THE CANCER LETTER

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Obama Plan Would Double Cancer Funding, Increase Clinical Trial Enrollment To 10%

By Paul Goldberg

The Obama campaign laid out a clear plan for combating cancer, and now the question is how closely President Obama would follow the plan.

The Obama cancer plan calls for doubling federal expenditure on cancer research over the next five years, increasing accrual to clinical trials to 10 percent of all cancer patients, reinstating the requirement that Medicare pay for routine care costs associated with clinical trials, and instituting public health measures that include colorectal cancer screening and smoking cessation.

Though the authors aren't listed on the plan, sources close to the campaign said the document was written by Harold Varmus, president of Memorial Sloan-Kettering Cancer Center and former NIH director, Gilbert Omenn, professor of internal medicine, human genetics and public health

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FDA News:

Cancer Groups Urge FDA To Spell Out Standards For Data Collection In Time-To-Progression Trials

By Paul Goldberg

Several cancer groups, pharmaceutical companies, and NCI are lobbying FDA to spell out how data collection procedures and evidence requirements have changed as a result of the agency's decision to approve drugs based on their ability to delay cancer progression.

In the process of approving recent applications, the agency has asked for a variety of changes in the methods clinical trialists use to collect data. Demanding these changes, the agency argued that unlike survival, the old, unambiguous metric that used to be the gold standard for drug approval, time to progression is subject to bias and therefore requires different methodology.

Many issues now discussed by the agency, cancer groups, and industry crystallized in the context of the controversy over the trial of the Genentech drug Avastin (bevacizumab) that was used as a basis for the supplemental New Drug Application in metastatic breast cancer (The Cancer Letter, Dec. 14, 2007; Feb. 15, Feb. 22, Deb. 29, 2008).

The application received an accelerated approval earlier this year.

Now, drug companies and NCI-sponsored clinical trials cooperative groups are eager to hear the agency answer some fundamental questions.

—Should trials that seek supplemental approvals collect as much data on minor toxicities as trials designed to support New Drug Applications? If

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Plan Restores Clinton's Order To Pay Routine Costs In Trials

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at the University of Michigan, Francis Collins, former director of the National Human Genome Research Institute, and Eric Whitaker, executive vice president for strategic affiliations and associate dean for community-based research at the University of Chicago Medical Center.

A Call To Eliminate Barriers To Coordination

In addition to increasing the research budget, the plan calls for boosting funds for FDA's cancer programs and coordinating the oncology portfolio throughout the government.

"Currently, several federal agencies are focused on different aspects of tackling cancer," the document states. "NCI focuses on research, CDC on cancer control, FDA on regulating cancer-related drugs, and the Centers for Medicare and Medicaid Services on paying for cancer-related care. Too often, efforts across these agencies are poorly coordinated, leading to gaps in our national strategy to combat cancer. As president, Barack Obama will immediately direct his Secretary of Health and Human Services, in collaboration with agency officials, academic researchers, cancer survivors and advocates for people with cancer, and state public health officials, to comprehensively examine the various cancer-related efforts of federal agencies, and provide recommendations to eliminate barriers to effective coordination across federal agencies and between the federal government and other stakeholders."

The NCI-funded clinical trials cooperative groups, the cash-starved program that has the capacity to address research questions pharmaceutical companies wouldn't address, stands to get a boost under the Obama plan.

The plan would increase "NCI reimbursement for patient participation in clinical research." Currently, the groups receive $2,000 per patient, not nearly enough to cover costs.

Also, the NCI director would be instructed "to identify regulatory barriers that prevent the timely implementation and completion of successful clinical trials." The government would be able to meet its 10-percent accrual goal by requiring coverage of clinical trial costs in the public and private insurance plans that would be offered through the proposed National Health Insurance Exchange.

The cancer centers stand to benefit from funds for training clinical researchers. "In addition, investing in health information technology and practice redesign will free up time of physicians and clinical personnel to care for patients, not cater to insurance companies," the document states.

Centers for Disease Control and Prevention would be directed to "develop and carry out an epidemiologic study on cancer survivors to understand their long-term health needs," the document sates. Also, CDC would be directed to "identify and replicate successful support group programs for cancer survivors."

CDC would receive $50 million new funds to "determine the most effective approaches that assist not only navigation of cancer patients through diagnosis and treatment processes." The "cancer navigator" program is being developed by NCI.

Though NCI directors are Presidential appointees, their positions haven't been viewed as political. As a result, some directors have remained on the job for some time after changes of administrations.

Samuel Broder, a George H.W. Bush appointee, stayed on for a year through the beginning of the Clinton administration, and Richard Klausner, a Clinton appointee, stayed on for nearly a year into the George W. Bush administration.

Obama's plans reflect considerable depth of thought about oncology. The Clinton administration promised a "national action plan on breast cancer" and a reform of the healthcare system, but both programs quickly bogged down, and Clinton's vision appeared to develop as he went along.

Bush appeared to have adopted his parents' cancer

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cause, the National Dialogue on Cancer, and ultimately appointed one of the Dialogue leaders, Andrew von Eschenbach, to run NCI.

During his three years as director, von Eschenbach politicized the institute, reorganizing it around his blatantly unachievable goal to "eliminate suffering and death due to cancer" by the year 2015. Von Eschenbach was so political that he made a campaign appearance, endorsing a Florida Republican congressman member who was facing serious opposition (The Cancer Letter, Feb. 3, 2006).

Does Obama Have A Candidate For NCI?

Though the current NCI director, John Niederhuber, has signaled to associates that he would like to stay on in the job after Bush leaves the White House, his chances of success would depend on how effectively he distances himself from his predecessor who recruited him to NCI and the administration that appointed him.

In this regard, Niederhuber's balance sheet is complicated. He is credited with having saved the Specialized Programs of Research Excellent (SPORE) grants from elimination by von Eschenbach, and, as soon as his predecessor moved on to head FDA in 2006, Niederhuber abandoned the 2015 goal, thereby ushering the institute back into the world of real things.

However, Niederhuber's signature program—the NCI Community Cancer Centers Program—is difficult to distinguish from the institute's long-running Community Clinical Oncology Program, which functions as a component of the cooperative groups.

Niederhuber's $9-million pilot program, which supports community hospitals to enter patients on clinical trials and begin biospecimen banking, is funded through a contract with SAIC-Frederick, the institute's contractor for the NCI-Frederick campus. The program was never formally reviewed by NCI's advisory groups (The Cancer Letter, Nov. 10, 2006).

Some advisory board members, as well as CCOP and cooperative group insiders view Niederhuber's program as an ill-advised waste of resources and a vote of no-confidence in the work of the groups.

Niederhuber's job performance may not have any bearing on his chances of staying on, as the new administration may have identified a candidate who stands poised to implement its detailed plans for oncology.

It's unclear whether Obama's plans, which were made public before the onset of the economic crisis, will be feasible at the time he moves into the White House. However, science groups are taking the President-elect at his word. Richard Marchase, president of the Federation of American Societies for Experimental Biology, applauded Obama pledge to double science funding, which extends to NIH, National Science Foundation, and Department of Energy Office of Science.

"Still, we acknowledge that the President alone cannot accomplish all that is needed to fulfill the great promise of biomedical research, and we will be reaching out to both parties in the new Congress to see that the promises of the campaign season are realized," Marchase said. "We also encourage Mr. Obama to appoint a Science Advisor by Jan. 20 and to promote the advisor to cabinet rank."

Pharmaceutical industry sources are expecting the new Administration to look for a way to force pharmaceutical companies into negotiations over the price of drugs covered by Medicare. A shift to generic drugs is also likely, and generic biologics have become more likely to be approved.

Three Bills On Health Care Reform, So Far

On Capitol Hill, at least three bills will address healthcare reform. One of these bills, introduced by Sen. Ron Wyden (D-Ore.) was recently introduced in the Senate. Sen. Max Baucus (D-Mont.), chairman of the Finance Committee, is expected to introduce a white paper on the principle of health care reform.

Sen. Edward Kennedy (D-Mass.), chairman of the Health, Education, Labor and Pensions Committee, has been working on a new version of the National Cancer Act.

Health systems researchers see an opportunity to find an alternative to the fee-for-service healthcare.

"CMS will need to accelerate projects and demos on different forms of payment to get costs under control," said Ezekiel Emanuel, an oncologist and chairman of the NIH Clinical Center's Department of Bioethics, whose book "Healthcare, Guaranteed: A Simple, Secure Solution for America" was published this summer.

"The President will have to decide how comprehensive a health care reform to propose," said Emanuel, whose brother, Rep. Rahm Emanuel (D-Ill.), was named the White House chief of staff. "Everyone seems to agree there needs to be payment reform to both hold down costs and improve quality. But we do not know the best way to pay doctors. So we need to have innovation in delivery system, which is going to be catalyzed by changes in payment. Everyone seems to agree fee-for-service is a terrible payment system, but no one knows the best payment mechanism. We need experiments to improve it."

FDA News:

Questions Of Standards Stem From E2100 Trial Of Avastin

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a drug's toxicity profile was established in the process of obtaining the initial approval, should trials aimed at obtaining supplemental approvals be required to compile comprehensive databases on Grade 1 and 2 toxicities?

—Should trials that measure time to progression be required to have central review of radiological data? In the past, when survival was the FDA gold standard, the agency required commercial sponsors to have central review of radiological images, but exempted the cooperative groups from this requirement.

However, during the Avastin breast cancer controversy, the agency changed that requirement, asking for a central reanalysis of data from the pivotal trial, E2100, conducted by Eastern Cooperative Oncology Group.

Tied to this are questions of whether all radiological data should be subjected to central review, or whether a randomly selected portion of cases should be reviewed by auditors.

—In addition to regulatory issues arising from E2100, the agency is being asked to define standards for approval of drugs and diagnostics that are intended for use together.

Diagnostics can be used to selecting patients who stand to benefit from specific oncology drugs. Alternatively, bad assays can be as harmful as bad drugs, in part because they can lead to misuse of drugs.

The problem is so daunting that new legislation, a restructuring of FDA, and new policies at Centers for Medicare and Medicaid Services would likely be required to fix it, insiders say.

"A bad tumor marker is as bad as a bad drug, but if we raise the bar, we need to reimburse appropriately to keep people in the field," said Daniel Hayes, clinical director of the Breast Oncology Program at the University of Michigan Comprehensive Cancer Center.

Hayes took part in a recent workshop that explored the need for change in the way FDA regulates oncology. The meeting was conducted by the Brookings Institution's Engelberg Center for Health Care Reform.

Cancer Groups Must Formulate Proposals To FDA

"Development of standards for collection of data or for monitoring of studies in cancer trials would help to move the field forward," said Jeffrey Abrams, acting associate director of the NCI Cancer Therapy Evaluation Program. "The whole community, both industry and the cooperative groups, would embrace some guidelines from the FDA that would help us to speed up drug development. That's what we are trying to do."

FDA appears to be willing to listen to these proposals. In fact, the agency's top officials took part in the Brookings workshop. However, any recommendations would likely go through the FDA Oncologic Drugs Advisory Committee.

"We are not saying that one needs 100 percent review of every single x-ray, and I think we are very interested in taking a look at alternative strategies that are the least burdensome, but provide to us an assurance that there is not a systematic bias that could be influencing the results," Richard Pazdur, director of the FDA Office of Oncology Products, said at the Brookings meeting Sept. 26.

Now it's up to the cancer groups to come up with specific proposals for the agency, sources said.

Insiders say that the most feasible would be a proposal to free drug developers from collecting comprehensive data on milder, Grade 1 and 2, toxicities in the context of sNDAs. This part of the agenda is coordinated by the American Society of Clinical Oncology.

Also, drug developers, particularly Avastin's sponsor Genentech, are mining their databases to determine the value of data on low-grade toxicities in previously conducted studies.

The questions related to the agency's requirements for central radiographic review are being spearheaded by NCI. The institute has conducted at least one retrospective study of biases inherent in central review, and additional studies of this sort are underway.

The remaining piece of the agenda—the development of assays used in conjunction with drugs—doesn't appear to have clear mechanism for follow-up, insiders said.

Several drug companies, Friends of Cancer Research, and the American Association for Cancer Research, the Pharmaceutical Research Manufacturers of America, are also involved in follow-up to the workshop.

The rules are of vital importance to NCI-funded cooperative groups, said Richard Schilsky, chairman of the Cancer and Leukemia Group B and president of ASCO, who took part in the Brookings meeting. "One thing we know for certain is that the most influential factor in whether or not a patient decides to participate in clinical trials is the doctor, whether or not the doctor recommends participation in a clinical trial," Schilsky

said at the meeting. "We also know that the majority of oncologists in this country are not happy with the cancer clinical trials process. And paper work is one of the reasons."

The pursuit of supplemental NDAs has become a major area of research for cooperative groups at a time when NCI isn't providing budget increases for the groups.

Changes in coverage policies also make these questions more important. In the past, it was enough for drug companies to get approvals for any indication, leaving it to physicians to prescribe these drugs off-label. However, with new drugs costing $10,000 or more a month, the companies have to get all uses on the label to make it possible for patients to obtain drug coverage.

The groups receive $2,000 in NCI funds for every patient placed on clinical trials, and can accept additional funds from drug companies to pay for expenses not covered by the institute.

FDA Envisions "Decision Tree" Guidance

In the context of sNDAs, low-grade toxicity data are gathered, but often not even looked at. "Most of the data are kept in a vault somewhere at the FDA or the sponsors' offices and never sees the light of day," Schilsky said.

"We had a general agreement on our panel that data collection for new drug applications should remain comprehensive," said Schilsky. "When we are bringing a drug that has never before been marketed for any human indication, we need to have confidence that this drug is safe and effective.

"But data collection requirements for supplemental applications should be based on a number of factors. What is the existing safety database for the agent that has been developed as part of this initial indication? What is its known pharmacology and known drug interactions? In a supplemental indication, what are the similarities of the study population to the initial indication, and what's the intended use in that population? If a drug is now going to be used in a combination, whereas previously it was evaluated as a single agent, what is the similarity of the new drug regimen to what the drug is already approved for? And, finally, we need to consider whether a supplemental application follows the initial full or accelerated approval of the agent."

However, Janet Woodcock, director of the FDA Center for Drug Evaluation and Research, said that in some cases, comprehensive collection of data is justifiable.

"Even after FDA approves a drug, there still is a great deal of remaining uncertainty about the performance of that drug out in the population," Woodcock said at the meeting. "If you have a model that your drug is going to be a home run and will have a survival advantage, that's one thing. But often you see marginal benefits at the end of the day. That's how it is in drug development, especially cancer drug development."

Collection of data can be in the sponsor's interest, Woodcock said. "Sponsors might want to go back and want to salvage that drug, and all of a sudden you are talking about a different benefit/risk analysis," she said.

If FDA issues a guidance, it would likely be in the form of a "decision tree," Woodcock said.

"Extensive data collection can lead to compilation of large amounts of unimportant data, and we only know the data are truly unimportant retrospectively, when we look back and we say that none of this really mattered," she said. "Minimal data collection may miss data elements that end up being critical if the trial results are not what was hoped, which is usually the case. How do you choose?

"How do we know what type of data collection we should do? How much do we know about the drug already? In effect, that influences what questions you are asking about the drug in a particular trial.

"Your factors for an already marketed drug would include how much data are available from previous trials? What questions do these data answer? How about the marketing experience? Often we learn a tremendous amount about drugs just by using them in the clinic. How much exposure is there? How different is the new patient population being studied? What is the indication?"

Woodcock said the agency exercises discretion in asking for comprehensive toxicity datasets for sNDAs.

Schilsky disagreed. "Many of us who go to end-of-phase II meetings actually pretty much hear the same thing in every discussion, and it usually surrounds comprehensive data collection, " he said.

The Value of Low-Grade Toxicity Data in sNDAs

Woodcock said FDA analyzes toxicity databases "in very detailed manner."

"You can see sub-clinical laboratory abnormalities," Woodcock said. "That's why FDA likes to see databases. Because often you won't see a clinical event in a trial, but you would see sub-clinical abnormalities that we will see that some patients are going to develop toward clinical symptomatology when the drug is more widely used. Often we are going to go back and analyze the trial

to see if there is a horrendous toxicity in the trial."

Gwen Fyfe, Genentech's vice president for clinical hematology and oncology, said that while data on Grade 3 and 4 toxicities are largely reliable, the data on Grade 1 and 2 toxicities aren't.

"What is enough when a randomized controlled trial has already shown that the drug is safe and effective?" Fyfe said at the meeting. "We already know in one context at least the kinds and severity of adverse events that we've seen. We know the impact on various laboratory values. We know the time course of those adverse events and whether they appear to have a cumulative effect."

Consider a typical patient, Mrs. Jones, Fyfe said.

"She is a 66-year-old white female who has just been diagnosed with metastatic breast cancer. Her physician agrees to refer her to a site that may be many hundreds miles away. She enrolls in a RCT of chemotherapy with biologic compound, which has already been approved in an RCT. However, it is being investigated for the first time in breast cancer.

"She is randomized to an oral 5-FU agent, plus a second investigational agent, and she will now be seen every three weeks at the trial site. But she will be followed by her local physician during cycles.

"She is treated at the site, she goes home, and in the first week she has severe nausea, vomiting and fatigue. She feels terrible. She has mild moderate diarrhea, dehydration, she feels weak. She has a sore throat, she has one episode of dizziness, some abdominal pain, she isn't hungry. Most of these symptoms resolve or substantially improve over seven days. She has a skin rash, or her hypertension gets slightly worse. She doesn't know that.

"All of these are expected adverse events in the context of this chemotherapy and this investigational agent. What will she remember when she goes back to her trial site three weeks later?"

Once the Mrs. Jones's symptoms are classified based on the NCI common toxicity criteria, the data become problematic.

"When Mrs. Jones goes back to the site, she needs to know when she started vomiting, when she stopped vomiting, what day was the worst, how many times she vomited or had diarrhea, how tired was she?" Fyfe said. "All those things are supposed to be relayed to the trial site and put into an adverse events database. If you go back to anything that happened to you three weeks ago, it's probably inappropriate to try to apply a lot of precision to what happened. Did you vomit five times or did you vomit six times? That could change the grade of your adverse event. As we look at adverse event reporting, we have to remember that the data come from the patients, and the patients will remember the two or three things that most bothered them, and that's probably what matters.

"If Mrs. Jones remembered everything, I estimate she had three Grade 3 or 4 adverse events, which is 24 fields on a case report form. She would have nine Grade 1 and 2 events, which is 72 fields on a case report form. All these events resolve, if she is going to be retreated. All will need to be re-entered, when they will almost certainly happen again on every cycle.

"If you just add up the number of events and the number of cycles, you can see that there is an enormous amount of paperwork describing something that has already been expected for these agents. We also have to ask, what will Mrs. Jones remember? Will it be as precise and complete as the NCI CTC would seem to suggest?"

Fyfe said a more reliable adverse event reporting system monitors what the doctors did to manage the patient's toxicities.

"Did they discontinue the treatment? Did they dose-modify the chemotherapy or the investigational agent? There is also a serious adverse event collection system, which will absolutely capture every life-threatening event, hospitalization requiring intervention, disability or anomaly. These adverse events are generally described in a little vignette or a history, and are often far more informative than Grade 3 and 4 frequency rates.

"If an event is not expected, it's reported right away, to protect a patient on the trial in case there is an unexpected interaction between the investigational agent and the background chemotherapy."

Meeting materials, which include Fyfe's slides, are posted at http://www.brookings.edu/events/2008/0926_cancer.aspx

Audits vs. Comprehensive Review of Radiology?

The controversy over central review of radiological data stems from the E2100 trial of Avastin in breast cancer.

The data—a spectacularly statistically significant increase in time to progression—triggered a standing ovation at the 2005 ASCO annual meeting. However, in September 2006, FDA bounced back the application, seeking additional documentation (The Cancer Letter, Sept. 15, 2006).

The problem was, E2100 was an open-label trial that wasn't designed to lay the foundation for an sNDA, and, at least initially, data collection wasn't scrutinized

as rigorously as it would be in a registration trial.

Until FDA's decision to send back the Avastin application for re-analysis, the agency required drug company trials to have central review, but exempted cooperative groups from this requirement.

Was FDA saying that acceptance of TTP had changed the rules of the game, and that *all* cooperative group trials would henceforth have to have central review? For cooperative groups, the agency's requirement amounted to a substantial increase in the cost of doing business.

Insiders wanted to know whether the agency had data to justify the view that the absence of central review introduced systematic bias in cooperative group trials measuring TTP.

In August, the Journal of Clinical Oncology published a paper by Lori Dodd *et al*., which suggests that blinded independent central review may be useful as an auditing tool to assess the reliability of marginally positive results. Based on a retrospective analysis of a randomized phase II trial, the paper argues that central review itself introduces bias because of informative censoring, which results from having to censor unconfirmed locally determined progressions.

Dodd is a biostatistician at the NCI Biometric Research Branch.

"In a standard case of an open-label, randomized superiority trial, when and how much blinded central review do we actually need?" James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis, said at the Brookings meeting. "Let's talk about the goal of actually deciding that we don't need to review every single case, and then, in fact, agree than an audit function is appropriate for some fraction of the cases, which by itself—if we agree on how it could be done—would save an enormous amount of time and energy. The goal is to be sure that there is no meaningful ongoing evaluation bias that can be discerned by central review."

At the meeting, NCI officials said they planned to conduct further analyses of randomized trials in order to derive sampling strategies that could provide a basis for replacing central radiology review. The studies could be published within six months, NCI officials said.

FDA hasn't demanded that cooperative groups conduct independent assessment for all their trials. "I certainly can't speak for the experiences of all the groups, but for CALGB, we have had a few phase 3 trials with PFS endpoints where FDA has recommended prospective collection of the images in the event that an independent radiology committee review is necessary, but has not been firm in requiring an independent review," Schilsky said in an email.

At the Brookings meeting, FDA's Pazdur indicated that the agency is open to seeing the data, especially if prospective studies are added to justify a move from central review.

The text of Pazdur's remarks follows:

I will start out with a little vignette here, a personal experience, I had when I was reviewing with our staff the Avastin trial, E2100, and the controversy that exists with PFS.

I don't think there is unanimous agreement in the oncology community regarding the use of this endpoint. During this review, I received probably 300 emails from one group saying "Dr. Pazdur, do not approve this drug. You are lowering the standard of oncology drug approval if you approve it."

The next week, I got 300 emails saying, "Dr. Pazdur, please use PFS as an endpoint for the approval of drugs, because we believe it is clinically important, and it's important for patients to have treatment options based on the use of this endpoint.

Although we have here a group that is "the converted," we also should know that there is a group out there that FDA also will hear from that might not be in the converted status.

There must be continued dialogue in this area, but I think from our previous action we can see that there is a willingness of the FDA to view this endpoint for registration.

Let me go back and ask the question: Why PFS?

It goes back to the previous panel and the comment about the word "minimal."

"Minimal" connotes to many people a reduction in standards. And I'd like to replace that word when we discuss PFS and looking at streamlining data as "optimal," as opposed to "minimal." What it represents is a more comprehensive look at what are the resources available and what are we get at the end of the review process.

It's not an attempt to lower standards. It's an attempt o make optimal use of the existing resources. I have mentioned to many companies that have come to see us that rather than doing a PFS endpoint with an exhaustive review of the clinical data, costing millions of dollars, this money may be better spent by having more patients enrolled in the trial.

So we understand what goes along with the use of PFS.

We have had a continuing dialogue with the oncology community regarding the use of this endpoint in various diseases.

We have had numerous conferences with ASCO, AACR, ASH on different approval endpoints for a variety of malignancies.

There seems to be an ongoing theme here, and an argument at all of these conferences. Is PFS is a surrogate for survival? Is it or isn't it? And it keeps going back and forth, and back and forth. And I realize that we are looking at PFS in brackets, as if it were an absolute value, and we are ignoring a very important aspect—the magnitude of effect on PFS--in the discussion of a relationship between PFS and survival.

One problem that we have in [assessing] a relationship between PFS and survival is that many of our therapies have a relatively modest impact on PFS and overall survival, and, hence, one has a difficult time in [assessing] this relationship.

If you are talking about an effect on PFS that has an improvement of 80%, that's a much different effect in its relationship to overall survival rather than a drug that has an improvement of 20% on PFS.

So I think we have to look at also at questions we have been discussing at the FDA. Is PFS of clinical value in itself? Let's get away from this surrogacy issue. Could we take a look and say that for patients that have an underlying malignancy that is rapidly progressive would a delay in progression be of clinical benefit in itself? During the approval of Avastin, I made a comment that we were making that decision in the context limited to that application for that specific disease.

We always have to examine the risk/benefit relationship of based on the available information that we have, given a particular product at the particular time.

We look at the totality of information. We have to look at past approval of that drug in other diseases and the secondary endpoints that we have embedded in the trial that would corroborate the impact on PFS.

In oncology, we have a different situation than in many other therapeutic areas. We approve drugs based on single trial even for the in initial approval. That usually is not the case in other areas. So we are starting out behind the ball here, with [less] data?

How did we get to the point of [requiring] independent review committees? I am not quite sure exactly how this evolved over time. These committees probably stem from the approval and evaluation strategies of contrast agents. These are obviously different questions than one is asking for the approval of an oncology agent.

Is there any bias in this relatively subjective endpoint that could be manipulated?

That's what we are interested in reviewing the radiographs. We are not saying that one needs 100% review of every single x-ray, and I think we are very interested in taking a look at alternative strategies that are least burdensome, but provide assurance that there is not a systematic bias that could be influencing the results.

There are many questions as far as which of these strategies to take into widespread use. For example, should one take a look at a specific percent of patients? Should there be concordance on the patient-by-patient basis, or should the concordance be on the total results of the trial at a specific interim analysis? How many patients should one take a look at? How many investigators? There are many questions that need to be worked out here before we move away [from current standards] and say this is what we want. But I think it's doable.

Here again, I think we can take a look at retrospective data.

But I would like to see a prospective evaluation embedded into ongoing trials that looks at some of these proposals and compares them to a standard review.

In the Cancer Centers:

WILLIAM NELSON, a member of the Johns Hopkins University School of Medicine faculty since 1992, has been selected to lead the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

Nelson, who specializes in prostate cancer genetics and treatment, is nationally known as a leader in translational cancer research who with fellow Johns Hopkins colleagues discovered the most common genome alteration in prostate cancer. The discovery led to new diagnostic tests for the disease and has fueled interest in new drug discovery.

Nelson served as associate director for translational research and the co-director of the Prostate Cancer Program. He has been in a leadership role for the partnership program with Howard University Cancer Center. He was one of three co-chairmen of NCI's Translational Research Working Group, and has been a member of the scientific advisory boards of several companies. He is a member of the American Association of Cancer Research Board of Directors, president of the National Coalition for Cancer Research, and a member of the Scientific Advisory Board of the Prostate Cancer Foundation.

Nelson said he plans to emphasize continued growth of the center with clinical faculty recruitments and expanded research opportunities.

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Business & Regulatory Report

FDA News:

Firm Withdraws Ovarian Cancer Test After Receiving FDA Warning Letter

By Paul Goldberg

Laboratory Corporation of America has withdrawn its test for ovarian cancer after receiving a warning letter from FDA.

Though clinical evidence justifying the test is inconclusive, the company attempted to sell it as a "home brew," a regulatory category that's typically not regulated by the agency.

In this case, FDA argued that OvaSure isn't a home brew, because the home institution of its developers, Yale University, had licensed it to

(Continued to page 2)

Oncology Management:

US Oncology Becomes Member Of RTOG; Practices Gain Access To Clinical Trials

Radiation Therapy Oncology Group and **US Oncology Inc.** said they have entered into a collaboration that gives US Oncology affiliated practices access to RTOG clinical trials for brain, head and neck, lung, gastrointestinal, genitourinary, cervix, and breast cancers.

US Oncology said it is the first multi-state, national organization to become an affiliate member of RTOG. Members include large regional practices and academic practices with facilities in metropolitan areas.

"Our collaboration with US Oncology and its network of member practices is attractive due to the organization's strong commitment to clinical trial participation, leadership and accrual," said Walter Curran, group chairman of RTOG and professor and chairman of the Department of Radiation Oncology of Emory University School of Medicine. Curran is also chief medical officer of the Winship Cancer Center at Emory University. "We were confident their track record as a multi-site organization with significant accruals in a variety of clinical trials would be a good fit."

The participating affiliated practices include: Texas Oncology practices at Sugar Land, Medical City Dallas, Sherman, Methodist Dallas, Klabzuba, and Bedford Harris; Kansas City Cancer Center's North, South, and Southwest sites; Willamette Valley Cancer Center; Central Indian Cancer Center-South; Arizona Oncology Associates-Tucson; Rocky Mountain Cancer Center-Aurora, and New York Oncology Hematology-Albany.

The collaboration gives RTOG access to the US Oncology patient population, making radiation therapy trials more accessible to cancer patients

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OvaSure Focuses Attention On FDA Diagnostics Rules

(Continued from page 1)

LabCorp. Also, FDA argued that the assay is, in effect, a medical device.

The case of OvaSure is noteworthy since it focuses attention to FDA rules on diagnostics, observers say.

On the one hand, these rules are lax enough to allow introduction of unregulated home brews.

On the other hand, critics say that the agency lacks appropriate mechanisms for regulating assays that are designed to work with therapeutic agents, either by selecting patients who are most likely to benefit from a drug or to monitor a patient's progress after getting therapy.

Such assays can be an important tool for matching the right patient with the right drug.

Last year, the agency issued a draft guidance on "in vitro diagnostic multivariate index assays." The document is posted at www.fda.gov/cdrh/oivd/guidance/1610.html. A final guidance is yet to be issued.

The agency's warning letter to LabCorp is posted at www.fda.gov/foi/warning_letters/s6947c.htm

In the Oct. 20 letter to FDA, LabCorp's Senior Vice President and General Counsel F. Samuel Eberts III disputed the agency's rationale for the enforcement action.

The following is the text of his letter, which was also included as a regulatory filing to the Securities and Exchange Commission:

We are writing to you in response to the Warning Letter issued to Laboratory Corporation of America dated September 29, 2008.

The OvaSure test that is the subject of the Warning Letter is performed at a laboratory that is licensed under the Clinical Laboratory Improvement Amendments. LabCorp is a CLIA-certified high-complexity testing laboratory.

The OvaSure test meets all applicable CLIA regulatory requirements. LabCorp bears full responsibility under CLIA for the performance of its tests, including OvaSure, and independently validates its tests on an ongoing basis. The testing service developed by LabCorp and all subsequent changes to standard operating procedures for OvaSure™ were rigorously validated pursuant to CLIA requirements.

LabCorp does not agree with the assertion in the Warning Letter that OvaSure is a medical device subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FDC Act"). As we have previously stated, we believe that laboratory developed assays are not medical devices within the meaning of the FDC Act and that they are not subject to regulation as medical devices.

We also do not agree that our interactions with Yale University provide FDA any basis for exercising jurisdiction over the test. LabCorp has licensed intellectual property from Yale University; we did not purchase any products or materials from Yale. Yale's role in LabCorp's test is limited to licensing to LabCorp certain intellectual property. Yale has no control, contractual or otherwise, to influence the development, methodology, validation, performance characteristics, use, distribution or any other aspects of LabCorp's testing service.

Cooperative agreements between laboratories and academic researchers are prevalent. Many tests currently offered by laboratories were initially developed by academic research centers; these tests rely heavily on the research performed by leaders in their respective disciplines. Licensing agreements permit this research to be translated into innovative diagnostic test services, while providing academic centers with critical funding to continue their ground breaking research.

Restricting the ability of laboratories to utilize information and knowledge generated by academic researchers will have a negative impact on the availability of diagnostic tests that offer substantial health care

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benefits to patients and health care professionals. We are also unaware of any basis – and the Warning Letter cites none – for asserting that a laboratory assay is a device under the FDC Act because the laboratory allegedly did not establish the specifications for materials that the laboratory purchased from a third party vendor.

LabCorp is an industry leader in responsible scientific innovation. We are deeply concerned that the unprecedented position FDA has advanced in its Warning Letter will limit the dissemination of information and expertise, and will stifle the ability of laboratories to provide innovative diagnostic tests. Nevertheless, LabCorp is committed to positive and responsible relationships with regulatory agencies. Accordingly, despite our disagreement with FDA over this test offering, LabCorp will voluntarily discontinue offering the vaSure™ test effective October 24, 2008.

LabCorp continues to believe that OvaSure offers significant health benefits to women. We therefore request a meeting with you and your staff to discuss our testing service and the associated regulatory issues. LabCorp will be contacting you shortly to schedule this meeting.

Deals & Collaborations:

Eli Lilly, ImClone Directors Approve Merger Agreement

Eli Lilly and Co. (NYSE: LLY) and **ImClone Systems Inc.** (Nasdaq: IMCL) said the boards of directors have approved a definitive merger agreement under which Lilly will acquire ImClone through an all cash tender offer of $70.00 per share, or $6.5 billion.

The offer represents a premium of 51 percent to the ImClone closing stock price on July 30, the day before an acquisition offer for ImClone was made public, the company said.

The oncology franchise will offer both targeted therapies and oncolytic agents along with a pipeline in all phases of clinical development, the company said. The combined oncology portfolio will target solid tumor types including lung, breast, ovarian, colorectal, head and neck, and pancreatic, positioning Lilly to pursue treatments of multiple cancers. Importantly, the combination also expands biotechnology capabilities of Eli Lilly.

The ImClone development and commercial manufacturing facility will provide flexibility to develop and manufacture complex biomolecules, the company said.

"We think very highly of ImClone's ground-breaking work in oncology, particularly its success with Erbitux, a blockbuster targeted cancer therapy, and its ability to advance promising biotech molecules in its pipeline," said John Lechleiter, president and CEO of Eli Lilly. "By bringing together the Lilly and the Imclone marketed oncology products, pipelines, and biotech capabilities, we are taking a very important step forward in addressing the challenges of patent expirations we will face early in the next decade."

Erbitux is marketed by Merck KGaA and Bristol-Myers Squibb, ImClone's two partners, and ImClone co-promotes the treatment in North America together with BMS. The drug is indicated as both a single agent and with chemotherapy for certain colorectal cancers and as a single agent or in combination with radiation therapy for head and neck cancers.

In 2007, worldwide sales of Erbitux grew 18 percent to approximately $1.3 billion, the company said.

ImClone pipeline molecules include: IMC-1121B, a fully-human monoclonal antibody that targets the VEGF receptor to deprive tumor blood vessels of the nutrients for further growth; IMC-A12, a fully-human monoclonal antibody that targets the insulin- like growth factor-1 receptor; IMC-11F8, a fully human monoclonal antibody that targets the epidermal growth factor receptor, the same receptor targeted by Erbitux.

Upon the closing of the transaction, Lilly will incur a one-time charge to earnings for acquired in-process research and development, the company said. The company said it expects the transaction to be accretive to earnings on a cash basis in 2012 and on a GAAP basis in 2013.

AstraZeneca of Wilmington, DE, and the **University of Texas M. D. Anderson Cancer Center** of Houston said they have renewed and are extending for another five years their collaboration to integrate pre-clinical and clinical research in cancer.

The collaboration is unusual in its focus on pre-clinical research and the transition to clinical trials and was the first of its kind for both institutions, the collaborators said.

Both parties said they intend to build on their two dozen joint research projects and broaden the original focus from aerodigestive diseases to include targets in cancer settings.

"Earlier access to drugs destined for the clinic has permitted the identification of biomarkers and combinations with existing agents that will permit individualization of cancer treatment," said Robert Bast

Jr., vice president for translational research at M. D. Anderson. "In an atmosphere of trust and collaboration, it has been possible to eliminate unnecessary delays in moving drugs into the clinic. In one case, we reduced the time to initiate a phase I clinical trial by three months, while fully meeting regulatory requirements."

While the terms of the collaboration remain confidential, it covers the sharing of intellectual property, M. D. Anderson's rights to publish research results and funding commitments by AstraZeneca.

CEL-SCI Corp. (NYSE:CVM) of Vienna, Va., said it has entered into a Material Transfer Agreement with the NIH Clinical Center and the laboratory of Francesco Marincola, to investigate the molecular basis of changes to the tumor microenvironment caused by the CEL-SCI cancer drug Multikine.

Marincola is chief of the Infectious Disease and Immunogentics Section, Department of Transfusion Medicine in the NIH Clinical Center.

Under the agreement, CEL-SCI will provide tumor samples of Multikine treated and untreated matched control patients to the NIHCC, which will use molecular genomic microarray technology developed by the laboratory of Marincola to look for molecular genomic differences in the tumor microenvironment in squamous cell carcinoma of the head and neck.

Should the pre-clinical experiments find differences between the Multikine treated and untreated patients, a formal collaboration between CEL-SCI and the NIHCC may expand the study to include patients from the CEL-SCI pivotal phase III trial, the company said.

Fox Chase Cancer Center of Philadelphia said it is working with **Vericom Corp.** of Atlanta to provide hospital-wide healthcare communications via digital signage with ChannelCare, the Vericom Content Management System software.

The web-based, user-friendly software includes a library of digital signage content, including high-end 3D animations focusing on health and prevention topics, Vericom said.

"We needed a turn-key digital signage platform that could be tailored to accommodate our diverse audiences and venues," said Julia Goplerud, senior director of regional marketing at Fox Chase.

Both ChannelCare and SoundCare allow us to create, deliver, and change messages in real-time, in sync with our mission and values, said Goplerud.

ChannelCare will be used in waiting rooms, lobbies, eating areas, and hallways, the center said. Fox Chase said it would use both ChannelCare for internal audiences and SoundCare for callers who are briefly placed on hold.

The Vericom systems target audiences with information relevant to where they are within the health system. Messages on ChannelCare monitors in the imaging center are different from messages delivered to staff in break rooms.

Nerviano Medical Sciences of Nerviano, Italy, said it has entered into a multi-year agreement with **Genentech Inc.** of South San Francisco to discover antibody drug conjugates as anticancer agents.

The research agreement is the second collaboration agreement signed between Genentech and NMS in less than twelve months, the company said.

Genentech will have the exclusive license to fully develop and commercialize licensed products that contain such antibody drug conjugates, the company said. During the research program, NMS will be responsible for synthesizing and manufacturing drug reagents, while Genentech will generate antibody drug conjugates with such drug reagents and further evaluate their therapeutic utility.

Terms include a one-time-license-fee, milestones and royalties for licensed products as well as milestones on a target-by-target basis, the company said.

Nerviano Medical Sciences is owned by Congregazione dei Figli dell'Immacolata Concezione of Rome.

Sigma-Aldrich (NASDAQ:SIAL) of St. Louis said **Memorial Sloan-Kettering Cancer Center** has joined the RNAi Partnership Program.

The program gives members access to products in the Sigma-Aldrich functional genomics portfolio, including shRNA libraries developed by The Rai Condortium, or TRC, consisting of 15,000 human genes and 15,000 mouse genes

"Many of our researchers are interested in targeted gene knockdown on an individual or gene-focused basis, as well as a genome-wide scale for which we are fully equipped," said Hakim Djaballah, director of the High Throughput Screening Core Facility at Memorial Sloan-Kettering Cancer Center. "Access to the Sigma-Aldrich MISSION shRNA libraries will enhance our gene scanning capabilities and will enable us to discover and validate cancer-causing genes and pathways."

Sigma-Aldrich said it would like to establish collaborations with academic institutions through the RNAi Partnership Program. Existing members of the

RNAi Partnership Program include the Cleveland Clinic, Harvard Stem Cell Institute, Washington University of St. Louis, Princeton University, the Wistar Institute, and Rutgers University.

Sigma-Aldrich is a life science company and member of The RNAi Consortium.

Swedish Neuroscience Institute of Seattle said it is collaborating with the **Institute for Systems Biology** to fundraise and to collaborate on research in brain and nervous system diseases.

Greg Foltz, neurosurgeon at SNI and head of the new Center for Advanced Brain Tumor Treatment at the SNI Cherry Hill Campus, is leading the project with Leroy Hood, co-founder and president of ISB.

"This is the first time that such a large group of established researchers have been brought together from the fields of neurosurgery, neuropathology, systems biology, genomics and biostatistical analysis to address diseases affecting the brain, such as malignant brain tumors," said Foltz. "Also of significance is that the SNI and ISB researchers are focused solely on developing early diagnostic tools and treatment solutions for human disease rather than theoretical pursuits."

"The SNI and ISB collaboration represents a strategic partnership that joins the clinical expertise of Swedish with the systems biology, technology and computational expertise of ISB," said Hood.

The partnership has created a brain tumor tissue bank and associated genomic database derived from samples removed during surgery.

"One thing that's made learning about the tumors difficult is that there are few patients at any one center and the tumors progress so rapidly without treatment," said Foltz. "With the tissue bank and associated genomic database, we are establishing the foundation for one of the largest brain tumor research projects in the country."

Foltz has developed a way to analyze brain tumor blood and look for markers that can determine the best course of chemotherapy for the type of tumor, the group said.

Fundraising will be headed by Randy Mann, senior director of Campaign for the Swedish Foundation, and Laurence Herron, vice president of development for ISB.

Velos of Fremont, Calif., said **Duke University Health System** has completed a successful go-live of the Velos eResearch system.

The clinical trials management system is now operational with a basic set of functionality and in cancer research, the company said,

Go-live completes beginning phase activities related to the DUHS enterprise-wide strategic business model of clinical trials informatics. Velos said its eResearch will execute site based clinical research, financial standards and compliance with regulatory responsibilities. The Velos platform will provide infrastructure for strategic directions that include collaboration with other institutions on a national and international scale, the company said.

DUHS is using Velos eResearch to register protocols and subjects for all cancer trials. The first part of the phase began with registration of protocols and subjects and completed with the conversion of all cancer protocols and subjects. Implementation will continue by therapeutic area until all research is in the system.

"At that time, we'll be managing research subjects in a common system and taking advantage of the financial aspects of the Velos product," said Steve Woody, associate chief information officer for translational and clinical research for Duke Medicine. "We've laid out the next logical set of functionality. It's a pretty healthy list that includes going to other disease specialties."

Clinical Trials:

ACOSOG Selects Cryoablation System For Phase II Trial

American College of Surgeons Oncology Group selected the Visica 2 Treatment System from **Sanarus Medical** of Pleasanton, Calif., as the exclusive technology in the cryoablation portion of an NCI-funded phase II trial for invasive breast cancer.

The study is titled, A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma.

Z1072, the designated study protocol, will evaluate not only cryoablation but also the ability of MRI to evaluate post-cryoablation efficacy in 100 patients and 20 clinical sites, with enrollment beginning in early 2009.

The trial is similar to a pilot study conducted by Gary Levine, medical director at Hoag Breast Care Center in Newport Beach, Calif., and Steven Poplack, co-director of Breast Imaging at Dartmouth Hitchcock Medical Center. Both the pilot study and pending ACOSOG clinical trial share the common clinical protocol elements of cryoablation followed by MRI, surgical resection of the tumor and subsequent

pathological evaluation, the group said.

"Cryoablation has been used effectively for years to treat a number of medical conditions, including benign breast tumors, so it is a natural progression to study its use in the treatment of breast cancer," said Levine. "We are very encouraged about the promising initial results in our pilot study and believe further research is warranted in order to develop and refine this potential breakthrough breast cancer treatment."

The Sanarus Visica System has been used in the cryoablation of fibroadenomas, non-cancerous tumors, since its FDA market clearance in 2002, the company said. The office-based procedure, which usually takes less than 20 minutes, places a small needle into the center of the tumor using ultrasound guidance and subsequently freezing and killing the tumor.

Peregrine Pharmaceuticals Inc. (NASDAQ: PPHM) of Tustin, Calif., said it has completed first stage enrollment in its phase II trial of a combination regimen of bavituximab with carboplatin and paclitaxel in non-small cell lung cancer.

The primary objective is to assess the overall tumor response rate in the combination therapy, the company said.

In the Simon two-stage design, 21 NSCLC-patients will be in Stage A of the study, with the trial expanding to 49 patients depending upon results of the cohort. Secondary objectives include assessing time to tumor progression, duration of response, overall survival and safety parameters. Treatment would consist of bavituximab and up to six cycles of carboplatin and paclitaxel, and continued treatment with bavituximab as long as there is no cancer progression and side effects are acceptable, the company said.

The trial is being conducted in India according to International Conference on Harmonization and Good Clinical Practices standards.

Bavituximab, a monoclonal antibody that binds to the cellular membrane component phosphatidylserine, mobilizes the immune system to destroy the tumor and the tumor blood vessels, the company said.

The agent is in two separate phase II combination therapy trials for advanced breast cancer, as well as the phase II combination therapy trial for NSCLC. A phase I bavituximab monotherapy trial in advanced solid cancers is also continuing.

Rosetta Genomics Ltd. (NASDQ: ROSG) of Rehovot, Israel, said it has begun a clinical assessment study with **Johns Hopkins University School of Medicine** to compare the Rosetta Genomics miRview squamous, which differentiates squamous from non squamous non small cell lung cancer, with available immunohistochemistry methods.

An approved angiogenesis inhibitor for NSCLC has demonstrated severe side effects in squamous-cell lung cancer, the company said.

The targeted therapy includes a black-box warning about higher rates of severe or fatal hemorrhage in NSCLC with predominantly squamous histology. Patients with squamous-cell histology have therefore been regarded as inappropriate candidates for therapy with the drug. In addition, other targeted drugs for NSCLC under development may require accurate differentiation due to different side effect profiles or different levels of efficacy, the company said.

Earlier in the year, the Columbia University Medical Center High Complexity Molecular Pathology Laboratory received the approval of the New York State regulators for a test differentiating Squamous NSCLC from other NSCLC. The test, which is based on Rosetta Genomics technology, exhibited sensitivity of 96 percent and specificity of 90 percent, the company said.

SpectraScience Inc. (BULLETIN BOARD: SCIE) of San Diego said it has shipped its non-invasive WavSTAT Optical Biopsy System to the **University of Southern California** to identify dysplasia or cancer in the esophagus.

The study, which has been conduced over the three years, is in its final phase, the company said. SpectraScience also said it had delivered WavSTAT Systems to the Mayo Clinic and San Diego VA Hospital for similar studies. Other participants in the study include Minnesota Gastroenterology, P.A. and the Boston University VA Hospital.

The clinical use of the WavSTAT System to improve the clinical sensitivity in identifying dysplasia or cancer in the esophagus will be evaluated, the company said. The hypothesis that the sensitivity of a WavSTAT-assisted endoscopic examination improves that of standard endoscopy alone will be tested. If the hypothesis is correct, there would be fewer physical biopsies, the duration of the exam would be decreased and discomfort minimized.

The system uses a low power, non-significant risk laser to scan tissue, which allows physicians to determine whether small polyps are normal or pre-cancerous without removing the tissue. If polyps are determined pre-cancerous, they can be removed during the same procedure.

Product Approvals & Applications:

Cell Therapeutics Submits sBLA For Zevalin In NHL

Cell Therapeutics Inc. (Nasdaq and MTA: CTIC) of Seattle said it submitted a supplemental Biologics License Application to FDA for Zevalin ([90Y]-ibritumomab tiuxetan) as consolidation therapy after remission induction in untreated follicular non-Hodgkin's lymphoma.

The company said it has requested priority review. CTI said it gained access to the First-line Indolent Trial, or FIT, data through an agreement with Bayer Schering Pharma AG, of Germany who used the data to obtain approval for the therapy as first-line consolidation treatment in Europe.

"If the sBLA is approved there would be 18,000 additional patients that receive first-line treatment that would be eligible to use Zevalin under the proposed expanded label," said James. Bianco, CEO of Cell Therapeutics.

Zevalin is approved in the U.S. for relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, including rituximab refractory follicular NHL. Zevalin is also indicated, under accelerated approval, for relapsed or refractory, rituximab-naive, low-grade and follicular NHL based on studies using an endpoint of overall response rate, which is a surrogate for progression free survival, the company said.

The multinational, randomized phase III FIT study evaluated the benefit and safety of a single infusion of Zevalin in 414 patients with CD20-positive follicular non-Hodgkin's lymphoma who had achieved a partial response or a complete response after receiving standard first-line chemotherapy regimens. The trial demonstrated that when used as a first-line consolidation therapy for follicular non-Hodgkin's lymphoma, the drug improved the median progression-free survival time from 13.5 months (control arm) to 37 months (Zevalin arm) ($p < 0.0001$), the company said.

The study concluded that the drug consolidation of first remission in advanced stage follicular non-Hodgkin's lymphoma is highly effective, resulting in a total complete response (CR + CRu) rate of 87 percent and prolongation of median progression-free survival (PFS) by two years, with a toxicity profile comparable to that seen with the Zevalin use in approved indications. Zevalin-treatment had reversible grade 3 or 4 hematologic side effects including neutropenia in 67 percent, thrombocytopenia in 61 percent, and anemia in 3 percent. Nonhematologic toxicities were 24 percent Grade 3, 5 percent Grade 4, and Grade 3/4 infection was 8 percent.

Cephalon Inc., (NASDAQ: CEPH) of Frazer, Penn., said FDA has approved Treanda bendamustine hydrochloride) for injection for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

In March, Treanda received approval for the treatment of chronic lymphocytic leukemia.

"Because most patients with indolent non-Hodgkin's lymphoma eventually become resistant to existing treatments, new treatment options like Treanda are needed to improve patient outcome," said Bruce Cheson, Professor of Medicine at Georgetown University Hospital and Treanda clinical investigator. "The Treanda pivotal trial shows that it is an effective and well-tolerated chemotherapy that offers a delay in disease progression for more than nine months."

The FDA approval is based on a trial of 100 patients with indolent B-cell NHL who had progressed during or within six months of treatment with a regimen that included rituximab. The study demonstrated that patients had a high response rate to treatment with Treanda, and these responses to the treatment were durable. The results from the pivotal study showed that treatment with Treanda as a single agent resulted in an overall response rate of 74 percent, which means that after treatment, the cancer diminished or disappeared in approximately three out of four patients, the company said.

Patient response to treatment in the pivotal study lasted a median of 9.2 months and patients remained alive and their disease did not progress for a median of 9.3 months.

In the pivotal and secondary studies for Treanda in indolent NHL, the most common non-hematologic adverse reactions (frequency greater than or equal to;15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decrease, dyspnea, rash and stomatitis. The most common hematologic abnormalities (frequency greater than or equal to;15%) are lymphopenia, leukopenia, anemia, thrombocytopenia and neutropenia.

Eisai Corp. of North America of Woodcliff Lake, N.J., said FDA approved an efficacy supplemental biologics license application for Ontak (denileukin diftitox) solution for intravenous injection in persistent or recurrent cutaneous T-cell lymphoma where malignant cells express the CD25 component of the interleukin -2

receptor (CD25+).

A separate efficacy supplement that included data of CTCL where malignant cells did not test positive for the CD25 component of the IL-2 receptor received a complete response letter, the company said.

The FDA action, following a priority review, marks the conversion of an accelerated approval indication to full approval and is based on data from a phase III of randomized, double-blind, placebo-controlled trial that evaluated the overall efficacy and safety of the drug in CTCL.

The study met its primary endpoint of overall response rate, the company said. The ORR was 46 percent for the 18 mcg/kg/day dose of Ontak (p=0.002 vs. placebo) and 37 percent for the 9 mcg/kg/day dose (p=0.03 vs. placebo) vs. 15 percent for placebo. In addition, analysis of a secondary endpoint, progression-free survival, suggested a 73 percent reduction in risk of disease progression in the 18 mcg/kg/day group (hazard ratio=0.27, p=0.0002, 95 percent CI 0.14, 0.54) and a 58 percent reduction in risk of disease progression in the 9 mcg/kg/day group (hazard ratio=0.42, p=0.02, 95 percent CI 0.20, 0.86) compared to placebo.

"The data confirm the benefit of the safety and efficacy profiles of Ontak," said Francine Foss, professor of medicine, assistant director of clinical investigation, hematologic malignancies at Yale Cancer Center. "In addition, the data indicate a significant reduction in risk of disease progression compared to placebo."

The 144 patients with CTCL whose malignant cells expressed the CD25 component of the IL-2 receptor, were randomized to receive either of two doses of Ontak [18 mcg/kg/day (n=55) or 9 mcg/kg/day (n=45)] or placebo (n=44) for up to eight cycles of therapy. Two-thirds (67 percent) of had stage IIa or lower and one-third (33 percent) had stage IIb or III. They were randomized to receive Ontak via intravenous infusion on days one to five of each 21-day cycle. The median number of cycles for all Ontak-treatment was six for the 18 mcg/kg/day group (range 1-11) and seven for the 9 mcg/kg/day group (range 1-10), the company said.

"The efficacy data suggests that dermatologists and oncologists should collaborate to ensure that CTCL patients are treated appropriately at each stage of their disease," said Madeleine Duvic, professor of internal medicine and dermatology, deputy chairman Department of Dermatology, University of Texas MD Anderson Cancer Center. "Patients with CTCL may also wish to visit a CTCL center of excellence, in which both specialties are represented, to discuss treatment options."

Oncology Management:

US Oncology Expands Support Service Care Advantage To CA

(Continued from page 1)

in the community setting nationwide. The US Oncology presence in parts of the country expands RTOG clinical trial participation into areas where it has few or no enrolling members.

US Oncology of Houston said **OncologyRx Care Advantage** has expanded its service to 50 states and Puerto Rico, with the addition of the state of California.

Since 2006, Care Advantage has offered therapy support services to 4,000 patients and home delivery of 22,000 prescriptions, the company said.

The Care Advantage pharmacy provides home delivery of oral cancer therapies and the additional support for safe and supervised use of the oral therapy treatments, the company said.

The program utilizes oncology certified nurses to monitor patient compliance with the prescribed therapy and support adherence by managing their side effects. In addition to the ongoing support of a team of care experts, Care Advantage has 24-hour access to oncology certified pharmacists.

Innovent Oncology of Houston said **Rocky Mountain Cancer Centers** has signed an agreement with the **Public Employees Retirement Association** of Colorado to provide patient support services to the PERA retired members undergoing cancer treatment at RMCC.

"We also expect the program will help us manage overall cancer treatment costs for both our retirees and our plan," said Wendy Tenzyk, insurance director for Colorado PERA. PERA has more than 80,000 retirees and operates a self-insured health plan administered by Anthem Blue Cross and Blue Shield of Colorado that covers 36,000 retirees and their dependents. The agreement with RMCC covers the Anthem members.

Innovent Oncology said it bundles core services and offers them to health plans on a per participant basis. By integrating the services, patients benefit from added support services throughout their treatment; physicians gain access to evidence-based treatment Pathways; and payers benefit from the information available through enhanced data capture and analysis, outcomes measurement and utilization review, the company said.