THE CANCER LETTER

Vol. 33 No. 23
June 15, 2007

Three NCAB Members Say They Cannot Offer "Strong Endorsement" Of P-4 Trial

By Kirsten Boyd Goldberg

A three-member subcommittee of the National Cancer Advisory Board said it can't "offer strong endorsement" of the P-4 STELLAR trial that would test letrozole vs. raloxifene in nearly 13,000 healthy women at high risk of developing breast cancer.

"While P-4 is a well-designed, interesting, and relevant clinical trial, even if positive, it is unlikely to change the practice of preventive oncology," NCAB member Bruce Chabner, clinical director of the Massachusetts General Hospital Cancer Center, said to the board at its June 14 meeting. "In view of

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ESA Controversy:

NEJM Papers, Interview With NCI's Doroshow, Provide Justification For Regulatory Action

By Paul Goldberg

A package of three papers in the June 14 issue of New England Journal of Medicine provides further scientific justification for the efforts by FDA and the Centers for Medicare and Medicaid Services to curtail the use of erythropoiesis stimulating agents in oncology.

The three papers focus on the history of ESAs and urge further assessment of their safety, and an accompanying interview on the journal's Web site offers guidance on their use in the clinic.

In the interview, James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis and a member of the FDA Oncologic Drugs Advisory Committee, said that the agents generally shouldn't be administered to patients whose hemoglobin level is above 9 g/dL.

This is consistent with the proposed National Coverage Decision, which is now being finalized by the Centers for Medicare and Medicaid Services. The CMS proposal doesn't discuss its rationale for selecting 9 g/dL as the initiation level.

Oncology and hematology professional societies oppose the lowering of the hemoglobin threshold from the current level of 12 g/dL. In comments submitted to CMS, the American Society of Clinical Oncology said the 9 g/dL initiation level has "no basis in clinical evidence."

Doroshow said that little is known about these agents' risk-benefit ratio when they are given in a manner consistent with the FDA label, to patients with the hemoglobin levels between 9 and 12 g/dL.

The agents were approved for use in this hemoglobin range based on

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NCI Director Niederhuber On P-4 Trial: "I'm Tired Of It"

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the cost of the trial, the patent status of letrozole, and the need for expanded research on biomarkers for risk, we cannot offer strong endorsement of its funding."

The statement, which amounts to a recommendation to NCI Director John Niederhuber not to fund the trial, was the culmination of an unusual review process for the trial that would cost NCI $54 million over its first five years.

The NCAB voted unanimously to accept the report of the assessment group, but didn't make a public statement on whether NCI should fund the trial.

Initially, the trial was approved by a "special emphasis panel," a grant review committee, the Clinical Trials Operating Committee, and the NCI Executive Committee (The Cancer Letter, April 20 and March 2). However, on Jan. 23, Niederhuber blocked the trial from proceeding and asked for additional review, which was conducted by a specially-formed panel, called the P-4 Chemoprevention Trial Assessment Group.

The group met once in a closed session on March 23 to discuss the trial, but under federal advisory committee rules, it wasn't allowed to vote or make a recommendation on whether NCI should go forward with the trial. Instead, the conclusion was presented to the NCAB by Chabner and two other members of the board who were also involved in the review.

Chabner said that in reaching that conclusion, he was speaking for the three-member NCAB subcommittee, not the assessment group. He presented the assessment group's 25-page report to the NCAB, which provided a mixed view of the trial. Yet, he said that during the group's meeting on March 23, there were "strong opinions for and against" the trial.

The report didn't address issues of the peer review of the trial.

The three NCAB members said more research needs to be done to better identify women at higher risk of developing breast cancer, so that chemoprevention trials would take less time, enroll fewer participants, and test therapies that offer a better risk-to-benefit profile for healthy women.

Few women have been taking the previously tested chemoprevention drugs, tamoxifen and raloxifene, Chabner said. Since Novartis' exclusivity for letrozole would end in 2011, the company wouldn't have an incentive for marketing the agent for prevention, he said. Nonetheless, the company had agreed to provide $30 million to help support the P-4 trial.

The National Surgical Adjuvant Breast and Bowel Project, an NCI-funded cooperative group, proposed P-4 as the third in a series of breast cancer chemoprevention trials of selective estrogen receptor modulators and aromatase inhibitors. Representatives from the cooperative group weren't invited to the NCAB meeting.

Speaking with reporters, Niederhuber said he planned to make a final decision about the trial soon. "Obviously, I have to get it off my table," he said. "I'm tired of it."

NCI's Division of Cancer Prevention had planned to fund the trial through the Community Clinical Oncology Program, which has accrued participants to previous NSABP prevention trials. The cooperative group's CCOP Research Base grant—of which P-4 was an integral part—was renewed earlier this year by the NCAB.

The Pittsburgh-based NSABP has received support from Sen. Arlen Specter (R-Penn.), who wrote a letter to Niederhuber seeking an explanation for the trial's delay (The Cancer Letter, May 25). Also, the cooperative group said investigators and participants in its P-2 trial, the Study of Tamoxifen and Raloxifene, have sent 2,000 letters to Congress. NSABP's Canadian investigators and participants have sent letters to the U.S. Ambassador to Canada, David Wilkins, former speaker of the South Carolina House of Representatives and state chairman of the 2004 George Bush-Dick Cheney presidential campaign.

THE CANCER LETTER

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Subscription $365 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

NSABP officials declined to comment on the subcommittee's statement.

DCP Director Objects

Peter Greenwald, director of the NCI Division of Cancer Prevention, said he strongly supported the trial.

"I feel this P-4 trial should be a top priority of NCI," Greenwald said. "I don't know any other approach that holds the possibility for women who opt to take a pill for prevention of potentially preventing 70 percent of breast cancer.

"The final common pathway to most progress is a clinical trial," he said. "Even if you focus on biomarkers, they would have to be validated in the context of a clinical trial. When you get a suspect one, you are going to have to add on a clinical trial. This trial, with a depository, at least adds the possibility of looking back and seeing which ones to go forward with."

Greenwald said Chabner's presentation inflated the cost of the STAR trial by more than $20 million. Chabner said it cost $129.5 million while NCI's estimate is $102 million. Also, he questioned Chabner's estimate that P-4 follow-up period of five to 10 years could cost "$80 million or more" after the first five years of the trial.

"I don't know how, at this point, without knowing the result, you can estimate what the cost of the next period of follow-up would be," Greenwald said.

"I have been here a long time, and I remember when the Women's Health Initiative, which cost eight or nine times the cost of this trial, [was proposed] and people were aggressively against it—more aggressive than this committee—and now it's one of factors leading to the current decline of breast cancer" due to the drop in use of hormone replacement therapy, Greenwald said.

Greenwald said the National Heart, Lung and Blood Institute developed educational programs on heart disease and hypertension to help people make an informed decision about whether to use newly available therapies. "With a dedicated staff, it took five to 20 years, and it's still going on," he said. "It's not something were all of a sudden with the first trial, people know whether or not to take it."

Between NSABP's first breast cancer prevention trial and the STAR trial, 33,000 women decided to participate and accrual for the trials was ahead of schedule, Greenwald said.

"Raloxifene you can't judge yet, because obviously, we wouldn't do an education program without an approved indication," he said. "If it goes to FDA and gets approved for breast cancer prevention, I would like to see us develop an education program so people can make a balanced judgment about whether to use it or not."

Another argument for P-4 is that "the more options of different drugs for prevention, the better," Greenwald said. "People are going to have different risk factor situations and we need more than one option."

Finally, Greenwald said P-4 would be the most expedient action NCI could take in breast cancer prevention right now. "People say there are other ways to approach prevention," he said. "There are, but those are going to take many, many more years than this one. There are none that I know of where, within seven years, we will get an answer to this trial. If we come anywhere near knowing how we can advise women about what's a useful option if you are at high risk, I think this trial will give us very good information and will give us a way of judging one approach versus another approach."

Peer Review Issues Not Addressed

At the NCAB meeting, Board Chairman Carolyn Runowicz, director of the Neag Comprehensive Cancer Center at University of Connecticut, made no comment about the report, saying that it would be discussed in further detail during its closed session.

NCAB Executive Secretary Paulette Gray, director of the Division of Extramural Activities, said the board couldn't publicly discuss the peer review of a specific grant that is pending before NCI. "We cannot have any mention of grant applications here," Gray said, interrupting NCAB member Diana Lopez, who began to do just that. "This has to be a generic discussion about the chemoprevention program, chemoprevention trials, etc.," Gray said.

Lopez, one of the three subcommittee members and professor of microbiology and immunology at University of Miami, said she didn't support P-4 because "chemoprevention can be quite toxic," and use of tamoxifen for that purpose is low.

NCAB member Kenneth Cowan, director of the Eppley Cancer Center at University of Nebraska and one of the three subcommittee members, complimented NSABP on its previous prevention studies.

"I think we all want to recognize fact that [NSABP's] two previous trials are probably the most important things that have been done in cancer prevention by the NCI, in terms of demonstrating reduction in risk of occurrence of any type of cancer," Cowan said. "So we have got to give credit to the idea that these trials have identified an approach to looking at prevention of cancer that may have some benefit.

"Yes, these trials are incredibly expensive to perform, and they take a long time, and when you are working with a large cohort of patients, many of which are not going to get cancer, there are serious issues related to side effects that have to be taken into account in terms of developing these strategies," Cowan said. "The question is how to move the field forward in a way that still offers hope to women at risk. I think everyone wants to see research in prevention move forward in a way that we can identify the most at-risk populations, and to define agents which have a very good safety profile, and long-term benefit.

"We support the NCI moving forward in the field, but in a way where there is a consensus on who should really be eligible for [chemoprevention], and how to best identify the patients at risk," Cowan said.

Cowan disagreed with Chabner's characterization of the clinical use raloxifene as "low."

"I think it's unfair to assess the role of raloxifene right now, because the data are really new," Cowan said.

Raloxifene hasn't been approved by FDA for breast cancer prevention, and so it would be illegal for the sponsor to market it for that use. Earlier this week, the agency announced that its Oncologic Drugs Advisory Committee would review the data on raloxifene at a meeting July 24.

NCAB member Jean deKernion, chairman of urology at University of California, Los Angeles, asked whether the trial could be limited to women at extremely high risk of developing breast cancer. "If you could confine it to highest risk group as you could identify to date, would it not be salvageable?" he said.

"If you did that, effectively you would exclude some subgroups from the study that needed to be included," Chabner said. "I think it related to exclusion of minority women."

"The model chosen for the two previous studies used the Gail model with the cutoff of 1.67 years," Cowan said. "You could ratchet it up. In fact, the average person on the study has about 3.5—over 4. I think if you built the study to accepting higher risk, you could use the model, but I think what everyone was trying to point out was that, we are trying to make more advances in the field, more than [the Gail model's] five questions, many of which don't identify a lot of people."

Cowan said he never read the P-4 protocol. "I never saw the actual study itself," he said.

NCAB member David Koch, executive vice president of Koch Industries, asked what it costs to take chemoprevention. "Would it be so expensive that it's really not practical?" he said.

"First of all, this drug [letrozole] is unlikely to be the drug that's taken," Chabner said. "There are two other trials going on with AIs, and if those are successful, those companies will be asking for NDAs."

Chabner said his staff estimated the total cost of taking chemoprevention for breast cancer is $100,000 for each year of cancer-free life. "I can't tell you the annual cost of the drug for patients that take it, but you have to understand that only a fraction of them would benefit," he said.

Tamoxifen costs about $100 a month, and raloxifene costs about $75 a month, Greenwald said. "Bruce is right that letrozole will be off patent by the time the trial is done," but if a generic version is made, the cost would decrease, he said.

CHABNER: "I guess, Peter, the question is, who will put in an NDA for this drug? If it's off patent, what would be the incentive?"

GREENWALD: "Why would Novartis put in $30 million for the trial if they aren't willing to do this? Also, a generic company could put in for the NDA."

CHABNER: "They won't own the data."

GREENWALD: "I believe the NSABP owns the data and can work with whomever they want to put in the NDA."

NCAB member Lloyd Everson, vice chairman of US Oncology Inc., said he felt "ambivalent" about P-4. "I have read this report and followed the science in these trials for a number of years. I deeply respect Peter [Greenwald] and Leslie [Ford, associate director for clinical research], and the folks at NSABP," he said. "They have significantly contributed to prevention research. I am trying to sort through in my own mind… this difference of perspective on the impact on cancer and where we should be going…. We established in the scientific community at NCI, to our credit, a whole process of review and this particular trial has been through than process—"

Gray interrupted him. "Anything that's related to review, budget, a specific grant, cannot be discussed in open session," she said.

"I find myself coming down on the side of saying, 'I want to listen to the people we have entrusted at the board level to look at this,' and furthermore, Dr. Niederhuber has the ultimate fiduciary and scientific duty to make a decision, based on the best advice, and these may be very hard decisions," Everson said. "We have listened to some of our best scientists, the report from Bruce and his group, but ultimately, this is a decision of John, and I certainly will back Bruce and

the panel's recommendation."

NCAB member Daniel Von Hoff, director of translational drug development at the Translational Genomics Research Institute, Phoenix, spoke in support of NSABP.

"The thing that still is bothering me is that this is a team that has given us so many terrific insights into breast cancer," he said. "And this is a trial they worked very hard to come up with. Whenever you are taking care of a patient, you ask for a consultation. You don't have to take it, but you ask the best people that you can. So my greatest concern is, you have the best team that's ever been fielded in this area and they feel very strongly about doing this, so that weighs very heavy on my mind, were you have the world's best.

"Obviously, the NSABP feels extremely strongly about doing this," Von Hoff said. "But it's such an expert team that to say, 'Don't do this,' that's tough to say that, to experts who have always had the best interests of women with breast cancer, or potentially in prevention, in mind. We have heard that they have done the most important work in this area. It's hard to turn down an expert group."

"I'll just respond that our job was to listen and try to interpret what we heard, but it is really John's decision," Chabner said. "I presented the pluses and minuses of the trial as I see it. All of us saw it and agreed on the assessment, but it's the institute that has to make the decision."

Report Summary

Following is the introduction to the P-4 assessment group's report, "Summary of Issues/Recommendations from the NCAB P-4 Subcommittee":

1. The ultimate value of the study will be determined by whether it provides sufficient positive data to change the practice of preventive medicine. To date, the prevention trials in breast cancer have provided positive results with both tamoxifen and raloxifene, but despite their ability to decrease the numbers of tumors by 50 percent, neither has been widely adopted, probably because of concerns about side effects and the relatively low risk for a major segment of the female population of interest. Prior studies have not defined a survival benefit, and the cost-benefit analysis of the P-1 trial predicted a surprisingly high expenditure ($1.3 million) for each year of life saved. Thus, if we are to undertake another such study, in a relatively low-risk population, we need to be sure that (1) the expected risk-benefit ratio is clearly defined by the study, (2) the U.S. Food and Drug Administration agrees with the design and the planned collection of data as a "registration" trial, and (3) the company in question (Novartis) is backing the study.

2. Regarding these three key points, at the [March 23] meeting, it was not clear that the risk/benefit ratio for AIs would be clearly defined by this study. The AIs have the potential foor serious toxicity in at least two areas, bone and lipids/heart attacks. These toxicities may not become evident in the first five years of the trial. Thus while the cancer prevention impact may become clear quite early in the trial, it may take five-10 years to assess the drug's safety and its impact on mortality. There is no placebo control group for comparative assessment of these important toxicity rates. Secondly, regular toxicity assessment is planned only for the first five years on the study. Thereafter, late-occurring toxicities will be monitored through voluntary reporting, as events happen. This may well be inadequate for purposes of registration. Regarding points 2 (FDA) and 3 (Novartis) above, both the FDA and Novartis need to reassure the NCI that the trial design has their full support as a registration effort.

3. The costs of the trial are not clear. NSABP says the prices is $55 million for five years, not counting indirects. NCI says the total cost is likely to be $110 million or higher, if one takes into account the need for longer followup. This figure needs to be clarified. In addition, we need to know what Novartis is actually willing to contribute to the trial. If it is aimed at registration, the company should fund a major part of the cost.

4. Everyone agrees that the greatest need is for identification of biomarkers that define a high-risk population. The proposed trial does not incorporate a strategy for defining such markers, and uses a selection strategy based primarily on age and piror breast pathology. Many of our advisers were reluctant to see the NCI embark on a 10-year trial with basically a 15-year-old approach, Drug A versus Drug B, in an unselected population.

5. There were various suggestions for amending the trial, including one that proposed a look at shorter durations of therapy for the two agents in a 2 x 2 design. It is unclear whether the addition of randomization steps would add to the cost of the trial, and might lead to both less toxicity and lower efficacy in the new arms.

6. The trial should become a platform for research on identifying higher risk subgroups. Key to this effort is the collection of tumor tissue and normal cells (whole blood) for molecular studies. These samples must be available to outside investigators. NSABP should establish a transparent process, with outside

representation and NCI participation ensuring access to samples for qualified investigators.

These are the primary concerns expressed at the meeting. It will be important to add the missing information for our discussion in June, particularly a clear definition of the cost and the support of the FDA and Novartis in aiming for registration. To summarize, while virtually all the participants thought that interesting and useful information would come from the trial, as proposed, there was uncertainty that the trial would lead to registration. Even if the trial meets its goal regarding tumor prevention, as currently designed, it was the dominant opinion that, because of concerns about toxicity, its effect on the practice of preventive medicine might be modest.

ESA Controversy:

NEJM Commentary At Odds With Oncology Societies

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their ability to prevent blood transfusions, and early studies didn't measure the agents' impact on survival or time to disease progression. The current FDA label allows starting ESAs for patients with the hemoglobin of under 12 g/dL, and payers generally reimburse for therapy at this level.

"I think that using these agents for individuals with the hemoglobin level of less than 8 to 9 g/dL is certainly appropriate," Doroshow said.

Doroshow said he wouldn't use ESAs in breast cancer patients, one of the diseases where studies showed a decrease in survival, "unless there were other associated medical conditions that strongly push me to try to ameliorate the anemia, and there were symptoms clearly associated with it."

In such settings, which also include head-and-neck cancer, "I personally would not use them in the range of 9 to 12 g/dL, unless it was in the context of an appropriate clinical trial with an appropriate informed consent," Doroshow said.

In his interview with the journal, Doroshow said ESAs are best used in patients who are not candidates for blood transfusion. "Let me give you an example where the risk-benefit ratio may be very much in favor of benefit: If I had a patient with the hemoglobin of 8 who had history of coronary artery disease, who therefore is not a good candidate for transfusion, and who was having symptoms related to his anemia while on chemotherapy," he said. "It is a very different circumstance if one is trying to judge where it is not so clear-cut, namely a patient doesn't have other extenuating circumstances or other illnesses that make transfusion something to be avoided."

At a meeting May 10, ODAC recommended that FDA impose further marketing restrictions on ESAs, and that the new label should specifically state that these agents aren't indicated for tumor types where clinical trials have demonstrated adverse safety signals. The committee also said that should define hemoglobin levels where ESAs should be initiated, but declined to identify a target level where ESAs should be suspended.

"In the diseases where an adverse effect on survival has already been demonstrated when the target hemoglobin is above 12, we simply don't know whether or nor at lower levels of hemoglobin the agents are safe," Doroshow said. "The problem, I think, is that it will be difficult to obtain accrual to clinical trials investigating the issue to definitively answer the questions around safety in that range of hemoglobin."

Viewed together, the three papers point out that the scientific ambiguity that allowed ESAs to become a $4.854 billion product in oncology last year is now hurting the franchise.

Many fundamental questions remain unanswered in the ESA controversy, wrote Robert Steinbrook, the journal's national correspondent.

"For ESAs, the unfinished business includes completing and reporting on better studies; assessing the risks posed by the agents as compared with those of blood transfusions in specific clinical situations; and gaining a better understanding of the relationships among erythropoietin doses, hemoglobin concentrations, and cardiovascular risk," he wrote.

The question of potential tumor promotion must be urgently addressed, wrote Gregory Longmore, associate professor of medicine and cell biology at Washington University, St. Louis.

"The concerns regarding the use of erythropoietin in patients with cancer make the question of whether cancer cells in the patient express functional erythropoietin receptors important to answer unequivocally, using tools permitting the analysis of clinical specimens," Longmore wrote. "Even a finding that erythropoietin receptors present in cancer cells are not functional, however, would not necessarily vindicate erythropoietin, since such receptors might stimulate tumor progression through the effects of endothelial cells and angiogenesis or through the elaboration of other factors that influence tumor growth.

The issue of receptors figures in the CMS proposal. Though ODAC wasn't asked to consider the evidence on EPO receptors, the committee recommended that these

agents could be restricted in some indications.

FDA should continue to restrict the drugs' indications, wrote Fadlo Khuri, head of hematology and medical oncology at Emory Winship Cancer Institute.

"In the face of media attention to the hyperbolic advertising by the companies that make ESAs and the substantial profits accrued by physicians who use such agents aggressively, the FDA has sought guidance in exercising prudent, evidence-based judgment," Khuri wrote. "In order to maintain the public trust, the agency should act transparently in adopting new guidelines, and medical oncologists should begin using these agents in a compassionate but disciplined fashion, placing patient benefit above all other considerations."

The journal is sending a clear message to the medical profession, Khuri said to The Cancer Letter. "What all four of us are saying, from different perspectives, is very consistent: these agents should be used cautiously, certainly not until hemoglobin drops below 10 g/dL," Khuri said. "I personally don't give them to patients who don't have known cardiovascular risks until their hemoglobin drops below 9."

The papers expose a schism between respected scientists and clinicians who view the absence of hard data as a cause for caution and the oncology and hematology professional societies and patient groups that are urging CMS to scale down its coverage decision.

In addition to submitting their own comments, the sponsors of the ESAs have been lobbying patient groups and professional societies to come to their defense.

"We have a lot of self-interest in this so it is easy to discount our point of view," said Jim Daly, an Amgen senior vice president for North America Commercial Operations. "What is most important is for the professional societies and for the patient advocacy groups to step up, [and] the good news is they are stepping up in a major way. ASCO has been very clear on their position. ASH, very clear, and the patient groups have been very clear. So I think CMS has received a very strong response during the comment period on a number of areas, and we are hopeful that they will incorporate that feedback in their final decision."

Daly spoke with analysts at the Goldman Sachs healthcare conference June 13.

In its letter to CMS, ASCO urged the agency to delay any changes until FDA decides on additional changes to the label. In the letter dated June 8, Joseph Bailes, chairman of the society's government relations council, wrote that a 1993 amendment curtailed the CMS authority to decline payment for agents used in cancer therapy. This applies to FDA-approved indications as well as off-label indications listed in the compendia.

"Therefore, CMS lacks authority to make coverage decisions that are narrower than the FDA-approved indications," Bailes wrote. "Moreover, additional uses unapproved by FDA but referenced in the statutorily identified medical compendia must be covered by Medicare absent a specific decision by the [HHS] secretary that such uses are medically appropriate."

ASCO's concerns included:

—*Myelodysplastic Syndromes*. ASCO does not believe there is evidence to support the non-coverage of ESAs in "anemia of myelodysplasia." While it is not an approved indication, use of ESAs in the context of myelodysplastic syndromes (MDS) is well established in practice, supported by listing in a statutorily accepted compendium, and recommended in the joint guidelines of ASCO and the American Society of Hematology (ASH).

A number of published studies have confirmed the safety and efficacy of ESAs in MDS. Most significantly, a randomized, double-blinded, placebo-controlled trial compared ESAs with placebo in patients with low-risk MDS not receiving chemotherapy, with significantly more patients achieving a hematologic response in the ESA group; adverse events were the same in both the ESA and placebo groups. Many prospective and retrospective cohort studies and single-institution reviews have confirmed the findings in the randomized trial. Accordingly, there is a clear evidence basis for coverage of ESAs in

MDS, and the Medicare law requires a positive coverage determination on account of the compendium listing.

—*Erythropoetin Receptors*. CMS proposes imposition of coverage limits in connection with "ESA use by beneficiaries with tumors with erythropoietin receptors." This proposal is not only unsupported by medical evidence; it is also completely impractical, as there is no reliable test to identify such receptors, nor is there proven clinical significance to their existence. Responsible coverage policy should provide predictable and transparent results, which would be impossible with respect to the theoretical and unsubstantiated role of erythropoietin receptors. In short, there is no demonstrated clinical significance to the existence or not of erythropoietin receptors, and they should not serve as the trigger for non-coverage decisions that are inconsistent with the Medicare law as well as with evidence-based medicine.

—*Treatment Regimens Including Anti-Angiogenic*

or Anti-EGFR Drugs. With virtually no evidentiary support, CMS proposes to restrict use of ESAs with treatment regimens including drugs such as bevacizumab that have anti-angiogenic properties or drugs like panitumimab that are directed against the epidermal growth factor receptor (EGFR). There is no basis in law or in medical evidence to support such restrictions, and ASCO strongly opposes them. While it is true that these agents are unlikely to induce anemia when used individually, they will in many circumstances be administered in conjunction with chemotherapy drugs that do have anemia-inducing qualities. In any event, the proposed restrictions are inconsistent with the FDA-approved labeling and the compendia.

—*Initiation of ESA Therapy.* CMS's proposed restrictions on initiation of ESA therapy appear to have no basis in clinical evidence. The proposed initiation levels are less than those indicated by relevant clinical trials. Indeed, in contrast to the CMS proposal, the overwhelming majority of clinical trials involving ESAs enroll patients with hemoglobin above 9 at baseline.

—*ESA Dosing.* There is no evidentiary basis for the dosing restrictions proposed by CMS, leaving the perception that the restrictions are proposed for the sole purpose of limiting expenditures. CMS should cover ESAs consistent with the FDA-approved labeling, as required by law.

—*Duration of ESA Therapy.* The CMS proposal would limit duration of ESA coverage to a total of 12 weeks per calendar year. This limit has no basis in evidence and could be extremely detrimental to patient care. Many chemotherapy regimens continue beyond 12 weeks, and patients may receive more than one such regimen per year, particularly in the recurrent, metastatic or palliative setting. An arbitrary limit of 12 weeks of coverage per calendar year could require patients either to forgo medically necessary additional chemotherapy or alternatively to endure transfusions as a result of treatment.

—*Limiting Coverage of ESAs to Clinical Studies.* ASCO strongly opposes the suggestion that ESAs, as products approved for marketing by FDA, should be available to Medicare beneficiaries only in the context of clinical studies.

That suggestion is inconsistent with the cancer coverage provisions imposed on CMS by Congress, is unmindful of the critical role of FDA in determining the safety and efficacy of marketed products, and is insensitive to the needs of cancer patients who benefit from these products. We reject the notion that products that have passed through the rigorous safety and efficacy screen of FDA review should be subjected to additional review through clinical studies required by Medicare officials as a precondition of reimbursement.

The complete text of the letter is posted at www.ASCO.org.

The ASH letter urged CMS to continue to pay for the use of ESAs for anemia of myelodysplasia, an off-label indication that is included in the draft decision.

The MDS indication hasn't been brought before ODAC, and at the May 10 meeting of the committee FDA officials said the sponsors should conduct studies and put the indication on the label.

In addition to objecting to the proposal to deny payment for MDS, ASH argues that:

—The proposed policy maximum covered treatment duration of 12 weeks is without support in clinical evidence. ASH believes this proposal is arbitrary and could hurt Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year.

—The proposed policy maximum covered treatment dose is inconsistent with the FDA-approved dosing regimen for ESAs.

—The proposed policy to discontinue use of ESAs in non-responders after four weeks is not based on scientific evidence.

—The proposed policy to all ESA therapy for beneficiaries with cancer only within clinical research studies is inappropriate and unprecedented for any Medicare covered drug or biological, and is not justified based on the multitude of published evidence supporting ESA use. The ASH comments are posted at www.hematology.org/policy/news/06132007.cfm

The sponsors' comments, too, are posted on their Web sites, www.orthobiotech.com and www.amgen.com.

Amgen's Daly said CMS is pursuing a "rationing objective."

"The evidence is clear that if you start initiation level at 9 g/dL, you are going to significantly increase the number of transfusions," Daly said at the Goldman Sachs conference. "And then the idea of limiting therapy to 12 weeks. There is no science for that; it clearly appears to be a rationing objective, disguised as a scientific objective. How do you ration to 12 weeks per year when you have patients who receive multiple courses of chemotherapy?

"Our encouragement is CMS, stick with the science. If your agenda is to reduce your budget, decrease utilization, let's talk about that. There's probably more rational ways to approach it than doing that.

"What is the interaction between CMS and the FDA? We're not sure. But based on recent history we know there is some type of interaction there. And so we are watching that very closely," Daly said..

CMS is expected to take up to 60 days to publish the final version of the coverage decision. The proposed decision is posted at www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203.

Dingell Asks FDA To Account For Failure To Curtail ESA Ads

By Paul Goldberg

A Congressional committee has asked FDA to explain its failure to strike the quality of life claims from the labels of erythropoiesis-stimulating agents.

The agents were approved for their ability to reduce the need for blood transfusions, but the sponsors used direct-to-consumer advertising that marketed ESAs as a treatment for cancer fatigue.

The request for information was sent by the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce and signed by Rep. John Dingell (D-Mich.), chairman of the full committee and Rep. Bart Stupak (D-Mich.), chairman of the subcommittee.

Dingell and Stupak first announced their investigation in March, when they asked the sponsors of the ESAs, Amgen Inc. and Johnson & Johnson, to produce documents related to promotion of these products and adverse events associated with their use (The Cancer Letter, March 23). At the time, the committee didn't seek comment or documents from FDA.

The latest letter was dated June 15 and addressed to HHS Secretary Michael Leavitt. *The text of the letter follows:*

Under Rules X and XI of the United States House of Representatives, the Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations are investigating the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with prescription drugs. As part of that inquiry, the Committee has noted with increasing alarm reports that indicate that Erythropoiesis-Stimulating Agents (ESAs), commonly known as EPO products, when used at higher than recommended doses, appear to increase blood clots, stimulate tumor growth, and are associated with significantly higher mortality rates than placebos.

Appropriately, the FDA convened an Oncology Drugs Advisory Committee (ODAC) meeting on May 10, 2007 to consider the overall safety of ESAs, including Procrit, Aranesp, and Epogen. During this meeting, ODAC members, as well as FDA officials, expressed skepticism about not only the safety claims of the sponsors, but also the "quality of life" claims contained in ESA labels. On March 9, 2007, FDA instituted an ESA class label change, which eliminated all references to improvements in quality of life from labels. The question remains, however, as to why these claims were allowed on ESA labels when the only approved indication for ESAs is to reduce the need for blood transfusions.

Moreover, the unapproved "quality of life" claims contained in the patient information section of the labels paved the way for misleading direct-to-consumer advertising, which led patients and doctors alike to the unsubstantiated belief that ESAs improve quality of life. Similar to many ODAC members, this Committee is interested in learning why FDA did not act sooner to both correct the labels and prevent the misleading advertising that was based upon the labeling.

Accordingly, we request that you produce the following documents relating the ESA "quality of life" claims:

Any and all records reflecting communication between Johnson & Johnson and FDA, FDA Office of Chief Counsel (OCC) or elsewhere within the Department of Health and Human Services (HHS) relating to advertising of Procrit between 1998 and 2005;

Any and all records reflecting communication between Amgen and FDA, OCC, or elsewhere within HHS relating to advertising of Aranesp, separately or bundled (for example with Neulasta or Neupogen);

Any and all records between Amgen and FDAm OCC, or elsewhere within HHS relating to "quality of life" claims including the claim that Aranesp may "relieve the symptoms of anemia" contained in the Aranesp package insert or label information; and

Any and all records between Johnson & Johnson and FDA, OCC, or elsewhere within HHS relating to "quality of life" claims contained in the Procrit label, including the claim that "symptoms [of weakness, dizziness, chest pain] may improve" with use of Procrit.

We appreciate your cooperation in this investigation. Please deliver copies of the requested records to the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, Room 316 of the Ford House Office Building, by no later than 15 business days from the date of this letter.

FDA News:

Experts Sought For Committee On Risk Communication

FDA said it is seeking experts to serve on a new advisory committee on the communication of risks and benefits of FDA-regulated products to the public.

The Risk Communication Advisory Committee will help FDA better understand the communication needs and priorities of the general public; advise FDA on the development of strategic plans to communicate product risks and benefits; and make recommendations to FDA on what current research suggests about crafting risk and benefit messages, as well as how to most effectively communicate specific product information to vulnerable audiences.

FDA said it formed the committee in response to a 2006 Institute of Medicine report on drug safety. The advisory committee will be made up of 15 voting members that include experts knowledgeable in risk communication, social marketing, health literacy, cultural competency, journalism, bioethics, and other relevant behavioral and social sciences. The committee also will include consumers, patients, caregivers and health professionals.

A Federal Register notice seeking nominations for members is posted at http://www.fda.gov/oc/advisory/OCRCACCFN060407.htm. Nominations received by July 20 will be given first consideration. The primary contact is Lee Zwanziger, Office of Planning, Office of the Commissioner (HFP-1), FDA, email: rcac@fda.hhs.gov.

Advocacy:

Komen To Give ASCO $10M For Programs And Grants

Susan G. Komen for the Cure said it will provide $10 million over the next four years to the American Society of Clinical Oncology for programs and grants that will support improvement in cancer care access and delivery, particularly in disparities in care and access to clinical trials.

"Even with great advances in science, there is a great divide in the delivery of quality cancer care," said Hala Moddelmog, Komen for the Cure president and CEO. "Far too many people—racial and ethnic minorities, the poor, and those with little or no insurance—run up against barriers to access every day and are less likely to receive quality cancer care and are more likely to die from this disease. We believe this situation is entirely unacceptable, which is why we are working with ASCO and The ASCO Foundation to initiate sweeping changes."

The initiative will also focus on solutions to the projected shortfalls of the oncology workforce in the next decade by sustaining an adequate workforce, particularly those with large underserved populations.

"We face a growing culture of complacency. We claim to be waging a 'war' on cancer, yet we are losing our outrage and urgency over a disease that still kills more Americans every year than died in all the wars in the 20th century," said Nancy Brinker, founder of Susan G. Komen for the Cure. "Partnerships like this are the new norm —providing immediate help to the growing cancer needs in this nation and worldwide—as it is estimated that the number of new cancers diagnosed globally each year will double by 2030 to 27 million cases and 17 million deaths every year."

NIH News:

Working Groups To Examine NIH Peer Review Process

NIH officials formed two working groups to examine the peer review process.

The working groups—one external and one internal—will study the context, criteria, and culture of peer review to make sure the most talented individuals and reviewers are engaged in the process.

Results from the external working group will be presented to the full Advisory Committee to the Director in December. The internal working group will present its findings to the NIH Director's Steering Committee the same month. Both working groups will meet in January to develop a set of integrated recommendations for next steps.

Members of the External ACD Working Group on Peer Review: Co-Chairmen, Keith Yamamoto, University of California-San Francisco, and Lawrence Tabak, National Institute of Dental and Craniofacial Research. Bruce Alberts, University of California-San Francisco; Mary Beckerle, University of Utah; David Botstein, Princeton University; Helen Hobbs, University of Texas-Southwestern; Erich Jarvis, Duke University; Alan Leshner, American Association for the Advancement of Science; Philippa Marrack, National Jewish Medical and Research Center, University of Colorado; Marjorie Mau, University of Hawaii; Edward Pugh, University of Pennsylvania; Tadataka Yamada, Bill and Melinda Gates Foundation; Norka Ruiz Bravo, NIH Office of Extramural Research, ex officio; and Antonio Scarpa, NIH Center for Scientific Review, ex officio.

Members of the Internal Steering Committee Working Group On Peer Review: Co-chairmen: Jeremy Berg, National Institute of General Medical Sciences, and Lawrence Tabak,

National Institute of Dental and Craniofacial Research. Story Landis, National Institute of Neurological Disorders and Stroke; Marvin Kalt, National Institute of Allergy and Infectious Diseases; Roderic Pettigrew, National Institute of Bioimaging and Bioengineering; Norka Ruiz Bravo, Office of Extramural Research; Antonio Scarpa, Center for Scientific Review; Lana Skirboll, Office of Science Policy; Brent Stanfield, National Institute of Diabetes and Digestive and Kidney Diseases; Jane Steinberg, National Institute of Mental Health; Betty Tai, National Institute on Drug Abuse. Ex officio members: John Bartrum, Office of Budget, Jack Jones Jr., Acting Chief Information Technology Officer; Catherine Manzi, Office of General Counsel; and Jennifer Spaeth, Office of Federal Advisory Committee Policy.

In Brief:

Lustgarten Commits $18M To Pancreatic Genome Project

LUSTGARTEN FOUNDATION for Pancreatic Cancer Research has committed $18 million to the Pancreatic Cancer Genome Initiative to sequence the genome of pancreatic cancers. **Bert Vogelstein**, of Johns Hopkins Kimmel Cancer Center, leads the initiative. Former President **Jimmy Carter** will appear in a public service announcement to raise awareness for the project. . . . **GREGORY CURT** was named U.S. medical science lead for emerging products in oncology at AstraZeneca LP, of Wilimington, Del. He has been the company's senior medical director for medical affairs, emerging products and global development, since 2003. Previously, Curt was director of clinical affairs for NCI. . . . **ELLEN FEIGAL** was named chief medical officer of Insys Therapeutics, a new pharmaceutical company moving from Chicago to Phoenix, specializing in medicines and delivery systems for pain management, oncology, and neurological disorders. Also, Feigal was appointed as adjunct professor at University of California, San Francisco, School of Pharmacy. She is working with UCSF, industry, universities, and FDA to develop and direct a new educational program, the American Course on Drug Development and Regulatory Sciences (http://acdrs.ucsf.edu). Feigal, who received her M.D. from the University of California, Davis School of Medicine, also became the first recipient of the 2007 Transformational Leadership Award given by the school on the 35th anniversary of its founding June 9. Feigal moved from NCI in April 2004 to the Translational Genomics Research Institute in Phoenix, where she was vice president of clinical sciences and deputy scientific director. . . . **CORRECTION**: The last name of **Vinni Juneja**, an FDA medical reviewer, was incorrectly spelled in a June 1 story about ESAs.

Cancer Letter Editor Wins Washington Journalism Award

Paul Goldberg, editor of The Cancer Letter, received a 2007 Dateline Award from the Society of Professional Journalists, Washington, D.C., Pro Chapter, for his story, "I-ELCAP 'Soundbites' For Investigators Were A Protocol For Spin, Critics Say," published Nov. 22, 2006.

The award recognizes enterprising newsletter reporting from Washington for a national audience.

Goldberg's story described a document distributed to physicians involved in the I-ELCAP trial titled "I-ELCAP Soundbites." The document told the physicians what to say and what not to say in talking to the media about the study that tested CT scanning for lung cancer. Physicians were urged to use the word "compelling" when describing the results, refrain from mentioning other trials, avoid using the terms "observational" or "noncomparative" in describing the study, and urge people to get screened.

The document was evidence of an effort to make the public think that the data are more reliable than they are, health ethicists said. Goldberg's story also examined the way the I-ELCAP results were covered in the general media. The word "compelling" caught on and was used in many news media outlets.

Funding Opportunities:

PAR-07-377: Omics and Variable Responses to CAM: Secondary Analysis of CAM Clinical Trials. R01. Application Submission/Receipt Date: Aug. 14; 2007, 2008, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-377.html. Inquiries: Carol Pontzer, 301-435-6286; pontzerc@mail.nih.gov.

PAR-07-378: Omics and Variable Responses to CAM: Secondary Analysis of CAM Clinical Trials. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-378.html.

PAR-07-379: Behavioral and Social Science Research on Understanding and Reducing Health Disparities. R01. Letters of Intent Receipt Date: Aug. 20; Aug. 20, 2008; Aug. 20, 2009; Application Submission/Receipt Date: Sept. 19; Sept. 19; 2008, Sept. 18, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-379.html. Inquiries: Shobha Srinivasan, 301-435-6614; ss688k@nih.gov.

RFP N02-CM-77002-21A: Storage and Distribution of Chemicals and Drugs used in Preclinical Evaluation and Development. Response Due Date: July 12. Full text: http://www.fbodaily.com/archive/2007/05-May/24-May-2007/FBO-01300123.htm. Inquiries: Drake Russell, or MaryAnne Golling Treatment and Support Branch, P.O. Box B, 244 Miller Dr., Rm 121, Fort Detrick, Frederick, Md. 21702-1201.

In the Cancer Centers:

NCI Funds New Centers At Stanford And Baylor

NCI recently designated two new cancer centers: **Stanford Comprehensive Cancer Center** and the **Dan L. Duncan Cancer Center at Baylor College of Medicine**.

At Stanford, the new status is shared with the Fremont-based Northern California Cancer Center, which worked with Stanford to achieve the designation. The designation will provide about $1 million per year for three years.

Reviewers noted the excellence of the school's basic research and cancer care, particularly its molecular imaging, cancer biology, and bone marrow transplant programs, each of which received an outstanding rating from the review committee. **Philip Pizzo**, dean of the School of Medicine, said he hopes the NCI designation will help propel additional cancer programs to the same level. "The future contributions of the Stanford Cancer Center are likely to be extraordinary," the review committee said.

Beverly Mitchell, deputy director of Stanford's Comprehensive Cancer Center, said the designation is the culmination of a three-year effort on the part of clinicians and researchers at Stanford. "To be an NCI-designated cancer center in this time of decreased NCI funding is quite an achievement," she said.

The Duncan Cancer Center joins M.D. Anderson Cancer Center as one of two designated cancer centers in Houston. The third cancer center in the state is University of Texas Health Science Center at San Antonio.

"It is most appropriate that Houston, the fourth largest city in the nation and home to the largest medical center in the world, have two designated cancer centers," said **Peter Traber**, BCM president and CEO. "We have collaborated with M.D. Anderson, the top-ranked cancer center in the world, on many projects and, in fact, share a department chair. We see this as an opportunity to continue to strengthen that relationship, with patients receiving the greatest benefit."

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ROBERT YOUNG was appointed chancellor at Fox Chase Cancer Center, a position he assumed on June 1 after having served as the center's president and CEO for 18 years.

Reporting to the new president, **Michael Seiden**, and working with the board of directors and senior leadership, Young will lead several efforts including serving as the chairman of the NCI Board of Scientific Advisors and advocating for Fox Chase at the national and state levels. Young will continue to work on the completion of the Cancer Research Pavilion and expansion projects, and with donors and staff to complete the center's Centennial Campaign.

"The creation of this new position reflects my confidence that Dr. Young's experience and energy will be important in leading a variety of local, regional, and national initiatives important to our cancer center as well as the National Cancer Institute," Seiden said.

Later this month, the center's Cancer Prevention Pavilion will be named the Robert C. Young, M.D., Pavilion for Cancer Research. Also, Fox Chase board member **Margot Wallace Keith** and her husband, **Robert Keith Jr**., will endow a $1.5 million chair in Young's honor. The Robert C. Young, M.D., Endowed Chair in Cancer Research will help stimulate innovative research leading to novel treatments, diagnostic and prevention techniques, the Keiths said.

Young became president of Fox Chase in December 1988 after serving as chief of NCI's medicine branch and associate director of the NCI cancer centers and community oncology program. He announced his plan to step down as Fox Chase president last September.

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FADLO KHURI, deputy director for clinical and translational research at Emory University's Winship Cancer Institute, was elected to the American Society of Clinical Investigation. Khuri is the Blomeyer Professor of Hematology and Oncology; professor of hematology and oncology, otolaryngology, medicine and pharmacology; and chief medical officer and co-director of the cancer drug discovery, development, and delivery program at Winship. In 2006, his translational research in lung cancer received an NCI P01 grant of $7.9 million. . . . **KENNETH ANDERSON** was named editor-in-chief of Clinical Cancer Research, published by the American Association for Cancer Research. He is the Kraft Family Professor of Medicine at Harvard Medical School, chief of the Division of Hematologic Neoplasia and director of the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute. Anderson succeeds **William Hait**, president of AACR, as editor-in-chief. . . . **JEFF BOYD** was named director of the Curtis and Elizabeth Anderson Cancer Institute at Memorial Health University Medical Center in Savannah. He replaces **William Hoskins**, who is retiring. Boyd will retain his title of vice president, research, and director of development and operation of the laboratory and clinical research programs at Memorial Health.

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