THE CANCER LETTER

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Cooperative Groups Get Reprieve From Cut As Budget Is Flatlined At Fiscal 2006 Level

By Kirsten Boyd Goldberg

CHICAGO—NCI's clinical trials cooperative group program will receive a flat budget for the current fiscal year, not the 10 percent cut that the groups expected, institute officials told the group chairmen during the American Society of Clinical Oncology annual meeting.

Last fall, the groups were instructed to prepare for a nearly $14.5 million budget cut. Earlier this week, institute officials said the program's budget would be restored to the FY 2006 level of about $155 million.

The additional money isn't likely to revive many of the activities the groups curtailed over the past six months in anticipation of shortfalls, group chairmen said to The Cancer Letter. To adjust to the lower budget, the groups delayed or eliminated 95 phase II and III trials, and cut enrollment to current

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Scientist's Interpretation Of Meta-Analysis On ESAs Turns 180 Degrees Over 72 Hours

By Paul Goldberg

CHICAGO—Last week, Charles Bennett prepared to present a provocative and potentially important finding:

According to his meta-analysis, patients who took erythropoiesis stimulating agents had a statistically significant increase in the relative risk of venous thromboembolism and death.

The Cancer Letter published a story about his findings in the June 1 issue, and on June 3, hundreds of people showed up at Bennett's poster at the annual meeting of the American Society of Clinical Oncology in Chicago.

But instead of delivering a message of caution, Bennett said that his findings weren't newsworthy, and that ESAs pose no previously undisclosed risks to 90 percent of patients.

"We break no new ground," Bennett, an oncologist at Northwestern University, said to Reuters reporters who came to interview him at his poster. "What we do have is what people said all along: When the drug is used on label, there are no hidden safety signals."

This statement contradicted the claims Bennett made to The Cancer Letter as well as the findings on the poster behind him.

"Our data show that since 2003, trials of treatment with EPO/DARB for anemic cancer patients identified increased risks of VTE and death, compared to control," the poster read. "Prior to 2003, similar trials were associated with increased risks of VTE, but not mortality. Our findings are worrisome

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Group Budgets To Be Restored But Many Cuts Already Made

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clinical trials by about 3,000 patients. Several groups took additional measures to reduce costs, including eliminating trials in brain cancer, melanoma, sarcoma, and pediatric cancers, and laying off staff.

"Most of these cuts have already taken place," Allen Lichter, executive vice president of ASCO, said a press conference June 1. "The trials have been curtailed or ended. Though the groups will receive the same amount as last year, over the past five years, the cooperative groups have taken a funding hit."

ASCO drew attention to the funding plight of the cooperative groups by giving the 12 organizations its 2007 Distinguished Service Award for Scientific Leadership. Representatives from the groups accepted the award during the meeting's opening session.

"This is the first time that we have given an award to a group of recipients," said Sandra Horning, chairman of the ASCO Special Awards Selection Committee. "It was my feeling that the time had come to reward what is now called 'team science.' Much, if not most, of the accomplishments in oncology come from groups of individuals working together."

The award recognizes the groups' "more than 50 years of contributions to programs that support the design of clinical trials, many of which have led to the development of new cancer treatments," according to the citation.

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"The cooperative groups are highly deserving for their many scientific achievements over the years," Horning said. However, "they are under siege a bit currently from the present funding climate."

ASCO has joined other medical societies and advocacy organizations to call for a minimum 6.7 percent increase in NIH funding.

The cooperative group program, begun in 1956, has sponsored more than 4,000 clinical trials that treated more than 500,000 patients. The groups consist of multidisciplinary networks of researchers, cancer centers, and community physicians in the U.S., Canada, and Europe.

"It is fitting not only to honor these groups—which have dedicated incredible amounts of energy, power and resources to bring to our patients the highest quality evidence—but also to recognize that they were created thanks to the long-range perspective of the National Cancer Institute," said Gabriel Hortobagyi, who completed his term as ASCO president during the annual meeting.

The 12 groups that accepted the awards were: American College of Radiology Imaging Network; American College of Surgeons Oncology Group; Cancer and Leukemia Group B; Children's Oncology Group; Eastern Cooperative Oncology Group; European Organisation for Research and Treatment of Cancer; Gynecologic Oncology Group; National Cancer Institute of Canada, Clinical Trials Group; National Surgical Adjuvant Breast and Bowel Project; North Central Cancer Treatment Group; Radiation Therapy Oncology Group; and Southwest Oncology Group.

U10 Awards To Be Restored

NCI had asked the groups to prepare for a 10 percent decrease "because that's what we were asking every program within NCI to look at, not knowing what we would have in terms of dollars," NCI Director John Niederhuber said at ASCO's June 1 press conference.

After Congress provided the institute's FY07 appropriation in February, NCI officials began "working feverishly across the board to put funding plans in place for these rather large and complex programs—SPOREs, centers and cooperative groups," he said.

"It took me a bit longer to do the cooperative groups, because as a new person now completing only my second year at NCI, and only my first year as director, it was clear to me that no one had tried to get their hands around the whole cooperative group program, rather than as separately funded groups," Niederhuber said.

The cooperative group program is funded through an assortment of NCI grants to various institutions and entities, with separate awards for each group's operations center, as well as U10 awards to institutions that take part in the groups.

"If we are gong to be effective, we need to work across the groups in a coordinated way," Niederhuber said. "I took steps to understand and force the understanding of that budget…. What I am trying to do with the clinical trials cooperative groups is to provide some more stability to that, rather than having it treated as one grant and another grant, but treat it as a program, to take some of the risk out of it."

Most of the U10 grantees will receive a restoration of their awards back to 2006 levels, except for the sites whose budgets are being reduced due to performance issues, Jeffrey Abrams, head of the NCI Clinical Investigations Branch, said to The Cancer Letter. "The exact '07 award amount is still being calculated but we believe it will be around $155 million, which will make it quite comparable 2006. That is the entire group budget for treatment" including the U10s, but not including cancer prevention and control funding or the Community Clinical Oncology Program.

Niederhuber met privately with the group chairmen during the ASCO meeting to discuss the program's budget.

"We had a very productive meeting with Dr. Neiderhuber," said Robert Comis, chairman of the Eastern Cooperative Oncology Group and president and chairman of the Coalition of Cancer Cooperative Groups. "He reiterated that the cooperative group budget would remain flat at the '06 level and also announced that there would be an additional $4 million made available this year for accrual reimbursements for highly productive sites."

The plan for distribution of the additional $4 million is yet to be completed, said Richard Schilsky, chairman of the Cancer and Leukemia Group B and president-elect of ASCO. "This was an unexpected and greatly appreciated show of support for the cooperative groups," he said.

However, the group chairmen said their networks still face severe financial constraints that will slow clinical research.

"We did make it clear to John that, even at this level of support, the groups are still operating at a significant budget reduction compared with FY 2002-03 and, with inflationary adjustments, our purchasing power is still down about 15 percent compared to that period of time," Schilsky said.

"We also pointed out that much of the damage has been done for this year," Schilsky said. "Studies that have been closed will not be re-opened, committees that have been disbanded will not be re-convened, and clinical trial accrual is likely to be down this year. The flat funding at FY '06 levels is certainly better than a 10 percent cut, but should not be interpreted to mean that all is well in the cooperative group program."

Many groups stopped trials, cut staff, delayed trials, and disbanded work in some areas, Comis said. "Due to unique grant cycles, each of the groups were in varying stages of implementation of their FY07 budgets during the six-month interval from first notice of the planned reduction in November 2006 and the May 22 notification that a decision was reached," he said. "Now that we have received clear direction from the NCI on the status of FY07 funding, the groups are working together to assess the overall impact that period of uncertainty has caused across the system.

"Ultimately, a reversal of the downward trend and an increase in funding is needed to keep pace with the rising costs of clinical research and the grater number of new molecules and compounds that need to be tested and brought through development to cancer patients," Comis said.

"We are still terribly under-funded for the work that we do," Schilsky said. "Both academic and community sites are feeling the budget pinch, and many are no longer able to 'subsidize' the cooperative groups from local revenue sources.

"The system remains quite fragile and still in jeopardy of collapse unless NCI funding can be substantially increased in future years," Schilsky said.

"We discussed with Dr. Neiderhuber the fact that the most recent crisis has energized the public and the advocacy community because of their desire to have the opportunity to participate in cooperative group trials, which are increasingly driven by the newest technologies and targeted therapies," Comis said. "As I mentioned in my remarks in the ASCO opening session, we now need to work together with advocates, the NCI and Congress, if need be, to obtain the level of funding needed to ensure continued patient access to clinical studies."

Leadership Change At CTEP

In another development that affects the groups, Michaele Christian, director of NCI's Cancer Therapy Evaluation Program for the past 10 years, announced her plans to retire on June 30. CTEP coordinates NCI's extramural cancer treatment trials.

"It has been a tremendous privilege to do cancer therapeutics development in the public interest for the past two decades and to work with the extraordinarily committed and very talented staff of CTEP," Christian said to The Cancer Letter. "I hope that some of the initiatives of the past 10 years will have a lasting positive impact for cancer patients, especially the clinical trials of combinations of molecularly targeted agents which have required that multiple pharmaceutical partners work together to allow the NCI to sponsor these important trials, and the Cancer Trials Support Unit which provides an infrastructure to allow national access to important clinical trials for cancer patients and to accelerate the evaluation of promising new treatments by facilitating participation across the entire clinical trials network."

Christian said she plans to pursue "some of my many other interests over the coming years and having the time to enjoy the good fortune with which I have been blessed."

Christian came to medicine as a second career. She was an arts administrator with the Friends of the Kennedy Center and the Duke Ellington School of the Arts in Washington, D.C., and she currently serves as president of the Board of Directors of the Duke Ellington School of the Arts Project and a trustee of the Black Student Fund.

She received an M.D. from Georgetown University, where she completed residency training in internal medicine and fellowships in hematology and oncology. She worked in the NCI Investigational Drug Branch on clinical development of new anti-cancer drugs as acting chief and head of the Developmental Chemotherapy Section. In 1995 she established NCI's Clinical Trials Monitoring Branch, which oversees quality assurance and compliance for NCI clinical trials. She was named director of CTEP in 1997.

Jeffrey Abrams, head of the Clinical Investigations Branch, will serve as acting director of CTEP.

Fisher Speaks Out On Breast Cancer Prevention

At an ASCO session on global cancer prevention, Bernard Fisher, Distinguished Service Professor at the University of Pittsburgh and former chairman of the National Surgical Adjuvant Breast and Bowel Project (1967-1994), argued for continued support for breast cancer prevention research, both to continue what he called the "current strategy" of chemoprevention trials, as well as to pursue fundamental research in molecular biology.

Fisher didn't mention by name NSABP's P-4 breast cancer prevention trial, which NCI has been reviewing for the past year and a half (The Cancer Letter, May 25, April 20, and March 2). However, his remarks could be interpreted as a reproach of the "multiple review committees" that "debate about how limited resources for breast cancer prevention research should be spent."

In his presentation, Fisher reviewed the NSABP P-1 and P-2 studies, as well as breast cancer chemoprevention trials in other countries. "Collectively, those studies opened a door, revealing the road to the future for breast cancer prevention," Fisher said. "Recently, a sign was posted on that road to indicate that just ahead, there's a fork in the road.

"One branch leads to the frontier of science, where fundamental research in genetics and other aspects of molecular biology will determine and eliminate the cause of breast cancer. It will obtain information that will make it possible to unequivocally identify women who will get breast cancer, and among them, women who will respond to targeted interventions that will prevent it. Many consider that to be the preferred route to the future, and one would have a hard time disagreeing with that position.

"However, pursuing the current strategy also has merit and should be viewed as an acceptable route to the future," Fisher said. "Traversing that path would permit addressing questions that have arisen from current findings, the answers to which would enhance the acceptability of those findings. Moreover, it would establish the worth of new preventive agents, generate new hypotheses, and most important, while work is in progress, prevent cancers, and by doing so, eliminate the need for surgery, radiation therapy, and chemotherapy in countless women, thus making the use of prevention cost-effective.

"All of the above are worthwhile accomplishments in my view. So here we are today facing a critical decision. What should we do? Do we continue to dwell obsessively on the side effects of preventive agents, without acknowledging that there are countless women in countries where these trials were conducted who could stand to derive a net benefit? Or do we relegate all that has been accomplished to the dustbins of history and abandon the current pathway of prevention research?

"To appropriately answer that question, we can invoke an aphorism by the American baseball player Yogi Berra, who stated, 'When you come to the fork in the road, take it.'

"Simply speaking, that malapropism suggests that progress relative to the prevention of breast cancer can best occur by providing free access and unbiased support

to those who have legitimate reason to travel on either or both of the roads.

"Berra's aphorism is, in a way, supportive of two other more erudite statements. One by Sir Austin Bradford Hill in 1965, who said, 'All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action it appears to demand at a given time.'

"Another statement was made by [NCI Division of Cancer Prevention Director] Peter Greenwald, who in 1988 said, "The exigencies of public health problems require prudent action wherever reasonable evidence is available, despite imperfect knowledge.'

"Once again, it is important to emphasize that the way in which breast cancer prevention is pursued in the United States will have a profound affect on global breast cancer prevention.

"Finally, while multiple review committees, think tanks, and pundits debate about how limited resources for breast cancer prevention research should be spent, i.e., which road to take, it must be realized that there are forces outside their domain that will eventually influence what is apt to occur. No longer can the fact that the shape of our planet is rapidly changing be ignored. As Tom Friedman of the New York Times described in his recent book, as result of technologic, economic, and intellectual integration, the world is becoming flat. As a result, increasing numbers of countries are experiencing unparalleled prosperity, and as they do so, the health of their populations assume greater importance…. Their clinicians and scientists must be supplied with whatever support is needed to become full participants in prevention research and in the application of findings.

"Until that time, we in the United States must adjust our mindset to accept the premise that prevention is the ultimate strategy for minimizing the breast cancer problem.

"We must stop quibbling about the pathway to take in order to reach that goal," Fisher said. "We must do our part, and the rest of the world must do its part. And only then can breast cancer prevention become a reality."

Physician Attitudes And Trial Enrollment

The majority of cancer survivors would have considered enrolling in a clinical trial if their physician had made them aware of the option, according to a study of attitudes towards cancer clinical trials conducted among cancer survivors by the Coalition of Cancer Cooperative Groups and Northwestern University.

According to the study, presented at the ASCO meeting, 65 percent of cancer patients would have been somewhat or very receptive to enrolling in a cancer clinical trial had they been made aware at the time of their initial diagnosis, and the vast majority, 87 percent, would have considered participating in a trial if their initial treatment had failed.

Of those cancer survivors who did enroll in a clinical trial, 84 percent were encouraged by their physician to participate, while 83 percent said their physician also made a determined effort to help them find a suitable trial, the study found.

Conversely, 100 percent of cancer patients who declined to consider enrolling in a clinical trial said they were discouraged by their physician from participating, with the majority indicating that their physician exerted little effort to either educate them on the pros and cons of clinical trial participation (69 percent) or help them find a suitable trial (67 percent).

Also, of those patients who tried unsuccessfully to enroll, only 7 percent said their physician encouraged them to participate, and 11 percent made an effort to help them find a suitable trial.

"Clearly, there is an enormous disparity between patient receptivity to cancer clinical trials and overall enrollment," said Jon Miller, who analyzed the data as co-primary investigator on the study and who is now director of the International Center for the Advancement of Scientific Literature and Hannah Professor of Integrative Studies, Michigan State University. "The data from our study show that physician communication and encouragement are essential to closing this enrollment gap."

Between 2000 and 2005, reliance on one's personal physician for information increased from 38 percent to 51 percent, while physicians surpassed all other health care resources as the most trusted information source. Patients and the public turned to cancer organization web sites, patient education materials, advocacy groups, family members, other health care professionals and the media to a lesser degree.

For cancer survivors, reliance and trust in a personal physician was even stronger, with 73 percent of survivors indicating that they learned of clinical trials from a physician.

"These findings show that the lack of communication between patients and physicians about clinical trial opportunities can no longer be overlooked," said Robert Comis, MD, president and chairman of the coalition and the study's primary investigator. "We have more than 5,000 cancer clinical trials available, but too few

patients are made aware of them and encouraged by their most trusted source—their physician—to participate. To continue our progress in discovering new cancer treatments through clinical trials, a serious effort must be made to develop strategies that address barriers to physician involvement."

Miller and colleagues at Northwestern and the Knowledge Networks conducted the survey in March and April 2005. The survey was supported by unrestricted educational grants to the coalition from Amgen Inc., C-Change, and the Lance Armstrong Foundation. Participants were obtained from a sample of 40,000 adults recruited by Knowledge Networks. Participants agreed to weekly surveys in exchange for a free WebTV box and ISP service. Of the 2,029 who reported a cancer diagnosis, 1,788 agreed to participate.

Scientist's Remarks At Odds With His Poster, Experts Say

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because of the high penetration of EPO and DARB in the oncology setting. Although we did not have access to source data to evaluate outcomes such as tumor progression and cancer-specific survival, our findings suggest that observed increased death rates associated with EPO/DARB administration were probably not due to chance alone."

EPO, or erythropoietin, is an agent sold by Johnson & Johnson under the trade name Procrit, and DARB, darbepoetin alfa, is sold by Amgen Inc. under the trade name Aranesp.

"The content of Dr. Bennett's poster is at odds with the remarks quoted by Reuters," said Donald Berry, chairman of the Department of Biostatistics at M.D. Anderson Cancer Center. Berry, who reviewed a copy of the poster provided to him by The Cancer Letter, said the data didn't differ substantially from previously published meta-analyses.

According to Bennett's poster, his meta-analysis found a statistically significant increase in the relative risk of death in studies reported since 2003, hazard ratio of 1.11 (95% CI: 1.0-1.2). The relative risk of VTE was 1.6 (95% CI: 1.3-2.0), also statistically significant.

"There is a contradiction between the poster and his spoken words," said Howard Ozer, chief of hematology and oncology and Eson chair and professor of medicine at the University of Oklahoma Cancer Center. "If you take the poster at face value, it looks very scary, but if you are telling me that you can demonstrate an 11 percent increase in relative risk of death, that's a big deal, and you better be able to back it up with hard data, not with a meta-analysis."

In a May 28 email to this reporter, Bennett claimed to be breaking new ground.

"Where we are is that the findings of increased VTE risks is more solid than previously published, and that the increased risks of death, while debated (FDA-yes; companies -no) appears to be real and identifiable when a complete meta-analysis is done," he wrote.

In the story published in The Cancer Letter last week, Bennett is quoted stating that the VTE finding is seen both in the on-label and the off-label settings. "The signal on VTE is a very clear signal that's independent of whether you measure on-label or off-label usage," he said.

Speaking with The Cancer Letter, Bennett appeared to be losing patience with his colleagues and drug regulators:

"How much more do we need to show you to stop overuse of these drugs?" he said. "How many safety signals do we need before we get to the idea that we have to reconsider what we are doing here?"

The appearance of these quotes in The Cancer Letter couldn't have surprised Bennett. To ensure that his findings were accurately represented, Bennett was asked to review the final draft.

Bennett provided The Cancer Letter with a manuscript of a paper he was submitting to medical journals, the slides he had presented at the plenary session of the May 22 meeting of the Society for Clinical Trials, and a draft copy of a his ASCO poster, which was in the process of being updated. Moreover, The Cancer Letter spoke with seven experts in the field, two of whom were quoted in the story.

Experts pointed out the limitations of Bennett's meta-analysis, and suggested alternative approaches. All of this was included in the story.

Bennett's past role in the ESA controversy and his expertise in adverse drug reactions made his findings newsworthy. He is an NCI-funded investigator who runs a program that assesses drug toxicities, a participant in the Cochrane Collaboration of meta-analysts, and a co-author of the current ASCO and the American College of Hematology guidelines for using ESAs.

Bennett made his final comments on the draft of The Cancer Letter story in the morning of May 31, and a few hours later, the issue was posted. Later that day, Morgan Stanley analyst Steven Harr issued a note based on the story, and a Reuters story cited the findings. Had Bennett stayed with his original conclusion, more coverage would likely have been generated by his ASCO poster presentation.

Why did Bennett's interpretation swing 180 degrees over 72 hours?

In a brief telephone conversation June 3, Bennett confirmed that the comments he made to Reuters June 3 reflected his current views, but declined to elaborate.

In an email June 7, Bennett wrote that "because of commitments to the sensitivities of the peer-review manuscript process, Kara [Gleason, the lead author of the abstract] and I must withhold additional comments on ESAs until the manuscript is accepted and in print.

"I know that this is a disappointment, but it is necessary," he wrote.

Bennett's change of position has benefited the sponsors of the two drugs. At a conference with analysts June 4, Roy Baynes, Amgen's vice president for global development, noted that Bennett regarded his findings as "neutral."

"I think the author was actually quoted in the press today as saying that he has broken no new ground there, and that essentially this is a neutral finding, but that essentially there is a time difference which may relate to the mix of studies that were represented in that, so really no new story there," Baynes said, responding to a question from Morgan Stanley's Harr.

According to Baynes, the ESAs should still be regarded as safe when used on-label. "There have been five studies, which have shown some adverse signals," Baynes said. "These have all been in off-label indications. The off-label indications have generally related to high hemoglobin targets in therapeutic modalities other than chemotherapy induced settings, or they have been in the setting of anemia of cancer where patients who had active disease were not getting chemo, not getting radiation, had a worse outcome, and there were many possible confounders as the to the explanation for that."

Baynes argued that Bennett's selection of the year 2003 as a cut-point was arbitrary. "I think the author himself did the best description of that that essentially this was a descriptive exercise," Baynes said. "When you look at the overwhelming analysis from that particular pooled study, the finding was exactly the same as what has been reported at [the FDA Oncologic Drugs Advisory Committee] by us. The 2003 cut-point is not necessarily a logical cut point, because that's essentially just picking a particular point."

However, Baynes noted that Bennett's data point to a survival *advantage* for ESAs, an extraordinary claim to make at the time when large studies are pointing in the opposite direction, and while FDA is working on further restrictions on the use of the agents.

Studies conducted before 2003 pointed to a survival benefit, Bennett's analysis shows. These small, randomized studies usually focused on the ability of the ESAs to decrease the need for blood transfusion. After 2003, a new generation of trials, which focused on harder endpoints and tested ESAs in off-label settings, wiped out the survival advantage and raised concerns about the agents' safety.

"Now, interestingly, if you would take that point, prior to 2003, there was a survival benefit, so if you're going to do that sort of analysis, you really have to describe both sides of survival benefit before 2003; a slightly adverse survival after 2003 and the magnitude of that was roughly a 20 percent benefit before 2003 and potentially 11 percent detriment afterwards," Baynes said. "I think the person that conducted this analysis was quite clear that the post 2003 is heavily influenced by those off-label indications, in settings where, in fact, they are in deep confounders as well."

Data don't justify resurrecting the claim to a survival advantage, said Ozer.

"There was great skepticism then, before 2003, and now, about whether there was a survival advantage," he said. "There really was only one study that showed a survival advantage, and a lot of it was derived from historical literature. If you go do a meta-analysis of data prior to 2003, yes, you will show a survival advantage, but what that reflects more than anything else is the limitation of meta-analysis."

J&J, too, has made use of Bennett's analysis. At a presentation for analysts June 7, Jay Siegel, group president, research and development for Johnson & Johnson Pharmaceuticals, cited that study's overall survival data, which didn't reach statistical significance, and the survival data for off-label use, which suggested a statistically significant 14 percent decrease in survival, HR 1.14 (95% CI: 1.02-1.27).

Bennett's changing interpretation creates an uncertainty that ultimately harms patients, said Robert Erwin, president of the Marti Nelson Foundation, an advocacy group that specializes in expanded access and drug approval issues.

"The importance comes down to data integrity and data clarity," Erwin said. "It's very important for patients to make decisions based on objective analysis of all available data, and when we see this kind of dramatic reinterpretation being made within such a short period of time, it raises questions about the integrity of the data analysis.

"It's a matter of extreme importance that this be resolved," Erwin said.

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Business & Regulatory Report

Product Approvals & Applications:

FDA Approves Wyeth's Enzyme Inhibitor Torisel For Renal Cell Carcinoma

Wyeth Pharmaceuticals Inc. of Philadelphia said FDA approved Torisel (temsirolimus) for renal cell carcinoma.

Data on Torisel, an enzyme inhibitor, showed prolonged survival, the company said. The product is a protein that regulates cell production, cell growth and cell survival.

"We have made significant advances in the battle against kidney cancer," said Steven Galson, director of the FDA Center for Drug Evaluation and Research. "Torisel is the third drug approved for this indication in the

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Clinical Trials:

SWOG Closes Enrollment In Phase III Trial Testing Revlimid For Multiple Myeloma

Celgene Corp. (NASDAQ: CELG) of Summit, N.J., said Southwest Oncology Group has closed enrollment in the phase III randomized controlled SWOG study S0232, comparing a standard drug therapy, dexamethasone, with a combined therapy of dexamethasone plus Revlimid (lenalidomide) for newly diagnosed multiple myeloma.

SWOG announced that participants be given the choice of switching to Revlimid with dexamethasone, the company said. The SWOG data and safety monitoring committee based its recommendation to close enrollment on the preliminary one year survival results from the Eastern Cooperative Oncology Group phase III study E4A03. The ECOG study is evaluating a low dose of dexamethasone in combination with lenalidomide as compared to the higher, standard-dose of dexamethasone that is used in combination with lenalidomide for newly diagnosed multiple myeloma.

According to SWOG, the 198 patients enrolled prior to the trial closure, are sufficient to provide data analysis and evaluate the primary endpoint of progression-free survival in the two arms of the trial, the company said. Data analysis is ongoing and results will be presented and released in the usual fashion.

Revlimid is approved by FDA in combination with standard-dose dexamethasone for multiple myeloma with at least one prior therapy, the company said. The agent also is approved for transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid recently received a positive opinion from the European Medicines Agency in combination with dexamethasone

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Torisel Is Third FDA Approval In Kidney Cancer Since 2005

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past 18 months, and one that shows an increased time in survival for some patients."

The approval follows the December 2005 approval of Nexavar (sorafenib), which was based on a delay in progression of disease, the company said. In January 2006, Sutent (sunitinib) received accelerated approval based on durable response rate, or tumor size reduction, and was later demonstrated to delay tumor progression.

The safety and effectiveness of Torisel were shown in a clinical trial of 626 patients divided into three groups. One group received Torisel alone, another received a comparison drug called Interferon alfa, and a third received a combination of Torisel and interferon, the company said.

The Torisel alone group showed a significant improvement in overall survival, the company said. The median overall survival was 10.9 months for Torisel alone versus 7.3 months for those treated with the interferon alone. Progression-free survival increased from 3.1 months on the interferon alone arm to 5.5 months on the Torisel alone arm. The combination of Torisel and interferon did not result in a significant increase in overall survival when compared with interferon alone.

The most common adverse reactions, occurring in at least 30 percent of Torisel-treated patients, were rash, fatigue, mouth sores, nausea, edema, and loss of appetite. The most common laboratory abnormalities were high blood sugar, elevated blood lipids and triglycerides, elevated liver and kidney blood tests, and low red cell, white cell, and platelet counts.

* * *

Ortho Biotech Products L.P., of Bridgewater, N.J., said FDA has approved the use of Doxil (doxorubicin HCl liposome injection) in combination with Velcade (bortezomib) for Injection for multiple myeloma with one prior therapy treatment that was not Velcade.

The approval is based on the results of an international phase III trial comparing the Velcade + Doxil combination to Velcade alone, the company said. When used together to treat relapsed/refractory multiple myeloma, the two medications extended the median time to disease progression from 6.5 months to 9.3 months ($p<0.0001$; HR 0.55; 95 percent CI (0.43, 0.71)) over Velcade alone, the company said.

"This approval means that the Velcade + Doxil combination offers an important new option for treating relapsed or refractory multiple myeloma," said Robert Orlowski, of the University of North Carolina, Lineberger Comprehensive Cancer Center and principal investigator. "This is particularly significant because we need treatment options that improve the prognosis for patients whose disease has not responded to their first round of therapy."

* * *

AutoGenomics Inc. of Carlsbad, Calif., said it has obtained clearance from FDA to market its Infiniti Analyzer as stand alone instrumentation for multiplexed assays.

The company said it had obtained clearance for its Infiniti System Assay for Factor II & Factor V as an in vitro diagnostic device that consisted of reagents and instrumentation.

AutoGenomics said it has submitted another 510(k) application to FDA for its Infiniti 2C9 / VKORC1 Multiplexed Assay to assess Warfarin sensitivity and will file for FDA clearance for additional applications in its expanding test menu in pharmacogenetics, genetic disorders, infectious diseases and cancer diagnostics.

* * *

Dendreon Corp. (NASDAQ: DNDN) of Seattle said it has received confirmation that FDA will accept either a positive interim or final analysis of survival from its ongoing IMPACT study to supplement the Biologics License Application for Provenge (sipuleucel-T).

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The information was obtained in a follow up meeting with FDA to discuss the additional clinical data required to support the licensure of Provenge requested by FDA in the Complete Response Letter the company received on May 8, 2007, the company said.

"FDA indicated that either a positive interim or final analysis of survival, as described in the IMPACT Special Protocol Assessment Agreement, would address their request for the submission of additional clinical data in support of our efficacy claim," said Mitchell Gold, president and CEO of Dendreon. "We should complete enrollment in the IMPACT study this year and anticipate interim survival results in 2008. We are committed to making Provenge available as rapidly as possible to help the many men with late-stage prostate cancer who currently have few appealing treatment options."

Dendreon said it submitted the BLA under a Fast-Track designation and was accepted for filing by FDA in January 2007. The BLA was based on a multi-center, randomized, double-blind, placebo-controlled phase III study, D9901, that showed that the group with asymptomatic, metastatic, androgen-independent prostate cancer who received Provenge had a median survival time 4.5 months longer than the median survival seen in the group that had been assigned to receive placebo. For the men who received Provenge, there was a 41 percent overall reduction in the risk of death (p-value = 0.010; HR = 1.7). In addition, 34 percent of those receiving Provenge were alive 36 months after treatment compared to 11 percent of those randomized to receive placebo, the company said.

Treatment with Provenge was generally well tolerated, the company said. The majority of side effects were mild, including infusion-related fever and chills that were usually of low grade and typically lasted for one to two days following infusion.

* * *

Indevus Pharmaceuticals Inc. (NASDAQ: IDEV) of Lexington, Mass., said the European Medicines Agency Committee for Medicinal Products for Human Use has finalized the referral procedure for Vantas (histrelin acetate subcutaneous implant).

Following approval in Denmark in 2005, Indevus said it filed for Mutual Recognition Procedure in the U.K., Ireland, Germany, Spain and Italy. The CHMP action allows for marketing authorization to occur in those countries.

Indevus said that following the acquisition of Valera, the company met with Spepharm Holding B.V., the Valera European marketing partner for both Vantas and Supprelin LA, and the companies have agreed to terminate their investment and shareholder agreement, as well as, their European license and distribution agreement. The finalization of the termination is subject to third-party consents, the company said.

Separately, the company said it also has begun shipment of commercial supplies of Vantas to South America and Asia following approvals in Argentina and Thailand.

Vantas is a soft and flexible 12-month hydrogel implant that provides histrelin, a luteinizing hormone-releasing hormone agonist, for advanced prostate cancer. Vantas is contraindicated in hypersensitivity to GnRH, GnRH agonist analogs, or any components in the product, the company said.

* * *

Pfizer of Woodcliff Lake, N.J., and **Eisai Inc**, said FDA approved a new indication for its anticoagulant Fragmin (dalteparin sodium injection) for the extended treatment of symptomatic venous thromboembolism and/or pulmonary embolism to reduce the recurrence of VTE in cancer.

The agent is the first low-molecular-weight heparin approved in the U.S. for the indication, the companies said.

Data from the CLOT study showed Fragmin reduced the recurrence of blood clots in cancer by 50 percent compared to standard anticoagulant therapy, the companies said.

"Cancer treatments and the disease itself put this patient population at significantly higher risk than non-cancer patients for developing DVT or PE, the two conditions described as VTE," said Frederick Rickles, clinical professor of medicine at George Washington University Medical Center and a CLOT study investigator.

The CLOT trial evaluated the safety and efficacy of Fragmin in reducing the recurrence of DVT/PE in with cancer, compared to an oral anticoagulant, the company said. Patients with acute DVT, PE or both were randomized into two groups of 338 each. One group received the drug for six months. The other group received Fragmin for five to seven days, followed by Warfarin for six months. During a six-month period, nearly twice as many treated with Wafarin experienced at least one episode of DVT or PE compared to those treated with a once-daily administration of Fragmin. Most of the difference occurred during the first month of treatment. The benefit was maintained over the six-month study period. Mortality rates were similar between the study groups at the end of the study. The

safety findings were numerically higher for the Fragmin group versus the Warfarin group for major bleeding, thrombocytopenia and liver enzyme elevations, the companies said.

Eisai said it licensed exclusive U.S. rights to promote Fragmin from Pfizer Inc in September 2005, and has assumed responsibility for product distribution.

* * *

Roche of Basel, Switzerland, said the European Commission has approved Herceptin (trastuzumab) in combination with an aromatase inhibitor for postmenopausal patients with HER2 and hormone receptor co-positive metastatic breast cancer.

The approval is based on data from the international phase III TAnDEM study which showed that the addition of Herceptin to hormonal therapy doubled the median progression-free survival from 2.4 months to 4.8 months, the company said.

TAnDEM is the first randomized study to show that this specific subset of patients with co-positive disease, both HER2 and hormone receptor-positive, are at an increased risk of relapse, making the positive results with Herceptin even more meaningful, the company said.

Herceptin is approved for early and metastatic HER2-positive disease, and has demonstrated a survival benefit in both settings, the company said. The new approval will also allow Herceptin to be used in combination with hormonal therapy for advanced breast cancer.

The TAnDEM study is a randomized phase III trial which evaluated Herceptin in combination with the hormonal therapy anastrozole versus anastrozole alone as first-line therapy (or second-line hormonal therapy) in postmenopausal women with advanced (metastatic) HER2-positive and hormone receptor-positive (ER-positive and/or PR-positive) breast cancer, the company said. Enrolment began in 2001, and 208 patients with HER2 and hormone receptor co-positive disease were randomized at 77 centers in 22 countries.

Median progression-free survival, the primary endpoint of the trial, was 4.8 months for the combination compared to 2.4 months for hormonal therapy alone ($p = 0.0016$), the company said. The combination arm also responded better to treatment (overall response rate was 20.3 percent versus 6.8 percent; $p = 0.018$). a positive trend was seen in median overall survival (28.5 months versus 23.9 months; $p = 0.325$); this is despite the fact that in the hormonal therapy alone arm, more than half (58/104) crossed over to receive Herceptin during the trial when the disease had progressed, and an additional 15 (out of 104) received Herceptin at a later point.

Overall safety data in both arms were acceptable given the known safety profile of each of the drugs in the advanced breast cancer setting, the company said. Patients will be followed for side-effects.

Clinical Trials:

Celldex Begins Phase II/III Trial Of CDX-110 In Gliobastoma

(Continued from page 1)

for multiple myeloma with at least one prior therapy, the company said.

* * *

Celldex Therapeutics of Phillipsburg, N.J., said it has initiated the ACT III study, a randomized, multi-institution phase II/III trial.

The study will investigate the clinical efficacy and safety of the Celldex epidermal growth factor receptor variant III peptide vaccine CDX-110 added to standard-of-care for newly diagnosed glioblastoma multiforme that express the variant III mutation of the EGFR receptor.

The CDX-110 investigational immunotherapy activates the immune system against EGFRvIII, a unique protein on cancer cells, recruiting the immune system to attack existing tumor, the company said. Research led by John Sampson of Duke University showed promising results of the EGFRvIII vaccine in a phase II for brain tumors.

The phase III trial would evaluate CDX-110 in 90 patients, randomized to receive the investigational vaccine treatment or standard therapy in a 2:1 ratio (vaccine to control), the company said. Over 20 tertiary brain tumor centers across the U.S. and Canada will participate in the phase II portion of the study.

The investigational immunotherapy targets the tumor specific molecule EGFRvIII, a functional variant of the epidermal growth factor receptor, which is a protein that has been well validated as a target for cancer therapy. The variant, EGFRvIII, was discovered in a collaborative effort between Bert Vogelstein and Albert Wong at Johns Hopkins University and Darell Bigner at Duke University. Unlike EGFR, EGFRvIII is not present in normal tissues, suggesting the target will enable the development of a tumor-specific therapy for cancer, the company said.

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Cell Therapeutics Inc. (NASDAQ and MTAX: CTIC) of Seattle said it agrees with FDA Special Protocol Assessment comments for its trial in relapsed

or refractory indolent non- Hodgkin's lymphoma.

Pixantrone for relapsed or refractory indolent NHL received Fast-Track designation in May, the company said.

"FDA acknowledged that pixantrone may address unmet medical needs for relapsed indolent NHL, and that the agency is working with us on designing a trial which, if successful, would provide the basis for expanding the indication for pixantrone into this larger segment of the lymphoma population," said James Bianco, president and CEO of CTI.

The PIX303 300-patient trial will examine the time to disease progression for the combination regimen of fludarabine, pixantrone and rituximab compared to the combination of fludarabine and rituximab in patients who have failed up to five prior treatments for relapsed or refractory NHL.

Prior results demonstrated the addition of pixantrone to a fludarabine/rituximab-based regimen in relapsed or refractory indolent NHL yielded a 70 percent confirmed response/unconfirmed response rate, the company said. In that phase I/II study the estimated median duration of response was 25 months (range 2.3 to 43 months) and the estimated progression-free survival rate at three years was 50.4 percent. A phase III trial of rituximab compared to rituximab plus pixantrone in relapsed or refractory indolent NHL had a 61 percent overall improvement in time to tumor progression compared to rituximab alone (395 days vs. 245 days). In that randomized trial, the median TTP estimate for pixantrone/rituximab was 13.2 months compared to 8.1 months for rituximab alone (hazard ratio 0.13, log rank $p<0.001$). The overall response rate in the pixantrone/rituximab arm was 75 percent versus 33 percent in the rituximab arm with a CR rate of 30 percent in the pixantrone/rituximab arm versus 11 percent in the rituximab arm, the company said.

* * *

CuraGen Corp. (NASDAQ: CRGN) of Branford, Conn., and TopoTarget A/S (Copenhagen Stock Exchange: TOPO) said they have initiated a 24-patient phase I/II open-label, multi-center trial evaluating the efficacy and safety of intravenous belinostat (PXD101), an HDAC inhibitor, in combination with doxorubicin, for soft tissue Sarcomas.

Ole Steen Nielsen, head, Department of Oncology, Aarhus University Hospital, DK, is principal investigator, the companies said. Additional sites include the Royal Marsden Hospital, London and Herlev Hospital, DK.

During the initial dose escalation, the aim is to define the maximal tolerated dose of belinostat in combination with doxorubicin, the companies said.

The trial will then advance into phase II and enroll an additional 20 to 40 STS patients who have not received prior chemotherapy, the company said. Standard chemotherapy of doxorubicin will e administered every 3 weeks to which belinostat will be added in a 5-day intravenous regimen. Demonstrated complete or partial response will mean treatment will continue with the combination for up to eight cycles or until disease progression.

The primary objectives are to determine the MTD, and to assess the anti-tumor activity of belinostat and doxorubicin combination treatment as defined by RECIST criteria, the company said. Secondary objectives include the time to disease progression, overall survival, and duration of response. The pharmacokinetic profile and aspects of pharmacodynamic activity of belinostat will also be evaluated.

Belinostat, a small molecule HDAC inhibitor is being investigated for solid and hematologic malignancies either as a single-agent, or in combination with other active anti-cancer agents, including 5-FU, carboplatin, paclitaxel, cis-retinoic acid, azacitidine and Velcade (bortezomib) for Injection, the companies said. Intravenous belinostat is being evaluated in multiple clinical trials for multiple myeloma, T- and B-cell lymphomas, AML, mesothelioma, liver, colorectal, ovarian cancers, either alone or in combination with anti-cancer therapies, the companies said.

* * *

EntreMed Inc. (NASDAQ: ENMD) of Rockville, Md., said it has begun a phase II combination study with Panzem NCD (2-methoxyestradiol or 2ME2) and Temodar (temozolomide) for recurrent glioblastoma multiforme.

Annick Desjardins, associate in medicine at the Preston Robert Tisch Brain Tumor Center at Duke University Medical Center will serve as principal investigator, the company said. The single center, open-label study would determine progression free survival, pharmacokinetics and safety in GBM with treatment consisting of orally- administered Panzem NCD in combination with Temodar.

Panzem NCD is an orally-administered anticancer agent that attacks tumor cells through multiple mechanisms of action and blocks the development of new blood vessels, the company said. The drug MOAs include apoptosis, tumor cell cycle inhibition at the G2/M phase of mitosis, and disruption of angiogenesis through the inhibition of hypoxia inducible factor-1 alpha, the company said.

Panzem NCD is being evaluated in multiple phase II studies for cancers including GBM, prostate cancer, ovarian cancer, carcinoid tumors, and renal cell carcinoma. The drug has been well-tolerated with an acceptable safety profile, allowing it to be combined with other anticancer therapies such as Temodar, the company said.

* * *

Exelixis Inc. (NASDAQ: EXEL) of South San Francisco said it has begun a phase II trial of XL647 for non-small cell lung cancer with prior benefit from treatment with erlotinib or gefitinib or documented T790M mutation in the epidermal growth factor receptor.

Although the T790M mutation confers resistance to the inhibitory effects of erlotinib and gefitinib, preclinical data indicate that the agent inhibits the mutation and other mutant forms of EGFR, the company said. XL647 simultaneously inhibits the activity of multiple receptor tyrosine kinases, including EGFR, HER2, and vascular endothelial growth factor receptor type 2, the company said.

A phase II trial evaluating XL647 as a first-line therapy is ongoing for stage IIIB or IV NSCLC with adenocarcinoma histology and either a demonstrated activating mutation in EGFR or at least one of the following criteria: Asian, female, or no/minimal smoking history, the company said.

Based on the ongoing trial data, Exelixis said it notified GlaxoSmithKline that it had achieved proof-of-concept for the product under the collaboration agreement between GSK and Exelixis.

Under the agreement, GSK has three months to review the data and decide whether to exercise its option to select the compound for further development. If XL647 is selected, Exelixis said it would receive milestone and commercialization milestones, royalties on product sales and, an option to co-promote in North America.

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Mersana Therapeutics of Cambridge, Mass., said it has initiated a phase I open-label, dose-escalation trial of its lead product candidate, XMT-1001, for solid tumors.

XMT-1001 is a polymer-based prodrug of camptothecin, a well-characterized topoisomerase I inhibitor with potent anti-tumor activity, the company said.

The primary objectives are to determine the safety, tolerability and pharmacokinetic profile of the drug, the company said. Patients also will be assessed for evidence of anti-tumor activity. The study is being conducted at three clinical sites: University of Maryland, Greenbaum Cancer Center under Edward Sausville; TGen Clinical Research Services at the Scottsdale Heathcare Virginia G. Piper Center under Stephen Anthony, and Daniel Von Hoff; and U.S. Oncology in Albany under Lawrence Garbo.

XMT-1001, a Fleximer-based product candidate, utilizes a dual release mechanism to liberate a camptothecin prodrug, which is then converted within cells into camptothecin, a DNA topoisomerase I inhibitor, the company said. In pre-clinical studies, XMT-1001 was better tolerated and more efficacious than either camptothecin or irinotecan in models of human cancer, showing extended plasma half-life and high concentrations in tumor tissue.

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Oncolytics Biotech Inc. of Calgary (TSX: ONC, NASDAQ: ONCY) said NCI has filed a protocol with FDA for a phase II 47-patient trial for metastatic melanoma using systemic administration of Reolysin, the Oncolytics proprietary formulation of the human reovirus.

NCI is sponsoring the trial under its Clinical Trials Agreement with Oncolytics, while Oncolytics said it would provide clinical supplies of the drug.

* * *

Spectrum Pharmaceuticals Inc. (NASDAQ: SPPI) of Irvine, Calif., said it has begun phase III registrational trials for EOquin, its proprietary drug candidate for non-invasive bladder cancer.

The trials will be conducted under the recently agreed upon Special Protocol Assessment with FDA, the company said.

"There has been no new treatment approved and marketed for noninvasive bladder cancer in more than 20 years," said Mark Soloway, professor and chairman, University of Miami School of Medicine, and principal investigator of the EOquin phase III trials. "EOquin is among the most promising new therapies we have observed, with potential to treat this very common, yet difficult-to-treat, cancer."

The EOquin SPA calls for two double blind, placebo-controlled, randomized studies, each with 562 patients with Ta G1 G2 non-invasive bladder cancer, the company said. Randomization will be done in a one-to-one ratio to EOquin or placebo. The primary endpoint will be the difference in the rate of tumor recurrence between the two treatment groups by year two, the company said. More than 55 centers will participate.

EOquin (apaziquone for intravesical instillation),

an anti-cancer agent that becomes activated by reductase enzymes found in cancer cells, is formulated for administration directly into the urinary bladder. In a phase II pilot study for which patient accrual was completed this year, the agent instilled into the bladder following TUR-BT was well tolerated and was not absorbed in any detectable amount from the bladder wall into the bloodstream and therefore, would carry a low risk of systemic toxicity, the company said.

Spectrum Pharmaceuticals said it completed a multi-center, phase II trial in Europe. The results showed that EOquin was well-tolerated and produced a 67 percent CR in patients, many of whom had been treated multiple times. The data from this study were presented to the FDA in early 2006.

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Tapestry Pharmaceuticals Inc. (NASDAQ: TPPH) of Boulder, Colo., said it has begun its phase II trial program for its next generation taxane, TPI 287.

The company said it opened enrollment in a phase II trial hormone refractory prostate cancer. Also, the company said it would begin an additional phase II trial this year for glioblastoma multiforme. A third phase II trial is also planned this year for cancer of the pancreas. In all of the studies, TPI 287 will be administered in an intravenous dosage form.

Tapestry said it would initiate a phase Ib/II study evaluating the combination of TPI 287 and temozolomide in primary brain cancer. Exploratory phase II trials in other tumor types may be initiated as well, based on preclinical and clinical data.

Tapestry said it is developing an oral formulation of TPI 287. An oral phase Ib/II pharmacokinetic trial of TPI 287 would begin in the summer of 2007 to evaluate its bioavailability in humans. No taxane is approved for oral administration, the company said.

Data on the TPI 287 oral bioavailability and activity in human glioblastoma mouse xenografts was presented at this year's American Association of Clinical Research annual meeting.

TPI 287 overcomes multiple drug resistance in solid tumors that are innately resistant to taxane therapy or have become resistant to taxanes following exposure to chemotherapy drugs, the company said. In preclinical testing, the taxane inhibited tumor cell growth in a number of in vitro cell lines and has shown inhibition of human tumor growth in certain animal xenograft models when tested against standard comparative agents. The in vitro activity was seen across multiple cell lines including cell lines known to be sensitive to taxanes as well as cell lines known to be resistant to taxanes. Taxane sensitive cell lines in which TPI 287 has shown activity include cell lines derived from breast cancer, uterine cancer and non-small cell lung cancer. Taxane resistant cell lines in which TPI 287 has shown activity include cell lines derived from breast cancer, colon cancer and prostate cancer, the company said.

* * *

VION Pharmaceuticals Inc. (NASDAQ: VION) of New Haven, Conn., said it would suspend enrollment and further treatment in its phase II study of Cloretazine (VNP40101M) for relapsed adult myelogenous leukemia pending a detailed review of all of the data.

The decision was based on the recommendation of the independent Data Safety Monitoring Board after a planned interim analysis, the company said.

The trial is a double-blind placebo-controlled randomized evaluation of an experimental treatment consisting of Ara-C plus Cloretazine (VNP40101M) versus a control arm regimen of Ara-C and placebo, the company said. The trial is designed to accrue patients in first relapse AML whose first complete remission was more than three months but less than twenty-four months in duration. Stratification was done according to: (i) age, greater than or less than 60 years and (ii) length of the first CR, more than or less than 12 months in duration.

The primary endpoint is the objective response rate, defined as CR plus CRp, the company said. Secondary endpoints include time to progression, duration of response, overall survival and toxicity, the company said.

The DSMB review of clinical data from the first 210 treated patients resulted in a recommendation that enrollment and further treatment of patients on study be suspended because any advantage in complete remission could be compromised by the observed on-study mortality to date, the company said.

The study will remain blinded while a complete medical review is conducted, the company said.

The company also it is evaluating Cloretazine (VNP40101M) as a single agent in a phase II trial in the elderly with de novo poor-risk AML.

Deals & Collaborations:

Genzyme To Pay $345 Million For Bioenvision, Clofarabine

Genzyme Corp. (NASDAQ: GENZ) and Bioenvision Inc. (NASDAQ: BIVN) said they have reached an agreement under which Genzyme will acquire Bioenvision in an all cash transaction valued at

$5.60 per outstanding common share, or $345 million.

Genzyme said it would gain exclusive, worldwide rights to clofarabine. The companies co-developed clofarabine in Europe where Bioenvision markets the product for acute lymphoblastic leukemia in relapsed and refractory pediatric patients.

The drug also is being developed by the companies for indications including as a first-line therapy for adult acute myeloid leukemia.

Clofarabine is branded as Clolar in the U.S. and Canada, where it is marketed by Genzyme for relapsed and refractory pediatric ALL. The product has been granted Orphan Drug status for ALL and AML in both the U.S. and European Union.

Bioenvision also markets Modrenal (trilostane), approved in the U.K. for post-menopausal breast cancer following relapse from initial hormone therapy, and has a pipeline in development for unmet needs in autoimmune disease and infectious disease, the companies said.

The acquisition of Bioenvision will take the form of an all cash tender offer, which is expected to be completed in July, the companies said. The transaction has been approved by both boards of directors.

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Cedara Software (NASDAQ: MRGE; TSX: MRG) of Toronto said it has concluded a licensing agreement with **Varian Medical Systems** of Palo Alto, Calif., giving Varian exclusive global rights to distribute the Cedara I-Response technology within the radiation and medical oncology market.

Cedara I-Response has received FDA 510k clearance and the company said a commercial release could come in June.

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Medarex Inc. (NASDAQ: MEDX) of Princeton said it expects to receive an undisclosed milestone payment from its licensing partner, Amgen, for the advancement of an antibody into a phase II trial.

The antibody was generated using the Medarex UltiMAb technology and is the second UltiMAb-derived antibody to be advanced into phase II development by Amgen. Medarex said it may receive future milestone payments and royalties should the product candidate progress through clinical development and achieve commercial sales. Two additional UltiMAb antibodies are in phase I development by Amgen, the company said.

Medarex said it applies its UltiMAb technology and product development and clinical manufacturing experience to generate, support and commercialize a range of fully human antibody product candidates for itself and its partners. ANX-201 Drug Combination Demonstrates Synergistic Activity Against Human and Bird Flu Viruses

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Morphotek Inc. of Exton, Penn., said it has entered into an agreement with CMC Biopharmaceuticals of Copenhagen to develop MORAb-028, a therapeutic antibody for advanced melanoma and other cancers.

The product is a human IgM monoclonal antibody that recognizes a cell surface antigen over-expressed on a fraction of metastatic melanoma, brain cancers and non-small cell lung carcinoma, the company said.

* * *

Novacea Inc. (NASDAQ: NOVC) of South San Francisco and Schering-Plough Corp. (NYSE: SGP) of Kenilworth, N.J., said they have entered into an exclusive worldwide license agreement to develop and commercialize Asentar (DN-101).

Novacea said it is conducting an international 900-patient phase III trial, ASCENT-2, evaluating the drug for androgen-independent prostate cancer. Asentar is a proprietary, high-dose oral formulation of calcitriol, a hormone that exerts its effects through the vitamin D receptor.

Under the agreement, Novacea said it would receive an upfront payment of $60 million, including $35 million as reimbursement for past research and development expenses, a license fee of $25 million, and a commitment by Schering-Plough to purchase $12 million of Novacea common stock at a predetermined price within 10 days of the closing. The agreement provides Novacea with pre-commercial milestone payments of up to $380 million, and tiered royalties on worldwide sales of Asentar, the companies said.

Schering-Plough said it would be responsible for all forward development costs in exploring indications for earlier stages of prostate cancer, such as androgen-dependent prostate cancer and adjuvant therapy and will lead all global commercialization efforts for Asentar. Novacea said it would provide medical support to the Schering-Plough commercial operations for Asentar in the U.S., including deployment of their medical science liaisons, which will be funded by Schering-Plough.

* * *

Peptech Ltd. and **EvoGenix Ltd.**, both of Australia said they would merge to form a biotechnology company focused on the antibody and protein therapeutics sector. The merged company will be led by John Chiplin, CEO of Peptech and a board made up of directors from both companies. Merilyn Sleigh, CEO of EvoGenix, will be retained in a senior advisory role.