin disrupts the interaction between the Nucleolin protein and a G-quadruplex DNA structure in the ribosomal DNA template, a critical interaction for rRNA biogenesis and one that is amplified in cancer cells. As a result, quarfloxin selectively induces apoptotic cell death in cancers, the company said.

Eisai Corp. of Woodcliff Lake, N.J., said it initiate the first clinical trial evaluating Dacogen (decitabine for injection) compared to Vidaza (azacitidine) in intermediate-1, intermediate-2 or high-risk myelodysplastic syndromes.

The head-to-head trial will directly compare the agents with a primary endpoint of complete response rate, including marrow complete response, the company said.

"Previous to the introduction of the hypomethylating agents, supportive care was the only treatment option for living with MDS," said Hagop Kantarjian, chairman of the Leukemia Department and professor of medicine, University of Texas M.D. Anderson Cancer Center. "This study, for the first time, will provide physicians with important information to understand how these two agents compare when treating patients with MDS, who have a generally poor prognosis, with life expectancies shorter than those with lung cancer."

The randomized, multi-center, open-label 228-patient study in intermediate-1, intermediate-2 and high-risk MDS, will be randomized on a 1:1 ratio to either Dacogen or Vidaza, the company said. Each treatment arm will be stratified by IPSS risk group and type of MDS, primary vs. secondary.

"Findings could clarify the fundamental differences between Dacogen and Vidaza and ultimately help clinicians with treatment selection," said Anastasios Raptis, co-director, Myelodysplastic Syndrome Program, attending, Stem Cell Transplant Program and clinical assistant professor of medicine, University of Pittsburgh School of Medicine. "The study takes into account recent data that suggest that treatment should continue for as long as they receive clinical benefit or until their disease progresses."

Dacogen was approved by FDA in 2006 for myelodysplastic syndromes including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, chronic myelomonocytic leukemia), and Intermediate-1, Intermediate-2 and High-Risk International Prognostic Scoring System groups.

EntreMed Inc. (NASDAQ: ENMD) of Rockville, Md., said it has met the primary endpoint for the efficacy portion of the open label phase I/II study of MKC-1 in combination with pemetrexed (Alimta) in non-small cell lung cancer.

The study was designed to first evaluate a dose of MKC-1 to be used safely in combination with Alimta. Patients were subsequently enrolled into the phase II portion where the primary endpoint was tumor response. The primary endpoint has been met and EntreMed said it is considering options for further studies in NSCLC. Options include the continuation of the current single arm study or a randomized phase II study in the same population.

MKC-1 is an orally-active cell cycle inhibitor with in vitro and in vivo efficacy against a range of solid tumor cell lines, including multi-drug resistant cell lines, the company said. Data from studies with MKC-1 demonstrate broad-acting antitumor effects, showing tumor growth inhibition or regression in multiple preclinical models, including paclitaxel-resistant models.

The agent inhibits mitotic spindle formation, prevents chromosome segregation in the M-phase of the cell cycle, and induces apoptosis, the company said. Furthermore, MKC-1 inhibits the Akt-mTOR signaling pathways, which may occur through inhibition of the mTOR/rictor pathway.

ImClone Systems Inc. (NASDAQ: IMCL) of New York, N.Y., said it has begun enrollment in a randomized phase II trial of IMC-A12 in previously treated HER2-expressing locally advanced or metastatic breast cancer.

IMC-A12 is an IgG1 anti-insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibody.

The primary objective is to evaluate the antitumor activity of the combination of capecitabine and lapatinib with and without IMC-A12 in HER2-expressing stages IIIB, IIIC, or IV breast cancer that has progressed on trastuzumab-containing treatment, the company said. The study is being conducted by the North Central Cancer Treatment Group, sponsored by NCI.

NCCTG, which is comprised of a network of more than 1,000 community-based cancer treatment clinics in the U.S., Canada and Mexico that work with Mayo Clinic, also is working with other cooperative groups to recruit patients through the NCI Cancer Therapy Study Unit. The study is one of 10 phase I and II trials of the drug sponsored by the NCI Cancer Therapy Evaluation Program.

"The study of IMC-A12 is a rationally designed study based on preclinical evidence suggesting that there are interactions between the HER2 and IGF-IR that may be exploited to improve treatment outcome for women with HER2-expressing breast cancer," said Eric Rowinsky, chief medical officer and executive vice president of ImClone. "The NCCTG is seeking to determine if the anticancer activity of the combination with lapatinib and capecitabine, which is an approved treatment for HER2-expressing breast cancer that is no longer responsive to trastuzumab, can be improved by the addition of IMC-A12."

The 154-patient study of IMC-A12 will be randomized for either capecitabine and lapatinib (one-third) or the same treatment plus IMC-A12 (two-thirds), the company said. Treatment in both arms will be continued as long as benefit is shown. The primary endpoint is progression-free survival.

"Research asserts that HER2-positive breast tumors may resort to the IGF-1R pathway as an adaptive growth mechanism to therapies that target the HER2 cell proliferation mechanism," said Paul Haluska, assistant professor of oncology at Mayo Clinic and lead scientist on the phase II study. "The IGF-R pathway is a key mechanism of resistance in cancers that adapt to HER2-targeted therapy, as well as chemotherapy. Now that we have a therapeutic agent in IMC-A12 to block IGF-1R, we are able to conduct this study to determine if co-inhibiting IGF-1R and HER2 in combination with the chemotherapy agent capecitabine will benefit patients with HER2-positive breast cancers."

Light Sciences Oncology Inc. of Bellevue, Wash., said it has completed enrollment in a global phase III trial of Light Infusion Therapy for unresectable hepatocellular carcinoma.

The two-armed, randomized 200-patient trial is taking place at sites in the Philippines, Korea, India, Malaysia, Thailand, Hong Kong, Singapore, Serbia, Poland, Croatia, and Italy, the company said. The primary endpoint is to assess survival with Litx therapy treatment versus standard-of-care therapies.

The single-use, disposable Litx device uses light-emitting diodes to activate LS11 (talaporfin sodium), a light-activated, water-soluble drug, the company said. An LS11 molecule activated by the system results in the production of singlet oxygen, which kills target tissues with minimal side effects. The system uses low-intensity light that causes vascular closure and apoptosis. Illumination with low-intensity light activates each molecule of LS11 many times, resulting in a continuous supply of singlet oxygen molecules, the company said.

There is no evidence that Litx produces the typical side effects from the systemic damage to rapidly-dividing normal cells caused by chemotherapy, radiation, and other cancer treatments, the company said.

Medarex Inc. (NASDAQ: MEDX) of Princeton said it has initiated a phase Ib trial for MDX-1106 (ONO-4538: development code of Ono Pharmaceutical Co. Ltd.), a fully human anti-PD-1 antibody for cancer treatment.

Studies suggest the PD-1 signaling pathway plays a role in tumor evasion and escape from host immune responses and promotes the persistence of chronic viral infections, the company said.

The open label 76-patient trial would evaluate the safety and tolerability of repeated dosing of the agent in solid tumors and will also assess the anti-tumor activity of multiple doses of MDX-1106 (1, 3 or 10 mg/kg).

The tumors to be studied include malignant melanoma, renal cell cancer, castrate-resistant prostate

cancer and non-small cell lung carcinoma.

"Anti-PD-1 antibodies could represent the next stage in immunotherapy with a promising mechanism of action and potential for marked synergy with anti-CTLA4 antibodies," said Geoffrey Nichol, MBChB, senior vice president of product development at Medarex. "Preliminary results from our single-dose phase I study demonstrated an acceptable safety profile and initial evidence of anti-tumor activity in cancer."

In May 2005, Ono entered into a collaboration agreement with Medarex to research and develop a fully human anti-PD-1 antibody in cancer.

The companies would share the costs and responsibilities of research and product development up to the completion of a phase II study in each party's territory. Thereafter, each company will be fully responsible for any continued development and any commercialization in its exclusive territory; the Medarex exclusive territory is North America, and the Ono exclusive territory is all areas outside of North America.

MDX-1106/ONO-4538 is a fully human antibody that targets and inhibits the function of PD-1, a receptor expressed on the surface of activated lymphocytes. The binding of PD-1 with one of two ligands (PD-L1 or PD-L2) is a negative regulation pathway that suppresses or inhibits activated lymphocytes. Research has noted increased PD-1 expression levels on antigen specific T-cells in both the oncology and chronic infectious disease settings, as well as a strong correlation between increased PD-L1 expression on tumors and a negative survival prognosis in cancer.

Preclinical studies indicate that antibodies targeting the PD-1 signaling pathway reinvigorate antigen-specific T-cell responses and promote an immune response to fight tumors and infectious diseases, the company said.

PTC Therapeutics Inc. of South Plainfield, N.J., announced the initiation of two clinical trials of the company's product candidate PTC299 in adult patients with solid tumor cancers and Kaposi Sarcoma, a HIV-related cancer.

PTC299 is an orally delivered, investigational new drug that offers an innovative approach to anti-angiogenesis, limiting the formation of new blood vessels for tumors.

Based on the pre-clinical and clinical studies to date, PTC299 has the potential to meet significant unmet medical need for patients with different types of cancer, the company said.

An open-label phase 1b clinical trial will enroll up to 42 patients with locally advanced or metastatic solid tumors in order to evaluate the safety and efficacy of multiple doses of PTC299 alone and in combination with Taxotere (docetaxel) chemotherapy. The primary objective of the study is to determine the maximum tolerated dose of PTC299.

The trial will also assess the overall safety profile of the drug when administered alone and in combination with chemotherapy, evaluate its effect on the production of vascular endothelial growth factor (VEGF), its antitumor activity, and its pharmacokinetics.

The study will be conducted at Memorial Sloan-Kettering Cancer Center.

A second open-label phase I/II clinical trial will enroll up to 45 patients with Kaposi's sarcoma associated with human immunodeficiency virus infection. Kaposi's sarcoma, a cancer that develops from the cells that line blood vessels, is the one of the most common HIV-related cancers.

The primary objectives of the study are to determine the maximum tolerated dose of PTC299 and to evaluate the overall safety and efficacy profile of the drug as therapy for Kaposi's sarcoma. The study will be conducted by the AIDS Malignancy Consortium, a multicenter clinical trials group supported by the National Cancer Institute, and will be conducted at AMC sites in the U.S.

The study will be led by Susan Krown, of the Melanoma and Sarcoma Service, Memorial Sloan-Kettering Cancer Center, who chairs the AMC's Kaposi's Sarcoma Working Group.

PTC299 is an orally administered small-molecule investigational drug that in preclinical models selectively blocked the pathological, or disease-related, production of the protein VEGF in tumors acting upstream of current therapies, while sparing physiological VEGF expression. VEGF plays a critical role in angiogenesis, or the formation of new blood vessels, the company said.

SuperGen Inc. (NASDAQ: SUPG) of Dublin, Calif., said it has received clearance to initiate clinical trials with SGI-1776, an inhibitor of Pim kinases.

The clearance of its original Investigational New Drug Application triggers a $5.2 million milestone payment to the former stockholders of Montigen Pharmaceuticals Inc, the company said.

The milestone payment will consist of $2.8 million in cash payments and the issuance of $2.4 million in equity, representing 1.5 million shares of SuperGen

common stock.

SuperGen said it would begin a phase I trial to evaluate the safety, tolerability and pharmacokinetic profile of the agent, a novel, orally administered, small molecule anticancer compound.

The trial program would target solid tumors with emphasis on hormone refractory prostate cancer and refractory non-Hodgkin's lymphomas, the company said.

The solid tumor types overexpress the Pim kinase family of proteins at a high frequency, the company said. Overexpression of Pim-1 kinase is a marker of poor prognosis. A second phase I/II study is planned in refractory leukemias in which Pim kinases are also overexpressed, and correlated with poor prognosis and drug resistance, the company said.

The clearance of the SGI-1776 IND application represents a validation of our CLIMB technology platform and its ability to generate first-in-class drug candidates," said James Manuso, president and CEO of SuperGen.

Treatment with SGI-1776 produces significant tumor regressions in animal models of acute myeloid leukemia and suppression of solid tumor growth and biomarker modulation in models of prostate adenocarcinoma and non-Hodgkin's lymphoma, the company said.

In non-clinical studies, SGI-1776 has shown good oral bioavailability and sustained inhibition of Pim kinase targets in vivo following both single and repeated oral dosing.

The three Pim kinases, Pim-1, Pim-2 and Pim-3, are conserved serine-threonine kinases that are regulators in signaling pathways implicated in cancer, the company said.

Deals & Collaborations:

BioWa Licenses Technology To GSK For Therapeutics

BioWa Inc. of Japan said it licensed to **GlaxoSmithKline** (NYSE:GSK) its Potelligent Technology in developing and commercializing select GSK antibodies with enhancement of antibody-dependent cellular cytotoxicity.

Under the agreement, BioWa said it would provide GSK with non-exclusive commercial rights to the technology for multiple antibodies. In return, BioWa would receive technology access fees, and milestone payments and royalties from resulting GSK products.

Potelligent Technology improves antibody therapeutics by enhancing ADCC, one of the mechanisms of action for antibody therapeutics. The technology reduces the amount of fucose in the carbohydrate structure of an antibody using a proprietary fucosyltransferase-knockout CHO cell line as a production cell.

BioWa is a wholly owned subsidiary of Kyowa Hakko Kirin Co. Ltd..

Fujirebio Diagnostics Inc. of Malvern, Penn, and **Roche Diagnostics** of Basel, Switzerland, announced a worldwide license and supply agreement for the HE4 ovarian cancer test. Under the agreement, Roche will develop an assay kit utilizing Fujirebio Diagnostics' HE4 test on its automated immunoassay analyzers.

The HE4 test was developed by Fujirebio Diagnostics to be used in conjunction with the company's existing CA125 biomarker, the current gold standard for monitoring ovarian cancer.

This combination of biomarkers, as published clinical data shows, provides clinicians with a diagnostic tool that can provide higher sensitivity and specificity than CA125 alone. Improved sensitivity and specificity should allow clinicians to distinguish between benign and malignant pelvic masses more accurately, helping to ensure that patients receive appropriate therapy earlier.

HE4 in a manual format is currently FDA-cleared for monitoring recurrent or progressive disease in patients with epithelial ovarian cancer (EOC), and CE-marked in Europe as an aid in estimating the risk of EOC in premenopausal or postmenopausal women presenting with pelvic mass. The HE4 manual test and corresponding Risk of Ovarian Malignancy Algorithm are pending clearance by the FDA for use in women who present with a pelvic mass.

Mylan Inc. (NYSE: MYL) of Pittsburgh said it subsidiary, Mylan Pharmaceuticals Inc., has entered into a settlement agreement with **Novartis Pharmaceuticals Corp**., Novartis Corp. and Novartis International AG, related to Letrozole Tablets, the generic version of the Novartis drug, Femara.

Under the agreement, Mylan said it would provide a patent license to market Letrozole Tablets, 2.5 mg, prior to its expiration.

Letrozole Tablets, which are used in breast cancer treatment, had U.S. sales of $470 million for the 12 months ending Sept. 30, the company said.

Mylan said it was the first company to file a complete Abbreviated New Drug Application containing a Paragraph IV certification for the product.