THE CANCER LETTER

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NCI Director Halts STELLAR Trial, Seeks "Brilliant Ideas" To Prevent Breast Cancer

By Kirsten Boyd Goldberg

NCI Director John Niederhuber abruptly halted a large, randomized breast cancer prevention trial the day after one of the institute's cooperative groups was told to begin the national study.

Niederhuber stopped the Study to Evaluate Letrozole and Raloxifene (STELLAR) on Jan. 23, the day after the NCI Executive Committee voted 8-2 in favor of going ahead with the trial. Niederhuber and NCI Deputy Director Anna Barker cast the two nay votes. Niederhuber then assigned Barker to form an ad hoc committee to review the study.

In an interview with The Cancer Letter, Niederhuber indicated that it is unlikely that the trial would open this year, "if at all." He will ask the committee to look more broadly at the issue of breast cancer prevention, he said.

"Maybe what will come out of this are some bright, brilliant ideas

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EPO Controversy:

FDA's ODAC To Review EPO Agents In May; SEC Probes Amgen Delay In Study Disclosure

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee is scheduled to review the entire class of erythropoietin agents at its May 10-11 meeting.

At that time, the committee will be able to consider the results of an Amgen-sponsored small cell lung cancer study, which is widely believed to be a make-or-break trial for EPO products in cancer treatment.

It's also likely that the committee will be able to review the results of a meta-analysis of EPO data, which is being updated with data with recently reported negative studies. The meta-analysis, conducted by the Cochrane Collaboration, has been inconclusive, a fact that is frequently sighted by the sponsors of EPO agents,

Even before the ODAC meeting, FDA is likely to add a "black box" warning on the labels for EPO agents. The warning would almost certainly reflect the results of recent studies in cancer-related anemia and chemotherapy-related anemia, Amgen officials acknowledged in a March 1 conference call with financial analysts.

Also, Amgen said the Securities and Exchange Commission has launched an informal inquiry stemming from the company's failure to report the negative results of a Danish study of Aranesp in head and neck cancer.

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NCI Division Director Calls P-4 "Crucial" To Reducing Cancer

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about how this should be done in a way that's going to give the American people—women—a much better opportunity to answer this question, and maybe in a much more timely fashion, to bring better science into this," Niederhuber said.

The trial would compare raloxifene (Evista)—the apparent winner of a previous randomized trial between that drug and tamoxifen (Nolvadex)—to letrozole (Femara), an aromatase inhibitor that prevents the formation of estradiol. The trial was slated to begin enrolling participants in April.

The NCI director's move surprised clinical trialists, who regarded this study as the next logical step in breast cancer prevention. NCI's infrastructure of Community Clinical Oncology Programs has been waiting for several months to begin recruiting the 12,800 postmenopausal women needed for the study.

"It's a shock," said James Wade III, principal investigator of the Central Illinois CCOP in Decatur, Ill. "We would love the study to open so we can get women on it and we can find out, is there a better drug than raloxifen or tamoxifen to prevent breast cancer? It's still a national problem, since 175,000 women a year get breast cancer. We have a drug that may be better. It would be wonderful to do the study so we can cut down on the number of women who get breast cancer. Isn't that a job for the federal government to help pay for? The trial has gone through all the scientific approval processes. Every committee has approved it and it's scientifically valid."

STELLAR, in development since 2005 by the National Surgical Adjuvant Breast and Bowel Project, an NCI-supported clinical trials cooperative group, was approved by an 18-member peer review committee last April. The trial then was reviewed and approved by the Clinical Trials Oversight Committee, the NCI Division of Cancer Prevention, and FDA.

The trial, also known as P-4, for NSABP's fourth prevention trial, would be the third in a series of large, randomized trials for breast cancer prevention. In 1992, NSABP began the Breast Cancer Prevention Trial (P-1), which found that tamoxifen reduced the incidence of breast cancer in women at increased risk for the disease by almost 50 percent. That finding led to the Study of Tamoxifen and Raloxifene (STAR, or P-2) to compare those two drugs. The study enrolled 19,000 women between 1999 and 2004, and results were announced last April.

STAR found that the two drugs were equivalent in reducing breast cancer risk for postmenopausal women at increased risk of the disease. However, the women who took raloxifene had fewer serious side effects than those who took tamoxifen, including fewer uterine cancers, blood clots, and cataracts. Menopausal side effects were mild to moderate for both drugs, and both are known to protect bone health.

STELLAR would determine if letrozole is better than raloxifene in reducing the incidence of breast cancer in postmenopausal women at increased risk of the disease. Secondary aims of the study are to compare the incidence of ductal carcinoma in situ and lobular carcinoma in situ, osteoporotic fractures, cardiac events, vascular events, non-breast cancers, toxicity and side effects, deaths, and quality of life.

Peter Greenwald, director of the NCI Division of Cancer Prevention, said he supports allowing the trial to start as planned. "The P-4 breast cancer prevention trial, or STELLAR, is at the heart of NCI's program to prevent breast cancer," he said to The Cancer Letter. "It is a crucial next step to build upon the major reduction of breast cancer occurrence seen in the first breast cancer prevention trial and the demonstration that this can be done with fewer adverse events in the STAR trial. We expect that STELLAR may demonstrate that breast cancer occurrence in post-menopausal women can be reduced even further. It also will provide women with a balanced view of benefits and risks to allow them to consider what is the best option for each individual.

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This will grow in importance as research using new technologies provides us with better ways to assess individual breast cancer risk.

"The National Surgical Adjuvant Breast and Bowel Project, in association with the CCOP program and the Cooperative Groups, has done more for progress against breast cancer than any other group in history," Greenwald said. "This is true for both prevention and treatment. They did extremely well in the peer review of the P-4 proposal. We hope the trial will start soon."

Estimates of the cost of the trial vary, but the peer review committee recommended that NCI give NSABP $66 million in direct funding for the trial over five years, with $12.3 million for the first year. Novartis, the maker of Femara, and Eli Lilly, which makes Evista, have agreed to provide the drugs and look-alike placebo pills for free, including the packaging and distribution costs. In addition, Novartis had agreed to provide additional funding for recruitment.

NSABP Chairman Norman Wolmark said he didn't see a rationale for delaying the study. "We would be very willing to work with the NCI and any group of scientific experts to enhance the value of P-4," he said to The Cancer Letter. "On the other hand, we think that delays to initiating P-4 would have extremely dire consequences for the participants who are ready to enroll in this trial, for the institutions that are poised to proceed with it, for the infrastructure, and for the additional money that's been allocated for this trial by industry. Our hope would be that we could get the trial started, and then if there is a need to amend it to augment the science, fine. But there's no rationale for delaying it further."

NSABP sought funding for P-4 through a supplemental grant request to its CCOP Research Base Award. This was the same mechanism that was used to fund the STAR trial. After P-4 was reviewed and approved by a Special Emphasis Panel, NSABP's CCOP Research Base grant underwent its five-year competitive renewal, and received approval for another five years for its prevention program, including the P-4 trial. The priority score for that review was 131, the best NSABP has ever received.

Niederhuber: Look At State of the Science

In a March 2 interview with The Cancer Letter, Niederhuber said he asked Barker to form a new working group under a subcommittee of the National Cancer Advisory Board to examine the trial and look more generally at NCI's approach to breast cancer prevention.

With NCI heading into its fifth year of "below-inflation appropriations," the institute's programs are under "a great deal of stress," Niederhuber said. "This proposed trial, P-4, represents a lot of NCI resources, and it also represents a lot of out-year commitment over some 12 or 13 years. One person who called to question this some months ago made the comment to me, 'In that time, will anyone really care about the answer?' If we can't do better in terms of understanding how to prevent this and other cancers in that period of time, then we are really in trouble. So this has really been not a straightforward kind of decision for me or for the leadership of NCI. It has been quite controversial.

"As you might imagine, there are a lot of strong feelings on the part of the scientific community, our R01 community, that this is not good science, that this is not the best investment of scarce resources," Niederhuber said. "Even some of our advocacy community has been very much against this. Others have been, on the other hand, supportive, and felt that this is something we definitely should do, to continue to build on the previous trials, P-1 and P-2….

"I thought that it was in the best interest of NCI, the best interests of the community and patients, that we at this time, faced with this kind of financial decision, seek outside advice," Niederhuber said. "That's something the director of the NCI not only has a right to do, but I think has an obligation to do, especially when budgets are as tight as they have been."

The working group will consist of about 25 members, including some with affiliations to NSABP, he said. The first meeting is scheduled for March 23, and the sessions will not be open to the public. The group will submit a report to the NCAB, which will discuss it in a public session.

"Hopefully, they will look at this, not just at the trial itself, but at the state of science in 2007 and what we anticipate our technologies will be able to do for us over next few years, and how we can best apply the resource platforms that we have to asking these questions," Niederhuber said.

"Do we need to do this in 13,000 women? Are there other ways we might use the technology that we have to look at smaller numbers of patients, or women at risk? Are there other endpoints we could use? Are there other ways to approach prevention questions today that maximizes the information that we can get, and what we can do to benefit patients.

"I'm a little bit surprised that our colleagues don't really welcome this as a sound approach, because I think everyone would agree that in these times, we absolutely

need to put our best brainpower to bear on what are the best approaches to asking these kinds of important questions," Niederhuber said.

"One of the issues that concerns a lot of us is that, while these [trials] have been important steps forward in prevention of breast cancer, we all know there are lots of tradeoffs to those interventions," Niederhuber said. "There has been a significant reluctance on the part of patients to embrace those. So, there is more to this that I think needs very careful consideration."

Aromatase inhibitors such as letrozole have "significant tradeoffs," Niederhuber said. "There is significant evidence out there that we don't know that women will embrace them."

Niederhuber said he didn't know how long the working group might take to complete its review. When asked whether NSABP would be able to open the trial later this year, if at all, Niederhuber replied: "If at all. Or in this form.

"Maybe a better way to say it is, maybe what will come out of this are some bright, brilliant ideas about how this should be done in a way that's going to give the American people—women—a much better opportunity to answer this question, and maybe in a much more timely fashion, to bring better science into this," he said. "I don't know. I'm very interested in hearing what people have to say about it. It could be that everyone will say this is the best we can do. If that's the case, then we have to look at resources very carefully and say, OK, can we afford to make this long-term out-year commitment? Do we have to find other resources?"

NSABP made a "strong argument" that the study has been peer reviewed, Niederhuber said. "But actually, I think our scientific community would have a few questions about that process that has been used to ask to commit over $100 million.

"First of all, this was really a concept review as a follow-up to previous trials, and it has been proposed to be funded as a supplement," he said. "This is a little bit different than developing a Request for Application, for example, which would be something that would be a more normal course of action for something as important and as big as this project is. And, one would ask the community to respond with applications of their best science and their best approach to this question. Then those would go to study section for review and for priority score and decision about which was the best, which could be funded, what resources could be applied to that.

"There was no competition involved in this," he said.

"There has been a tendency over the years, and I have been as guilty in this as others have been, in the clinical trials arena, especially in the large trials, the proof-of-principle phase III trials or the prevention trials, of finishing one thing and then asking what are you going to roll into next. Rather than stopping and carefully looking at where you are scientifically and how science is changing and how science might direct the next approach to clinical research….

"When I went back and reviewed the report from the concept review, it was very clear to me that that group also had some significant concerns and felt there were some weaknesses of this proposal as well," he said.

NCI's Clinical Trials Oversight Committee, established last year to review and prioritize clinical trials, reviewed P-4 "with a great deal of debate and discussion, especially about the resources, and sort of kicked it up" to the NCI Executive Committee, Niederhuber said. "There were considerable concerns. It came early in the formation of CTOC, when CTOC is still getting its sea legs and learning how to function."

"Should The Trial Proceed As Designed?"

NCI's Barker sent a letter outlining Niederhuber's concerns about the trial to prospective members of the working group, who were invited to travel to Bethesda at the institute's expense to participate in the March 23 meeting.

The text of Barker's letter follows:

As you are aware, over the past several years the National Cancer Institute's Division of Cancer Prevention has performed a series of important clinical trials to study the effect(s) of tamoxifen, raloxifene (Selective Estrogen Receptor Modulators – SERMS) and, subsequently, aromatase inhibitors such as letrozole on reducing the incidence of invasive breast cancer in defined populations of postmenopausal women.

As follow-on to this series of breast cancer prevention trials, a new trial in the sequence, the P-4 trial, has been proposed and peer-reviewed. The P-4 trial is designed to perform a 10-year study in risk-eligible, postmenopausal women to determine whether letrozole is more effective than raloxifene in reducing the incidence of invasive breast cancer in this otherwise healthy population. The trial will accrue 12,800 patients over 4 years. The primary endpoint for this trial will be the first occurrence of invasive breast cancer. Secondary endpoints will include DCSI; LCIS; ischemic heart disease; fracture of the wrist, hip, and spine; DVTs; PEs; TIAs and stroke; death; other invasive cancers;

and quality of life.

The P-4 trial would cost the NCI approximately $55 million, with the private sector also contributing an undetermined amount to the costs of the trial. The total cost of the trial will approach $80-100 million. Given the magnitude of this investment, the rapid acceleration of progress in molecular genetics and molecular biology, and the disparate range of views on the trial, Dr. John E. Niederhuber has requested that we convene a group of experts to review the proposed P-4 trial and provide feedback to him. It is anticipated that the group will provide guidance in addressing several important questions. For example:

•Should the trial proceed as designed?

•If it proceeds as designed, will the results accrue major benefit to patients, and will there be uptake of the results?

•Should the trial proceed—but imbed in it molecular, imaging and other studies that could conceivably provide new mechanistic insights into breast cancer and/or serve as clinically relevant biomarkers?

•Should a new trial be developed that would address some of the issues highlighted above – e.g., focused on molecular mechanisms of these types of agents and/or molecular markers of breast cancer disease progression?

Of course, there are many other questions that could be raised by this group and all issues should be considered open for discussion.

Convening this group in no way questions the quality of the design of the current trial to achieve its stated objectives or the peer review process that recommended it, but rather this P-4 Chemoprevention Trials Assessment Group represent what is becoming relatively routine procedure for NCI's investments of this magnitude—assessment of the initiative/trial by the extramural communities at multiple levels to ensure that the best science/trials are being funded. Our intent is to ensure that our funds are invested optimally to achieve outcomes that utilize the best of clinical and molecular sciences to answer key scientific questions, produce extremely valuable data sets for the community, and, in this instance, provide maximal benefit to breast cancer patients.

On behalf of Dr. Niederhuber, I am pleased to invite you to participate in the deliberations of this Group. We will send out the protocol and other supporting materials for your review prior to a 1-day meeting that will be held on March 23, 2007, at the Hyatt Hotel in Bethesda, Bethesda, Maryland. The thoughts and input from the Group on the P-4 trial will be summarized in a report to Dr. Niederhuber and the NCI leadership following the March 23, 2007, discussion.

"Extensively Reviewed And Fully Approved"

On Feb. 20, NSABP Associate Chairman Lawrence Wickerham sent a memorandum to the cooperative group's members, titled "IMPORTANT INFORMATION FOR NSABP MEMBERS CONCERNING THE STATUS OF THE PROTOCOL NSABP P-4, THE STELLAR TRIAL."

The text of the memo follows:

We would like to take this opportunity to give you an update on the status of the NSABP Breast Cancer Chemoprevention P-4, STELLAR Trial and to enlist your support in getting the trial activated. Attached to this e-mail is a summary of the trial.

Reviews and Approvals of the P-4 Study to Date

The P-4 study has been extensively reviewed and fully approved by every NCI Committee and panel that has considered the study to date.

—This process began in Fall 2005, when the NSABP submitted a detailed concept of the P-4 study to the NCI's Division of Cancer Prevention. The concept underwent review and was subsequently approved by the NCI's Executive Committee in October of that year.

—The NSABP then submitted a supplemental grant request to the NCI's Division of Cancer Prevention. This 340 page document plus appendices was reviewed by a Special Emphasis Panel selected by the NCI and comprised of 18 respected and esteemed experts in a variety of fields including oncology, pharmacology, biostatistics, endocrinology, nursing and consumer representatives. Included in the group were Dr. Angela Brodie of the University of Maryland, Dr. William Gradishar of Northwestern University, Dr. Carol Fabian of the University of Kansas and Dr. Rowan Chlebowski of UCLA. Following a reverse site visit in April 2006, the application was recommended for approval with the best priority score that any NSABP chemoprevention proposal has received.

—The trial proposal was reviewed and approved by the newly formed Clinical Trials Oversight Committee (CTOC) in May 2006.

—Subsequently, a full protocol document was developed and submitted to the NCI's Division of Cancer Prevention; this was reviewed and conditionally approved in October 2006, pending FDA review, which subsequently took place in December 2006.

—Our full competitive renewal of the NSABP CCOP Research Base Award, which includes the breast

cancer prevention program, underwent peer review at the NCI and in December 2006, was awarded a priority score of 131, the best priority score received by any grant proposal in the 50-year history of the NSABP.

—The P-4 document was reviewed by the Food and Drug Administration in December 2006, and may proceed pending submission of the data forms to the FDA.

—Regarding funding of the trial, the Special Emphasis Panel recommended that the NSABP receive approximately $66 million dollars of direct funding over a 5-year period, with $12.3 million dollars recommended for Year 1. The NSABP has been awarded slightly less than $4 million for Year 1 of the trial to allow it to be fully developed and activated.

—On January 22, 2007, the NSABP was notified that the protocol had once again been reviewed and given final approval by the NCI's Executive Committee, which is comprised of the NCI Director and the Directors of each of the NCI divisions. After 18 months during which time the trial underwent no less than 7 reviews and passed each with outstanding ratings, this call was very good news.

P-4 Study on Indefinite Hold

On January 23, 2007, one day after the NCI Executive Committee's final approval of the P-4 study, the NSABP was told that Dr. Niederhuber put the P-4 study on hold. Dr. Niederhuber subsequently informed the NSABP that he was planning to convene an expert panel to consider adding elements of molecular analysis and other new technologies to the proposed protocol. According to Dr. Niederhuber, these additions to the P-4 study were being considered to ensure that the study would provide as much information as possible, particularly concerning the molecular aspects of breast cancer.

If Dr. Niederhuber's proposed additions to this trial add value, they will be welcome. However, it is the NSABP's hope that such efforts will occur without excessive burden to the women in the trial or to our investigators. More importantly, the trial must begin without further delay. It is this decision to arbitrarily delay the trial that is of greatest concern. Many of our sites have potential participants who are waiting for the activation of the trial and we suspect you and your associates are also anxious to begin this trial. The NSABP has developed the most successful breast cancer chemoprevention program in the world and it would be a terrible and irrevocable loss to see it evaporate because of these unexpected delays.

The trial represents a public-private partnership that involves the NSABP and the National Cancer Institute, and also Novartis and Eli Lilly and Company. Both companies are providing drug and placebos without charge, but these unexpected delays can adversely impact the packaging and labeling time slots already scheduled with their drug supply departments. Novartis has also agreed in principle to provide additional funding to help with recruitment and adherence efforts at the local centers. NCI funding for recruitment is $1,000 per participant entered and that has been unchanged since 1992. It is our experience for breast cancer prevention trials that our sites evaluate as many as 20 women in order to enroll 1, clearly showing that the $1,000/case is nowhere near sufficient to cover all recruitment costs. This partnership with industry is a critical factor in the successful conduct of this trial. From time to time we are asked why the P-4 trial and all of its costs should not be covered by industry. The patent for letrozole is likely to expire before the results of this trial are available and, therefore, Novartis is unlikely to directly benefit from the study. Conducting the trial as an NCI-sponsored study ensures the independence of the design, conduct and analysis of the trial with all of the necessary oversight mechanisms.

We certainly support the Director's idea to obtain the maximum information possible from this trial including molecular analyses and the incorporation of new technologies. The Human Specimen Bank components of our first two prevention trials have been highly successful. Over 95% of the participants submitted serum and lymphocytes. Blocks or slides were submitted on more than 80% of our cancer events (breast cancer and other cancers). In the P-4 trial we will continue to collect blocks or slides on breast cancer events and other cancers. We will also obtain serum and lymphocytes at the time of entry, at 1 year on study, and at the time of any breast cancer event. As in the prior prevention studies, we have chosen not to include specific ancillary studies that would mandate the allocation of materials. This trial will require 4 years to accrue participants and an additional 2-3 years of follow-up before analyses can be conducted. It is our experience that questions of interest today may have already been answered or may no longer be of interest by the time the P-4 materials and the clinical outcomes are available. When P-1 began in 1992, BRCA 1 had not yet been identified, but by 1998 when the results of the trial were available, we were able to analyze both BRCA 1 and BRCA 2. Specimens from all of our NSABP Human Specimen Banks are available to the entire scientific community, not just NSABP members.

The details concerning the process to access bank materials are listed on our NSABP Web site and involve the scientific review of proposals by an external panel of experts. In our treatment trials we have developed a partnership with Dr. Sheila Taube and her group at the NCI to promote the availability of the specimens. The Breast and GI SPORE PI's have been personally briefed on the bank's inventory of specimens and the process to obtain them. Among the studies already completed utilizing samples from the P-1 specimen bank is the evaluation of BRCA 1 and BRCA 2 abnormalities conducted by Dr. Mary Claire-King, and an evaluation of endogenous sex hormones, breast cancer risk, and tamoxifen response conducted by Drs. Walter Willet, Steve Cummings, and their associates. Dr. Judy Garber and her associates at Dana-Farber and Yale evaluated the relationship of Factor V Leiden and Prothrombin G20210A mutations to venous thromboembolism disease in P-1. Drs. Barbara Dunn, Mark Green and Ken Buetow from the NCI evaluated SNPs in estrogen and tamoxifen metabolizing genes. With the maturity of the STAR data, additional studies are being considered, including a project from the Consortium on Breast Cancer Pharmacogenetics looking at ER polymorphisms and Quality of Life and a separate project from the Mayo Clinic looking at CYP2D6.

EPO Controversy:

ODAC To Review Results Of Amgen Lung Cancer Trial

(Continued from page 1)

In a filing, the company reported that on Feb. 19, it received "an informal inquiry from the SEC's Atlanta District Office regarding the Danish Head and Neck Cancer (DAHANCA) 10 study."

According to the document, "the SEC's Atlanta District Office has requested that Amgen voluntarily provide certain information and documentation related to the Study. We intend to fully cooperate with the request."

The Danish study was temporarily stopped last Oct. 18, and the decision not to resume the study was made on Dec. 1, after finding an increase in local disease progression. However, the company didn't acknowledge the study's conclusion in its filings or during its Jan. 25 earnings call. The results were first disclosed in the Feb. 16 issue of The Cancer Letter.

Kevin Sharer, Amgen president, CEO, and chairman, acknowledged "a miss" by the company in failing to disclose the negative results. "Our policy for disclosure is to be as prompt and complete as we think investors would be interested," he said at the conference March 1. "Given what we know now, even though [the Danish study] was on a website, I wish we talked about it on the [Jan. 25] call. That was just a miss on our part, not some policy shift. We are going to keep telling investors in a timely way what's going on and be available like we are today."

Sharer described the SEC inquiry as a routine occurrence. "You never minimize a question from any government agency, whether it's the FDA, or the SEC, or the IRS," he said. "But I would say that this inquiry is informal, it's not unexpected. They saw us comment on the [Danish] study, the stock moved a little bit, and they are doing their work to just ask a few questions. We are going to respond to this seriously, and take it seriously, but we get a number of these inquiries throughout the year on various matters, and most large companies do. We are doing our darnedest here to be as open and responsive and complete as we can so investors have all the information they need to make judgments."

Amgen Paints (Mostly) Rosy Picture

In the March 1 call, organized by Goldman Sachs, Amgen officials attempted to reassure restless investors. The company's stock price has been dropping steadily from over $77 per share on Jan. 25 to under $62 at the end of trading March 1.

Amgen officials painted an optimistic picture:

The studies that raised questions about the EPO agents were in off-label indications, Sharer said. "When we look at the totality of the data, we believe our products are safe and effective when used on label," he said.

Amgen officials said that anemia due to cancer, an indication that is almost certain to be cited in a black box warning, contributes roughly $500 million to the company's sales. Altogether, U.S. Aranesp sales in oncology were $2.8 billion last year. Together with the competing product, Johnson & Johnson's Procrit, EPO sales in the U.S. oncology field were $4.9 billion last year, making EPO the most costly component of cancer care.

Company officials defined anemia of cancer as "a diagnosis of exclusion"— anything not classified as chemotherapy-induced anemia or myelodysplastic syndrome.

Three types of patients receive EPO for anemia of cancer: hospice patients, patients with chronic disease, and cancer survivors in remission.

Patients receiving palliative care account for 70 percent of all individuals receiving this treatment, but

account for far less than half of the sales, said George Morrow, Amgen executive vice president for global commercial operations.

"They are going to be on the drug for shorter time than cancer survivors in remission and chronic disease patients, who could be on the product for quite some time," Morrow said. "They are gravely ill and would die soon."

Giving EPO to patients in a curative setting has become particularly controversial in light of studies that show toxicity and disease progression. Some physicians said to The Cancer Letter that they give the drug mostly for palliation.

Though the anemia of cancer segment of the Aranesp market is in danger, the agent has room for growth, as anemia induced by chemotherapy continues to be under-treated, Sharer said.

"The penetration of the cancer market gives substantial room for further growth, based on the numbers of unmet patient need," Sharer said. "We are not remotely topped out in terms of the patients who need the drug, compared to who is getting it."

Recent studies "have created a shift in attitudes toward a more conservative view toward [EPO] treatment for cancer patients, particularly in [anemia of cancer]," Morrow acknowledged. "While a modest reduction in [EPO] utilization in cancer patients, particularly in [anemia of cancer] is likely, the unmet need in [chemotherapy induced anemia] remains substantial, and, barring any major shift in reimbursement policy, we would expect to see a continued significant utilization in the oncology segment."

Amgen officials said they haven't detected an increase in denials of claims for Aranesp for anemia of cancer or chemotherapy induced anemia. Though the US Pharmacopeia has dropped its listing of Aranesp as a treatment for anemia of cancer after a company trial showed an increase in mortality on the Aranesp arm, that use of the agent hasn't been stopped, Morrow said. He described the Pharmacopeia action as a result of a "snap decision."

"Medicare carriers must not deny Part B coverage based only on the absence of FDA-approved labeling if that use is supported in one of the compendia," Morrow said. "The reverse, however, is not true. Carriers can cover without compendia listing.

"The majority of payers have understood the complexity of the issue, the need for thorough scientific review, and the importance of taking the appropriate amount of time to evaluate the new clinical data."

Morrow said the company isn't aware of any payers who have changed their reimbursement policies for Aranesp in anemia of cancer. "However, there are several payers who have expressed an interest in reviewing this issue in the near term," he said. "We are uncertain of what impact, if any, that these reviews will have on future coverage."

At a conference call two weeks ago, Amgen officials said that the lung cancer trial would be concluded by the end of the year. However, Sharer said that all the deaths on the trial have occurred and are being adjudicated, to be presented to ODAC.

The trial has 80 percent power to show a 42 percent improvement in survival and has gone through two interim analyses.

"I know how much interest everybody has in this trial, and we have exactly the same interest ourselves," Sharer said at the March 1 conference. "All we can do now is wait for the analysis. I sure as heck wish I had an answer for you today, one that was good for patients and the drugs, but we are just going to have to wait and see. All I can say is that the trial is done, and we are analyzing the data and we are going to have to wait. Probably the most frustrating part about this business for all of us. But that's just the way it is.

"Clearly, if this trial is neutral or beneficial to patients in survival, that would be very positive," Sharer said. "If it is not, that would be a serious factor we are going to take into consideration."

Meanwhile, the company's situation remains uncertain, Sharer acknowledged. "Handicapping exactly what trajectory we are going to have in this business is very, very difficult right now," he said.

Is Neutral Positive?

Experts in lung cancer and clinical trials in general disagree with Sharer's assertion that a tie in the lung cancer trial would amount to a positive development for the company or for EPO products.

"A matching curve is a lose for the original design of the trial," said Howard Ozer, chief of hematology and oncology and Eson Chair and professor of medicine at University of Oklahoma Cancer Center. "The original design was hoped to show a survival advantage, and if it doesn't, it's a lose. And from what we know now, I would not expect Aranesp to be better."

The fact that Amgen's 600-patient trial is underpowered to detect a realistic survival difference will not escape notice by ODAC.

"A superiority trial that fails to meet its endpoint is clearly a loss," said Richard Schilsky, former ODAC chairman, associate dean for clinical research

at the University of Chicago, chairman of Cancer and Leukemia Group B, and the incoming president-elect of the American Society of Clinical Oncology.

"You cannot conclude non-inferiority in such a case, as the trial was not designed to demonstrate non-inferiority. All one can conclude in the hypothetical scenario you describe is that the new treatment failed to produce superior survival."

Amgen officials said the trial has gone through review by an independent data and safety monitoring board, which means only that the trial hasn't been stopped for futility or glaring safety issues, clinical trials experts say. This would be consistent with a trial where survival curves sit on top of each other, but where there is still a chance that one therapy would be ultimately shown to be superior.

"This was not designed as a non-inferiority trial," said Mace Rothenberg, the Ingram Professor of Cancer Research at Vanderbilt-Ingram Cancer Center. "Therefore, I can't conclude that the addition of Aranesp in this situation is overall 'neutral.' A higher rate of toxicity or a higher cost of treatment if Aranesp were purchased through commercial sources could make the addition of Aranesp 'worse' in this sense."

Also, oncologists may find it problematic to give patients a drug that doesn't add to efficacy, and any potential toxicity would be factored into the decision, experts say.

Skeptics say that the manner in which EPO has been studied makes it difficult to assess the contribution the doses of the agent might make to the toxicity or the loss of efficacy of cancer treatment. Discussion has to focus on the target levels of hemoglobin or hematocrit, said Dennis Cotter, president of the Medical Technology & Practice Patterns Institute.

"To the extent that it's high hemoglobin, there is an abundance of literature that talks about concerns with hypertension and peripheral vascular disease and cardiac events," Cotter said to The Cancer Letter. "However, nobody reports on the high dose, because the industry-sponsored studies do not want to focus on the effect of dose. That's their income source. So they never design studies that control for the dose. They would never unravel the mystery based on the dose, because it's their income stream."

Cotter is working with Medicare claims data to unravel the EPO dose-response relationship in nephrology. This analysis is possible in nephrology, because Medicare requires doctors to report the monthly dose and the end-of-month hematocrit. In oncology, such studies would be impossible, because the CMS form used to reimburse the treatment of cancer doesn't require reporting of the patients' hematocrit or hemoglobin levels.

At least in nephrology, "from a population standpoint, the dose-response relationship appears to be an S-shaped curve that flattens out at the high end, at a certain point the increased dose doesn't contribute to improved hematocrit, so high doses that are being administered do not result in improved hematocrit." Cotter said. "They are trying to get the patients to that high target, but patients who are resistant are being exposed to greater amount of EPO, so the risk from EPO exposure is more pronounced."

Amgen's Sharer said that "hypo-responders," patients who are resistant to EPO and who therefore end up receiving greater doses of it, could be at greater risk than the rest of the patients.

"The hypo-responders seem to have a predilection to have problems here," Sharer said. "I don't know what the market looks like, but that is an observation that some people who have looked at the data have made. I can't imagine that hypo-responders are a meaningful part of the market that we are serving today."

In an apparent effort to discuss how much of its market is at risk, Amgen officials presented proprietary data on Aranesp use.

The company said that on initiation of treatment with Aranesp, 98 percent of patients in the cancer area are started at the hemoglobin level below 12 g/dL, a level consistent with the guidelines of the ASCO and American Society of Hematology.

The company said that 84 percent of the patients have hemoglobin levels below 11 g/dL a week before treatment is initiated, and the vast majority is initiated below 10 g/dL.

On repeated treatments, 97 percent of patients are being treated below 13 g/dL and 86 percent are treated below 12 g/dL

"So a very small sliver of patients are being treated above 13," said Amgen's Morrow, summarizing company data drawn from an electronic medical record database covering about 50,000 admissions throughout 2005 and 2006. "I think what that says to us is that the vast majority are targeting hemoglobin of 12, and the new safety information shouldn't precipitate a major shift in prescribing, based on this utilization alone," Morrow said.

Experts contacted by The Cancer Letter say that these figures point to an aggressive and potentially harmful overuse of Aranesp by U.S. physicians.

A patient who has the hemoglobin of 13 g/dL a

week before treatment with Aranesp would be pushed to 14 g/dL or beyond, a clear danger zone following treatment. A patient at with the hemoglobin of 12 g/dL before treatment could be pushed beyond 13 g/dL, and in some cases, hemoglobin can go up by as much as three points as a result of treatment.

According to Amgen's numbers, 14 percent of patients receiving Aranesp are being treated at levels of 12 and 13 g/dL, which would take them to the edge of overtreatment or beyond, since treatment can deliver a hemoglobin boost of up to 3 g/dL, experts say.

"It's ridiculous that 14 percent of patients are getting Aranesp at 12 g/dL and above," Ozer said. "You will be pushing them above 13 g/dL. The guidelines are to target 12 g/dL. A patient who is at 12 g/dL shouldn't get Aranesp."

Charles Bennett, an oncologist at Northwestern University, agreed that Amgen's numbers point to overtreatment. "If you start getting closer to 12 g/dL, and then you treat, you might be getting into the 13 or 14 range when you actually get treated, which would be worrisome in terms of side effects," said Bennett, a participant in the Cochrane Collaboration and one of the authors of the ASCO-ASH guidelines on EPO use.

"Now that we are getting closer and closer to understanding that there might be some problems with too much hemoglobin, there is going to be some careful thought about it now," Bennett said.

Ozer said that after new data have come out over the past two months, he stopped giving EPO to patients whose hemoglobin is above 10 g/dL. "If somebody were below 10, I would treat them to above 11, and that's it," he said. "If a patient comes in with 11, I say, wait until you fall further, and then maybe we have something for you."

The Cancer Letter asked Amgen to disclose how many patients had the hemoglobin levels of 10 or 11 g/dL a week before receiving repeated treatment with Aranesp, but the data were not provided.

Payers See Widespread "Overutilizaton"

Lee Newcomer, head of oncology services at United Healthcare, has been fighting what he describes as overuse of EPO for years, and now his company is doing something abut it.

Starting next month, oncologists will be required to confirm that their patients' hematocrit level is at 36 percent or below. This hematocrit count, a measure of both the number of red blood cells and the size of red blood cells, would correspond to the hemoglobin level of 12 g/dL. The requirement applies to both Amgen's Aranesp and J&J's Procrit.

Another major insurer, WellPoint Inc., plans to revisit the clinical guideline for the use of EPO based on recent literature and FDA warning information at the next Medical Policy and Technology Assessment Committee meeting March 8, said Jim Gavin, a spokesman for the company that insures 34 million people.

Last summer, United Healthcare, a company that covers 18 million people, launched a pilot study at one of its plans, Oxford Health Plan, to see how EPO agents were used in the clinic.

Oxford was chosen because it was the only plan to require pre-certification of some medical services, Newcomer said.

"At Oxford, if a physician wanted to begin erythropoietin therapy, he needed to call in with the medical indication and the hemoglobin level of the patient.," Newcomer said. "And if the starting level that was too high, our reviewers would talk that through, and they also talked about not treating above the hematocrit of 36 [hemoglobin 12 g/dL]."

This pilot study yielded important data, which remain proprietary.

"Oxford was our laboratory for finding out whether or not there was excessive use of EPO, and the answer was yes," Newcomer said. "We had people being treated with hemoglobins of 15 g/dL."

Also, patients were being started at too high a level. However, when changes were implemented, utilization of EPO dropped by more than 30 percent, Newcomer said. Another proprietary study showed a similar result.

The two studies addressed starting EPO at too high a level, which is something the new United Healthcare procedures will not do. However, by monitoring hematocrit, Newcomer hopes to decrease EPO use by 15 to 20 percent. "That's still a huge amount of drug," he said. "We are just trying to address the over-utilization. We are not trying to address every problem that EPO has today."

Newcomer said excessive use of EPO seems to be "more of a systemic issue than it is physician malfeasance."

"What's probably happening there, is that standing orders are written, and people forget to check the hemoglobin levels," he said.

Beyond that, the problem is difficult to gauge, he said. "I can't tell in the claims system what the true indication is for the treatment, whether the patient has anemia of cancer, whether it's chemotherapy-induced anemia," Newcomer said.

Claims experts said that anemia is often coded as chemotherapy-induced in patients who had received treatment months or even years earlier. Diagnosis codes used by Medicare aren't always informative, either. A sample Medicare form CMS-1500 posted on Amgen's website suggests that physicians use code 285.22, "anemia in neoplastic disease." Presumably, physicians can also use what looks like a catch-all category, code 285.9, "unspecified anemia."

"If Medicare doesn't discriminate, physicians, whose priorities lie with patient care and reimbursement aren't going to correct diagnoses that don't get spit back at them," said a manager of a physician practice who spoke on condition of not being identified by name.

"There is no way we can tell what condition the patient has through claims data," Newcomer said. "We just get cancer. That's all we get. So se don't know if they are on active therapy. We don't know if they are being observed.

"That patient can be in remission, on therapy. That patient could be getting adjuvant treatment. That patient could be getting palliative chemotherapy. That patient could be on hospice. It's a critical problem with claims data in oncology. I might see an office visit for a patient without any chemotherapy, but that may be their interval check between treatments. I can't make many inferences from that."

Since CMS has little information about EPO use, it will be unable to distinguish anemia of cancer from chemotherapy induced anemia, or make sure that patients receive appropriate doses of EPO, experts say.

"There is no way CMS could deny these claims," said Newcomer, whose company acts as a contractor for CMS. "What will stop it is oncologists realizing that they may be giving a drug that's harmful. If these studies show increased death rates, that's going to stop oncologists cold.

"But from an enforcement standpoint, CMS can't do anything about it."

In the Cancer Centers:

Giles Named Director, IDD, Chief Of Oncology At UTHSC

FRANCIS GILES was appointed vice president and director of the Institute for Drug Development at the Cancer Therapy & Research Center. Giles also was named chief of the Division of Hematology and Medical Oncology at the University of Texas Health Science Center, and director of the experimental therapeutics program at the San Antonio Cancer Institute. He will hold the AT&T Distinguished Chair in Drug Development at CTRC.

Giles is professor of medicine and chief of the section of developmental therapeutics for the Department of Leukemia and co-chair of the Division of Cancer Medicine Phase I group at the M.D. Anderson Cancer Center in Houston. Giles will join CTRC and UTHSC on April 1, said **Karen Fields**, CTRC president and CEO. As IDD director, he will succeed **Anthony Tolcher**, who is leaving for private practice.

"The recruitment of Dr. Giles strengthens the mission of the San Antonio Cancer Institute and marks another significant step towards recapturing our Comprehensive Cancer Center status," SACI Director **Tyler Curiel** said in a statement. "I also look forward to Dr. Giles' contributions towards developing targeted therapies and expanding our translational portfolio in immunotherapies for cancer."

Giles said his vision for the IDD is to "build on its international reputation for Phase I clinical and preclinical pharmacology studies of novel anticancer drugs by broadening the range of patients, especially by including patients with hematologic malignancies and by increasing synergies between the CTRC and UTHSC pre-clinical, translational, and clinical scientists."

Giles is the founder and chairman of the International Oncology Study Group, a cooperative research group formed in 1993 and composed of over 170 oncologists from 90 institutions worldwide.

* * *

VANDERBILT-INGRAM Cancer Center Henry-Joyce Cancer Clinic waiting room space and exam rooms will double to meet the needs of increasing number of cancer patients. "The numbers have skyrocketed by about 60 percent since 2002," said **David Johnson**, deputy director of Vanderbilt-Ingram. The estimated $15 million multiphased renovation project will begin in May and take a year and a half. Also, a new infusion area will be added with its own elevators and stairwell so that immune-compromised patients are not put at risk by traveling alongside other Vanderbilt patients. . . . **CITY OF HOPE** Graduate School of Biological Sciences received a $750,000 grant from the Ralph M. Parsons Foundation for a teaching laboratory. The 1,057 square foot Ralph M. Parsons Foundation Teaching Laboratory will provide students with research space and equipment for training in molecular, cellular, chemical, biochemical and genetic disciplines during their first year. The laboratory is slated for construction within the Arnold and Mabel Beckman Center for Cancer Immunotherapeutics & Tumor Immunology

at City of Hope. Groundbreaking for the Arnold and Mabel Beckman Center is scheduled for April. . . . **MARIA BAER** was appointed head of the Hematologic Malignancies Program at the University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore. She also joins the faculty of the University of Maryland School of Medicine. Baer has been chief of the leukemia section in the Department of Medicine Roswell Park Cancer Institute since 1998. She was professor of medicine at University at Buffalo School of Medicine and Biomedical Sciences, professor of oncology at RPCI, and associate professor of molecular pharmacology and cancer therapeutics, Roswell Park Graduate Division, University at Buffalo.

In Brief:

Former FDA Chief Crawford Sentenced To Probation, Fined

LESTER CRAWFORD, former FDA commissioner, was sentenced Feb. 27 to three years of supervised probation and fines of about $90,000 for lying about stocks he owned in companies regulated by the agency. Magistrate Judge **Deborah Robinson** also ordered Crawford to conduct 50 hours of community service and pay the cost of his probation. Crawford, 69, pleaded guilty last October to charges of conflict of interest and false reporting about stocks he and his wife owned. Starting in 2002, Crawford filed seven incorrect financial reports with the government. The two charges are misdemeanors and each carries a maximum penalty of one year in prison and a $100,000 fine. The Crawfords made about $39,000 in dividends and from exercising options from the illegally held stocks. Crawford resigned from the FDA in September 2005 two months after his confirmation by the Senate. . . . **AMERICAN SOCIETY OF CLINICAL ONCOLOGY** appointed **Douglas Pyle** as senior director of international affairs. Pyle will lead ASCO's efforts to broaden the reach of the society's educational programs, products, and resources to oncologists around the world. Pyle was director of business solutions for the American Red Cross' International Services division. Previously, he managed the Red Cross' daily financial operations of international projects including the Tsunami Recovery Program. . . . **PROSTATE CANCER FOUNDATION** named **Howard Soule** executive vice president, discovery and translation. He was executive vice president and chief science officer at PCF from 1997 to 2004. Most recently, he was managing director of Knowledge Universe Health and Wellness Group, a private investment firm.

NCI Sponsors Meeting On Breast Cancer Therapy

NCI is sponsoring a meeting scheduled for March 26-27 to determine the state of the science on clinical use of preoperative therapy in breast cancer, as well as identify future research agendas.

Leading breast cancer physicians will present the state of the science and engage in a panel discussion in which audience participation is encouraged.

The conference, "Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions" is scheduled to take place in the Natcher Conference Center on the NIH campus.

The conference is open to the public, but pre-registration is requested. The meeting will be webcast at http://videocast.nih.gov. Continuing Medical Education credit is available.

Information about registration, the agenda, and faculty list are available at http://ctep.cancer.gov/bcmeeting.

Funding Opportunities:

RFA-CA-07-045: Comprehensive Minority Institution/Cancer Center Partnership. U54. Letters of Intent Receipt Date: March 13. Application Receipt Date: April 13. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-045.html. Inquiries: H. Nelson Aguila, 301-496-7344; aguilah@mail.nih.gov.

PAR-07-230: Feasibility Studies for Collaborative Interaction for Minority Institution/Cancer Center Partnership. P20. Letters of Intent Receipt Date: March 13; March 15, 2008; March 15, 2009; Application Receipt or Submission Date: April 13; April 15, 2008; April 15, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-230.html. Inquiries: H. Nelson Aguila, 301-496-7344; aguilah@mail.nih.gov.

PAR-07-239: Global Research Initiative Program, Basic/Biomedical Sciences. R01. Letters of Intent Receipt Date: Aug. 21; Aug. 21, 2008. Application Receipt Date: Sept. 21; Sept. 22, 2008. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-239.html.

PAR-07-235; Continued Development and Maintenance of Software. R01. Application Submission/Receipt Date: May 17 and Sept. 13. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-235.html. Inquiries: Jennifer Couch, 301-435-5226; couchj@mail.nih.gov.

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