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Experts Raise Questions About Influential Swedish Trial Of Mammography Screening

By Kirsten Boyd Goldberg

Breast cancer screening experts are raising questions about a Swedish trial that has influenced clinical practice and screening guidelines worldwide for the past 20 years.

Comparing official Swedish breast cancer statistics to the data reported in the Swedish Two-County trial of mammography screening, researchers from Norway and Denmark allege that 192 breast cancer cases and 43 breast cancer deaths are missing from the trial report. Their findings were published last November in the Danish Medical Bulletin, but have not been widely discussed.

In 1985, the Swedish Two-County trial demonstrated a 31-percent reduction in breast cancer mortality—the largest mortality reduction ever reported in a randomized trial of mammography screening. In an update published in 1992, the study investigators modified the mortality reduction

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FDA Advisors Uphold Broad Mandate To Limit Use Of ESA Products In Cancer Indications

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee May 10 gave the agency a broad mandate to regulate the use of Erythropoiesis Stimulating Agents in cancer.

In their votes and their comments, the committee members overwhelmingly upheld the view that the ESAs grew into the single largest product category in oncology despite the near-absence of data on their impact on either survival or time to progression.

The committee upheld the "black box" warning the agency placed on the ESA products, and opened the doors for refining it as data come in.

Committee members concurred with the agency that no data exist to support "quality of life clams" for the ESAs in oncology or to correlated the ESA doses with responses.

Also, the impact of ESAs differ from setting to setting, thereby requiring the agency to regulate ESA uses in some diseases.

Committee members voiced no objections to the agency's devastating review of the data on ESA use, which stated that the sponsors of ESAs have made insufficient efforts to answer questions posed at the May 4, 2004

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Swedish Trial Influenced Screening Policies Worldwide

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to 24 percent, still a large result in a field fraught with intense debate over trial methods, statistical analysis, and the overall balance of risks and benefits of screening for women.

"It is of note that the differences in the number of breast cancer deaths between the study and control groups in the Two-County trial are small," the article in the Danish journal stated. "The mortality reduction would therefore no longer be statistically significant if only a few more breast cancer deaths were added to the study group."

In the article, the investigators wrote that their method of estimating the numbers of breast cancer cases and deaths was "simple and crude," but nevertheless, the "differences are large and cannot be explained by random fluctuations in the cancer occurrence." Cause-of-death determinations in the Two-County trial were not blind, the article said.

The authors said they conducted the comparison because the 24 percent reduction in breast cancer mortality reported for the Two-County study was much higher than the 10 percent reduction reported by a 2002 meta-analysis of all Swedish studies—excluding one of the counties in the Two-County study.

"We think that this discrepancy is so large that it alone casts serious doubts about the reliability of the Two-County study," Peter Gøtzsche, of the Nordic Cochrane Centre in Copenhagen and one of the authors, said to The Cancer Letter. "It is because of this and because of other irregularities in the Two-County study that we decided to study whether cancers and cancer deaths were missing from the trial reports of this study. Historically, the Two-County study has had tremendous importance. It was because of this study and its results that mammography screening was introduced, not only in Sweden, but also in the U.K. and in many other countries."

Other authors of the article were Per-Henrik Zahl, of the Norwegian Institute of Public Health, in Oslo; and Jannike Mørch Andersen and Jan Mæhlen of the Department of Pathology at Ullevål University Hospital in Oslo.

The paper, titled "Results of the Two-County trial of mammography screening are not compatible with contemporaneous official Swedish breast cancer statistics," is posted at http://www.danmedbul.dk/Dmb_2006/0406/0406-artikler/DMB3890.htm.

The article escaped the attention of the news media, and even some screening experts, despite a controversy that involved three scientific journals, and withdrawal of the article from one of the journals.

The strong sentiment in the U.S. that mammography screening provides a major benefit to women, with very little risk, makes it difficult for investigators to raise legitimate questions, because "it undermines the core beliefs," said Cornelia Baines, professor emerita in the Department of Public Health Sciences at University of Toronto. "You can get abused for saying things people don't want to be said. I speak from personal experience."

Baines was co-investigator of the National Breast Screening Study of Canada that was widely criticized by mammography proponents because it showed no reduction in breast cancer mortality from screening.

"The Swedish Two-County study has been the motivator for all of the screening policy in North America," Baines said. "There have been a number of observations made as to anomalies in the report of the Two-County data, not least of which was the inconsistency in the number of cancers diagnosed, the number of women screened, and the number of deaths recorded. Over the years, there have been a number of hints that all was not as clear-cut as appeared to be the case."

The Two-County trial's investigator, László Tabár, professor of radiology at the Falun Central Hospital in Falun, Sweden, has repeatedly refused to submit his data on one of the counties in the trial to groups

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conducting meta-analyses of randomized screening trials. Following a 1997 NIH consensus conference on breast cancer screening, NCI researchers proposed to conduct a meta-analysis, but Tabár refused to participate, sources said. He declined to submit his data for the 2002 meta-analysis by Umeå University epidemiologist Lennarth Nyström et al. He also declined to participate in a Cochrane Collaboration review of breast screening trials that was published in 2006.

In an email to The Cancer Letter, Tabár attacked the Zahl article as "beset by elementary errors and fallacious assumptions." His response appears on page 4.

A Call For An Independent Audit

Donald Berry, professor and head of the Division of Quantitative Sciences at M.D. Anderson Cancer Center and an expert in the statistical analysis of mammography screening trials, said Tabár could clear up questions about the study by submitting his data for an independent audit.

"These are enormous differences," Berry said. "Zahl doesn't have any direct evidence. Maybe there is an explanation for all of these things, but it would be imperative for somebody to answer this.

"Who's right? I cannot say," Berry said. "There is no question that Zahl et al. are on shaky ground. They are saying to Tabár et al., 'But your results don't fit well with some crude calculations that we have made.' I would like to have seen more specifics from Tabár, using actual numbers cited by Zahl, and showing why and by how much they were wrong."

"Since this trial is so important, I would like to see it audited by an independent Swedish group," Berry said. "This would resolve any uncertainties regarding the suggestions from Zahl et al. And I wish the Kopparberg half of the Two-County trial had been included in the Nyström meta-analysis of 2002. Such inclusion and update would have diffused some of the Zahl et al. concerns."

The controversy over the Zahl article is marked by unusual roles played by three scientific journals:

—The European Journal of Cancer, which originally posted the article on its website on March 9, 2006, and then withdrew it without comment three weeks later;

—The Danish Medical Bulletin, which published the paper in November with a editor's comment on the EJC withdrawal of the article; and,

—The Lancet, which published a letter by Gøtzsche, Mæhlen, and Zahl last November describing the EJC actions.

Berry likens the dispute between the Scandinavian researchers to the region's Great Northern Wars, a series of conflicts that lasted from the 16th to the 18th centuries. It's not the first time that Zahl and Gøtzsche, together or separately, have called Tabár's data into question. Nor is it the first time that Tabár's supporters have defended the Two-County trial and launched counter-attacks, particularly against Gøtzsche, whose work with the Cochrane Collaboration influences screening guidelines worldwide.

Seven years ago, Gøtzsche and his colleagues published a paper in the Lancet that pointed out that mammography screening in the major randomized trials resulted in a rate of overdiagnosis of about 35 percent. Since then, the investigators modified that to 30 percent. "There was a huge fuss," Gøtzsche said. "Screening advocates have tried hard to conceal to the public that there is a problem with overdiagnosis."

The battles have been played out in the pages of scientific journals, and in emails and letters sent to journal editors, other researchers, and journalists attempting to cover the debate.

Within three hours of sending an email to Tabár requesting comment for this story, this reporter received a phone call from Peter Dean, professor of diagnostic radiology at University of Turku, in Turku, Finland, who introduced himself as a friend and collaborator of Tabár's for 30 years. Dean said Tabár's response would be waiting in this reporter's email. It was.

Tabár was traveling in China, but woke up in the middle of the night to write his response, Dean said. "He is brilliant and he works all the time," said Dean, who wrote a lengthy opinion article on Gøtzsche published by the American College of Radiology in 2004, titled, "Gøtzsche's Quixotic Antiscreening Campaign: Nonscientific and Contrary to Cochrane Principles."

"Gøtzsche and Zahl have taken the approach that the best way to advance their criticisms of breast cancer screening is to attack László Tabár's personal integrity," Dean wrote in an email to The Cancer Letter. "This is effective—attacking any individual, no matter how unjust the accusations, will sow the seeds of doubt in the minds of the reader."

Eight days after the Zahl article appeared as an "article in press" on web site of the European Journal of Cancer, Dean wrote a letter to the journal's editor-in-chief, John Smyth, director of the Cancer Research UK Clinical Centre at Edinburgh, and chairman of medical oncology at the University of Edinburgh. Dean sent copies of the letter to 80 other people, he said.

The authors, Dean wrote, "make the serious claim

'…the numbers of breast cancer deaths in both the study group and in the control group have been changed in favour of screening.' I contend that this accusation of scientific fraud amounts to deliberate defamation of character."

"You have allowed your journal to become a platform for calumny and slander," Dean wrote to Smyth.

Dean titled the letter, "La vérité est en marche et rien ne l'arrêtera" (the truth is marching forward and nothing can stop it), a quote from "J'accuse," Emile Zola's 1898 letter to the French president Félix Faure, accusing the government of anti-Semitism in the imprisonment of Jewish army captain Alfred Dryfuss.

Dean also sent a letter to Steve Cowden, general counsel and company secretary for Reed Elsevier Group, the publisher of the EJC. The Zahl article "amounts to scientific libel and defamation of character," Dean wrote in the letter dated March 20, 2006. "[T]he accused scientists were never contacted in advance to offer an opportunity to set the record straight."

Smyth also received a letter from Jack Cuzick, professor of epidemiology at the Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics. "Unless the journal has clear evidence to support the potentially libelous claim of numbers being changed, this statement should be removed from the printed version and an apology issue[d] to the trialists," Cuzick wrote.

The statement does not appear in the Zahl article as published in the Danish Medical Bulletin.

In an email to The Cancer Letter, Smyth declined to comment. "The paper you refer to had to involve legal advice and therefore I would prefer not to comment further," Smyth wrote.

In their Nov. 25, 2006, letter in the Lancet, Gøtzsche et al. charged that the EJC inappropriately removed the article from the journal's web site, without giving the authors the opportunity to respond to the complaints, or see the full text of letters or peer review comments. The authors revised the manuscript and "deleted a sentence that might have been interpreted (wrongly) as suggesting that the trial authors had deliberately changed the cause of death in favour of screening," they wrote. "We never intended this, hence the amendment to our paper to delete this sentence."

However, on May 25, 2006, Smyth told the authors that he decided to withdraw the paper. Smyth "did not retract our paper but removed it entirely from the journal's website without leaving a trace of it, without sharing essential information with us, without discussing the issues with us, and without even notifying us in advance," Gøtzsche wrote.

The Danish Medical Bulletin published the Zahl article without further peer review. The editor-in-chief, Torben Schroeder, wrote in a note at the end of the article that he shared the author's concerns.

"First, the process that led to removal of the accepted and published paper was unilateral," Schroeder wrote. "Second, a withdrawn or removed paper invariably leaves you with an impression of scientific fraud. Therefore, DMB has decided to publish the paper."

The EJC withdrawal of the article was "appalling," Baines said. "That a published, peer reviewed article would be withdrawn because of the protestations of the researchers or the cabal that supports the researchers, is just unbelievable to me," she said.

"Although truly libelous things have been said about the Canadian researchers, including committing fraud, we have never attempted to prevent anything being published, because we do have freedom of the press and it's up to people to find out what's true information and what's not true information," Baines said.

Baines said mammography's Great Northern War is likely to continue until another screening method emerges. "Ultimately, mammography is going to be a thing of the past, and there will be better ways of making early diagnoses of cancer," she said.

The 2006 Cochrane review concluded that, "Screening likely reduces breast cancer mortality. Based on all trials, the reduction is 20%, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15% relative risk reduction. Based on the risk level of women in these trials, the absolute risk reduction was 0.05%.

"Screening also leads to overdiagnosis and overtreatment, with an estimated 30% increase, or an absolute risk increase of 0.5%," the review stated. "This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. It is thus not clear whether screening does more good than harm. Women invited to screening should be fully informed of both benefits and harms."

Tabár's Reply To The Zahl Article

"You should not be surprised that the article by Zahl and colleagues was withdrawn, as a result of the strong critique from the scientific community," Tabár

wrote in an email to The Cancer Letter. "You should rather be surprised that this 'study' has ever got as far as it did.

"My comments address Zahl et al's withdrawn article as it appeared briefly in the European Journal of Cancer's website," Tabár wrote. "This is because, instead of reprinting that article as the editor of the Danish Medical Bulletin claimed, the authors have made a large number of substantial changes which were not acknowledged."

Following are comments Tabár submitted to The Cancer Letter:

1. The critique of the Two-County Trial by Zahl et al[1] is beset by elementary errors and fallacious assumptions. To begin with, randomization started in W-county in July 1977 and not Oct. 1977 and ended in March 1981 in E-County, not in December 1979, as they state. Also, they claim that the "trial was closed after the first screening round," which is simply not true, since the trial was closed after the termination of the first screening round of the control group in each district in succession. This occurred in W-county in Dec 1986 and in E-county even later, in September, 1988. Their claim that the trial ended "at Dec 31st, 1984" is nearly four years in error! During the trial period, 2,468 breast cancers were diagnosed, as has been repeatedly published but which is totally ignored by Zahl et al.

2. Most surprisingly, Zahl et al[1] fail to account for the precise method of randomization. The Two-County trial was randomized in stepwise fashion, district by district, from July 1977 through March 1981, as published in 1993[2]. Screening started some weeks after randomisation in study group areas, the first screens taking place in October 1977. When the first district had been randomized and while it was being screened, hundreds of cancers were diagnosed in the remaining districts that had not yet been inducted into the trial. This fact explains why their use of a "simple and crude method" to assess the incidence and mortality in this trial leads to fatal errors. Twenty-nine years after the initiation of the study and 13 years after publication of the results of the Swedish Cancer Society's independent Overview Committee, Zahl et al chose an arbitrary start date for each county in this trial. Realizing that this strategy was clearly wrong, they attempted to correct it by picking another arbitrary date during the randomization period, guessing the expected incidence from their erroneous first date to their erroneous second date, using prior national incidence data, then, bizarrely, adding this figure to the trial's reported results. This is yet another mistake, since it fails to take time trends in breast cancer incidence into account, further compounding their errors. Thus, the main reason for the difference between the Trial's reported results and the flawed estimates derived by Zahl et al from national registry figures, is their use of an arbitrary single entry date coupled with their naïve attempt to correct for it, instead of using precise data covering the stepwise trial entry design, which was published in 1988 in a book chapter previously cited by Gøtzsche.

3. The effect of these errors is further compounded because the strategy of Zahl et al includes women older and younger than the cut-off ages of 40-74 years at the actual time of randomization in the trial. The surprising phenomenon here is not the existence of a difference between the two figures: the surprise is that supposedly serious researchers ever expected them to be the same. Similar considerations apply to their comparison of breast cancer death, since they have included cases that never belonged to the study.

4. Zahl et al also criticize two publications on the basis of different results without noticing that one of them described results from follow-up to 1996 using data from the national death registry[3] while the other used the expert committee's results from follow-up to 1998[4]. When trying to explain any discrepancy, it is important to point out that in 1993 the independent Overview Committee's expert group of the Swedish Cancer Society published results nearly identical to those of the local expert committees. At their second publication, however, when the cause of death was taken from the national death registry, instead of being based on the decision of their own expert committee, a difference is to be expected, since the national registry figures are derived from death certificates while those determined by expert committees are based on each patient's hospital records, including autopsy reports. Again, the surprise is that anyone should expect the results to be identical.

5. Perhaps the most egregious error in Zahl et al.'s paper is their interpretation and comment that "the differences in the number of breast cancer deaths between the study and control groups in The Two-County Trial are small." Can it really have escaped their attention that the study group was more than 30% larger than the control group? Regrettably, Zahl et al imply that deliberate alteration of the data provides the only explanation for their findings, failing to appreciate that their results are merely approximations based on their own flawed estimations and a misreading of the literature.

6. In view of these elementary errors, sadly, I feel

it necessary to make the following observation. If one is asserting that the world has got it wrong about breast screening, and that only a handful of relative newcomers to the subject have the answer, it is surely not too much to ask that these "instant experts" read the literature carefully and get their facts right. Before showing off one's expertise it is advisable to acquire some.

There is one point of agreement between me and Zahl et al. They state: "We have used a simple and crude method…." Indeed.

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4. Tabár L, Vitak B, Chen HH, et al. The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am 2000; 38: 625-51.

Missing Cancers & Deaths in the Two-County Trial

Gøtzsche, Mæhlen, and Zahl reply:

Tabár's "explanations" are not helpful and his comments about our research are either wrong or seriously misleading. We have noted earlier that the randomization process and the definition of the date of entry have been inconsistently described in various publications (1), and that the recent peer review comments (2) we received related to our paper on the missing cancers and deaths in the Two-County trial (3) added to this confusion. However, the crucial assumption for our analyses is not time of randomization but that the average follow-up was 6.0 years as Tabár stated in his initial trial report (4). If the mean time of randomization is later than first published, as Tabár indicates above, our results would still be highly significant, but the mean time of follow-up would then be less than 6.0 years (4).

Tabár's statement that we should have claimed that the trial was closed after the first screening round is entirely misleading. We wrote: "The trial was closed after the first screening round and new women were not invited" (3). Thus, by closed we referred to the fact that no more women were randomized, which was relevant for our calculations.

Tabár's statement that we should have claimed that the trial ended "at Dec 31st, 1984" is seriously misleading and his claim that we should be nearly four years in error is wrong, of course. We wrote: "the average length of follow-up was 6.0 years [1] December 31st, 1984" (3). Thus, we referred to the date when no more deaths were included in the results, which was relevant for our calculations.

Tabár's claim that the number of breast cancers diagnosed during the trial period was 2468 is misleading. Tabár has described this number in a report with long follow-up (5) but it is completely irrelevant for our results that are based on a shorter time period for which Tabár has published far lower numbers (4).

Tabár says it is surprising that we did not describe the precise method of randomization. What is surprising is that Tabár has never published it, and that what has been published is inconsistent. We asked Tabár about the method already in 1999 but could not find it in the references he advised us to read. Tabár now mentions a book chapter and claims he has described the randomization method there but does not give a reference to the book. Based on our initial correspondence with Tabár in 1999, we assume it is a book published by Huber (6), but there is no description of the precise randomization method there.

Tabár claims we have used arbitrary dates. Not so. We have studied all of his publications carefully, noted discrepancies in the information offered, have estimated what the likely dates must have been, and have calculated several estimates based on different assumptions (2,3).

Tabár says that the effect of our so-called "errors" is further compounded because we included women older and younger than the cut-off ages of 40-74 years at the actual time of randomization in the trial. This is not true (3). We first recorded cases in the age group 40-74 years in the randomisation period and then recorded new cases among those aged 40-74 years in the remaining period. This method underestimates the number of breast cancers in the screened group, but despite this, we found far more cancers (3) than Tabár reported (4).

Most importantly, Tabár does not explain how it was possible for him and his colleagues to publish an update of the Two-County trial where they reported a 24% breast cancer mortality reduction for the Östergötland part (5) when an updated overview of the Swedish randomised screening trials that was based on official mortality statistics found only a 10% reduction in breast cancer mortality for the Östergötland part (7)

(data were not made available for the Kopparberg part as the Kopparberg trialists—Tabár and colleagues—did not wish to collaborate with the other Swedish investigators) (7). Compared to the overview, Tabár et al. reported 10 fewer deaths from breast cancer in the study group in Östergötland despite the fact that the follow-up was slightly longer and the age group was identical, and 23 more deaths in the control group, i.e. all 33 discrepancies were in favour of screening. Such a large difference is extremely unlikely to have happened by chance ($p < 0.001$). Furthermore, it is not correct when Tabár says that the independent Overview Committee's expert group published results nearly identical to those of the local expert committees. The overview committee reported in 1993, after an average follow-up of 10.0 years, that 481 women in the Two-County trial aged 40-74 years at entry had breast cancer as underlying cause of death and that 496 had breast cancer present at death (8). In contrast, Tabár et al. reported only 466 deaths from breast cancer in the same age group, although the average follow-up was 10.8 years, or almost one year longer, which is very surprising, indeed (9).

Tabár's statement, "Perhaps the most egregious error in Zahl et al.'s paper is their interpretation and comment that 'the differences in the number of breast cancer deaths between the study and control groups in The Two-County Trial are small.' Can it really have escaped their attention that the study group was more than 30% larger than the control group?" is entirely misleading. We wrote: "It is of note that the differences in the number of breast cancer deaths between the study and control groups in the Two-County trial are small [1]. The mortality reduction would therefore no longer be statistically significant if only a few more breast cancer deaths were added to the study group" (3). Of course, we were aware that the groups were not of the same size but that is totally irrelevant for our argument.

Tabár also says that we should have implied that he deliberately altered the data. This is not correct. We wrote: "According to an investigator involved with the Two-County trial [9], other Swedish trialists [7], and an IARC/WHO report [10], cause-of-death assessments were not blind. This might be the reason why the cause of death determination by a local endpoint committee [11, 12] in Tabár and colleagues' update [8] appears to be seriously flawed" (3).

We believe our methods are adequate to allow us to conclude that many cancers and deaths are missing in reports of the Two-County study. This is supported by other data as well. We conclude that the handling of data was sloppy at best, that the assessment of cause of death was rather subjective in favour of screening, and that the Two-County trial is unreliable.

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FDA News:

No Data To Support QOL Claim For ESAs, FDA Advisors Say

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session of ODAC.

The document is posted at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#OncologicDrugs.

The committee voted 15-2 that "further marketing restrictions" would be warranted for ESAs.

The group voted 12-5 that labeling should "specifically state that ESAs are not indicated for use in the specific tumor types studied in trials that showed adverse safety signals."

The committee voted 15-2 that the product labels

should "define a hemoglobin level in asymptomatic patients at which ESAs should be initiated." However, the committee voted 11-6 against lowering the hemoglobin target for suspending ESAs. The current target is 12 g/dL.

In another highlight, the committee voted to recommend that the use of ESAs should be reconsidered each time a patient switches from one chemotherapy to another, since some therapies are less myelosuppressive than others. The committee voted 16-1 that ESAs should be discontinued after "completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen."

Also, the committee was asked to comment on strategies for informing patients that the use of ESAs in anemia of cancer could shorten their lives and to suggest new clinical trials of the agents.

Discussion by committee members, which usually influences the agency, will be covered in next week's issue of The Cancer Letter.

The U.S. sales for ESAs in oncology were at $4.854 billion.

Trying A Little Data-Dredging? Don't Do It, FDA Tells Sponsors

By Paul Goldberg

FDA has a message for anyone who contemplates "data-dredging," or looking for ways to squeeze a drug indication out of a failed trial:

Don't.

The agency started May 9 by telling Dendreon Corp. that it needed to provide additional clinical data on its agent Provenge. The "complete response" letter from the agency means that the application would not be approved.

The company was hoping to get an approval based on an unplanned analysis of negative trials. While these trials failed to show a delay in disease progression, the unplanned analysis appeared to show a survival advantage. Critics said that a premature approval would jeopardize the company's ongoing trial.

Sponsors who might have hoped that the agency's Oncologic Drugs Advisory Committee could be more tolerant of data-dredging were disabused of that notion later that day, as ODAC turned down two applications that failed to meet the primary endpoints, leading the sponsors to dredge for treasures in the muck.

In the morning, ODAC voted 12-2 against approval of Junovan (mifamurtide), a liposomal formulation of MTP-PE, an IDM Pharma Inc. agent for osteosarcoma, and in the afternoon, it voted 7-2 against approval of orBec (beclomethasone dipropionate), a DOR BioPharma Inc. agent for the treatment of graft vs. host disease involving gastrointestinal tract.

The orBec presentation was marred by an outburst from the vice chairman of the company's board, who seized the microphone at the public hearing to make hostile statements aimed at ODAC Chairman Maha Mussain, professor of Medicine and Urology at the University of Michigan, and the rest of the committee.

No security guards were on duty, and the company official was able to remain at the microphone for several minutes before being escorted out by FDA staff members and his colleagues. The official introduced himself as Steve Kanzer, and company staff confirmed his identity.

The company's web site identifies Kanzer as the vice chairman of the board of directors, an attorney and certified public accountant who is involved biotechnology venture capital.

Hussain, who remained composed through the incident, concluded the meeting and summarized the regulatory take-home message from the committee's session: "not meeting your primary endpoints is a fatal flaw."

"Barring phenomenal benefits in survival, something spectacular, what would be the point in bringing these discussions forward?" Hussain asked the FDA staff.

"To have public discussion," responded Richard Pazdur, director of the FDA Office of Oncology Drug Products. "I am very thankful for the discussion we had today." Pazdur noted that the vote notwithstanding, the agency would have "discussions internally" on orBEC.

Turning to the question of security, Pazdur said he had expressed concerns to the agency and was visibly irritated by the absence of response. "I will ask the executive secretary to contact her supervisors to ensure that, and please resend my email that I sent," he said.

Committee member Michael Perry said the agency should ensure security of the committee. "We perform this as a public service," said Perry, director of the Division of Hematology/Medical Oncology at the University of Missouri. "We take a lot of grief from the public people who speak, many of whom speak off-topic and look at this as a bully pulpit to criticize the members. I think at the very least we should have security."

"I couldn't agree with you more," said Pazdur. "I have brought this up to the FDA management staff, and I am directing Ms. [Joanna] Clifford [ODAC executive

secretary] to contact her boss. I think it's imperative that even before tomorrow, the next session, that something be in place."

Failing Primary Endpoints

In the case of Provenge, FDA requested additional clinical data in support of the efficacy claim contained in the application, the company said in a statement.

Dendreon said it is "seeking a clarification from the FDA as to the nature of the data that is being requested." Also, the company said FDA has requested "additional information with respect to the chemistry, manufacturing and controls section of the [Biologics License Application.]"

"Given our strong belief in the survival benefit and safety profile of Provenge, coupled with the positive outcome of the advisory committee meeting, we are disappointed that this decision will cause a delay in the availability of Provenge for patients who suffer from advanced prostate cancer," Mitchell Gold, president and CEO of Dendreon, said in a statement. "We are committed to working closely with the FDA to resolve these questions in a timely and efficient manner to bring Provenge to patients with advanced prostate cancer who currently have few appealing treatment options."

On March 29, the FDA Office of Cellular, Tissue and Gene Therapies Advisory Committee recommended approval for the agent. Critics, including Hussain, said the agent should have been sent to ODAC, which has the expertise needed for assessment of cancer therapies (The Cancer Letter, April 13).

Addressing the methodological questions posed by the Junovan application at the May 9 session of ODAC, FDA drew on advice of three biostatisticians: David Harrington of Dana-Farber Cancer Institute, Ralph D'Agostino of Boston University, and Stephen George of Duke University. On a typical application, the agency invites one biostatistician.

In discussion, the biostatisticians reiterated one of the fundamentals of clinical trials design: if a trial fails to meet its primary endpoint, the data it yields cannot be used to answer additional questions.

Also, the committee included four experts in pediatrics: Gregory Reaman, chairman of Children's Oncology Group, Peter Adamson of Children's Hospital of Philadelphia, Lee Hellman, director for clinical research at the NCI Center for Cancer Research, Susan Blayney of Texas Children's Cancer Center, and Angela Myers of the University of Missouri.

The company sought approval for newly diagnosed respectable and high grade osteosarcoma following surgical resection in combination with multiagent chemotherapy.

The application was based on a single cooperative group study. The four-arm factorial-design study compared two chemotherapy regimens, and each of these regimens was studied with and without Junovan. The study arms were pooled and analyzed for disease-free survival. Since that endpoint wasn't met, subsequent analysis for overall survival is meaningless, the agency said.

Pediatric oncologists on the panel said they were unsure about the role of the drug ifosfamide in one of the tested regimens of the trials, which compared the MAP regimen (methotrexate, anthracycline and platinum) and the MAP plus ifosfamide regimen, both of which were compared with and without Junovan.

"We desperately need better treatment for osteosarcoma," said Hellman. "We have patients from years ago that we've cured with ifosfomide. I have no doubt that ifosfomide cures some patients. I have no idea how to use it. I have no idea which patients benefit, which patients don't."

"I can say that if this drug were a huge advance, we wouldn't be struggling," Adamson said. "Nonetheless, we haven't had an advance in 20 years, and so we can't dismiss an incremental advance, if it's there." Adamson said he isn't convinced by the company's survival analysis. "I haven't reached that level of certainty," he said.

"We are disappointed with the outcome of today's advisory panel meeting," said Jean-Loup Romet-Lemonne, president and CEO of IDM. "As acknowledged by the panel, there is a significant unmet need for safe and effective treatments for children and young adults suffering from osteosarcoma, as there have been no new treatments in over 20 years. We will focus on working with FDA in the coming weeks to address the issues raised in order to complete the evaluation of our New Drug Application."

The company anticipates a decision in late August 2007.

DOR said it plans to initiate a phase 2 trial of orBec for the prevention of GI GVHD in which it. DOR said it has plans to further develop orBec for other gastrointestinal disorders characterized by severe inflammation, such as radiation enteritis, Crohn's disease, IBS and ulcerative colitis.

"I mentioned accelerated approval to Dr. Pazdur, and that's one thing we want to continue to have a discussion about," said Christopher Schaber, president and CEO of DOR.

"That was where the panel made their stance," Schaber said. "That was a black-and-white type of discussion. We are disappointed with the panel vote, and we will work with the FDA and see what direction we want to move next. "

The agency is expected to make a decision by July 21.

Schaber said Kanzer's behavior "was not in the company's control."

"On behalf of DOR, its employees, and our external advisors, we definitely apologize for that incident," Schaber said to The Cancer Letter. "The company does not condone that, and we are not pleased with that. It had nothing to do with the company. It was an individual."

In the Cancer Centers:

Arizona, New Mexico Centers Hold Regional Cancer Summit

By Kirsten Boyd Goldberg

University of New Mexico Cancer Center and the Arizona Cancer Center are holding the first Arizona-New Mexico Governors' Cancer Summit May 10-12 in Tempe, Ariz.

The two NCI-designated cancer centers will join with representatives of their state Departments of Health, the Navajo Nation, and American Indian Tribal Leaders and Healthcare Organizations, to develop collaborative programs. The four key areas of emphasis will be cancer health disparities, prevention and screening, bioimaging, and developmental therapeutics.

Arizona Gov. Janet Napolitano and New Mexico Lieutenant Gov. Diane Denish will give keynote addresses at the summit. New Mexico Gov. Bill Richardson will address the summit by video.

David Alberts, director of the Arizona Cancer Center, and Cheryl Willman, director and CEO of the UNM Cancer Center, will lead the summit.

The impetus for the collaboration came from NCI, which has mandated that centers work together regionally to solve problems, Alberts said. "No one center has all of the ability, in cancer prevention, treatment, or basic research," he said. "Arizona and New Mexico are a natural fit. Our two states have to some degree similar demographics. We have a number of worthwhile research programs that are intertwined, particularly educational outreach."

Willman said the collaboration is important for New Mexico, which is the newest NCI-designated cancer center. "It's an intensely competitive program," she said. "In the past two years, the NCI, CDC, the American Cancer Society and patient advocacy organizations have said collaboration among centers is important. The smaller centers in the NCI program need to reach out and develop these partnerships."

The idea for a summit involving the governors of the states was hatched at Willman's dinner table. One of the guests at the dinner was Napolitano, who grew up in Albuquerque. Her father, Leonard Napolitano, was the first dean of the University of New Mexico College of Medicine.

The UNM serves a 52 percent majority-minority population, predominantly Hispanic and American Indian. "One of things we see in our state are dramatic differences in cancers that affect minorities," Willman said. "We have a tremendous ethnic mix with different cancer patterns that are changing rapidly over time."

"Never before have two of the country's most prestigious cancer centers crossed state lines to work together to find a cure," Napolitano said in a statement. "This will be the first time Arizona's and New Mexico's leading physicians, scientists and public health workers will be collaborating to share and discuss their research, treatment and techniques in curing cancer."

"This is an important opportunity for the UNM Cancer Center and the Arizona Cancer Center to meet and discuss cancer biotechnology and address disparities by working to improve access to medical care," Denish said in a statement. "Our states share many of the same challenges, particularly with regard to addressing disparities in Hispanic and Native American populations. Arizona and New Mexico are the incubators to bring national solutions to these tough issues."

The three-day event will include presentations from physicians and research scientists, and panel discussions on overcoming the region's significant cancer health disparities; developing and delivering culturally appropriate cancer education, prevention, and screening programs through regional clinical trials for the multi-ethnic citizens of the Southwest; and very high technology new science including the development of novel isotopes for improved diagnostic imaging and treatment of cancer, and cancer drug discovery. As a result of the summit, the two cancer centers will develop strategic targets and goals to seek and secure joint funding.

Prior to the summit, the centers selected the areas of emphasis and established four panels to review research and develop up to three research hypotheses, with specific aims and methods, Alberts said. "We didn't

want this to be all fluff or Show-and-Tell. We want it to result in NCI-funded research projects," he said. "Up to 12 research projects could come out of this."

NCI didn't provide funding specifically for the summit. The centers received support from the American Cancer Society and pharmaceutical companies for the summit, Alberts said.

Arizona and New Mexico will alternate as hosts for the joint summit each year, and the 2008 meeting has already been scheduled for Santa Fe, New Mexico.

Arizona Cancer Center was established in 1976 and has been an NCI-designated cancer center for 30 years. The center brings in over $65 million per year in research grants and contracts and another $25 million a year from other sources. It has 274 physician and scientist members.

University of New Mexico Cancer Center was founded in 1971, and received NCI designation in 2005. It receives more than $50 million per year in federal and private grant support and generates over $23 million in revenue. The center has 62 cancer physicians and 110 research scientists.

* * *

DOUGLAS YEE, medical oncologist at the University of Minnesota, was named director of its cancer center. A breast cancer researcher, he succeeds **John Kersey**. Yee is professor in the Department of Medicine and Pharmacology, holds the Tickle Land Grant Chair in Breast Cancer Research and is head of the breast cancer research program at the cancer center. . . . **MEMORIAL SLOAN-KETTERING** Cancer Institute announced appointment and awards. **Joan Masague**, chairman of the cancer biology and genetics program, was awarded the 2007 Passano Award for his work in transforming growth factor-beta signaling. **Johanna Joyce**, also of the cancer biology and genetics program, was named the first incumbent of a Geoffrey Beene Junior Faculty Chair. . . . **JOHNNIE L. COCHRAN JR.** Brain Tumor Center opened May 3 at Cedars-Sinai Medical Center during National Brain Tumor Week. The center serves as a coordination point for physicians who specialize in clinical trials, data managers, and clinical research nurses who interface with FDA and institutional review boards to manage human studies, said **Keith Black**, chairman of Neurosurgery at Cedars-Sinai Medical Center. The center is made possible with the personal and financial support of **Dale Cochran**, widow of the late attorney of Cochran, Atkins & Evans, who died of a brain tumor. . . . **UNIVERSITY OF PENNSYLVANIA** School of Medicine, in association with Pennsylvania State University Medical College and Lincoln University, received $4.2 million to establish the Center for Gene-Environment Interactions in Lung Cancer. Research would focus on the study of gene-environment interactions that increase the risk of lung cancer in African American and Caucasian smokers and non-smokers. Steve Whitehead, professor of pharmacology, is director of the center. The study will be conducted under the Gene-Environment Initiative of Pennsylvania Center of Excellence in Environmental Toxicology, directed by Trevor Penning. The award comes from the Pennsylvania share of the national tobacco settlement for 2006-2007. . . . **CITY OF HOPE** received a two-year, $500,000 grant for early stage testing and development of cancer therapies from Phase One Foundation, a nonprofit organization for medical advances in cancer care. The grant was awarded to **Robert Figlin**, chairman of the Division of Medical Oncology and Therapeutics Research, associate director for clinical research of the Comprehensive Cancer Center, and Arthur and Rosalie Kaplan Professor of Medical Oncology. The grant will fund collaborative projects, clinical trials, experimental protocols and translational research, said Figlin. City of Hope will establish institutional grants to support phase I trials developed in collaboration with the Department of Clinical and Molecular Pharmacology and new programs during the two years of the award. Funds also will establish competitive awards in the developmental therapeutics and hematologic malignancies programs for translational research. . . . **BRIAN DRUKER**, leukemia program leader for the Oregon Health and Science University Cancer Institute, was elected to the National Academy of Sciences. Druker is the JELD-WEN Chair of Leukemia Research at the OHSU Cancer Institute and a Howard Hughes Medical Institute Investigator. In 2003 he was elected to the Institute of Medicine of the National Academies.

In Brief:

Bush Picks Weems For CMS

KERRY WEEMS, a longtime federal health official, has been nominated by President Bush as administrator of the Center for Medicare and Medicaid Services. If confirmed by the Senate, Weems would succeed **Mark McClellan**, who resigned last October. McClellan joined the AEI-Brookings Joint Center for Regulatory Studies. Weems is deputy chief of staff to Health and Human Services Secretary **Mike Leavitt**. He also has served as an acting assistant secretary overseeing budget and technology issues at HHS.

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