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NSABP Objects To "Closed Process" Of Review Of Chemoprevention Trial

By Kirsten Boyd Goldberg

The clinical trials group that hopes to conduct a breast cancer chemoprevention study that was halted by NCI earlier this year is objecting to the process the institute has employed to decide whether the study should go forward.

Norman Wolmark, chairman of the National Surgical Adjuvant Breast and Bowel Project, said he was disturbed by NCI Director John Niederhuber's actions to hold a closed ad hoc meeting to review the Study to Evaluate Letrozole and Raloxifene, also known as P-4.

"I am disturbed that the NCI director has initiated an unprecedented, closed process that will affect the P-4 trial, our NSABP members, and most importantly, women at increased risk for breast cancer," Wolmark said. "These

(Continued to page 2)

Aranesp Study Finds No Difference In Survival Or Progression In Small-Cell Lung Cancer

By Paul Goldberg

A study of Aranesp in 600 previously untreated patients with small-cell lung cancer found no statistically significant difference in the risk of death or investigator determined progression-free survival, the company said April 19.

According to Amgen, the overall safety profile, including thromboembolic events, was consistent with the U.S. label.

The trial, called the 145 study, was designed to evaluate whether increasing or maintaining hemoglobin concentrations with Aranesp, administered with platinum-containing chemotherapy in patients with previously untreated extensive-stage SCLC, could increase survival.

A deficit in survival or time to progression would likely have crippled the ESA products. However, a finding of no difference in a trial designed to show superiority is inconclusive. Also, experts say that small-cell lung cancer, which represents 15 percent of lung cancer, would not be predictive of results in other diseases.

"These results contribute to the growing body of evidence on ESA safety, reinforcing the neutral impact of ESAs on survival in cancer patients suffering from chemotherapy-induced anemia," said Roger Perlmutter, Amgen executive vice president of research and development said in a statement.

Responding to signals about toxicity and the loss of efficacy associated with ESAs, FDA has scheduled a meeting of the Oncologic Drugs Advisory Committee May 10. Meanwhile, FDA has warned physicians to use the lowest

(Continued to page 8)

NCI Director To Decide Fate Of P-4 Trial After June NCAB

(Continued from page 1)

highly unusual actions appear to be out of step with the way that the NCI functions and do not appear to be in the best interest of science, cancer prevention, or the long established process of peer review."

The trial went through seven levels of review over the past year and a half, culminating in what was to be its final vetting before the NCI Executive Committee on Jan. 22. At that meeting, the committee approved the trial on an 8-2 vote, with Niederhuber and NCI Deputy Director Anna Barker casting the two nay votes.

On Jan. 23, Niederhuber told NCI staff that he decided not to allow NSABP to begin the trial. He assigned Barker to form an ad hoc committee of outside advisors and NCI staff to discuss the study. The ad hoc group, called the "P-4 Chemoprevention Trials Assessment Group," held an invitation-only meeting March 23 that was not open to the public. Participants were asked to sign forms promising they "will maintain the confidentiality of the materials and discussions and not disclose this information to any other individual."

The controversy over the trial that would randomize 12,800 healthy women to letrozole or raloxifene will be resolved after the National Cancer Advisory Board reviews the trial at its next meeting, scheduled for June 14-15. After the NCAB review, Niederhuber will make the final decision on the fate of the trial, an NCI spokesman said.

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The trial would cost NCI a total of about $74 million and would take 10 to 13 years, according to a background document prepared by institute officials.

Niederhuber declined to comment for this story. However, last month, he voiced his concerns about P-4 in an interview with The Cancer Letter. "We are headed into our fifth year of below-inflation appropriations, and that has created a great deal of stress on the budget and on the programs," Niederhuber said. "This proposed trial, P-4, certainly represents a lot of NCI resources, and it also represents a lot of out-year commitment over some 12 or 13 years."

In that interview, Niederhuber said NCI's "scientific community, our R01 community" has "strong feelings" that the trial "is not good science." He raised questions about the peer review process that the trial went through at NCI and the appropriateness of the trial's proposed funding mechanism—an administrative supplement to the NSABP's grant. He indicated that it was unlikely the trial would open this year, "if at all" (The Cancer Letter, March 2).

The assessment group will report its deliberations to the NCAB Clinical Investigations Subcommittee of the NCAB, which will make public its recommendations at the board's meeting in June.

"[The trial] will get a full and fair hearing at the NCAB," said Bruce Chabner, chairman of the NCAB subcommittee, one of the participants in the March 23 meeting, and clinical director of the Massachusetts General Hospital Cancer Center. "All points of view will be represented."

NSABP Objects To "Aberrant Process"

Wolmark objected to having been barred from attending the March 23 meeting of the assessment group that will report to NCAB.

"The P-4 trial has undergone an extensive 18-month review and approval process by the NCI, FDA, and Health Canada," Wolmark said. "The study and its five-year budget were part of the NSABP's CCOP Research Base Competitive Renewal that underwent peer review in December 2006 and received a priority score of 131, the best of any CCOP Research Base under review. In February 2007, the CCOP Research Base was approved by council at the regularly scheduled NCAB meeting.

"As the chairman of the NSABP and the principal investigator for the P-4 study, I have grave concerns about a process that prohibited me from attending this meeting and prevents me from discussing it with the two NSABP protocol officers who were permitted to attend,"

Wolmark said. "I am confounded by the decision not to include representatives from the NCI's own Division of Cancer Prevention. How can that possibly be in the spirit of providing full information to the committee?

"What I do know is that these actions are delaying the activation of this important study and are harming the public-private partnership which we have crafted among the NSABP, the NCI, Eli Lilly and Novartis," Wolmark said. "Novartis, in addition to supplying letrozole and placebo, has agreed to provide over $30 million to support protocol recruitment and compliance at our membership sites. Because of these delays, we have forfeited the first quarter of funding in 2007 which is over $900,000.

"From the time we first heard rumors about this aberrant process, we have attempted to meet with Dr. Niederhuber to discuss his concerns about P-4, but our efforts have been unsuccessful," Wolmark said. "Dr. Niederhuber has also declined my invitation to articulate his perspectives to our NSABP members at our next group meeting on April 28, in Jacksonville, Fla. We remain willing to amend the trial to include additional opportunities to obtain maximum benefit from the study."

A "Contentious" Meeting

Several participants described the March 23 meeting as "contentious." NCI staff instructed the committee not to take any votes, and it seemed to some participants that the group didn't reach a consensus.

The NCI Division of Cancer Prevention, which has oversight for chemoprevention trials, was not represented. DCP Director Peter Greenwald and Deputy Director Leslie Ford were not invited. Greenwald strongly supported the study and had proposed to fund it out of the division's budget. No new funding was requested for the trial (The Cancer Letter, March 16 and March 30).

According to a draft version of the meeting agenda obtained by The Cancer Letter, Chabner and the assessment group's chairman, Martin Abeloff, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, provided introductions. Niederhuber outlined his charge to the group. Then NCI Deputy Director Barker had 15 minutes to present background information about breast cancer chemoprevention.

Lawrence Wickerham, NSABP associate chairman, was given 30 minutes to present the case for P-4. This was followed by a 30-minute question-and-answer session. Committee members had about two hours to talk over a series of "discussion topics" and questions.

According to the agenda, the discussion topics included:

—Overall impact on chemoprevention research and ultimate value of P-4 as designed.

—Beneficiaries and health impact of current trial design.

—Appropriate funding responsibilities (NCI, industry, foundations) for trial as designed.

—Adequacy of clinical and biologic endpoints.

—Alternate study designs—smaller mechanistic studies, evaluation of intermediate endpoints, other.

—Overall strategies in breast cancer prevention and chemoprevention research; is this an optimal time for a large phase III randomized trial?

—Consider expected benefits and toxicity of therapies in P-4 as well as adequacy of risk assessment methodologies, other factors.

—Future focus areas for investment in breast cancer prevention and chemoprevention research overall.

The "questions for the group" included:

—Relative to the P-4 trial, should the trial proceed as designed at the cost proposed?

—If the trial proceeds as is, who should pay for it and how should the support be organized?

—Should large expensive trials that compare two or more companies' agents be supported by the government? By industry? Or by a government-industry collaboration?

—What will be the projected uptake of the results? Timeliness of findings?

—If NCI invests $50 million in breast cancer prevention trials, what trails would be of highest value—randomized comparisons, in-depth studies of imaging, molecular markers, other technologies?

—What mechanistic studies will contribute most to our understanding and ultimate control of breast cancer?

—What are the highest impact areas for NCI investments in breast cancer prevention/ chemoprevention?"

"It was a very good meeting, with lots of information about breast cancer prevention and the place of this trial in that whole constellation of efforts," said Allen Lichter, executive vice president of the American Society of Clinical Oncology, who attended the March 23 meeting. "I don't know how it's going to come out. It's a difficult balancing act that Dr. Niederhuber has. I'm glad it's not my decision.

"My bias is toward doing the trial," Lichter said to The Cancer Letter. "Knowing how much better letrozole

could be than raloxifene, when we think it could be 40 to 50 percent better, not five to 10 percent better—we don't often get a chance to test that in oncology. Testing these drugs head-to-head is a very compelling piece of research right now.

"My sense is that Dr. Niederhuber listened very carefully and probably has all the wisdom he is going to have on this, and now will make a decision," Lichter said. "There is no perfect clinical trial."

Individual players and organizations appear to be taking sides in the controversy.

The National Breast Cancer Coalition, which had two representatives at the March 23 meeting, doesn't support P-4, said Fran Visco, NBCC president.

"We think there are a number of problems with the trial design of P-4," said Fran Visco, president of the coalition, who didn't attend the meeting. "The bottom line is that we do not think, given all that we know, that is advisable to proceed at this time. We don't have the biomarkers to assess which women are at risk. We are taking a healthy population in whom we do not know how to assess risk and we are giving them drugs with serious side effects in a trial that has important issues in its design. It's not just about the best use of the money, it's what's best for the women. We are putting lives on the line here."

The coalition has challenged NSABP's earlier breast cancer prevention trials, P-1 and P-2, also called the Study of Tamoxifen and Raloxifene (STAR).

"We remain unconvinced that [the] P4 trial meets a strategic need in breast cancer prevention," Carolina Hinestrosa, NBCC executive vice president for programs and planning, wrote in a letter dated March 22 to Niederhuber. "As those trials that preceded it, the P4 trial uses a method of risk assessment that is too imprecise to have a meaningful clinical impact. While it may be plausible that P4 would reach its goal of demonstrating a 40 percent relative reduction in breast cancer incidence, the reality is that in absolute terms, still over ninety five percent of the healthy volunteers to be accrued to the trial will not develop breast cancer if they took a sugar pill and still they will be exposed to potent drugs. Furthermore, it has not been demonstrated that risk reduction using this approach will be beneficial beyond seven years. We believe that much longer follow up (20 years or more) of any prevention study is necessary to demonstrate whether the principle of chemoprevention via hormonal therapy is proven. This has not been accomplished with P1 or P2.

"There is no question that prevention is an area of strategic importance in breast cancer and we urge NCI to explore innovative approaches," wrote Hinestrosa, who participated in the March 23 meeting. "In particular, we believe that any chemoprevention trial should be built on the basis of robust biomarkers of risk to pursue a targeted strategy."

The coalition also objected to the review process and the funding of the trial as an administrative grant supplement. "We understand that the trial was reviewed as a concept by a special panel, but it did not go through peer review," Hinestrosa wrote. "As an organization that has made federal funding for breast cancer research a top priority since our inception, we at the National Breast Cancer Coalition Fund believe peer review is critical in assuring the public that funded breast cancer research meets the highest scientific standards. Furthermore, we believe that the administrative supplement mechanism undermines the reasoned prioritization of scarce research dollars."

NCI Peer Review Process

As the first step in the review process for P-4, the NSABP submitted the concept for the study to the Division of Cancer Prevention, which brought it before the NCI Executive Committee about a year and a half ago for a process known as "awaiting receipt of application." The EC accepted the study for review, which implies—but doesn't guarantee—that if the study received a fundable score in peer review, it would be likely to be funded.

Next, the NCI Division of Extramural Activities assigned the study to be reviewed by a Special Emphasis Panel, comprised of 18 experts in the field. This was not a competitive peer review in which applications are scored against one another, but where the application is assessed by itself for its scientific merit. This review method is commonly used by NCI.

"My recollection of the discussion a year ago in Bethesda is a little foggy," said William Gradishar, associate professor of medicine and co-director of the Lynn Sage Breast Cancer Program at Northwestern University, who served on the SEP. "What I do recall is the greatest discussion on the part of the panel focused largely on [dollars] expended to conduct the trial. There was a recognition that such trials are expensive.

"We questioned issues of what the actual assigned tasks of individuals cited in the budget were to be over the course of the trial," Gradishar said. "We thought there was room for some modifications, whereas the NSABP was very clear that conducting the proposed trial with the submitted budget would be difficult.

"As to the science, the trial proposed was a natural

progression of previous trials (P-1, STAR)," Gradishar said. "All participants would be interested in designs that did not require 12,000 patients and years of follow-up. Unfortunately, no one had a substitute for what was proposed.

"At the end of the panel meeting, the primary concern was one of budget rather than significant criticism about the science."

In the interview with The Cancer Letter, Niederhuber said he reviewed the panel's report. "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.

Nevertheless, the protocol moved on to a routine staff protocol review within the division, and then to an FDA IND review, sources said.

The next step was peer review of NSABP's research base grant for its participation in the NCI Community Clinical Oncology Program. The plans for P-4 were a significant part of that review, sources said. It was a competitive peer review and the reviewers gave NSABP a score of 131, which is the highest that the cooperative group has ever received for its research base grant, sources said.

Moving up the chain of approvals, P-4 then went before NCI's newly formed Clinical Trials Operating Committee, a group of NCI staff chaired by Niederhuber. P-4 was approved with only one negative vote, sources said. Sources couldn't confirm whether it was Niederhuber who cast the nay vote.

At that point, it would have appeared that P-4 would have passed all NCI review processes, sources said. However, Niederhuber told NCI staff that he wanted the Executive Committee to look at P-4 again.

In the interview with The Cancer Letter, Niederhuber said the CTOC, which has the mandate to review and prioritize NCI-supported clinical trials, had only recently been formed and wasn't certain of its role. The committee's review of P-4 included "a great deal of debate and discussion, especially about the resources." The committee "sort of kicked it upstairs" to the Executive Committee, he said.

At its Jan. 22 meeting, the Executive Committee voted in favor of approval of P-4. Sources said DCP Director Greenwald called NSABP to inform them that the trial was approved and could begin.

The next day, Niederhuber told Greenwald that the trial couldn't proceed. He would have Barker form the ad hoc assessment panel to conduct yet another review of P-4. "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 in the interview with The Cancer Letter.

Proponents of P-4 question the unusual extra steps of review. "I understand that the NCI is facing a difficult time right now, and anyone who doesn't have grant funded is upset," said Patricia Ganz, chairman of the NSABP Behavioral and Health Outcomes Committee, and professor of medicine and public health at the University of California, Los Angeles. "But with P-4, all the usual processes were followed. The Executive Committee endorsed this, with only two dissenting votes. It's not clear what wasn't followed.

"What's hard is that this trial has been delayed by a number of these steps in the past year or so," said Ganz. "It's possible that the whole infrastructure of the NSABP might deteriorate. At the least, the more delay there is, the more expensive the trial will be."

Will Women Care About The Results?

P-4 would enroll 12,800 postmenopausal women who have a five-year probability of invasive breast cancer of at least 1.66 percent, assessed using the Risk Assessment Profile generated by the NSABP Biostatistical Center, or who have a history of LCIS, according to the study protocol. Enrollment would take place over four years.

Participants would be randomized to take either raloxifene (Evista, Eli Lilly) 60 mg plus a placebo for letrozole, or letrozole (Femara, Novartis) 2.5 mg plus a placebo for raloxifene, orally once a day for five years. The primary endpoint would be the first occurrence of invasive breast cancer.

According to NSABP's protocol document, the rationale for P-4 stems from letrozole's result as a more effective treatment than the selective estrogen receptor modulator (SERM) tamoxifen in the adjuvant therapy of postmenopausal women with receptor-positive invasive breast cancer, with fewer serious toxicities.

"In those same studies, letrozole was more effective than tamoxifen in the reduction of new primary cancers of the contralateral breast," the document said. "The results of the STAR trial demonstrate that raloxifene is as effective as tamoxifen in the prevention of invasive breast cancers, but has fewer serious toxicities, making it the new standard treatment for the prevention of breast cancer in postmenopausal women at increased risk for the disease. An appropriate next step is to determine if letrozole is more effective than raloxifene in reducing the risk of primary invasive breast cancer in a group of healthy postmenopausal women at increased risk for

breast cancer. The P-4 trial is designed to provide that information and to carefully evaluate a variety of other risks and benefits."

Both SERMS and aromatase inhibitors have side effects. The agents "can exacerbate vasomotor symptoms, and aromatase inhibitors can cause a variety of other symptoms due to severely diminished endogenous estrogen levels," the protocol said. "Other QOL studies document that SERMs may have central nervous system effects that are manifested by an increase in vasomotor symptoms as well as some local gynecologic effects that result in vaginal symptoms. In contrast, the aromatase inhibitors appear to have a lower rate of vasomotor symptoms than the SERMs, but breast cancer patients taking these as adjuvant endocrine therapy report increased rates of joint pains and musculoskeletal complaints, as well as more difficulties with vaginal dryness and sexual functioning.

"While the NSABP B-35 trial is studying the efficacy, safety, and health-related QOL of tamoxifen versus anastrozole in patients with DCIS, to date, there have been no head-to-head comparison trials comparing a SERM to an aromatase inhibitor in the prevention setting," the protocol stated. "We believe this assessment is a critical component of the P-4 trial, and we will build upon our past experience in the NSABP P-1, P-2, and B-35 trials for the development of this component of the study."

In the interview with The Cancer Letter, Niederhuber said women may not care about the results of P-4 by the time results are available, because the drugs have "significant tradeoffs" and better science could emerge.

Women aren't embracing tamoxifen or raloxifene, said Paul Goss, director of breast cancer research at Harvard's Massachusetts General Hospital Cancer Center. "At the moment, less than 1 percent of women who could benefit from preventative therapy are taking it," he said. "If you define 'standard of care' as a commonly used therapy for a certain situation in medicine, there isn't one for [breast cancer] prevention at all."

Goss attended the March 23 meeting of the P-4 assessment panel, but in an interview he declined to comment on either P-4 or the meeting. However, in an article in Science on March 16, Goss questioned whether the results of P-4 would come soon enough to be relevant to clinicians and patients.

Goss is chairman of the MAP.3 breast cancer prevention trial being coordinated by the NCI of Canada Clinical Trials Group in cooperation with Pfizer Inc. The trial will randomize 4,600 women in North America and Spain to Pfizer's steroidal aromatase inhibitor exemestane (Aromasin) or placebo in postmenopausal women at high risk of breast cancer.

The MAP.3 study is funded by Pfizer and the Canadian Cancer Society, a spokesman for NCICCTG said. Goss said the trial is "an academic trial, at arms length and disconnected" from Pfizer.

The study is placebo-controlled because of the lack of a true standard for breast cancer prevention, Goss said. An ASCO technology assessment panel wrote that breast cancer prevention trials should be conducted against placebo, he said.

"Although we acknowledge that tamoxifen and raloxifene have preventative data, we believe that the efficacy and toxicity profile in general is not favorable, specifically in postmenopausal women," Goss said. "Because those drugs become slightly more hazardous when women get older, we feel a placebo is appropriate."

Because exemestane is a steroidal aromatase inhibitor, it may have better efficacy and lower toxicity than nonsteroidal AIs, Goss said. "We like this drug among the three available aromatase inhibitors," he said. "We are very excited about the trial. The indirect evidence that this drug—indeed, this class of drugs—will prevent both invasive breast cancer and pre-invasive breast cancer is supported tremendously by tens of thousands of women that have been exposed to these drugs with early-stage breast cancer already, meaning that contralateral new primary lesions, both pre-invasive and invasive, of the opposite breast from the cancer, show a marked reduction under the influence of these pills.

"So this is a new type of therapy for breast cancer prevention is unbelievably exciting," Goss said. "Bear in mind that if any other solid tumor cancer had a pill that might reduce the risk by 60 or 70 percent, people would be really, really, excited—as are we."

Goss said that at the conclusion of MAP.3, he hoped that "we not only will be able to say, 'this aromatase inhibitor was highly effective in preventing breast cancer,' but also, we will have a much clearer idea of what type of women actually benefited, what type of women didn't benefit, and who got side effects and who didn't—in other words, to narrow the field substantially."

"I Don't Want To Practice Without Evidence"

Enthusiasm of women for breast cancer prevention drugs was dampened by the "negative play in the press"

about tamoxifen, said Ganz. That's unfortunate, she said, because many women could benefit, including those who have a strong family history of the disease, or have had multiple biopsies and precancerous changes.

"I have been taking care of these patients since the early '90s, and the information that we gained from P-1 was enormous," Ganz said. "So the natural evolution was to do P-2, which I think again was very important, because all we had were the placebo-controlled raloxifene trials, which were done in older women who had had osteoporosis, who were not approached about taking the medication for breast cancer prevention."

Those studies seemed to show about an 80 percent reduction in the risk of breast cancer in those women, making raloxifene look "phenomenally better than tamoxifen," Ganz said. "If we have only placebo-controlled trials with different patient populations, it's hard to make comparative inferences. The progress to P-2, where we actually were able to do this head-to-head comparison, was critical. In the community in which I practice, a lot of women were being put on raloxifene for prevention long before it was studied."

The results of P-2 were "an eye-opener, because there was no difference in efficacy in terms of the risk reduction," Ganz said. "There was perhaps some more significant reduction in pre-invasive disease with tamoxifen, but on other hand, there were significant differences in adverse events between the two drugs, making it possible now to have both of these drugs used for the prevention of breast cancer in postmenopausal women."

Having two types of pills to take gives women more options, Ganz said. "If we only had one drug for hypertension, or only one drug for diabetes, or only one drug for lowering cholesterol, then if a person had an adverse event or couldn't tolerate one of these drugs, we would have nowhere to go," she said. "It's very important strategically that we have more than one alternative, because when I approach women about doing something for prevention, I basically say, 'It's only a pill. If it doesn't agree with you, we can discontinue it. We are not taking out your ovaries, we are not taking off your breasts. It's something that can be reversed. If one of the drugs doesn't agree with you, we can move on to the other.'"

P-4 would be the natural progression, Ganz said. "We have had heavy marketing for the aromatase inhibitors in the management of women with early-stage breast cancer as adjuvant therapy," she said. "These drugs seem to be better in terms of disease-free survival. Without a head-to-head comparison with an alternative drug, we will not know in that exact patient population what the benefits are.

"This represents an ethical and natural evolution for us to be able to gain information for a strategy that I think is going to become increasingly important," Ganz said. "It took a long time before people were aggressively treating hypertension, diabetes, and high cholesterol, and as a result of a very concerted efforts in dissemination of evidence, now, these have been adopted and we have seen a substantial decrease in cardiovascular disease. The same thing is going to happen in cancer, and breast cancer is going to lead the way in terms of this being a strategy."

Ganz said she was concerned about the ethics of MAP.3. "If I were a woman with pre-invasive breast cancer, I would not want to take a placebo, particularly when there are two effective agents available," she said. "It still will not answer the question. It will not tell us what are the differential risks and benefits in the exact same population."

In Feburary, long-term follow-up data from IBIS-1, a prevention trial conducted in the U.K., confirmed that women at high risk for breast cancer continue to receive a risk-reduction benefit from tamoxifen years after they stop taking it. The study supports the follow-up data from P-1. The updated results of both trials were published in the Feb. 21 issue of JNCI.

The results "suggest a true preventive effect and not merely transient risk reduction" and "highlight [tamoxifen's] favorable risk-benefit ratio in younger women, among whom severe toxicity is rare," wrote Umberto Veronesi and colleagues of the European Institue of Oncology in Milan in an editorial.

Ganz noted that the cost of P-4 would be minimal compared to the cost to society if women take drugs that don't work or have toxicities that aren't well understood. "The Women's Health Initiative studies were absolutely critical," she said. "How many women were given estrogen and progesterone without knowing the risks and benefits? I don't know what other alternative anyone has to propose.

"I'm a clinician, and I don't want to practice without evidence," Ganz said. "That's why this study is very important to me."

P-4 Chemoprevention Trials Assessment Group

Following is a list of participants in the March 23 meeting:

Chair: **Martin Abeloff,** Professor and Chair, Oncology; Director, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

NCAB Subcommittee Members: **Kenneth Cowan,** Director, Eppley Cancer Center, University of Nebraska Medical Center. **Bruce Chabner,** Clinical Director, MGH Cancer Center. **Diana Lopez,** Professor of Microbiology and Immunology, University of Miami.

NCI Participants: **NCI Director John Niederhuber. Anna Barker,** Deputy Director, Advanced Technologies and Strategic Partnerships. **James Doroshow,** Director, Division of Cancer Treatment and Diagnosis. **Charles Goldthwaite Jr.,** Science Writer. **Paulette Gray,** Director, Division of Extramural Activities. **Gary Kelloff,** Special Advisor, Cancer Imaging Program, DCTD. **Anne Lubenow,** Special Assistant to the Director.

Participants: **D. Craig Allred,** Professor and Director, Breast Pathology, Washington University School of Medicine. **Christopher Benz,** Professor and Program Director, Cancer and Developmental Therapeutics Program, Buck Institute for Age Research. **Donald Berry,** Head, Division of Quantitative Sciences; Chair, Department of Biostatistics and Applied Mathematics, University of Texas M.D. Anderson Cancer Center. **Christine Brunswick,** Vice President, National Breast Cancer Coalition. **Nancy Davidson,** Director, Breast Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. **Matthew Ellis,** Associate Professor of Medicine, Director, Medical Oncology, Washington University School of Medicine. **Margaret Foti,** Chief Executive Officer, American Association for Cancer Research. **Judy Garber,** Director, Cancer Risk and Prevention, Dana-Farber Cancer Institute. **Paul Goss,** Director, Breast Cancer Research, Massachusetts General Hospital Cancer Center. **Lyndsay Harris,** Associate Professor of Medicine, Yale University School of Medicine. **Lee Hartwell,** President and Director, Fred Hutchinson Cancer Research Center. **Daniel Hayes,** Clinical Director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center. **Susan Hilsenbeck,** Professor of Medicine, Baylor College of Medicine. **M. Carolina Hinestrosa,** Executive Vice President, Programs and Planning, National Breast Cancer Coalition. **Shelley Hwang,** Associate Professor in Residence, University of California, San Francisco. **Kenneth Krohn,** Professor, Department of Radiology and Radiation Oncology, University of Washington Medical Center. **Allen Lichter,** Executive Vice President and Chief Executive Officer, American Society of Clinical Oncology. **Scott Lippman,** Professor and Chair, Department of Head and Neck Medical Oncology, M.D. Anderson Cancer Center. **H. Kim Lyerly,** Director, Duke Comprehensive Cancer Center. **Frank Meyskens Jr.,** Director, Chao Family Comprehensive Cancer Center, University of California, Irvine. **Hala Moddelmog,** President and Chief Executive Officer, Susan G. Komen for the Cure. **Kathi Mooney,** Professor, University of Utah. **Martin Murphy,** Executive Editor, The Oncologist Journal. **Lillian Nail,** Rawlinson Professor and Senior Scientist, School of Nursing, Oregon Health & Science University. **Olufunmilayo Olopade,** Walter L. Palmer Distinguished Service Professor, Department of Medicine and Human Genetics; Director, Hematology/Oncology Fellowship Program; Director, Center for Clinical Cancer Genetics, University of Chicago Hospitals. **David Parkinson,** Senior Vice President, Oncology Research and Development, Biogen IDEC. **Dwight Randle,** Senior Scientific Advisor, Susan G. Komen for the Cure. **Ellen Sigal,** Chairperson and Founder, Friends of Cancer Research. **Thea Tlsty,** Professor, Department of Pathology, University of California, San Francisco. **George Vande Woude,** Director, Van Andel Research Institute. **D. Lawrence Wickerham,** Associate Chairman, National Surgical Adjuvant Breast and Bowel Project. **Jerome Yates,** National Vice President for Research, American Cancer Society.

Superiority Trial Detects No Difference In SCLC

(Continued from page 1)

doses of erythropoiesis stimulating agents to gradually raise the hemoglobin levels to the lowest level sufficient to avoid blood transfusions.

Separately, insurers have started to limit over-prescribing of the agents and Centers for Medicare and Medicaid Services have initiated a national coverage analysis of the use of ESAs outside nephrology.

Amgen officials said they would discuss the results at a conference call to review the company's first quarter results April 23.

In the study, patients were randomized 1:1 to receive Aranesp 300 mcg or placebo every week (QW) for the first 4 weeks, followed by once every three week (Q3W) dosing (commencing on week 5) for the remainder of the 24-week treatment period. Patients were treated to a target Hb of 13 g/dL, which is higher than indicated by the FDA-approved product label, with dose withholding at 14 g/dL. The hemoglobin target in the U.S. label is 12 g/dL.

The study demonstrated no statistically significant difference in risk of death (overall survival Aranesp compared to placebo Hazard Ratio: 0.93, 95% CI: 0.78 to 1.11) (HR: 1.02, 95% CI: 0.86 to 1.21).

The study demonstrated a significant change in hemoglobin concentration from baseline in favor of Aranesp (a co-primary endpoint). Aranesp-treated patients also experienced a significantly lower risk of blood transfusions (HR: 0.40, 95% CI: 0.29 to 0.55).

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