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CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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Hilton Washington
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

Committee Participants:

Bruce D. Cheson, M.D., Acting Chairman
[a.m. session]
Johanna M. Clifford, M.S., RN, BSN, Executive Secretary

Otis W. Brawley, M.D.
John T. Carpenter, Jr., M.D.
James H. Doroshow, M.D.
Stephen L. George, Ph.D.
Antonio J. Grillo-Lopez, M.D.
Pamela J. Haylock, RN
Silvana Martino, D.O.
Gregory H. Reaman, M.D.
Bruce G. Redman, D.O.
Maria Rodriguez, M.D.
Sarah A. Taylor, M.D.

Consultants (voting)

For Procrit:
Kenneth Bauer, M.D.
Laurie Feldman, Ph.D.

For CRC Endpoints:
Ronelle DuBrow, M.D.
David Kelsen, M.D., Guest Chair [p.m. session]
Michael J. O'Connell, M.D.
Daniel Sargent, M.D.

Patient Representatives (voting):
Musa Mayer, New York, New York - For Procrit

Nancy Roach, Hood River, Oregon - For CRC Endpoints

FDA Participants
Clare Gnecco, Ph.D.
Harvey Luksenburg, M.D.
Patricia Keegan, M.D.
Karen Weiss, M.D.
Amna Ibrahim, M.D.
Steven Hirschfeld, M.D., Ph.D.
Grant Williams, M.D.
Richard Pazdur, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. CHESON: Good morning. Welcome to the Oncologic Drug Advisory Committee, May 4th. I'm Bruce Cheson from the Lombardi Comprehensive Cancer Center. I am the Acting Chair of the ODAC for today's session. I do not work for, very clearly, the FDA in any way, shape, or form. I do this on a voluntary basis. And I am delighted to have some excellent colleagues of mine on this committee today, and I would like to start off today's session by having everybody at the table introduce themselves, starting with my friend Antonio Grillo-Lopez.

DR. GRILLO-LOPEZ: Thank you, Mr. Acting Chairman. My name is Antonio Grillo-Lopez. I am a hematologist/oncologist with the Neoplastic and Autoimmune Diseases Research Institute.

MS. MAYER: I am Musa Mayer. I am the patient rep for this morning's session, and I'm a 15-year breast cancer survivor from New York City.

DR. BRAWLEY: I'm Otis Brawley. I'm a medical oncologist and epidemiologist, and I'm a

professor at Emory University.

DR. MARTINO: Silvana Martino, medical oncology, from the John Wayne Cancer Institute.

DR. TAYLOR: Sarah Taylor, medical oncology, palliative care, University of Kansas.

DR. REAMAN: Gregory Reaman, pediatric oncologist at the George Washington University and Children's National Medical Center.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan.

MS. CLIFFORD: Johanna Clifford, FDA, Executive Secretary to this meeting.

DR. DOROSHOW: Jim Doroshow, medical oncologist, Director, Division of Cancer Treatment and Diagnosis, NCI.

DR. GEORGE: Stephen George, Biostatistics, Duke University.

MS. HAYLOCK: I'm Pamela Haylock. I'm an oncology nurse and doctoral student at the University of Texas, Medical Branch in Galveston, and I'm the consumer representative.

DR. FELDMAN: Laurie Feldman. I'm a

research scientist at the Beth Israel Deaconess Medical Center in Boston.

DR. GNECCO: Clare Gnecco. I am the statistical reviewer for several of the epoetin products.

DR. LUKSENBURG: Harvey Luksenburg. I'm a medical reviewer at the Food and Drug Administration.

DR. KEEGAN: Patricia Keegan, Division Director, Division of Therapeutic Biological Oncology Products.

DR. WEISS: I'm Karen Weiss, Office of Drug Evaluation VI, CDER, FDA.

DR. CHESON: Thank you.

Today we have an interesting series of discussion, the morning of which will be a series of presentations and discussions concerning safety concerns associated with Aranesp from Amgen and Procrit from Johnson & Johnson, both of which are indicated for the treatment of anemia associated with cancer chemotherapy. I was approached earlier by someone from the press who said, "How come there

has been no buzz about this?" I think this is sufficient evidence that there is buzz about this, and I look forward to an interesting series of discussions.

We'll start off with opening remarks from Dr. Keegan.

MS. CLIFFORD: Well, actually, me.

DR. CHESON: Oh, excuse me. From Johanna first. Johanna Clifford, the conflict of interest statements.

MS. CLIFFORD: Thank you.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the

following exceptions:

Dr. Maria Rodriguez has been recused from participating in all matters related to the discussions of safety issues associated with Aranesp and Procrit.

Dr. Kenneth Bauer has been granted a waiver under 18 U.S.C. 208(b)(3) and 21 U.S.C. 505(n) for owning stock in the parent company of the sponsor. The stock is valued from $5,001 to $25,000.

Dr. John Carpenter has been granted a waiver under 18 U.S.C. 208(b)(3) for lecturing on an unrelated matter for the sponsor of Aranesp. He is awaiting final payment of his fee that is less than $5,000.

Dr. Otis Brawley has been granted a limited waiver under 18 U.S.C. 208(b)(3) because his employer has a contract with the sponsor to study Aranesp. The contract is less than $100,000 a year. Under the terms of the limited waiver, Dr. Brawley will be permitted to participate in the committee's discussions; however, he will be

excluded from voting.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Lastly, we would also like to note for the record that Dr. Antonio Grillo-Lopez, Chairman, Neoplastic and Autoimmune Diseases Research Institute, is participating in this meeting as an industry representative, acting on behalf of regulated industry. He would like to disclose that he is a scientific adviser to Chiron and receives speaker fees from Wersch(ph).

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose product they wish to comment upon.

Thank you.

DR. CHESON: Hearing no other comments, now we'll go to Dr. Keegan.

DR. KEEGAN: Thank you. I want to thank the committee and the companies who have come forward to present information about the erythropoietin products, both those licensed in the United States and two that are not. The purpose of this is to review information based on the results of in the context of recent findings from two studies from Europe that suggested that there are certain practices in the administration of erythropoietin products which may raise concerns for safety of the products.

I want to remind everyone that the erythropoietin products that were approved in the United States were approved as a means of treatment of anemia in a variety of settings that, over the period since original approval, there have been investigations into alternative uses of these products, looking at other benefits such as impact

on survival.

It is in that arena that two studies recently conducted in Europe identified the potential for some safety concerns with those particular strategies. And we felt that it was important at this time to review the available data that both supported the original approval of Aranesp and Procrit for treatment of anemia associated with cancer, to review the clinical trials in question conducted in Europe, and to consider what additional information should be obtained at this point in time to determine whether or not an issue would exist with Procrit or Aranesp for the treatment of anemia associated with cancer and what the design of those studies should look like or to hopefully rule out any problems at the labeled and recommended doses for those two products. So I would ask that the committee carefully consider the data presented and provide us with some guidance in the approach of these additional studies.

I would like to draw your attention to the

fact that there are some errors in the FDA briefing document, and we have provided an errata sheet that will provide corrections to those errors. In addition, we have revised Question 1 of the questions to the committee in the first sentence, and the modified questions are available as an errata sheet at the table outside of this room.

DR. CHESON: Thank you, Dr. Keegan.

Since we went around the table, we've been joined by another member. If you could please identify yourself and your affiliation? Turn on the microphone, please. Hit the button.

DR. BAUER: Ken Bauer from Harvard, from the VA Medical Center and Beth Israel Deaconess in Boston.

DR. CHESON: Thank you.

Okay. The first presentation from a sponsor will be about NeoRecormon, or epoetin beta, from Hoffman-LaRoche, Ltd. Since I don't have your name here, if you could also please introduce yourself.

DR. HUBER: Good morning. I'm Marty

Huber, an oncologist with Hoffman-LaRoche.

Given the Advisory Committee's discussion today of the safety of erythropoiesis-stimulating agents in the treatment of cancer patients, Hoffman-LaRoche volunteered to provide data from a study that was recently published in The Lancet, which we'll subsequently refer to as MF4449. Additionally, we'd like to provide some context for these findings, reviewing some other clinical trials that have been conducted with epoetin beta.

Just a quick background. NeoRecormon is the trade name for epoetin beta. It is a recombinant human erythropoietin with a well-established benefit/risk profile with more than one million years of patient experience. It has been available outside the United States since 1990. We did not apply in the United States for approval based on patent issues. There were no safety issues which prevented it from being brought into the United States. It was not reviewed by the FDA. It is approved for patients with renal anemia as well as oncologic indications in most of these

countries.

For the presentation today, we'd like to review MF4449 focusing initially on the primary study results as published in The Lancet. We will also show additional analyses that were performed on this study. We did a meta-analysis of the clinical trial data with epoetin beta, and, finally, we'll look at one of our large randomized studies in which we have a long-term survival follow-up.

MF4449 was a study which was looking at an investigational use of epoetin beta. It was looking at, Would increasing the hemoglobin with epoetin beta lead to better efficacy of radiotherapy? This was trying to invoke radiosensitization, and could that lead to improved progression-free survival in cancer patients? The primary endpoint was local progression-free survival. For the rest of the study, I will refer to this as PFS, or progression-free survival.

This is an overview of the study design. Patients with head and neck cancer--and it was

males with a hemoglobin less than 13, females less than 12--were randomized to receive either epoetin beta, 300 international units per kilogram sub-cu three times weekly, or placebo in combination with their radiotherapy. Then they were followed up until progression or another endpoint.

The idea was to start them two weeks before the radiotherapy, but this was not done in all cases. Therefore, patients received a total of either seven to nine weeks of epoetin beta maximum. Epoetin beta was not continued in the follow-up period.

An important factor in this study was how the patients were stratified. As you know, head and neck cancer is a very heterogeneous disease. Therefore, we stratified them on the basis of tumor TNM Stage IV versus III. In addition, they were stratified by resection status. Stratum 1 here was patients who had had a complete resection. Stratum 2 was patients who had residual tumor after resection. And Stratum 3 was, finally, patients who received no attempt at resection and were

essentially treated with radiotherapy as their primary therapy.

With regard to the population characs, the details are in your briefing document, and they were overall very well balanced. There were a couple of exceptions we'd like to point.

First was smoking status. This was not have a history of smoking but were they smoking at the time. We believe this is relevant because we know there is an interaction between active cigarette smoking and radiotherapy which may diminish the efficacy of radiotherapy. At baseline, 53 percent of patients on placebo were smoking; 66 percent in the epoetin beta group.

Furthermore, because the patients had had surgery and then were randomized, there were patients who had relapsed, even prior to randomization. This was in balance, with 10 percent in the epoetin beta group, 7.6 percent on placebo.

And, finally, for Stage IV TNM status, there was a minimal imbalance at baseline, 72

percent versus 75 percent. But what you will see is, as we start looking at subgroups, this imbalance is magnified in an important subgroup.

These are the data that were shown in The Lancet showing that there was a progression-free survival advantage for placebo over epoetin beta. This is follow-up from--this is month six. An important point here is during the first five to six months, there was no difference in progression-free survival. This will contrast with some of the other data that you will review later.

We had conducted a series of secondary analyses which were prospectively planned. The intent of these analyses--we looked at the robustness of the data--was: Were the findings robust throughout? And, also, was there heterogeneity in the important subgroups?

Furthermore, when we looked at the outcome, this inferiority of epoetin beta was very much unanticipated. So this was in contrast to all other clinical experience with epoetin beta. So based on that, we did further additional analyses.

These were the planned secondary analyses to look at the population robustness. What I'm showing here are the Kaplan-Meiers for three populations: intent to treat, radiotherapy correct, and, finally, per protocol.

The differences between these groups are: In the radiotherapy correct population, these are the patients who received the radiotherapy as specified in the protocol. The per protocol population on the far right is not only did they get the right radiotherapy, but they also got the right treatment with regards to epoetin beta/placebo according to dose and schedule in the protocol. The n's on this, this is approximately 350, this is approximately 260, and this is around 220.

What's important to notice is that as you get to the purer population, the treatment effect actually diminishes. This is contrary to what you would expect. Normally when we do these studies for robustness, we are looking to see the treatment effect getting larger in the population that's

treated who are in per protocol. So this indicated to us some lack of robustness in the data.

We did subgroup analysis. This is a forest plot. I just oriented this slide. This is the categories, and these were categories we normally look at in head and neck trial: stratum, location, staging, age, gender, smoking status, and baseline hemoglobin.

What we looked at is, to the left is outcomes better with epoetin beta, and to right is better with placebo. As you can see here, there is a divergence of findings on both sides of one. What we'd like to look at today is look at a couple of these subgroups in which there was the highest relative risk, specifically Stratum 2 and they hypopharynx.

Looking at the progression-free survival by stratum, this is Stratum 1, which were the patients who were completely resected. This is Stratum 2, which were the patients who had residual tumor. One of the things that we found was the actual progression-free survival in Stratum 2

placebo was better than placebo with completely resected patients. This goes contrary to the natural history of these tumors and numerous other publications. We would clearly expect that this curve should be better than this. So what we feel is there is obviously some evidence of something odd about this placebo group.

Furthermore, when we looked into the tumor site, if you look at the hypopharynx location, there is a wide difference; there's a major treatment effect. This is placebo, epoetin beta. However, all other locations there was no difference in progression-free survival. So when we do the subgroup analysis, the effect is restricted to the hypopharyngeal population.

We looked further in this population, and what we found was that we did have an imbalance with regard to Stratum 3--30 percent in placebo, 45 percent epoetin beta--within this subgroup. These are the patients who did not have resection or attempts at resection and were radiotherapy only. Furthermore, we had an imbalance in the number of

patients who were in Stage IV.

With regards to safety, I apologize for this slide. This is the non-cancer-related adverse events, but essentially they were balanced overall: 65 percent placebo, 68 percent epoetin beta.

I would like to point out one piece of data here. In your briefing document, there's a reference to placebo 5 percent, epoetin beta 11 percent for vascular disorders. In this terminology, vascular disorders includes hypertension. What we have historically done when looking at these issues, we've used the definition of thromboembolic events. It does not include hypertension. So if you see some differences in numbers, this is what accounts for it

When we looked at thromboembolic events, we saw placebo 3.5 percent, epoetin beta 5.6 percent, with some--sort of slight imbalances, with more on the epoetin beta treatment group.

Furthermore, one of the things you may have noticed in the briefing document, there was an imbalance in cardiovascular deaths: 10 deaths on

the epoetin beta group versus 5 on placebo in the cardiovascular category. Given the concerns about thrombovascular events, what's important to note is one epoetin beta and one placebo occurred around day 50. The remaining deaths occurred after day 100. Remember, treatment was only for a maximum of seven weeks, so these events are occurring well after cessation of epoetin beta treatment.

In summary, we believe that there was a heterogeneity of treatment effect across various subgroups such as stratum, baseline hemoglobin, age, gender, disease location, and that there were also imbalances in important baseline characteristics, smoking for the overall population, as well as stage and resection status for patients with tumors in the hypopharyngeal location.

With regards to meta-analysis, this was pooled results from nine controlled clinical trials, a total of 1,409 patients, with both solid and hematologic tumors. We looked at tumor progression, overall survival, and thromboembolic

events.

Once again this is a forest plot. What we look at is better with epoetin beta, better with placebo. This is the total population. These are the individual studies. And then this is solid versus hematologic.

What we saw was actually a reduction in risk of progression with epoetin beta, 0.79, with a difference approaching significance. The remaining studies are relatively consistent in that most of them are less than 1, with a couple of exceptions, but they're very close. Also, it's a consistent finding for solid and hematologic tumors. In all of these we saw a reduced risk of progression.

For survival, we saw a risk of 0.97, so it's essentially the same for epoetin beta and placebo. And, once again, these studies are around 1. This one study, which is a higher one of 3.39, if you notice, due to the wide confident intervals. Very few deaths were noted in this study.

We also looked at thromboembolic events in this study, in this pooled study, and the control,

of 609 patients, 4 percent, epoetin beta 6 percent. This was actually quite consistent with the findings I presented from MF4449.

So, in summary, there was no evidence of increased tumor progression in patients treated with epoetin beta. There was no evidence of decreased overall survival. There was a small increase in the incidence of thromboembolic events: 6 percent of epoetin beta versus 4 percent on placebo. But what I'd like to note is when we looked at patient years of observation and corrected for that, this difference disappeared.

The limitation of this meta-analysis is most of these studies were relatively short in duration because they were looking at endpoints such transfusion or hemoglobin. Therefore, we looked at MF4467 to see what there a long-term effect on survival. This was a double-blind, placebo-controlled study of epoetin beta in patients with lymphoid malignancies. The primary endpoint was transfusion-free survival, and as you can see, there was a robust effect on that

endpoint.

What we did was an overall survival on over 340 patients in this study. This is the Kaplan-Meier and, as you can see, there's no difference in overall survival between placebo and epoetin beta.

In conclusion, the MF4449 study results are inconsistent with the other epoetin beta studies in oncology. We believe the most likely explanation for the adverse outcomes observed in MF4449 are factors independent of epoetin beta. The large majority of existing data shows that epoetin beta does not adversely affect tumor progression or survival in cancer patients.

Thank you.

DR. CHESON: Thank you.

We're going to reserve questions until after the FDA makes its presentation.

Next, Dr. DeLap from Johnson & Johnson.

DR. DeLAP: Dr. Cheson, members of the panel, and guests, good morning. I'm Dr. Robert DeLap. I'm Vice President for Regulatory Affairs

at Johnson & Johnson Pharmaceutical Research and Development, and I will be providing a brief introduction to our presentation.

We are pleased to be able to be here today to participate in this discussion of the safety of erythropoietin products in patients with cancer and to present our data in support of this discussion. We will not have time to summarize all of the information that's been generated over the years in our extensive research programs, so our presentation will focus on the information that we deem most relevant to today's discussion. Of course, we will be pleased to elaborate further on any specific points of interest.

Erythropoietin products are approved for the treatment of anemia associated with chemotherapy. Chemotherapy-associated anemia is a common problem for patients with cancer, and this anemia can be associated with debilitating symptoms and may require transfusions of red blood cells. Erythropoietic products have substantial value in treating anemia and its symptoms and can

significantly reduce the need for transfusions. This benefits individual patients and also means that the units of red blood cells that are collected by blood banks can serve the needs of additional patients.

The safety profile of erythropoietin products has been well established in years of clinical use, both in chemotherapy-induced anemia and in other illnesses where anemia may occur. Epoetin alfa products have been the subject of may clinical studies and have been used worldwide to treat more than two million patients for this indication.

In the U.S., there are two products that are labeled for treatment of patients with cancer chemotherapy-induced anemia. These are Procrit, marketed by Ortho Biotech, a J&J company, and Aranesp, marketed by Amgen. Procrit became available for this indication in 1993, and Aranesp became available for this indication in 2002.

Products available outside of the U.S. include EPREX, an epoetin alfa product that is also

marketed by J&J companies, and NeoRecormon and Aranesp. All of these products share extensive homology with naturally occurring human erythropoietin, and all act by binding to the erythropoietin receptor with activation of downstream pathways leading to red blood cell production.

Our presentation will describe a number of studies that have been done in our extensive clinical research program, and we will be talking about two different types of studies. Studies in supportive anemia care are the studies that were used to establish the existing indication for use of these products in patients with cancer--that is, the treatment of anemia associated with cancer chemotherapy. In this use, anemic patients are typically treated with a goal to obtain at least 1 gram per deciliter rise in hemoglobin level, to raise the patient's hemoglobin to a target range that is still below normally, typically, but is sufficient to reduce the likelihood of a transfusion.

Beyond correction of anemia is the term that we will be using today to describe investigational uses that have evaluated the use erythropoietin products to treat patients to higher hemoglobin target levels. Recent studies evaluating the effect or erythropoietic agents on cancer treatment outcomes have often utilized this design.

It was hypothesized that any beneficial effects of treatment with erythropoietic agents on cancer treatment outcomes might be magnified with treatment to higher hemoglobin target levels. However, some of these studies have suggested unexpected risks, including decreased survival.

This has led to extensive work that is continuing at our company to better understand the observations from these studies and to ensure that patients and prescribers will continue to have all of the information necessary to support the safe and effective use of our erythropoietin alfa products.

Safety data we will be presenting data are

as follows: We will first summarize data obtained in our clinical studies of epoetin alfa in supportive anemia care, which, together with the extensive clinical experience over more than a decade, support the favorable risk/benefit ratio for epoetin alfa for the existing indication.

Second, we will summarize data from a number of investigational studies that have involved treatment of patients beyond correction of anemia, including indications of increased risks that have arisen in some of these studies using that treatment approach. We remain interested in studying the effects of epoetin alfa on cancer treatment outcomes, but we have modified the hemoglobin target levels that we are using in that research.

Finally, we will describe additional data that we are collecting and further research that we have currently under consideration.

We look forward to the advice of the Advisory Committee today as we work to do the best possible job of planning our future activities in

this area.

Our agenda for our presentation is as follows: Dr. Peter Bowers, who leads our clinical programs with Procrit, will summarize our data from epoetin alfa studies that have been done for supportive anemia care and investigational studies that have involved treatment beyond the correction of anemia. Dr. Martine George, who heads our entire hematology/oncology clinical development program, will then describe future clinical data relevant to this subject that we expect to have from our currently ongoing studies and an additional clinical study that we are considering to fill knowledge gaps in this area. Finally, Dr. George will conclude our presentation.

We have with us today several advisors to help facilitate the discussion, as noted on this slide, including Drs. Jesse Berlin, Kimberly Blackwell, Roger Cohen, George Demitri, Mark Levine, and Brian Leyland-Jones.

Now I would like to introduce Dr. Peter Bowers for his summary of information from our

clinical study database. Thank you.

DR. BOWERS: Dr. Cheson, committee members, during the next minutes I will present a summary of safety information available from studies of epoetin alfa conducted in two settings: supportive anemia care, our labeled indication, and studies beyond correction of anemia.

We undertook a combined analysis of ten completed randomized, double-blind, placebo-controlled studies evaluating the use of epoetin alfa, EPREX and/or Procrit, for supportive anemia care. These data from 1,976 patients represent all controlled studies in this setting for which we have full patient level data regarding survival available. We examined mortality hazard ratios for deaths during the double-blind phase plus 30 days, and also tumor response and disease progression information, the latter available in five of the ten studies. Thrombotic vascular event, or TVE, data from the combined analysis will also be presented.

Some points should be kept in mind

regarding these analyses. The studies represent a variety of tumors, and many include mixed tumor types. The studies were designed and conducted to assess the impact of epoetin alfa on reducing transfusion and correcting anemia. Thus, data regarding survival and tumor response or disease progression were collected as secondary endpoints and/or for safety purposes. Additionally, the study drug treatment period ranges from 12 to 24 weeks, plus 4 weeks follow-up.

These are the results from the combined analysis for mortality. The chart in the center of the slide displays the point estimates, the red dots, and the 95-percent confidence intervals, the white horizontal bars. Unity is the dashed vertical line. A point estimate less than one suggests lower mortality among epoetin-treated patients, and greater than one, higher mortality. This side of the chart would favor epoetin alfa; this side favors placebo.

Please note for the combined analysis the point estimate for mortality is 0.99, shown at the

bottom, with a confidence interval 0.76 to 1.28. This means mortality among epoetin alfa-treated patients was the same as placebo patients in these studies.

We reviewed tumor response and disease progression data from the five studies where this information was collected. As you can see, response rates were similar between treatment groups, and also as you see, disease progression assessed in four studies was also similar between treatment groups.

To summarize, the established benefits of epoetin alfa for supportive anemia care--that is, anemia related to cancer chemotherapy--include transfusion reduction and amelioration of the debilitating symptoms of anemia. An evaluation of the studies in the approved indication showed no signal of reduced survival and no indication of an adverse impact on tumor response or disease progression. Thus, the benefits of epoetin alfa therapy continue to be supported by a well-defined and acceptable risk profile when used for the

approved indication of anemia in patients receiving cancer chemotherapy.

Now I'm going to turn to studies from epoetin alfa used in settings beyond correction of anemia, and before presenting the clinical data, I'd like to review very briefly some key preclinical findings.

The preclinical literature suggests a potential benefit of erythropoietins on tumor growth. However, there are also reports that suggest the possibility of a deleterious effect. Many tissues, including tumor cell lines, express erythropoietin receptors. In experiments by Johnson & Johnson and external groups, involving more than 25 different tumor cell lines, including cell lines known to express erythropoietin receptor, erythropoietin did not cause tumor cell proliferation. Similarly, systemic administration of epoetin at doses of 20 to 2,000 international units per kilogram three times per week in in vivo models of breast, lung, and ovarian cancer in vivo did not increase tumor volume. Moreover, a

positive effect on tumor growth delay has been observed in animal models of concurrent administration of erythropoietins in chemotherapy or radiation therapy.

There are conflicting reports regarding the impact of erythropoietin on tumor cell growth. Some experiments in vitro indicate increased tumor cell proliferation at erythropoietin concentrations 5- to 100-fold greater than those achieved clinically using a dose of 40,000 international units.

Based on the balance of positive preclinical data and results from Study INT-10, published by Dr. Timothy Littlewood in the Journal of Clinical Oncology 2001, which suggested a potential positive survival impact, the company conducted Study INT-76. Details of this trial are summarized in your background briefing materials.

INT-76 is a large study, 939 women receiving first-line chemotherapy for metastatic breast cancer, with a simple design. EPREX or placebo was administered weekly and continued for

12 months, regardless of chemotherapy changes or disease progression.

Study drug was initiated at a hemoglobin of 13 or below and titrated to maintain hemoglobin in the range 12 to 14. The primary endpoint of the study was survival at 12 months. Objective confirmation of investigator-reported secondary endpoints, including disease progression and tumor response, were not require. The primary--excuse me. Study drug treatment was discontinued at the recommendation of the DSMB for the study, and at that time 88 percent of the subjects had completed planned study drug treatment or had been withdrawn from the study. The shortest duration of treatment was nine months. Blinded follow-up continued out to the 12-month endpoint. Groups were generally balanced with regard to prognostic factors.

This slide shows the Kaplan-Meier plot for survival. The vertical axis is probability of survival, and the horizontal axis, time in months. Below the horizontal axis are the numbers of patients represented at each time point. White is

placebo, blue represents epoetin alfa. Please observe the survival curves begin to diverge relatively early in the course of follow-up such that by month 4 the separation was near maximal, and the curves continued parallel out through month 12.

The primary endpoint, survival at 12 months, was 24 percent survival--excuse me, deaths in the placebo group, and 30 percent deaths of patients in the epoetin alfa group. This difference has a p value of 0.012. The hazard ratio for mortality at the 12-month time point was 1.37, the confidence interval 1.07 to 1.74.

In light of these unexpected results, extensive analyses were undertaken by the company. Post hoc analyses, including subgroup and Cox modeling, were undertaken, and results of these analyses should be considered exploratory and interpreted cautiously. No particular subgroup was identified as accounting disproportionately for most of the mortality difference.

Additional data were collected in a

retrospective blinded chart review of the medical records of all subjects in the study. While not conclusive, the analyses in chart review, together with data from other trials, provide some hypotheses that might explain the observed survival difference. An adverse impact of epoetin alfa on tumor proliferation is one hypothesis. Another is imbalance in fatal thrombotic vascular events. And we'll look at those a little further momentarily.

Now, looking in detail at the cause of death data we have from INT-76, investigators captured cause of death on a case report form page with check boxes for either disease progression or other. We looked at causes of deaths at 4 months, since most of the difference in mortality had been seen by that time point. Investigators attributed most deaths to disease progression with a difference between the groups, as you can see on the slide.

In the other category, investigators listed thrombotic vascular events, chemotherapy toxicity, again, with differences as shown.

The blinded chart review suggested a somewhat higher rate of thrombotic vascular events than was reported by investigators, as you see on the bottom of the slide: two among placebo group patients, 11 among the epoetin alfa group patients, at the 4-month time point.

This suggests the possibility that thrombotic vascular events may have been underdiagnosed or -reported as a cause of death in this study and may have accounted for more of the excess deaths in the epoetin alfa arm than was appreciated.

The high number of deaths within the first 4 months, more so in the epoetin alfa group, may indicate that a more sick patient population than usual for a first-line metastatic breast cancer study had been enrolled. As you can see, a greater number of deaths--as you have seen, rather, a greater number of deaths was attributed to disease progression by investigators.

Further supporting the observation that the observed early differences in mortality may

have resulted in substantial part from causes other than tumor proliferation, the time to disease progression curves shown here--placebo, again, white; epoetin alfa, blue--are superimposed. Response rates for the groups are similar: 46 percent and 45 percent. Thirty-eight percent of patients in the placebo group developed new lesions, whereas 30 percent of epoetin alfa patients did. These results are not consistent with an adverse impact of epoetin alfa on tumor growth.

Given that this is a large, randomized, double-blind study with unbiased, if incomplete, collection of tumor progression data, these results should be considered carefully.

To summarize, in INT-76, an early survival disadvantage was observed in the treatment group. Deaths were attributed to investigators in significant part to disease progression. However, investigator-reported disease progression and response rates were similar. Given these inconsistencies, other potential explanations for

the outcome merit consideration as well and, in particular, thrombotic vascular events may have been underdiagnosed as a cause of death in this study.

Now, I'd like to turn to data from other studies using epoetin alfa in settings also beyond correction of anemia. Here we see summarized several other studies that evaluated epoetin alfa use in these settings. These studies are grouped to reflect status, either completed or in follow-up at the top of the chart, or discontinued in the group at the bottom of the chart. INT-76 is included at the top for reference.

As you see, the table summarizes some key details of the studies. In general, these studies have used epoetin alfa in settings where patients are not anemic or are treated to hemoglobin levels that are somewhat or substantially higher than are needed for correction of anemia.

The mortality experience is shown here. For the completed or in follow-up study, with the exception of Study INT-76, mortality is not

significantly different. The five discontinued studies represent studies stopped as a result of unplanned interim analyses of safety conducted at the company's request. Following this review, more than 15 studies continued, some with modifications to reduce target hemoglobins.

All five studies were stopped based on an unplanned analysis, and, thus, it's not possible to draw definitive conclusions other than to note unfavorable survival trends for epoetin alfa-treated patients in some of the stopped studies. Follow-up data collection for these five studies is continuing to further understand the results.

Now, let's consider the data relevant to tumor proliferation or disease response, as indicated by the endpoints shown on the slide: response rates, time to disease progression, disease-free survival, and so forth.

Looking at the column on the right, the differences in outcomes related to tumor response or disease progression tend to be small. These

data show no signal that epoetin alfa is associated with an adverse impact on adverse impact on tumor growth.

Turning to clinically relevant thrombotic vascular events in this same group of studies, clinically relevant thrombotic vascular events, or TVEs, are those which would be regarded by clinicians as significant and include both the venous and arterial events, but exclude such occurrences as superficial venous thrombophlebitis or catheter-related thromboses.

Here I've ordered the studies by frequency of clinically relevant TVEs in the epoetin alfa-treated patients: 31 percent to 1 percent. Please note the substantial differences in the frequency of clinically relevant TVEs.

Study 1015 with the greatest difference in TVE rates, 27 percent, is among the studies with the highest target hemoglobin level.

In contrast to this is the frequency of TVEs in the ten studies of supportive care of anemia. The studies are ordered by TVE frequency

in the epoetin alfa group, high to low, 9 percent or lower. In general, the absolute frequency of TVEs is substantially lower than is seen in the group of studies beyond correction of anemia. Differences between the groups are also smaller, with a negative number indicating more TVEs in placebo group patients.

Overall, the odds ratio shown at the bottom of the slide is 1.55, indicating a modestly increase risk of clinically relevant TVEs in the epoetin alfa-treated patients, the confidence interval 0.96 to 2.5.

In conclusion, our data indicate a favorable benefit/risk profile for epoetin alfa with no signal of tumor proliferation or adverse survival impact in settings of supportive anemia care. In study settings using epoetin alfa beyond correction of anemia, adverse outcomes have been seen. However, there is no clear signal suggesting an adverse effect on tumor proliferation. There is an indication that thrombotic vascular events are more frequent in studies with higher target

hemoglobin levels. This may account for some, possibly much, of the observed survival signal.

Additional data are being collected, and a new trial is under consideration. Dr. Martine George, therapeutic area head of oncology and hematology at Johnson & Johnson PRD, will share further details with you.

T1B DR. M. GEORGE: Thank you.

Johnson & Johnson has been studying the potential benefit of epoetin alfa in the setting of beyond correction of anemia since 1999, and our work in this area continues. First, I will present a clinical trial design for a study considering the FDA guidance. Then I will review with you how populated and ongoing trials could be used to address the safety questions raised.

We considered several clinical trial designs according to the agency requests, and after critical analysis, we decided to select advanced breast cancer. Our proposed clinical trial will focus on breast cancer based on the signal observed in INT-76, on the EPO receptor presence on breast

tumor, which is well known, on the high incidence of the disease in the population, and also based on the need for homogeneity in terms of patient population and chemotherapy.

Furthermore, early clinical trials in anemic patients have suggested a favorable outcome in patients with anemia treated with erythropoietin. The unfavorable outcome of INT-76 doesn't preclude a potential benefit in anemic patients.

We are assuming a potential benefit, but the trial will have to be powered to exclude a negative effect, as requested by the agency.

The objective of the trial is simple. It's to evaluate the effects of EPO alfa on cancer outcomes in patients with metastatic breast cancer receiving first-line chemotherapy.

The proposed clinical trial will be double-blind, randomized, placebo-controlled, and will enroll patients with advanced breast cancer receiving first-line chemotherapy, including taxane and/or anthracyclines. Patients will be anemic at entry with hemoglobin at baseline equal to or less

than 11 grams per deciliter before their third cycle of chemotherapy. Patients will receive EPREX or placebo until tumor progression, end of chemotherapy, or death. The target hemoglobin level in the study will be 12 grams per deciliter, and we'll hold the drug if the hemoglobin goes over 13 grams per deciliter.

The endpoints of the clinical trial will be as follows: The primary endpoint will be progression-free survival, and because of lack of time, I won't expand on how we are going to assess progression-free survival. Secondary endpoints will include overall survival, thrombotic vascular events, response rate, and TTP.

Statistical methods will include a non-inferiority comparison, possibly followed by a superiority test. Two thousand patients will provide 80-percent power to exclude a 15-percent reduction in progression-free survival, assuming no difference. If non-inferiority is demonstrated, a superiority test will be done. There will be 80-percent power to detect a 15-percent gain in

progression-free survival.

There are some considerations when designing the trial in which we will particularly welcome your feedback. The first challenge is to run a placebo-controlled trial when anemic patients receive drug treatment as a standard of care. Crossover of placebo patients following the double-blind phase could obscure the assessment of overall survival.

Second, functionality of the EPO receptor is best addressed in fresh frozen samples. Collecting samples may significantly slow down patient enrollment into the trial and would delay study completion. However, more preclinical studies to assess ligand affinity, signal transduction, and gene expression are warranted to better understand the receptor and its functionality.

Providing patients with a homogenous chemotherapy regimen is complicated, but at least three elements: the previous adjuvant chemotherapy, the wide range of available

therapies, and constant innovation in therapy.

And, finally, this clinical trial should provide an opportunity to better understand and control the causes of thrombotic events.

In the next two to three years, as depicted on the slide, we will have considerably more information in the areas of tumor control and survival from the tumor types where we have observed a survival signal: breast cancer, head and neck cancer, lung cancer, as well as some more data in carcinoma of the cervix, all in studies beyond the correction of anemia.

In summary, we will have a significant amount of additional data in the next two to three years from those recently completed studies and ongoing studies. This data will provide significant information in various tumor types.

We welcome your advice and opinions on the timing, design, and challenges of the proposed study.

And now I would like to conclude the Johnson & Johnson presentation. As you have read,

seen, and heard, in the supportive care of anemia we have extensive clinical experience which supports the favorable benefit/risk profile of Procrit. We take very seriously the survival signal observed in metastatic breast cancer and head and neck cancer that occurred in studies assessing the benefit beyond the correction of anemia with two different products: EPREX and NeoRecormon. We have looked for and found no clear tumor proliferation signal as assessed by response rate and tumor progression.

We note that TVEs account for some, potentially much, of the negative signal we have observed in those trials. In contrast, some studies in supportive anemia suggest a potential benefit in cancer outcome, and future clinical evaluation in that setting may provide the answer to that question.

In summary, Procrit provides important benefits for patients with cancer by decreasing transfusion and alleviating anemia symptoms. We are committed to maximizing those benefits and

minimizing the risks associated with its use.

We look forward to working with ODAC and FDA to optimize our current and future development programs.

Thank you very much for your attention.

DR. CHESON: Now we will move on to the Amgen presentations, their partners for the day. Dawn Viveash will do the introductions.

DR. VIVEASH: Good morning, members of the committee, FDA participants, ladies and gentlemen. Amgen is pleased to be here today to present data regarding the benefit and safety of Aranesp in the treatment of patients with chemotherapy-induced anemia.

We have with us today a number of distinguished guests: Dr. Jeffrey Crawford, Dr. David DeMets, Dr. John Glaspy, Dr. Harvey Lodish, Dr. Douglas Losordo, Dr. Marc Pfeffer, and Dr. Joseph Eschbach.

In addition, we have a number of independent investigators who are currently conducting oncology studies with Aranesp. These

investigators are Dr. Overgaard, representing the Danish Head and Neck Cancer Study Group; Directors. Delarue and Bosley, representing the GELA Lymphoma Study Group; Dr. Nitz, representing the West German study; and Dr. Kahlert, representing the German Gynecological Oncology Study Group.

I will open the presentation with a brief overview on preclinical and clinical properties of Aranesp. There has been a change on our agenda. As you'll see, we have a different cast of presenters than is shown on the published agenda. We will have Dr. Harvey Lodish discuss considerations regarding the epoetin receptor. His lab was the first to clone the EPO receptor. He is professor of biology and bioengineering at MIT and is a member of the National Academy of Science. Dr. David Parkinson will describe the clinical observations with Aranesp, and he will also provide an overview of our clinical trial program.

Aranesp is a distinct erythropoietic molecule. The development of Aranesp represents the combination of over ten years of research

during which time more than 450 molecules were characterized. Aranesp is unique as a result of its novel amino acid sequence, which allows for two additional carbohydrate chains, leading to an increased negative charge and increase in molecular weight. The terminal half-life of Aranesp is three-fold greater than epoetin, and because of its longer half-life less frequent dosing can be utilized compared to erythropoietin.

Aranesp was initially approved in 2001 for the treatment of anemia associated with chronic renal failure in both dialysis and non-dialysis patients. It was subsequently approved in July of 2002 for chemotherapy-induced anemia.

I'd like to highlight some relevant safety information from the package insert. The warnings section represents prior observations from the Normal Hematocrit Study which was conducted with EPOGEN. This was conducted in dialysis patients with pre-existing cardiovascular disease. This section also addresses high hemoglobin, rate of rise, and mortality.

The dosing guidance recommends a hemoglobin target of 12 and provides instructions for dosage adjustment to avoid excessive rate of rise of hemoglobin.

The precautions section includes a statement regarding the theoretical concern of growth factor potential, and the adverse reactions section describes the thrombovascular events.

You are now well aware of the findings from studies with epoetin alfa and epoetin beta and their observations regarding survival, tumor progression, and thrombotic events. When Amgen became aware of these findings, we conducted a comprehensive review of preclinical and clinical data.

The preclinical data with respect to Aranesp does not support the contention that this agent stimulates tumor growth. Aranesp is not genotoxic. There were not proliferative or hyperplastic signals in six-month toxicology studies. In addition, there was no off-target binding of Aranesp, and no off-target effects were

seen with Aranesp or erythropoietin in toxicology studies.

In studies of tumor xenografts, one of which was performed by Dr. Blackwell from Duke University, who is present here today, there was no stimulation of tumor proliferation. In fact, to the contrary, there was a potential beneficial effect observed when Aranesp was administered in combination with radiotherapy in some models.

The clinical review includes epidemiological analysis of thrombotic events and a review of completed and ongoing Aranesp trials and also an assessment of post-marketing experience. Dr. Parkinson will review our observations from the clinical data.

Based on this comprehensive review of oncology data, we did not identify any adverse survival or tumor progression signal with Aranesp. The thrombotic event rate remains consistent with that represented in the product label.

One of the hypotheses that has been put forward from the signals observed in the BEST and

Enhanced studies relates to the role of the EPO receptor in tumor progression. I would like to ask Dr. Lodish to address the potential relevance of the EPO receptor on tumors and the utility of current methods to detect the receptor.

Thank you, Dr. Lodish.

DR. LODISH: Thank you.

To begin, I'd like to emphasize that mere detection of the EPO receptor on tumor cells--or normal cells, for that matter--does not mean that erythropoietic agents drive the oncogenic process. The EPO receptor is present at very low levels on many normal and tumor cells, but the EPO receptor does not possess any of the characteristics of an oncogenic receptor.

For example, as you know, established oncogenic tyrosine kinase receptors, such as HER2 or the epidermal growth factor receptor, are amplified and mutated in many types of human tumors. Receptors can be overexpressed as many as 100,000 or a million copies per cell in certain cancers. In other cases, mutation leads to

constituitive--that is, hormone independent--activation. Both cases are transforming, are prognostic markers, and are established therapeutic targets.

The situation is quite different for the EPO receptor. With the sole exception of erythroleukemia, where EPO gene amplification has been recognized, EPO receptor amplification has not been seen in human tumors. The presence of gene amplification into erythroleukemic cell lines illustrates that the failure to detect involvement of the EPO receptor in the vast majority of cancer samples is genuine and not simply a false negative result. And it's my understanding that Aranesp treatment of erythroleukemia is not recommended.

Importantly, there are no constituitive reactive--that is, hormone independent--EPO receptor mutants in any human or animal tumors. The one case of humans with mutations in the EPO receptor involve truncations of the cytoplasmic domain that render the receptors hypersensitive to erythropoietin. These individuals develop

polycythemia but have no increased tumor incidence.

And, in conclusion, then, the EPO receptor is not known to initiate tumorigenicity or cause primary solid tumors to proliferate. There are no known correlations of EPO receptor expression or mutation with any aspect of oncogenicity.

I've also been asked to comment on methodological aspects of existing and potential assays for functional EPO receptors on primary solid tumors. And before doing that, I'd like to point out several important aspects of EPO receptor expression on erythroid cells.

First of all, over 90 percent, well over 90 percent of the EPO receptors in erythroid cells are not on the cell surface. They're in the cytoplasm on various membranes. Erythroid cells have only 1,000 to 2,000 receptors on their surface. Non-erythroid cells are transformed or otherwise generally have much less. And, importantly, surface expression of the receptor requires expression of the JAK-2 protein tyrosine kinase and possibly other accessory proteins.

Finally, the high-affinity receptor that is seen on erythroid cells, the signaling receptor, forms a one-erythropoietin, 2-receptor complex that initiates downstream signaling. The low-affinity receptors that are seen on the vast majority of normal and tumor cells are low-affinity, as I said, and likely are forming a 1-erythropoietin, 1-erythropoietin complex and are not signaling.

Concerning the assays that one might think of for erythropoietin receptor detection in primary tumors, I'd like to point out several points. First of all, numerous publications discuss EPO receptor expression and function in tumor cell lines, but it's not clear that these translate to primary tumor samples in a clinical setting. And, importantly, only cell surface receptors are clinically and biologically relevant. Only these receptors can bind to erythropoietin and send signals to the inside of the cell.

It's important to note that there are no measurements for functional epoetin receptors possible in fixed or frozen tissues. Reverse

transcriptase polymerase chain reaction, RT-PCR, measures RNA copies or transcripts of the EPO receptor gene. That does not necessarily measure functional EPO receptor message and does not measure EPO receptor protein, and certainly not functional receptor. And, importantly, these studies would require separation of the tumor cells from the other cells in the tumor.

Immunohistochemistry measures erythropoietin receptors in the cytoplasm and is too insensitive to detect the minute numbers that might be expected on the surface of cells. And, importantly, the existing antibodies, commercial or otherwise, are simply not sufficiently specific to detect EPO receptors among other background proteins.

There are ways of detecting functional EPO receptors in fresh tumor biopsies, but they also present many problems. First of all, these measurements would require fresh samples of cells and samples in which the tumor cells have been separate from the non-tumor cells. Binding with

radiolabeled EPO to cell surface receptors is possible, but it is very difficult to detect the low numbers of low-affinity receptors--and by low numbers, I mean under 1,000 receptors--present in cells. And it's difficult to resolve the specific saturable binding to cell surface EPO receptors from the non-specific, non-saturable binding to other cell surface components.

Proliferation of tumor cells in culture and response to EPO is also not practical for the simple reason that, as you know, fresh tumor cells generally are not viable in culture. In my view, the only assay that would detect functional EPO receptors in tumor cells--or, for that matter, other types of cells--involve EPO-induced activation of downstream signaling proteins as measured by, say, phosphorylation of the erythropoietin receptor, the JAK-2 kinase, other signaling proteins. These are complicated assays that require, as do the others, on the order of ten million cells per assay. The cells, again, must have been purified from other cells, and in

non-erythroid cells, these immuno-precipitation Western blot analyses are quite insensitive and have a very low signal-to-background ratio.

So, in conclusion, there are no presently available assays suitable for routine measurement of functional erythropoietin receptors on primary solid human tumors. Development of such assays will take years, and it's unclear to me what form these assays might ultimately take.

I now turn the podium over to Dr. Parkinson, who will discuss the clinical observations.

DR. PARKINSON: Good morning. Thank you, Dr. Lodish.

Outlined are the clinical observations which I will discuss relevant to this morning's meeting. After briefly reviewing some of the benefits associated with the treatment of anemia, I'll present the results of Amgen's studies of the risk of thrombotic events in association with erythropoietins. Next I'll present the analysis of survival in completed clinical trials. And,

finally, I'll outline a program of ongoing trials involving Aranesp in different tumor treatment settings.

Together, these trials have power to detect a safety signal far smaller than those which have been discussed already this morning. We believe this represents a responsible and credible approach to definitively resolving the questions raise in this morning's meeting.

With regard to the cancer indication, today we're here primarily to consider risks. But no meaningful discussion of risk can occur in the absence of a consideration of benefit. Anemia, which translates in patients with cancer into the important symptom of fatigue, is a highly prevalent comorbidity which significantly affects the quality of life in patients with cancer. Without erythropoietic protein therapy, 90 percent of cancer patients undergoing chemotherapy will have some level of anemia, and some 40 to 60 percent of those patients will require transfusions.

Historically, chemotherapy-related anemia

has been treated with transfusion, with its attendant inconveniences and risks. Not only is fatigue common in cancer patients, but fatigue as a symptom is rated by the majority of patients to be more important even than pain.

The left side of this panel shows the hematopoietic response indication correction of anemia by Aranesp therapy. Portrayed to the right is the significant decrease in the rate of transfusion with Aranesp therapy utilizing dosing intervals extending as far as three weeks.

Extensive literature suggests the association of this anemia correction with improved fatigue and other quality-of-life scores. Recognition by the oncology community of the importance of anemia and the benefits of its treatment with erythropoietic proteins have led to the production of independent, evidence-based treatment guidelines. These include treatment algorithms and desirable upper levels for hemoglobin.

These evidence-based guidelines have been

incorporated by Amgen into our current trials and analyses. Furthermore, treatment recommendations in the product label are consistent with these guidelines.

We'll now present the results of our evaluation of thrombotic events in patients with cancer. First of all, it's well established that patients with cancer have a higher background rate of thrombotic events. A full description of the epidemiology of these events in patients with cancer is outlined in our briefing document. We have extensively reviewed that.

The increased risk of thrombotic events with Aranesp therapy is represented in the adverse events section of the Aranesp label, as has already been discussed by Dr. Viveash. But we proactively initiated a reevaluation of thrombotic event experience within Aranesp clinical trials--these are 11 completed trials as of late last year--involving more than 1,800 Aranesp-treated subjects relative to more than 400 placebo-treated subjects.

On this slide, we see that our own Amgen analysis of the Medstat Claims database reflecting patients treated primarily with erythropoietin alfa also shows an increased risk of thrombotic events with epoetin alfa therapy. This analysis is consistent with the Cochran meta-analysis involving cancer patients receiving either erythropoietin alfa or beta, presented by Bohlius, et al., at the December American Society of Hematology meeting, the relative risks of thrombotic events in our study and the Bohlius study being 1.4 and 1.55, respectively.

We'll now show you our analysis of survival in completed clinical trials.

We identified four suitable randomized, double-blind, placebo-controlled trials. Two of these, involving more than 600 patients, had long-term follow-up and with 360 events allow us to carefully evaluate Aranesp's effect on survival. One trial was conducted in lung cancer and included anemic patients beginning platinum-based chemotherapy. A second trial involved patients

with five different lymphoid malignancies. In this trial, Aranesp therapy was initiated when patients became anemic. Finally, Amgen conducted a pooled analysis involving these two trials and two additional controlled trials comprising more heterogeneous patient populations.

The first of the studies, in lung cancer, is represented on this slide. More than 300 patients with either small-cell or non-small-cell lung cancer beginning platinum-based chemotherapy were randomized to weekly Aranesp or placebo. The relatively homogeneous patient population, the fact that most patients were beginning chemotherapy, and the long-term follow-up make the study very appropriate for survival analysis. Seventy percent of these patients have been followed until death.

On this slide, we see the results of this study in lung cancer. There is no evidence of any decrease in progression-free survival with Aranesp. In the Amgen briefing document, we've provided a breakdown of small-cell and non-small-cell lung cancer subjects. These subsets behave similarly.

This slide shows similar results for overall survival. The sample size of the trial and the number of observed deaths were appropriate to detect reduced survival of the magnitude seen in the BEST and Enhanced or Henke trials. Yet there is evidence for any negative survival influence with Aranesp therapy.

Trial 161, this lymphoid malignancy trial, differs from the lung cancer trial, as I've indicated, since patients with multiple lymphoid tumor types were eligible, and these patients could be randomized anytime during the course of chemotherapy. In this study, 344 patients with one of five different lymphoid malignancies with chemotherapy-induced anemia were randomized to receive either weekly Aranesp or placebo. The distribution of the different malignancies is outlined here.

The slide illustrates the baseline characteristics of the patients in the lymphoid malignancy trial. The study, while it did include long-term follow-up, was again designed to study

anemia. As a consequence, patients were not stratified for malignancy-specific prognostic factors. This led by chance, as you can see, to patients with the worse prognosis for both non-Hodgkin's lymphoma and chronic lymphocytic leukemia to be assigned to the Aranesp arm.

This slide indicates the trial result. We see on this slide no evidence for a significant decrease in progression-free survival. The hazard ratio, which is adjusted for disease type, stage, and IPI score, is greater than 1 but the confidence interval extends below 1. We continue to follow these patients.

On this slide, we observe no convincing evidence for a significant decrease in overall survival in association with Aranesp therapy. Again, the hazard ratio is above 1, but the confidence interval extends below 1. We've presented data on individual lymphoid malignancy subset in the briefing document.

I will now review the pooled analyses for these completed trials.

As previously noted, two other randomized, double-blind, placebo-controlled short trials with short-term follow-up were considered to be appropriate for the pooled analysis and to contribute particularly to the study of the early part of the survival curve which seemed to be so important in the BEST trial results, as you've heard.

On this slide are demonstrated the number of patients and the breakdown by tumor type of the patients contributing to this pooled analysis with cumulative follow-up involved. Combined, these trials provide more than a 80-percent power to detect an effect on survival of the magnitude seen in the BEST and Enhanced trials.

I'll now review results starting with progression-free survival.

Portrayed here is the progression-free survival in the overall pooled analysis. Note here that the time scale extends to 16 weeks and that the progression-free survival percent extends from 80 to 100. We've magnified the scale. The hazard

ratio is close to 1, and there is no evidence of an effect of Aranesp on progression-free survival during this period.

On this slide, we again see no evidence for a negative overall survival influence in association with Aranesp therapy. In addition, as shown in our briefing document, the long-term follow-up from this pooled data set is a hazard ratio of approximately 1. The confidence interval for that analysis extends from 0.8 to 1.2, which excludes an effect of the size seen in the BEST and Enhanced trials.

I will now review the analysis by tumor type.

On this slide, I portray the progression-free survival results of the pooled analysis by tumor type. No clear association is observed between progression-free survival and tumor type. Results are similar with respect to overall survival.

Here we find an association with improved progression-free survival and overall survival is

observed with respect to achieving an on-study rise in hemoglobin of 1 gram per deciliter or more over 14 days. These hazard ratios are 0.51 and 0.43, respectively, with the indicated confidence intervals.

Note that a similar association is found with improved progression-free survival and overall survival with respect to achieving an on-study hemoglobin of greater than or equal to 13 grams per deciliter.

In summary, our more recent analyses have confirmed the appropriateness of the Aranesp prescribing information with respect to thrombotic event rate. In an evaluation of data from over 1,100 patients randomized to placebo-controlled oncology trials with Aranesp, we found nearly identical survival and progression-free survival with Aranesp and placebo. We believe that our detailed examination confirms the safety profile of Aranesp and that the benefit/risk ratio remains favorable and warrants continued examination of potential beneficial effects on survival.

I will now review a program of ongoing trials involving Aranesp in different tumor treatment settings. We believe this group of trials represents a robust approach to ultimately resolving the questions raised in this meeting. The trials to be described were initiated, I should point out, because of evidence regarding the positive potential benefits of anemia treatment on patient survival. Outlined here are the relevant preclinical and clinical observations providing the rationale for these trials.

On particular note at the bottom is the Cochran meta-analysis with a favorable relative risk and a conclusion by the authors that more trials to explore this finding were merited.

On the next several slides are outlined the Amgen-sponsored and the four independent investigator-initiated and -conducted studies. The Amgen response to the information from the BEST and Enhanced trials has already been described by Dr. Viveash, including our formal review of all ongoing clinical trials involving Aranesp being

conducted worldwide.

One of our goals in this review was to identify clinical trials in which the design, the size, and the patient population would be particularly informative with respect to answering the kinds of questions that we're dealing with today. We identified five such trials--one Amgen-sponsored and four utilizing Aranesp but being conducted by independent investigators. All of these studies are randomized and controlled. One trial is itself double-blind and placebo-controlled. The other four clinical trials involve randomization to Aranesp or no epoetin. In these trials, Aranesp treatment is administered proximate to the time of chemotherapy and not for the full duration of follow-up. These studies include long-term follow-up with collection of predefined progression and survival endpoints. In addition, of course, the studies will capture thrombotic and cardiovascular events. Each study includes homogeneous populations with stratification for disease-specific prognostic

variables.

One question posed by the FDA relates to the feasibility and appropriateness of conducting placebo-controlled studies. You will note that, as I've indicated, one of our studies includes placebo-controlled design. While these studies are currently ongoing in Europe, we can report that we are successfully accruing patients to a placebo-controlled trial of Aranesp in chemotherapy-induced anemia in the United States if that's relevant to your deliberations.

In fact, it is our opinion that controlled studies are essential in certain situations and that it is feasible to conduct such studies in the United States.

On this slide, we also indicate that the number of patients for each tumor type and the total number of patients for these five trials being over 3,500. We believe that there is particular value to an approach which incorporates a range of tumors with robust numbers of patients in both breast cancer and head and neck cancer. I

will now review each study design in detail.

Portrayed here is the Amgen-sponsored, double-blind, placebo-controlled study. Six hundred patients with newly diagnosed extensive small-cell lung cancer will be randomized to combination chemotherapy with Aranesp or placebo. As you can see, endpoints include survival, and this trial has accrued more than 200 patients to date. I'd like to point out again that this trial is placebo-controlled.

The first independent investigator-conducted trial which I will discuss is the neoadjuvant breast cancer trial being conducted by the German Gynecologic Oncology Group. Seven hundred patients with diagnosed breast cancer will be randomized to dose-intense or standard chemotherapy with a secondary randomization to Aranesp or observation. Following induction chemotherapy, surgery will be conducted. Endpoints are as listed; follow-up is long term.

By the nature of this patient population and by the nature of the study design and

investigator intent with Amgen support, tumor tissue is being collected and stored. The trial has accrued more than 400 patients, half of the projected total accrual. An interim analysis of the experience in the first 200 patients will take place in the next several weeks.

The second investigator-initiated study is the adjuvant breast cancer study being conducted by the West German Study Group. After definitive surgery, the projected 1,000 patients will be randomized to center-specific adjuvant chemotherapy with or without Aranesp. Endpoints are as listed, and this trial has recently initiated accrual.

The diffuse large-cell lymphoma study conducted by the French, Belgian, and Swiss GELA, is outlined here. More than 600 patients will be randomized to 14- or 21-day monoclonal antibody CHOP(?) chemotherapy treatment regimens. These patients are secondarily randomized to Aranesp or supportive transfusion. Endpoints are as listed; long-term follow-up is involved. This trial has recently initiated accrual.

The head and neck cancer study being conducted by the Danish Head and Neck Cancer Study Group is outlined here to test the hypothesis that anemia contributes to radiotherapy failure. A projected 600 patients with head and neck cancer are randomized to radiotherapy alone or to Aranesp with long-term follow-up. The principal investigator is Professor Overgaard, a well-recognized authority in the field of tumor oxygenation and radiation therapy. More than 260 patients have already been accrued to this trial.

In response to the Henke and Enhanced trial results, the investigators have conducted an interim analysis for safety. We are informed that this trial is proceeding.

On this slide, the five clinical trials are outlined with respect to the tumor types involves, projected and current accrual, and the detectable differences from the expected control arm results. Individually, these trials will accrue between 600 and 1,000 patients and have power to detect absolute differences in survival

between 7 and 11 percent. Note that these studies are ongoing outside of the United States, but we believe the findings should absolutely be applicable to United States practice.

This slide shows the statistical power of the individual trials to detect an increase in the risk of death. Each of these trials has reasonable power to detect a hazard ratio of 1.4 or 1.5. Even if the true hazard ratio is as low as 1.2, there is a greater than 85-percent chance that at least one of these trials will result in a statistically significant difference.

On this slide is outlined the projected accrual over time to these trials and the expected cumulative patient years of follow-up. Including all five ongoing studies, more than 3,500 patients will be randomized in trial settings in which the influence of Aranesp on survival can be compared.

This slide shows the power of a meta-analysis illustrated in yellow of all five trials. This analysis will have high power to detect a true hazard ratio as small as 1.15, which

is far smaller than that observed in the BEST and Enhanced trials.

Also shown on this graph in the purple is the power of the meta-analysis of the neoadjuvant and adjuvant breast cancer studies, a total of 1,700 breast cancer patients. This analysis will have 80-percent power to detect a true hazard ratio as small as 1.32.

So on this slide, I've summarized the strengths of the ongoing clinical trials activities. As I've discussed, these include design elements which involve either double-blind, placebo-controlled, or Aranesp versus epoetin elements, with predefined survival or tumor progression endpoints. I'd like to emphasize this in view of the agency's first question.

While it is true that these trials are all being conducted ex-U.S., we would point out that it is entirely possible to conduct placebo-controlled trials in the United States. These ongoing trials cross multiple tumor types with approximately 1,700 breast cancer patients and 600 head and neck cancer

patients. The cumulative meta-analyses of 3,500 patients will provide robust power for assessment of survival outcomes in this program.

Of note, these studies have already accrued close to 900 patients. These studies include careful safety monitoring, and the AGO breast cancer trial incorporates tissue collection to enable appropriate correlative biological studies.

In conclusion, we've outlined the known and potential benefits of therapy with Aranesp. We have found no adverse effects on tumor progression or survival to date in our Aranesp clinical trials. To the contrary, evidence exists for potential benefit from erythropoietic protein therapy, both in the settings of cancer and other conditions.

It is our position that this potential benefit should be studies, but that such studies must be carried out responsibly, with carefully designed and executed trials.

Thank you very much.

T2A DR. CHESON: I would like to thank the

sponsors for their very clear and on-time presentations.

And now I'd like to turn to the FDA presentation, Dr. Harvey Luksenburg--who is going out the door.

[Laughter.]

DR. CHESON: Harvey, come back, please. And for those of you who are standing against the side wall, if you would please, for fire safety reasons, stand in the back or you'll have to be asked to leave the room.

DR. LUKSENBURG: Dr. Cheson, members of the committee, ladies and gentlemen, I'm Harvey Luksenburg. I'm a clinical reviewer at the Food and Drug Administration, and I would just like to start off by noting that I am but a member of a team of very talented individuals who put in a tremendous amount of work in putting together the data which we'll be presenting today.

Now, two large randomized studies in cancer patients on chemotherapy plus or minus EPO have shown shorter overall survival, shorter

progression-free survival, and an increased incidence of thrombotic and cardiovascular events in the groups assigned to receive erythropoietins.

The erythropoietin products used in these two studies are not licensed in the U.S. They are NeoRecormon, epoetin beta, manufactured by Hoffman-LaRoche, and EPREX, epoetin alfa, would is manufactured by Ortho Biologics. Both of these studies used a treatment strategy to achieve a hemoglobin greater than 12 grams per deciliter, which is higher than that recommended in the labeling for U.S.-licensed products.

The clinical trials for U.S.-licensed EPO products were not designed to assess the impact on response rate, with one exception--the N93 study, which I'll describe momentarily; they were not designed to look at in a systematic way time to progression or progression-free survival; and they were not designed to look at overall survival.

Now, the goals of my talk are four-fold. First of all, I'll try to give some justification of why the FDA feels that the safety issues

observed with EPREX and NeoRecormon, the non-U.S.-licensed EPOs, may also apply to U.S.-licensed products. In addition, I will review results of trials with EPREX and NeoRecormon, the non-U.S.-licensed products, regarding the safety concerns. Thirdly, I will review data available regarding safety from trials of EPOGEN/Procrit and Aranesp, the U.S.-licensed trials, and finally will try to come agreement on the design of future studies regarding these safety issues.

Now, the three safety issues which I'm going to be discussing are, first of all, an increased risk of thrombotic and cardiovascular adverse events, an increased risk of tumor progression in patients receiving EPO products, and poorer survival in groups of patients receiving EPO products.

Just the cast of characters. Recombinant EPO products which are currently U.S.-licensed are epoetin alfa manufactured by Amgen and marketed under the name of EPOGEN; the same drug manufactured by Amgen and marketed as Procrit by

Ortho Biotech; and darbepoetin alfa, or Aranesp, manufactured and marketed by Amgen.

The EPO products which are not licensed in the U.S. are epoetin alfa, or EPREX, manufactured by Ortho Biologics; Epoetin beta, NeoRecormon, manufactured by Hoffman-LaRoche.

Now, the FDA considers all these products members of the same product class, and, thus, these evolving safety issues are assumed to apply to all products unless adequate and well-controlled trials demonstrate otherwise.

The differences between these products are as follows: epoetin alfa and beta have the same amino acid sequence, but they differ in glycosylation. Aranesp differs in the amino acid sequence (5) and in the degree of glycosylation.

The similarities are meaningful. All these exert their principal clinical effect by binding to the erythropoietin receptor. All these products have similar pharmacodynamic effects when they're used at recommended dosages. And there's a similar toxicity profile across all of these

products with the exception of pure red cell aplasia, which has been seen thus far only in EPREX.

Now, target hemoglobin, the labels for EPOGEN/Procrit and Aranesp have dosage guidelines based on safety data from registration studies performed in patients with chronic renal failure. Just to quote what is written on the current labels, for EPOGEN/Procrit, "The suggested target hematocrit range is between 30 and 36 percent." For Aranesp, "The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL."

In addition, for rapid increase in hemoglobin greater than 1 gm per deciliter, or four points in hematocrit, in any two-week period, the dose should be reduced. And the product should be held if the hemoglobin is greater than 13 until the hemoglobin falls less than or equal to 12 grams per deciliter and re-start the dose at 25 percent below the previous dose.

Now, the first safety issue which I'd like

to discuss is that of an increased incidence of thrombotic and cardiovascular adverse events. This is a road map, and I'll show this slide several more times, and for each safety issue--thrombotic events, tumor progression, overall survival--I'm going to discuss only one study done in renal patients, the Normal Hematocrit Study. These in yellow are the studies done in non-U.S.-licensed EPO, and the studies in pink are the studies done in U.S.-licensed EPO products. An "x" means that there's data available for evaluation for each of these safety concerns.

Now, the licensing studies for EPOGEN/Procrit and Aranesp demonstrated that there's a baseline risk of thrombotic and cardiovascular adverse events at their labeled target hemoglobin, that is, between 10 and 12 grams per deciliter.

A study which dramatically showed the potential adverse effects of increasing the hemoglobin was the so-called Normal Hematocrit Study, first author Besarab, published in the New

England Journal in 1998. The idea behind this study was that patients with chronic renal failure on dialysis who had clinical evidence of cardiac disease could do better clinically if they had their hemoglobin raised from the nominal low 30 range to a higher hematocrit, around 40. And so 1,200 patients with chronic renal failure on dialysis with clinical evidence of congestive heart failure or ischemic heart disease, they were all on EPOGEN at baseline and maintaining a hematocrit of between 27 and 33 percent.

Now, both arms received EPOGEN, but they were randomized to different treatment strategies. One was randomized to achieve a higher hematocrit, around 42, plus or minus 3. This was called the so-called normal hematocrit group. The other arm maintained the lower hematocrit group, as was customary in practice, around 30 percent. This was called the low hematocrit group.

This study had a composite primary endpoint of either death or non-fatal myocardial infarction, and here are the results. In the

normal hematocrit group, there's an increased incidence of death, 30 percent, versus 34 percent in the low hematocrit group. There's an increased risk of non-fatal myocardial infarction, 3.1 percent in the normal hematocrit group, versus 2.3 percent in the low hematocrit group. And there was an increased risk of vascular access thrombosis, 39 percent in the normal hematocrit group versus 29 percent in the low hematocrit group.

Here's a graph showing the increased probability of death in the normal hematocrit group, death or myocardial infarction in the normal hematocrit group, and in the low hematocrit group. This goes out to about 30 months.

Now, when I talk about target hemoglobin, a target hemoglobin is only a target, and many patients don't achieve that target. However--and this has been seen in both the renal studies and in the oncology studies--it's the dosing strategy, it is the idea of pushing the dose of the erythropoietin to a higher level in order to try to attain the target hemoglobin. However, we've seen

in all these studies that the adverse event signals seem to occur in the group assigned to the dosage strategy aimed at the target hemoglobin, despite whether they attained that hemoglobin or not.

Now, the next studies I want to discuss are the BEST and the Henke studies. These are the studies done in oncology patients using non-U.S.-licensed erythropoietins. And, again, I'm just talking about thrombotic events.

The Breast Cancer Erythropoietin Trial, or the BEST Trial, used EPREX. This was a randomized, double-blind, placebo-controlled trial in 939 patients with metastatic breast cancer who were receiving first-line therapy. They received EPREX or placebo for 12 months, and the therapy was not started until the hemoglobin was less than 13.

The primary objective of this study was to demonstrate superior survival at 12 months. The target hemoglobin, again, was higher than what is on the label, between 12 and 14, and this study was stopped by an Independent Data Monitoring Committee based on the first four months of safety data.

At four months, there was an increase incidence of fatal thrombotic and cardiovascular events. In the EPREX arm, it was 2.3 percent; in the placebo arm, it was 0.4 percent.

The next trial that got our attention was published in The Lancet last October by Henke and his colleagues, and it used NeoRecormon, or epoetin beta. This was a randomized, double-blind, placebo-controlled trial in 351 patients with head and neck cancer who were receiving concurrent radiation therapy. All these patients were anemic, less than 12 grams per deciliter in women, less than 13 grams per deciliter in men.

The primary objective in this trial was to demonstrate superior locoregional progression-free survival. The target hemoglobin was less than or equal to 14 in women and less than or equal to 15 in men.

Now, the incidence of cardiovascular and thrombotic events was higher in the epoetin beta arm, 11 percent, versus placebo--this included hypertension, hemorrhage, venous thrombosis,

pulmonary embolism, and stroke. In addition, the incidence of patients who died of cardiac disorders not otherwise specified was 5 percent in the epoetin beta group versus 3 percent in the placebo group.

Next, still in the thrombotic events column, I'm going to discuss the studies we have available to us on the U.S.-licensed epoetin products.

The registration studies for Procrit consisted of pooled analyses of six multicenter, randomized, double-blind, placebo-controlled studies constituting a total of 131 patients. They had various primary cancers. Three of these studies consisted of patients receiving platinum-containing chemotherapy and three of them consisted of patients receiving non-platinum-containing chemotherapy. All these patients were anemic, and the primary endpoint was proportion of patients transfused. There were no progression-free survival or survival endpoints incorporated in these studies.

The incidence of thrombotic and cardiovascular events in the pooled data was 12 percent in the placebo group and 3 percent in the Procrit group.

A post-marketing commitment study done after the approval of EPOGEN/Procrit for the oncology indication asked the question whether giving Procrit along with chemotherapy for small-cell carcinoma of the lung would have a potential adverse effect on the tumor's response to chemotherapy. This was a randomized, double-blind, placebo-controlled, non-inferiority study which was intended to enroll 400 patients with small-cell carcinoma of the lung who were receiving first-line therapy and their baseline hemoglobin was less than 14. So these patients did not necessarily have to be anemic.

The primary endpoint, as I mentioned, was the objective response rate, CR plus PR, after three cycles of chemotherapy to rule out a decrement of 15 percent in the overall response rate with Procrit. There was no target hemoglobin;

however, the Procrit dose was reduced if the hemoglobin exceeded 16 grams per deciliter. The study, however, was terminated because of poor accrual at 224 patients.

Now, the incidence of thrombotic and vascular events in this study--we did review the data after 224 patients--in the Procrit group was 22 percent and in the placebo group was 23 percent. However, the definition of thrombotic and vascular events included chest pain, not otherwise specified, as well as all the other well-known clinical entities. So we subtracted chest pain and came up with these figures: for the Procrit group, the incidence of thrombotic/vascular events went to 14 percent, and in the placebo group, it was 9.5 percent.

The Aranesp Oncology Registration Study was a randomized, double-blind, placebo-controlled study in 320 patients with both small-cell and non-small-cell lung cancer, all of who were receiving platinum-containing chemotherapy. All these patients were anemic.

The primary endpoint, again, was a transfusion endpoint, the proportion of patients transfused between week 5 and week 12 or the end of the treatment period. The dosage guidelines were that Aranesp was to be held for hemoglobin of greater than or equal to 14 in women and for greater than or equal to 15 in men.

The incidence of thrombotic events in this study was 5 percent in the Aranesp group and 3 percent in the placebo group.

So, to summarize the studies for the thrombotic/cardiovascular events so far, in the studies in which a signal was detected, the Normal Hematocrit Study done in patients with chronic renal failure, the incidence of non-fatal myocardial infarction, 3.1 percent in the normal hematocrit group versus 2.3 percent in the low hematocrit group. An increased incidence of vascular access thrombosis, 39 percent in the normal hematocrit group versus 29 percent in the low hematocrit group. In the BEST Study, done in 939 patients with metastatic breast cancer, there

was an increased risk of fatal thrombotic events in the arm randomized to receive EPREX, 2.3 percent, versus 0.4 percent in the placebo arm.

In the Henke Study in head and neck cancer and the patients were randomized to receiving epoetin beta, or NeoRecormon, or placebo, there was also an increased risk of cardiovascular and thrombotic events, 11 percent in the epoetin beta group versus 5 percent in the placebo group.

In the thrombotic and vascular events studies that didn't have a signal, the Procrit pooled studies, 3 percent in the Procrit group versus 12 percent in the placebo group. The N93 study in small-cell carcinoma of the lung, 22 percent Procrit versus 23 percent placebo. We put an asterisk next to this because after we subtracted the non-specific chest pain, we did find that there was an increased risk of thrombotic/vascular events in the Procrit group. And, finally, the Aranesp Oncology Registration Study, 5 percent incidence in the Aranesp group versus 3 percent in the placebo group.

Now, in September 2003, three placebo-controlled clinical trials in oncology patients in which one arm received EPO to target a higher hemoglobin were terminated because of unexpected rates of thrombotic events in the EPO arm.

Briefly, to summarize these studies, in one, the primary cancer was small-cell carcinoma of the lung; the target hemoglobin was between 14 and 16; the incidence of thrombovascular events, TVE, was 34 percent in the EPREX group versus 6 percent in the placebo group. The second study, patients who had cervical cancer, the target hemoglobin was between 13 and 14; the incidence of TVE, 16 percent in the Procrit group, versus 5 percent in the placebo group. And the third study, gastric or rectal carcinoma, target hemoglobin 14 or 15; the incidence of TVE, 24 percent in the Procrit group versus 6 percent in the placebo group.

Now, the next safety issue I'd like to discuss is that of tumor progression. There are a number of preclinical studies which have been

reviewed, but our selective take under the literature is that there are EPO receptors which are present on some tumor cell lines and on tumor vasculature, meaning endothelial cells.

EPO has been reported in some studies to inhibit apoptosis, stimulate angiogenesis, stimulate endothelial cell growth, migration, and proliferation, and reduce survival in some tumor xenograft models.

Now, studies supporting the approval of Procrit and Aranesp for the treatment of anemia in cancer patients on chemotherapy were not designed to assess the impact on tumor response, tumor progression, or survival. So there's a big lacunae in the information that we have for the U.S.-registered EPO products. And, again, I'm going to go through the two studies that utilized non-U.S.-licensed EPO products and then two studies which we have that have data that's useful for looking at tumor progression in the U.S.-licensed EPO products.

Again, just to remind you that the BEST

Study using EPREX, randomized, double-blind, placebo-controlled, 939 patients with metastatic breast cancer, first-line therapy, randomized to receive EPREX or placebo for 12 months, therapy started at less than 13.

The primary objective of this study was to demonstrate superior survival at 12 months. The target hemoglobin was between 12 and 14, and this study, again, was stopped by the Data Monitoring Committee based on the first four months of safety data.

At four months, there was a twofold increase in the incidence of disease progression. It was 6 percent in the EPREX group and 3 percent in the placebo group.

At four months, there was 2.5-fold increase in early mortality. It was 8.7 percent in the EPREX group versus 3.4 percent in the placebo group.

In the Henke trial, again, randomized, double-blind study in 351 patients with head and neck cancer receiving concurrent chemotherapy,

these patients were entered if women had a hemoglobin of less than 12 and men less than 13. The primary objective was to demonstrate superior locoregional progression-free survival. The target hemoglobin was less than or equal to 14 in women or less than or equal to 15 in men.

For locoregional progression-free survival as the primary endpoint, the relative risk was 1.62 favoring placebo, and the lower bound or the 95-percent confidence interval was greater than 1, with a highly significant p value.

For locoregional progression, again, the relative risk was 1.69 favoring placebo and the lower bound of the 95-percent confidence interval was greater than 1, with a significant p value.

Study N93, the post-marketing study which looked at small-cell carcinoma, this was a randomized, double-blind, non-inferiority study which was intended to enroll 400 patients who were receiving first-line therapy.

The primary endpoint, again, was objective response rate after three cycles of chemotherapy to

rule out a 15-percent decrement in the overall response rate in the Procrit arm. No target hemoglobin was determined. The Procrit dose was reduced for hemoglobins greater than or equal to 16, and the study was terminated at 225 patients out of a projected 400 for poor enrollment.

This study was not designed to assess the impact on time to progression, and survival was a secondary endpoint, and there was no formal hypothesis testing.

The results showed that for the placebo group the overall response rate was 67 percent; for the Procrit group it was 72 percent. The 95-percent confidence interval around the observed difference had a lower bound of minus 6 percent. So even though this study met its intended objective despite the early termination, it was able to exclude a difference of greater than 15 percent.

The Aranesp Oncology Registration Study, a randomized, double-blind, 320 patients with non-small-cell and small-cell lung cancer all

receiving platinum chemotherapy and all of whom were anemic.

The primary endpoint was a transfusion endpoint. The Aranesp was held for hemoglobins greater than 14 in women and 15 in men.

The median progression-free survival was five months in the Aranesp group and four months in the placebo group. This study, again, was not designed to assess the impact on progression-free survival.

And here are the curves. This is the placebo group here. Here is the Aranesp group. Here is a year, two years.

So, just to summarize, the data we have on tumor stimulation, first the studies in which a signal was detected. The BEST Study, EPREX, metastatic breast cancer, at four months an increased risk of deaths due to disease progression being 6 percent in the EPREX group versus 3 percent in the placebo group. In the Henke Study, head and neck carcinoma using NeoRecormon, EPO B, the relative risk for locoregoinal progression-free

survival favored placebo, 1.62.

The tumor stimulation studies without a signal, the Procrit group, the post-marketing commitment in small-cell carcinoma of the lung, the overall response rate was 72 percent in the Procrit group versus 67 percent in the placebo group. The Aranesp Oncology Registration trial, the median progression-free survival, four months for Aranesp, five months for placebo.

And, finally, I'd like to discuss the data we have concerning poorer survival in patients randomized to receiving erythropoietins.

Again, I'll be discussed the data we have on the BEST trial and the Henke trial as well as the U.S.-licensed erythropoietins.

Just to remind you once again, the breast cancer study, 939 patients with metastatic breast cancer, randomized to receive EPO or--EPREX or placebo for 12 months, and the primary objective of this trial was to demonstrate superior survival at 12 months. The target hemoglobin was between 12 and 14, and this study was stopped by the

Independent Data Monitoring Committee based on four months safety data.

The estimated 12-month survival was 70 percent in the EPO group and 76 percent in the placebo group. The relative risk of death was 1.4 favoring the placebo group, and the lower bound of the 95-percent confidence interval was greater than 1, with a p value of 0.12.

Here are the curves for the first 12 months, which was the primary endpoint. This is the placebo group on top, and here is the EPREX group.

In the Henke Study, again, 351 patients with head and neck cancer getting radiation therapy. The erythropoietin product used was NeoRecormon.

The relative risk of death was 1.4 favoring placebo; the lower bound of the 95-percent confidence interval was greater than 1. The median overall survival was not different, but there's a trend toward poorer survival in the NeoRecormon group--was 605 days in the NeoRecormon group versus

928 days in the placebo group.

Study N93, the post-marketing commitment done in patients with small-cell carcinoma of the lung, again, this study was not designed to assess an impact on survival. The median survival was 10.5 months in the Procrit group and 10.4 months in the placebo group. The overall mortality rate was 92 percent in the Procrit group versus 88 percent in the placebo group.

And here are the curves. The dotted line is the placebo group. The sold line is the Procrit group.

The Aranesp Oncology Registration trial, 320 patients with lung cancer receiving platinum-containing chemotherapy. This study was not designed to assess the impact on survival.

The median overall survival was ten months in the Aranesp group and eight months in the placebo group. The overall mortality rate, 14 percent in the Aranesp group, and 12 percent in the placebo group.

And this is the placebo arm here, and here

is the Aranesp arm. This is one year, two years.

And so, just to summarize the studies we had in which there was a survival signal, the BEST Study, metastatic breast cancer, the 12-month survival rate, the primary endpoint, poorer survival in the EPREX group, 70 percent, versus 76 percent in the placebo group, p value of 0.12. In the Henke Study using NeoRecormon, the median overall survival not significant but a trend, 605 days for NeoRecormon versus 928 days with placebo.

The studies that we have without a survival signal, the N93 Study, post-marketing study in small-cell carcinoma of the lung, 10.5 months in the Procrit group versus 10.4 months in the placebo group. The Aranesp Oncology Registration Study, ten months in the Aranesp group versus eight months in the placebo group.

So, to summarize, two large, multicenter studies--the BEST Study and the Henke Study--which were designed to show superior survival or progression-free survival, instead demonstrated an increased risk of thrombotic and cardiovascular

events, a shorter progression-free survival, and a shorter overall survival. Both of these studies used a treatment strategy to achieve hemoglobin levels greater than or equal to 12.

The multicenter, placebo-controlled trials using Procrit and Aranesp, the U.S.-licensed erythropoietins, were smaller in size; they were not designed to assess the impact on progression-free survival or overall survival. Their treatment strategy varied: Procrit was held in the N93 Study for hemoglobin greater than 14--the label recommends 12--and in the Aranesp study it was held for greater than 14 in women or greater than 15 in men.

So, to conclude, we have these evolving safety concerns. They cannot be dismissed. The current dosing recommendations we feel are adequate to minimize the risk of thrombotic events. However, there is insufficient information concerning overall survival and progression-free survival for U.S.-licensed products at approved doses to assess these risks. Amgen, Ortho Biotech,

and the FDA have agreed on the need for further studies to investigate these safety issues.

Now, the FDA recommends certain elements that should be components of all current and future studies which will be done to investigate these safety issues. First of all, there should be a homogeneous primary tumor type. There should be homogeneous chemotherapy or radiotherapy regimes. The studies should be designed to detect clinically meaningful decrements in response rate, progression-free survival, and survival. There should be prespecified definitions of cardiovascular and thrombotic events. And there should be Data Safety Monitoring Committee oversight.

We also recommend the determination of expression and ligand affinity of EPO receptor on specific primary tumor types, preferably through the analysis of clinical tissue specimens or through pre-existing tissue repositories representing common tumor types.

And I think that is the end of my

presentation.

DR. CHESON: Thank you, Dr. Luksenburg.

It's now time for questions from the committee to either the sponsor or Dr. Luksenburg. I'd like to start, while all the people are coming up, with questions for Dr. Luksenburg. On your various slides, Harvey, when you're talking about studies with signals, you mean with negative signals, since there are a number of studies with positive signals, including one of the ones on your slide, 98-0297, with the ten- versus eight-month survival in favor of the erythropoietin compound, right? So when you say with signal, you're referring to negative signal in your slides.

DR. LUKSENBURG: Yes.

DR. CHESON: Okay.

DR. KEEGAN: I would point out that the one that you're referring to as having the positive signal is actually not significantly different.

DR. CHESON: I know, but neither are some of the others.

Any other questions from the committee?

Any comments from the committee? Dr. Martino?

DR. MARTINO: I'm reminded of a quote from Enrico Fermi, which goes as follows: "Before I came here, I was confused on this topic. Now I'm still confused, but at a somewhat higher level."

[Laughter.]

DR. MARTINO: And I'm not sure who I want to sort of address this to, but whoever of you thinks you have an answer, I'd appreciate it.

It occurs to me that looking at the tumor tissue itself to see if it has receptors certainly is reasonable if it's doable. Simultaneous to that, it is likely that the mechanism, if there is any by which tumors grow, may not be by direct involvement of the tumor cell itself, but may be through some other mechanism. One of those, you know, is what it might do to the vascular system and neovascularization.

Is there some way to look at that parameter? Because some of us think that that may be the more likely mechanism by which tumor cell growth may occur, if, in fact, it does.

DR. CHESON: Dr. DeLap?

DR. DeLAP: Yes, I'd like to ask Dr. Francis Farrell to address that question. Dr. Farrell is head of our preclinical program for this area.

DR. FARRELL: Thanks for the excellent question. Francis Farrell, Johnson & Johnson.

We feel that your idea does have credence. Although we don't feel that the receptor on tumor cells is functional, there is enough preclinical data to show that EPO does have an effect on endothelial cell function, including some papers showing that EPO binds to endothelial cells. There have been some studies showing some chemotaxis with EPO on endothelial cells. There's also been some data that aortic ring formation can be formed.

The only caveat with these experiments, though, are that high doses of EPO are actually used to see this effect. And in one publication, the dose used was actually 50 units per ml, which would be very high compared to what the clinical maximal serum dose a patient would get with 40 IUs

per kg dose, which is approximately two units per ml.

So to answer your question, though, I think better preclinical modeling and xenograft models where you could actually look at vascular density, micro-vessel formation, I think are warranted, and that would be the direction that we would go in.

DR. DeLAP: If I could ask your indulgence, we also have Dr. Kimberly Blackwell here who could also contribute to this point, I think, as a consultant, if we have a minute.

DR. CHESON: Please. That would be fine.

DR. BLACKWELL: Hi. I'm Kim Blackwell from Duke University.

I, like the questioner, had some interest in was this tumor effect, was it endothelial cell effect, and we've embarked on a number of preclinical modeling, now with well over 500 animals that we've looked at, both in R3230, which is an ER-positive mammary carcinoma line. So it's as close as you can get to a rodent model to human

model. We've also looked at CT26, which is a colorectal model.

So, very briefly, our experiments have looked at tumor proliferation using Key 67, tumor growth using biodimensional tumor volume. We've also looked at micro-vessel density, and I think the best experiment is we've actually looked at in vivo angiogenesis using a dorsal window fold where you can actually measure vascular development in the mammary carcinoma model. And I will say that we've looked at erythropoietin in close to 16 mammary carcinomas and have failed to see any effect on tumor growth, tumor proliferation, or tumor angiogenesis. Obviously the in vivo angiogenesis models involve a small number, about 25 animals, because those are difficult experiments to do.

We've also looked at darbepoetin using similar models in both R3230 and CT26 that was alluded to the Aranesp presentation, and using biodimensional models in over 200 animals with R3230 tumors have failed to see effect on tumor

growth, tumor proliferation, and angiogenesis measured by micro-vessel density.

So I agree with Dr. Farrell that this really needs to be studied further in in vivo tumor models because the interaction between tumor endothelial cells, that's really the only way to study it as opposed to studying endothelial cells or tumor cells separately in cell culture models.

DR. VIVEASH: I'd like to ask Dr. Losordo to make some comments relating to this issue.

DR. CHESON: Please.

DR. LOSORDO: I'm Dr. Losordo from Tufts University and St. Elizabeth's Medical Center in Boston. My expertise is actually in cardiovascular where we've been studying actually the stimulation of angiogenesis for various ischemic disorders. And that experience I think has bearing here because the patient population that we study, which is generally aged and, therefore, it is somewhat higher risk for cancer than the general population, forces us to analyze the potential risk of stimulating angiogenesis in those patients in

various in vivo models. And so as a result of our work primarily using VEG-F to stimulate neovascularization of ischemic tissue, we've also conducted studies analyzing the impact of stimulating angiogenesis in that context on tumor vascularization and tumor progression by implanting tumors into animals and then stimulating angiogenesis by exogenous administration of angiogenic cytokines and have found, in fact, interestingly, that the angiogenesis that's stimulated is very context-dependent, meaning that in the region where angiogenesis seems to be deficient, for example, in the myocardium or the lower extremity where we've induced ischemia, the exogenous cytokine can stimulate and improve perfusion of that tissue. While the tumor itself regresses under the influence of chemotherapy, the vascularity of the tumor does not change at all.

And so what we've learned in a number of studies, and that would now include also studies in which we're using progenitor cells from the bone marrow or peripheral circulation, to also augment

neovascularization of ischemic tissue, and in those instances either stimulating the release of those progenitor cells from the marrow or directly implanting them into ischemic tissue also does not influence tumor progression.

So I would say that at the same time the study of these things is of great interest and something that we'll likely do and continue to do in the context of generating safety data for ongoing clinical studies. However, it also seems to me that all those preclinical studies, while generating interesting science, will not trump the sort of clinical trial data that's being generated and continuing to be generated, which I think will influence patients and clinicians to a far greater degree.

DR. CHESON: Thank you.

Are there any other investigators who would like to comment on this particular topic?

[No response.]

DR. CHESON: Okay. We can move on then. Other questions from the panel? Dr. George,

please.

DR. GEORGE: I have a question for Dr. Luksenburg. That was a very thorough presentation, but I was a little puzzled by the way it was presented with respect to studies that showed a signal, those that didn't show a signal, and I was left trying to do my own mental meta-analysis of things to try to get some bottom line there.

Did you do such things? Or can you help us out in that way?

DR. LUKSENBURG: No, we didn't. We obviously reviewed data which had come in over a number of years, and much of this data was from registration studies which were a few years old, and we looked, as did the sponsors, for evidence of--we looked at the data that was there for overall survival and progression-free survival. But since the studies were not designed to look at that, we, you know, just--we took the data as it was. We did not do any meta-analyses.

In general, our stance is that the studies that are valuable are studies--except for

thrombotic/cardiovascular disease, the studies that will provide the best quality data for overall survival, progression-free survival, time to tumor progression, are those with homogeneous tumor populations. And it's really difficult to do meta-analyses with variegated tumor populations.

DR. CHESON: Dr. Keegan, did you want to make a comment?

DR. KEEGAN: Yes. Actually, that was one of our concerns with several of the meta-analyses presented, that it's trying to put the data in there in a way that--and take studies that weren't intended to look at these events and provide information. And I think the quality of many of the studies included in the meta-analysis are not the same in terms of what information they can give you on progression-free survival or on overall survival simply because of the heterogeneity and the lack of control. So that, you know, I think if we were to choose to select the studies, we would try and find studies that were actually designed to look at these endpoints and have the qualities that

we are recommending further.

DR. GEORGE: Just a quick follow-up. I certainly agree with respect to some of those endpoints, but survival should be a clear one.

DR. KEEGAN: I think when you look at some of those studies--and many of them are fairly small studies, and they enrolled any patient with any tumor at any stage in their treatment. It might tell us something about transfusion rates. That's what they were intended to do. But they weren't really intended to give us a good comparison of impact on tumors. These studies were really done in a manner not well designed to assess impact on tumor, just given all the incredible variables so much more important in terms of impact on survival and time to progression.

Presumably, if there had been thousands of patients, all of those variables would probably have been evened out. But most of the studies, as you look at them, are not particularly large, with the exception of the ones that we tried to highlight.

DR. CHESON: Are you satisfied with that answer, Dr. George?

DR. GEORGE: Yes.

DR. CHESON: Okay. Ms. Mayer?

MS. MAYER: As I understand it, FDA is coming to ODAC not to ask us to assess if there is any level of risk associated with these products, but given that there may be a level of risk, to look at what kinds of clinical trials need to be done. And I'm wondering since the data doesn't seem to be conclusive, since there are different perspectives, if it's useful for us to continue to try to assess what we know already from the trials. It's just a question, I guess a clarification of what our task is.

DR. KEEGAN: I think you're right in saying that if we thought we knew the answer, we wouldn't be asking you to reinterpret the data for us. I think we're saying that we don't think it's been definitively assessed and could we seek some guidance on how to really address this question.

DR. CHESON: And the way I see it is we're

being asked to do one of several things: one, decide if the data are of sufficient concern; two, if they are of sufficient concern, are additional studies warranted; and, three, if additional studies are warranted, are those the studies that are already ongoing, as clearly elucidated by Dr. Parkinson and his colleagues.

Dr. Bauer, please?

DR. BAUER: Yes, maybe I could just follow up on that point, because some of the studies we've heard presented clearly are driven by safety concerns in terms of showing safety, but, you know, as I understand the studies that are being proposed, there's really a desire to show improved survival. And I guess we haven't heard a great deal about the rationale really in terms of showing survival. I think we know about effects on radiotherapy and tumor oxygenation. We also know some of the high hematocrits targeted there clearly are detrimental and a desire in all the studies going forward to keep the hematocrit below certain specified levels. I guess I would like to hear

more about really the rationale for really at this point believing that there really will be improved progression-free survival with the use of some of these erythropoietic stimulating agents, or survival overall, especially given the clear detrimental effect, albeit it small, in terms of thrombosis.

DR. CHESON: I think that most of these are probably non-inferiority trials, if I'm not mistaken. They just don't want to show that there is a negative effect.

Dr. Parkinson, since you were reviewing all those articles, would you like to comment on that, please?

DR. PARKINSON: Dr. Bauer, you're correct in that we did not spend a lot of time talking about the rationales. The time was short. Sponsors were many.

There is a wealth of preclinical evidence which I think there are a number of people who could discuss in more detail. There is a significant amount of clinical evidence. I

referred to the Cochran meta-analysis, independent analysis conducted, as you're aware, by the Cochran group, which was considered to be suggestive enough--not definitive, but suggestive enough to warrant further trials. I mention that because I think it's important. It's dissociated from any product-related.

We've shown you and you've seen from other sponsors quite interesting suggestions of patient benefit in a number of defined settings, both of radiotherapy and chemotherapy. Additionally, the trials that I described which were not Amgen-sponsored were initiated by independent investigators based on their own independent assessment of preclinical and clinical data designed to test particular hypotheses, which are actually superiority hypotheses. These were not trials designed to look for negative survival signals with erythropoietins. These were trials designed to look for benefit based on--we won't give you our assessment of the literature--their assessment of the literature and what they believed

were important therapeutic questions to ask.

You know, we can go into as much detail--there are actually investigators here from each of those particular clinical groups. There are preclinical investigators here from at least two companies. There's a wealth of evidence to support this kind of investigation. What we see here today are two signals from two trials which you've heard described and analyzed in great detail. You can make your own judgment as to what the value of those signals is.

DR. CHESON: Dr. DeLap?

DR. DeLAP: Since we've also done--obviously we've done a number of trials in this area. We clearly have a rationale for proceeding in this area. I'd like Dr. Adrian Thomas to address our thoughts in this area.

DR. THOMAS: Good morning and thank you. Adrian Thomas, Vice President, Drug Safety, Johnson & Johnson.

I think our view and position is entirely consistent with Dr. Parkinson. It's entirely

reasonable to look for survival benefits with these products, and we indeed embarked on INT-76 as a result of results from INT-10, in which we demonstrated as a secondary endpoint of survival advantage and, more particularly, when we looked at the subgroup of patients with breast cancer, they seemed to benefit the most.

So I think the rationale for pursuing a survival advantage is there. It's clearly in the context of what the risks might be in terms of, from our perspective, thrombotic vascular events and the appropriate targeting of hemoglobin levels.

DR. CHESON: Dr. Weiss?

DR. WEISS: Just to, I guess, reiterate what has been said, there is a wealth of data, there's a lot of information, lots of variability in terms of the quality of the different studies, and I know it's a difficult question to try to sort through it all. I think we all agree, though, that there's some provocative and interesting information that might suggest some benefits other than just minimizing or avoiding transfusions with

erythropoietin products, and I think we'd all like to be able to document that and have that well established. I think there's maybe a belief system that erythropoietins are benign, with the exception perhaps of some slight increased risk in thrombotic events.

So I think the question here is--and we've certainly had lots of discussions with both Amgen and J&J. I think we all agree that there is room for further studies and further exploration, and the best way to try to show a survival benefit or disprove some type of disadvantage is to do it in the context of very good, well-designed clinical trials. And I really think that's really the focus of this particular meeting.

DR. CHESON: Dr. Parkinson, pleaseS?

DR. PARKINSON: Just to say we totally agree and that, although I indicated that these trials were designed to look for superiority in terms of the therapeutic beneficial effects of Aranesp in our case, I just had a little note from my statistical colleagues that, you know, just

because they're designed to show superiority doesn't mean that they can't have a huge value in looking for negative survival signals. So to keep myself statistically in good company, I wanted to point that out.

DR. CHESON: Thank you.

Dr. Martino?

DR. MARTINO: I just need to be sure I'm clear before I say anything semi-intelligent here. I need to be sure that I'm understanding the following: It occurs to me that there really are two trials that have shown tumor-specific bad qualities, and those trials share at least one thing in common, which is that they've aimed for a hemoglobin above and beyond what most of us considered usual and appropriate and normal and the aim, at least within this country.

And so as we think about what questions we need to answer, it occurs to me that that's a key point as to are we trying to show that something bad happens, are we trying to show that something good happens, but the question has to be framed

within those two hemoglobin objectives, as I understand it.

Am I clear in my thinking on the evidence that exists?

DR. KEEGAN: I think you express very well the same impression we have of the two trials that showed a negative effect and the lack of information we have in the other areas of definitive information on the safety. If the companies want to show that there's a survival advantage associated with their products, we have no problem with that. Our issue is really that we would like for them to definitively address whether or not there could be an adverse effect.

DR. CHESON: Dr. Brawley? Oh, excuse me. Dr. Brawley will defer for the moment.

DR. M. GEORGE: I just wanted to follow up on the previous question and reiterate that the clinical trial we are proposing is to assess the activity on one single tumor trial using epoetin alfa within the label, so in the anemic patient population; and, lastly, that we're proposing a

non-inferiority trial, which explains why the trial is so large.

DR. CHESON: Thank you.

Dr. Brawley--or Dr. Parkinson first, and then Dr. Brawley. Sorry, Otis.

DR. PARKINSON: Just relevant to that is that most of the trial results that I presented here today were done with clinical trials during the development of Aranesp prior to development of the actual label. Our current recommendations are consistent, as I tried to make clear in the talk, with the evidence-based guidelines, the recommendations from ASH, from ASCO guidelines, and from the NCCM guidelines and reflect current practice.

Investigation of anything beyond that is a matter for clinical trials and careful clinical monitoring with carefully designed scientific hypotheses. We would completely support that.

DR. CHESON: Thank you. And now, Dr. Brawley?

DR. BRAWLEY: Actually, this is sort of in

follow-up to what Dr. Parkinson just said. My understanding is that the current indication for these drugs is for supportive anemia that is due to either renal failure or due to chemotherapy. There is no claim in the package insert that these drugs improve survival in any disease. Correct?

DR. KEEGAN: That's correct.

DR. CHESON: Dr. George?

DR. GEORGE: I have a question. It's in the Procrit area, I guess either for Dr. Bowers or Dr. George--a different Dr. George. That has to do with the endpoint chosen in the new study in that you chose progression-free survival even though in the study on which this was based, I guess, the indication was--the problem seemed to be a decrement in overall survival at 12 months and no indication of any progression-free survival problems.

DR. M. GEORGE: Overall survival is going be a secondary endpoint in the trial, and the reason why we chose progression-free survival is as follows: First, progression-free survival is the

best way to assess if there's any effect--if there is effect, if any, on the tumor. Second, we are talking about a placebo-controlled trial so there might be significant crossover if the tumor progresses, if things change. So that's one reason after the crossover. The second reason, which may even more obscure the survival endpoint, is if the patients fail the first-line chemotherapy, the patients are going to cross over to another regimen, and that may also obscure the survival endpoint.

So we thought that carefully designed progression-free survival endpoint--and, again, I didn't go through the detail on how we are going to assess it, how meticulously it's going to be assessed, review by a blinded independent panel will give us better enterprises. And I'm just reminded that we will have 80-percent power for a non-inferiority trial in survival.

DR. CHESON: Dr. Feldman?

DR. FELDMAN: I'm just wondering, are there any data available or are there any trials

planned to address the issue of the use of erythropoietin products in cancer patients not receiving additional treatment?

DR. M. GEORGE: I'm going to also--on behalf of Johnson & Johnson, yes, we currently have an ongoing trial comparing placebo to Procrit in patients who have cancer and are anemic and not receiving chemotherapy. The study is ongoing. Survival is going to be assessed in that trial as well as progression-related endpoints.

DR. CHESON: Dr. Parkinson, you should just probably stand there.

[Laughter.]

DR. PARKINSON: Thank you, Bruce. Yes, we have ongoing trials in anemia of cancer patients not actively receiving chemotherapy. Again, very careful monitoring, data monitoring committees that are independent, all of that.

I'd like to point out also the particular design of the AGO Study that I mentioned earlier. Those are neoadjuvant patients. They are biopsied, therefore, prior to initiating chemotherapy, and

Aranesp therapy or not. And a major endpoint of the trial is actually pathological endpoint at surgery. So, in addition to the status of the tumor, there will be the opportunity to examine carefully for any evidence whatsoever of angiogenesis differentials between Aranesp and not.

I think it's a very powerful design. Investigators are very sophisticated and very aware of the importance of the biological results in addition to the clinical results in this trial.

DR. CHESON: Don't go away. What are the endpoints on the previous trials that you mentioned in the non-treated patients?

DR. PARKINSON: In the anemia of cancer trials, endpoints are predominantly anemia related, but follow-up is long term. Those trials were designed prior to any of these discussions, and--

DR. CHESON: Is it possible to update the statistics on those to look for survival?

DR. PARKINSON: Absolutely. I think that there are a number of things that one may want to do at the end of the committee's deliberations and

recommendations. Absolutely.

DR. CHESON: Thank you.

Dr. Carpenter?

DR. CARPENTER: I just wanted to comment on the survival endpoint in the previous study. It's very hard to show a survival difference in advanced breast cancer with any treatment. Even though many people think certain things may confer survival benefit, it's hard to do a study large enough and pure enough to find that because of the large number of chemotherapy, hormonal, other, and now biological agents that are available. So I appreciate the company's diligence in trying to sort that out, but I think their use of disease-free of progression-free survival as a primary endpoint is going to be a lot easier to interpret and is going to be available a lot sooner than trying to sort out what's going to be a complicated bunch of information later.

DR. CHESON: I think what Dr. George is getting to is some consistency among trials with enterprises which, looking from the various trials,

there was some lack thereof.

DR. CARPENTER: Yes, but since it's going to be done in breast cancer, that's going to be a particularly hard thing to do.

DR. CHESON: Understood.

DR. CARPENTER: Where if it were done in some other tumor where there were many fewer options for treatment later--and this is going to be done with first-line chemotherapy. It's going to be a complex situation that might not be there in other tumors.

DR. CHESON: Thank you.

Dr. Redman?

DR. REDMAN: Just to follow up on the issue of the tumor-specific nature of the trials in which there were negative signals, do the sponsors have any plans to evaluate these agents in non-solid tumors, in hematologic malignancies, other than erythroleukemia?

DR. CHESON: Dr. Parkinson?

DR. PARKINSON: Yes, the GELA trial, a very large trial, 600 patients with aggressive

non-Hodgkin's lymphomas by a well-respected, very accomplished, cooperative group in France, Belgium, and Switzerland.

DR. CHESON: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I wanted to add to what Dr. Carpenter said, that an additional set of confounding factors would be that in any randomized trial where you have epoetin in one arm and not on the other arm, you are controlling for that during the course of the study. However, at some point when those patients have a relapse and go on to other chemotherapy, are you going to still require that they do not receive epoetin ever during the course of the remainder of their survival? I think that would be very difficult to require, very difficult to control and enforce. So at some point on both arms, patients will be getting some of these products, and I think that that's an additional reason why overall survival is probably not an appropriate endpoint for these studies.

DR. CHESON: Good point.

Dr. Martino, did you have a question?

DR. MARTINO: A question to anyone from industry. Are there any known or presumed clinical parameters for which a hemoglobin above 12 is known or felt to be of value?

DR. DeLAP: Dr. Adrian Thomas of our Drug Safety Group will address that question for us.

DR. THOMAS: Adrian Thomas, Vice President, Drug Safety Johnson & Johnson. I think in addressing that question, the benefits that have been seen in the chronic renal failure population with erythropoietin therapy have generally been seen at levels of hemoglobin less than or equal to 12. And one can postulate that by increasing the hemoglobin level by whatever mechanism, by having an effect on--a positive effect on the tumor, but I think we've seen indications of positive effects on tumor outcomes in some of our earlier studies at hemoglobin levels more typically within the anemic range that we would treat patients in clinical practice. I don't think that we need to pursue high-target hemoglobins to look for aggressive outcomes.

I also want to make a point around the concept of tumor-specific outcomes. I think what we've seen today is three very large meta-analyses of lots of tumors, and that, in fact, I'd challenge the word "tumor-specific." What we have, in fact, seen in terms of a biological signal is something that isn't consistent with tumors. We've seen no effect on tumor response. We've seen no effect on tumor response. We've seen no effect on tumor progression. We have seen no effect in our studies of new target lesions. What we've seen is a consistent signal both within oncology and from the Besarab study of fatal outcomes linked to high-target hemoglobins --[microphone off]-- need to be considered as a pharmacologically plausible mechanism.

DR. CHESON: Dr. Demetri?

DR. DEMETRI: I'd like to make one comment as a clinician who has done some of the studies on also patient-reported quality of life where patients have given data to support the benefits of how they feel in terms of better hemoglobin levels

beyond 12, interestingly, as well as some of the preclinical evidence that might support better oxygenation at higher levels. Now, the latter is more theoretical in terms of clinical outcomes, but that was part of the rationale for the beyond correction of anemia studies. And I think that is one key element to those investigational strategies. But there are data in the other studies for supportive care for benefits at higher levels.

DR. MARTINO: So are you saying, then, that we know from patient reports that self-reports of quality of life is somewhat better when a hemoglobin above 12 is maintained? I just want to be sure I'm understanding you.

DR. DEMETRI: I would say that is correct from the non-randomized large-scale studies that I've conducted, my colleague Dr. Glaspy has conducted, as well as others, yes.

DR. VIVEASH: Yes, I'd just like to comment that there's associative data in a number of disease settings, not necessarily in oncology,

that suggest higher hemoglobins are associated with better outcomes. And, in fact, we are going to be doing some work in patients with chronic renal insufficiency. I'd like to ask Dr. Pfeffer to just talk briefly about that program.

DR. CHESON: Briefly.

DR. PFEFFER: Thank you. So outside of oncology, there are some indications that there is real equipoise here and we need to do more research. And as a matter of fact, with the burgeoning problems with diabetes and renal insufficiency prior to dialysis, anemia is becoming a big factor, and the epidemiology suggests that this is a comorbidity and co-risk. So we're undertaking, if I could just have one slide just to show you the magnitude of the effort--no, that's not--we're undertaking a 4,000-patient study of people who are anemic, have diabetes, and who have renal insufficiency, not in dialysis,. with very hard cardiovasculars to determine if we can improve their outcome. Obviously, with a trial of 4,000 patients and over two years of follow-up, we'll

have a great deal of patient experience, randomizing to a strategy to maintain the hemoglobin to 13 or leave it where it is under 11. So that's a strategy that's going forward, so more information is going to be forthcoming, and there still is equipoise in the cardiovascular community.

DR. CHESON: Odd name for a trial when only half the patients actually get treated.

Ms. Mayer?

MS. MAYER: Just a comment on the form of reference to patient-reported responses to having their hemoglobin level at a higher level. I wonder how those patients might respond if they knew that by doing so they might be increasing their risk for thrombotic events. That might color patient perception.

DR. CHESON: Thus the need for clear and accurate informed consent.

MS. MAYER: Absolutely. I would be interested to know if in the informed consent in that trial that was an issue that was explained to patients, or if those findings of a higher risk for

those adverse events actually came from that trial.

DR. CHESON: Well, those are also in the package insert, but I would assume that they are in the informed consent.

One last comment from Dr. Keegan.

DR. KEEGAN: Actually, I did want to put into context the studies that Dr. Glaspy referred on quality of life were uncontrolled studies. So there was no way to put information in context.

The second is that he referred to patients who achieve hemoglobins above 12, and we would look at that as something of a responder analysis. You know, patients who do well do well. I think that one should consider those single-arm studies with a great deal of skepticism and caution given the amount of missing information that's generally not there from patients who were not doing well.

DR. CHESON: We will have additional time for discussion during the discussion period. Right now why don't we take a ten-minute break and reconvene here at about 12 minutes of.

[Recess.]

DR. CHESON: We are ready to get started. Now you can sit down, Dr. Parkinson.

[Laughter.]

DR. CHESON: The next part of this session involves the open public hearing. No one has approached us prior to this meeting to express an interest in presenting. At this point in time, is there anybody who has shown up for this purpose and has not talked to us?

[No response.]

DR. CHESON: If not, then we will move into the committee discussion. I just want to reinforce, for those of you who are new to this, that this is an Advisory Committee to the Food and Drug Administration. We clearly do not work for them, but hopefully we work well with them.

We have been given a number of questions, which are on a piece of paper that most of you got. Dr. Keegan has modified this to a minor extent. Dr. Keegan, would you just like to mention what your modifications are?

DR. KEEGAN: It was just a clarification

of the concern that arose about placebo-controlled trials, and I think the earlier wording might have led the committee and others to believe that it was the companies who felt that it was not feasible. But our understanding is that it isn't the companies but physician investigators who have raised feasibility concerns. So we just reworded that.

DR. CHESON: Clearly, from what we heard from the companies earlier, they feel it is feasible.

We have a series of questions before us, some of which are more compelling and some of which are less compelling, if the previous question is a negative one.

We've already talked about the possible reluctance of physicians to conduct and enroll patients in placebo-controlled trials. Do we have some sentiment around the table here as to whether this is a possibility? Dr. Martino?

DR. MARTINO: I was just kind of pondering. I wasn't ready to answer. But since

you've asked, I think there will be physicians for whom it will be an issue. You watch a hemoglobin going down, and you worry about--and I think to some degree physicians will be able to tell which patients are in active therapy and which are not. So a placebo in this context is a relative placebo. It is not a placebo in the sense that there are no clues of who is getting what. You can't always anticipate, you know, what that hemoglobin going down or up is from. But, you know, to a reasonable degree I think there will be at least the assumption that one knows what one's patient is on.

That being said, do I think that there will be physicians who will be willing and unwilling to enroll in a placebo-controlled trial asking these kinds of questions? I think there will be physicians in both of those camps, but I think there will be enough who will recognize the importance of the question, assuming the question is properly framed. And I'm not entirely comfortable that I know that the questions have been properly framed in the studies proposed. So I

have more of an issue with are the studies asking the questions that I consider of importance. I'm reasonably comfortable that there will be physicians who will randomize.

DR. CHESON: Dr. Taylor?

DR. TAYLOR: I would agree. I think that they're going to be looking at the other risks that we're trying to elucidate, and they're going to be willing to take those. And I think some patients will be more willing to take blood than Aranesp.

DR. CHESON: Dr. George?

DR. GEORGE: I don't have anything to add on whether it's possible or not, except to state that it would be desirable to do this if it is practical.

DR. CHESON: Anybody else have any comments on this? Dr. DeLap?

DR. DeLAP: I think our major concern is just we want to get studies done, and particularly when we're looking at a 2,000-patient study, even relative difficulties in accruing patients can be an issue, particularly in a disease like breast

cancer where the therapeutic regimens can change over time.

The studies need to be done; they need to be done efficiently and relatively quickly. And so I think we do still have some concerns in this area, although I would agree it's not a complete bar, but it is certainly an issue that has to be considered in the design of these studies.

Could I just ask Dr. Cohen to speak on this briefly?

DR. COHEN: I just want to speak as a clinical investigator. I would not underestimate the challenges of conducting placebo-controlled trials. I would conduct them in Europe and the United States because, to echo one of the committee members' comments, there will be investigators falling into both camps.

Also, the way that the question is framed is absolutely critical. In order to get patients to agree to be enrolled in these trials, I think we have to postulate that there is a survival benefit in using these drugs. Of course, the trials are

also powered to exclude a meaningful decrement in survival.

And I think the trials will need to be conducted by very mature clinical investigators with meticulously written informed consents to portray the issues accurately to the patients. But they are feasible. There are unmistakable challenges that will require a very prolonged and multinational approach in order to get the job done.

DR. CHESON: Dr. Martino?

DR. MARTINO: Patients are already aware of the two trials that have brought this issue forward, and those of us that practice oncology have lots of patients who have called and written. And so it's not entirely an issue of placebo. It is also an issue of patients knowing this newer data who may not want to be randomized to the treatment portion of this. So, you know, it isn't exclusively a placebo issue in my mind.

DR. COHEN: And I think in that regard we need to explain carefully to the patients what it

is we're trying to do. We are trying to treat anemia. We are not going into correction beyond anemia. If we explain the issues carefully to the patients, they will be less afraid and more willing to participate.

DR. MARTINO: I need to pursue this a little bit more if you'll allow me. Probably the thing of greatest concern to me right now is it appears to me that perhaps the real issue at gut here is, in fact, the level of hemoglobin. That to me is a reasonable explanation to the discrepancy in the data. And with the exception of the diabetic trial that was presented a few moments ago, I have yet to see--perhaps I've missed it, but I have yet to see a trial in cancer that addresses what I think may be the issue.

DR. CHESON: From the sponsors, is there such a trial that Dr. Martino is looking for that has been--

DR. DeLAP: Let me clarify the issues that you're trying to address here, whether there is an expectation of a benefit in the anemic population

or--

DR. MARTINO: No. My question is: The two trials that have shown a tumor-specific negative effect, okay? Both of them dealt with aiming for a hemoglobin above, you know, the usual 12 or so, okay? That may be exactly the issue. That may be exactly the issue. And if that is exactly the issue, then the proposed trials aren't addressing that. And you could be doing all kinds of things and never getting at the issue.

DR. DeLAP: You're correct in that there is the one trial that addresses the target hemoglobin level prospectively. That was the Normal Hematocrit Trial, which was in renal patients, not in cancer patients. We do not have a trial randomizing patients to different target hemoglobin levels.

We do have--actually, if I could just call up our slide DE3, I think it is. We do have one experience in our clinical trials program that I think speaks to this, which is one of trials where we have the biggest issue with these TVE events and

possibly some survival impact is this small-cell lung cancer trial which was terminated prematurely, again, for TVEs.

Now, the interesting thing about this trial is that, as originally designed, the patients were treated to a target hemoglobin of 14 to 16. In October 2002, for reasons unrelated to looking at any data but just that that seemed to be too high of a target, the target was modified to 12 to 14. Patients were randomized both before and after the amendment. Patients were treated for similar durations with erythropoietin therapy both before and after the amendment. And yet you can see that in the pre-amendment group, although the numbers are small, in the pre-amendment group 42 percent of the patients in the erythropoietin alfa arm had these TVE events. And in the post-amendment group treating to the lower target--which is still a higher target than we might like to use now, but, clearly, at the post-amendment point, it was 10.5 percent. So that's suggestive evidence, at least in a cancer population, that we're following the

right path by treating to a lower hemoglobin target.

DR. CHESON: Do you have any information on what the median hemoglobin was that was attained in the two arms--not in the two arms but in the two patient populations?

DR. DeLAP: Let me refer that to Dr. Adrian Thomas, who has more details about that study.

DR. THOMAS: I think this is certainly an interesting question. What we observed pre-amendment is, in fact, that the hemoglobins in the patients who developed TVEs were around the 15 level, and following the amendment the hemoglobins were around the 12 to 13 level. And so I think we can see, although not pre-defined, we can see some empiric evidence of the effect of changing the target hemoglobin level.

DR. CHESON: Dr. Parkinson?

DR. PARKINSON: Just a comment that, as I indicated earlier, the clinical trial results that I demonstrated were, in fact, conducted with trials

that took patients to target hemoglobins of 13. That doesn't reflect the current practice, but that's, in fact, what was the operative practice during the conduct of those trials. There are other reasons to go higher, which we could get into. Professor Overgaard is here, and he spoke to me at the break about the rationales for doing that. But I think that's not where you're coming from, Dr. Martino. Is that correct?

DR. MARTINO: I'm trying to figure out what the real question is that we want to answer here, and I guess one of the questions is: If you aim for 12, or thereabouts, is there an effect on tumor biology, survival, whatever endpoint you want to look at? And that's a very worthwhile question.

DR. PARKINSON: Okay. In that case, could I call upon Professor Overgaard, who is here from the Danish Head and Neck Cancer Study Group someplace? He told me he--oh, there he is. How could I miss you?

DR. OVERGAARD: My name is Jens Overgaard. I come from Denmark. The reason for this was that

earlier, before the break, there was a question as to what are the rationales for having a survival benefit of these trials here, and it was said that there were plenty. But it is fairly simple, basically, because this is a matter of oxygen delivery. And we must assume that what we really would like to have is more oxygen brought forward by more hemoglobin into the tumor. And that oxygen should do something in benefit for outcome. That means it should interact with the treatment, which will be better in one way or another if there is more oxygen delivered. And what you said, people know that might be very well the case because hypoxia is a key issue in the response to radiotherapy.

Now, if that treatment will be better issued in turn also influence the survival in the (?) , these are the fundamental simplicity of the design of the rationale. In such studies and the one we are doing in radiotherapy, it is a matter of lifting oxygen delivery from one level to a higher level. It is not a matter of lifting to some

specific level of 12 or whatever. It's just a matter of having a differential. And the only thing that puts a limit on that differential is the ceiling. So what we have to discuss here is more where is the ceiling, where is it halfway up to the ceiling, because we need to have the room for excess oxygen delivery if we have to do survival benefit trials.

DR. CHESON: Dr. Keegan?

DR. KEEGAN: Dr. Martino, is your question--and I think it's our question, too--that if studies are done using a higher hemoglobin, permitting or encouraging a higher hemoglobin target and they show that there is, in fact, a detrimental effect, we will have no information on whether or not at the approved dose and for the intended and licensed indication, which is avoidance of blood transfusion, whether or not these are safe? And so by not starting first at the approved dose and schedule and in the currently indicated population we may be actually prolonging our time to getting an answer?

DR. MARTINO: In the ideal world, what I'd like to see is both of these hemoglobin dose levels addressed and in each of those, the same question asked: Is it good? Is it bad?

Now, that's what I'd like in the ideal world. I do recognize that there's another issue here, which is a trade-off in the sense that it already is fairly apparent that there are more complications as you increase the level. So you get to this issue of, you know, relative good and relative bad. But it really is each of those levels which are of concern to me.

DR. VIVEASH: Could I just comment? I decided I'd give Dr. Parkinson a break for a moment.

He presented a number of studies, forward-looking studies, some of which are ongoing. The vast majority of those are actually using the current label target hemoglobin so we'll address the one question. The DAHANCA Study actually goes to a higher hemoglobin, and we feel both approaches are valid as long the studies are appropriately

conducted with the appropriate endpoints and appropriate safety monitoring.

DR. CHESON: Thank you.

Dr. Redman?

DR. REDMAN: This is regarding randomization, especially to Amgen and the European studies. Your target hemoglobin is somewhere between 13 and 14, it sounds, in most of the studies--the small-cell, the breast. I don't know what the policy is or what the benefit is in Europe. In the United States, the blood bank will not release blood for a hemoglobin of 13 unless the patient is actively bleeding. So how are you controlling for the transfusions in those?

DR. PARKINSON: These are not hemoglobin-controlled trials. These are trials of Aranesp to specified levels versus transfusions as used in regular clinical medicine. That will differ in different settings.

DR. CHESON: Are there any more comments? Ms. Mayer?

MS. MAYER: I'd like to return to the

issue of accrual to randomized trials. I have some concerns that patients may have difficulty submitting themselves to randomization, whether or not they're randomized to either arm, actually, because I think patients tend to come to their own conclusions in situations where it's really unclear and where there are complex risk/benefit ratios like the ones we're discussing. And in those situations, I think patients like to have choice. You know, given that this is on the market, some may choose to have transfusions and to avoid EPO until these issues are resolved, while others may decide it's a reasonable risk to take.

But the real question is: Will they be willing to be randomly assigned? And I think that will be also mediated by the kind of media coverage this gets and how it's presented to them. It's a really problematic issue because the drug is out there.

DR. CHESON: Okay. If we could summarize the first question, which boils down to: Is it reasonable to request that placebo-controlled

trials be conducted to assess the risks of or rule out a negative effect of EPO on time to progression and survival? And my feeling is that we all feel that it's not only reasonable but it's probably essential. Is that the sense of the committee?

VOICES: Yes.

DR. CHESON: Antonio?

DR. GRILLO-LOPEZ: Perhaps with the exception noted earlier in our discussion that overall survival may not be the best endpoint, but time to progression or progression-free survival could do it.

DR. CHESON: Okay. Dr. Redman?

DR. REDMAN: I'm sorry. The question between time to progression versus survival, is that what you're asking? Or just--

DR. CHESON: No, I was asking the concept of--I wasn't asking. I was summarizing the concept of doing the randomized controlled trial, whatever the endpoint we decide to be, is not just reasonable but is necessary.

DR. REDMAN: Yes, okay.

DR. CHESON: Now, as far as the endpoint, as we are going to be discussing this afternoon and have discussed in the past, this endpoint may differ from tumor type to tumor type. And there are pros and cons, as we've heard passionately from Dr. Grillo-Lopez, about one endpoint versus another, PFS versus overall survival. And Dr. Carpenter made that point also in breast cancer. It sounds like progression-free survival is probably a better endpoint.

Can we do this trial in the U.S.? The second part of this. And I think we heard from our patient advocate that it might be difficult, but I think we also heard from the sponsors that these trials are accruing, and hopefully they will succeed. So I think the answer to that one is probably also the--

DR. DeLAP: Could I ask Dr. George to -- [off microphone].

DR. CHESON: Please.

DR. M. GEORGE: If I have the chance to comment on accruing patients in the U.S., if I

think it's feasible, it's feasible. How feasible it is, that's the real question, because we want to have the answer to the question really, really fast and not wait. So we can have a trial up and enrolling patients in a placebo-controlled trial (?) period of time and wait for the answer or do it in a different way and including patients outside of the U.S. So the primary reason to the trial outside of the U.S. is speed.

DR. CHESON: Ms. Mayer?

MS. MAYER: I have some concerns, I guess, about our making use of patient populations outside the United States to avoid the ethical issues that may arise in doing trials here. It has to do with disclosure, I suppose, and how patients interact with their health care systems. I don't think it's a simple issue that we should just glide right over and say, yes, do the trials abroad.

DR. DeLAP: We're very sensitive to these ethical issues and, in fact, it's certainly the company's position--I'm sure it's also the position of Amgen--we will not pursue a study in a

particular region because, you know, there are ethical questions. It has to be a fully ethical and well-justified trial wherever it's done.

DR. CHESON: Dr. George--

MS. MAYER: Can I do a follow-up on that? I just want to point out that in countries where the blood supply is not as safe as it is in the United States, this may be a particular issue.

DR. PARKINSON: Just a comment. We work globally. Cancer is a global problem. It is solved by global cooperation. We work under the same rules globally, just as Dr. DeLap emphasized, same kinds of informed consent, same practice. We would not work in a place where those kinds of parameters were not in equipoise.

And with respect to the ability to work in the United States, as we heard, with mature investigators who can ask questions responsibly, even in the placebo-controlled setting, I just wanted to re-emphasize we've just accrued 145 patients over three weeks to a placebo-controlled study of Aranesp in chemotherapy-induced anemia.

Is it as--no, it isn't as easy, of course. It's never as easy in a randomized trial as it is in a single-arm trial. And it's never as easy in a randomized trial when there's a placebo control. But sometimes it's actually necessary to adequately--and we believe our responsibility is to answer these questions definitively. We believe patients have been confused by the reports of these studies, and we believe that it's our responsibility to them to answer this.

DR. DeLAP: To the extent that we're looking at a more homogeneous population, we've certainly done a lot of placebo-controlled trials in chemotherapy-induced anemia or in non-chemotherapy-induced anemia in cancer patients, we're studying that also in the U.S. in placebo-controlled trials. But when you start focusing in on a specific population with a lot of criteria to get as homogeneous a population as possible, you can't cast as broad a net as you can for chemotherapy-induced anemia.

Again, we're just saying--I think we're

all saying the same thing, but practicality demands that if we're going to do this kind of work efficiently, it has to be global.

DR. CHESON: Dr. George?

DR. GEORGE: I just wanted to clarify one thing. The FDA can correct me if I'm wrong, but there is nothing in the regulations or guidelines that prohibit exclusive use of, in fact, foreign data, if you want to call it that, in proving things, right? That's one point.

DR. KEEGAN: Yes, that's correct.

DR. GEORGE: But with respect to that little broader issue, it's certainly the case that medical practices and cultures differ in countries that would make it possible or more likely that you would enter more patients from one country than another. That's inevitable. And I don't think that has anything to do with ethics unless you believe there's some kind of universal ethics that doesn't--you know, that applies to all countries, which I think, you know, with respect to equipoise, is not really true. That is, it's been shown in

other studies that the Europeans are more skeptical of certain kinds of things that maybe we do, and vice versa. So it doesn't bother me, as long as, as Dr. Parkinson says, you're dealing in an area that's accepted all the usual rules and regulations.

DR. WEISS: If I can just add, it's also just an issue of whether or not you can generalize, as we've had some discussions, the results across--you know, overseas to U.S. populations and whether or not there are significant differences in practices that would make those results somehow not applicable.

DR. CHESON: Well, obviously, there are some agents which will require some pharmacogenomic differences, as we heard back last year with one particular drug that was more effective in one country than in another. But, in general, this shouldn't be that big a problem.

Dr. Martino?

DR. MARTINO: I want to deal a little bit with the issue of whether data which is generated

in Europe or elsewhere is accepted in this country. You know, we have a very mixed history in this country of what we accept that isn't generated here.

Now, there are things that the companies themselves can do to either enhance this separation or to not allow the separation. And so I just want to remind them that when their data is summarized and presented, whatever the results are, it becomes critical to present the data as it is meant, which is one study done internationally. Oftentimes with large studies, especially when the results aren't exactly what you had hoped for, there's a tendency to then separate the American group and its results, the European group and its results, and they're not always concordant.

And so there are ways to actually either accentuate the American desire to not accept non-American results, depending on how one handles the presentation of these data.

DR. CHESON: Point well taken.

Dr. Keegan?

DR. KEEGAN: Just one last comment about the European data. Dr. Weiss has summarized pretty much our position on that. But one nuance here is that Procrit is not approved or not marketed in Europe. So if there was a study either that had European sites or a separate European study, it might be conducted with EPREX rather than Procrit. We've already taken the position that these are class effects, to some extent, and we think it would at least address questions in the class. Would the conduct of a study in which certain patients received a related product in the class different in Europe than in the U.S. pose problems, or for instance, if the study was conducted entirely in Europe, the data were obtained with EPREX, would that be problematic, do you think, to the committee in looking at--

DR. CHESON: Well, the reason we're here is two studies conducted with a different product that's caused a flurry in this country. So I think the opposite would probably hold true. If those studies had not shown this potential problem, we

wouldn't be sitting here today.

So I personally would find these very similar compounds, the data from them to be applicable on both sides of the puddle.

Dr. Feldman?

DR. FELDMAN: Just one very brief comment, made perhaps out of the naivete of a non-clinician, but I was a little bit concerned by the comments of using European studies because it could be done faster. I don't think the speed of getting the answer should really be an issue here. I think the idea is to get the best answer and most complete answer to the questions.

DR. DeLAP: At J&J we agree with that, that speed per se is not the issue. Getting the best answer in a reasonable period of time is. But there is some interrelationship because there are changes, for example, in breast cancer them regimens. So if you're trying to have a study that has a relatively homogeneous approach to the treatment of patients, and then that study turns out extending out for six or seven years, it may

impact the quality of the study. Also, I think there is a strong desire to address this question as promptly as we can. Again, speed at all costs, no. But speed to get a good answer, yes.

DR. CHESON: Dr. Redman?

DR. REDMAN: I just want to make a comment about speed. As a clinician, I think if the trial is adhered to, the quicker the accrual goes to the trial, it is best. Speed does not imply a bad trial.

DR. CHESON: Dr. Reaman?

DR. REAMAN: I would echo the comment on speed. But for clarification, are we talking that trials will either be done in Europe or in the United States? Or if this really is a global initiative, would they be international trials?

DR. CHESON: To finish my summary of this before moving on to the next question, yes, these trials are necessary, and I think the studies are ongoing on both sides of the ocean, and that's how they should be done. And hopefully they will be completed alacrity in both situations.

Now, I think we already got to the other question, that if there are so many variables affecting response rate, survival, and safety, the tumor type, et cetera, et cetera, if you had one large trial that we all agreed on the endpoints, that was conclusive in one disease, since we are all here considering homogeneity of patients, would that one trial answer the question for all diseases? Or do we require now multiple trials in different tumor types?

I personally feel that if we can answer it in one very nice, well-done study in a common solid tumor, that would answer it for me. Dr. Martino?

DR. MARTINO: But it seems to me that the companies have already made these decisions, that, in fact, they are doing several trials in different tumors, and I have to say enough time has passed that I only remember a few of the studies.

And so I would be really happy if someone would succinctly review those trials because I thought what was wanted from us was our thoughts as to whether these trials were good, bad, or

indifferent.

Now, granted that they're already in progress, perhaps my views on any of them are irrelevant.

DR. CHESON: Could you state your name and affiliation, please?

[Laughter.]

DR. PARKINSON: Well, just to remind you about the clinical trials that we discussed, the first is an Amgen-sponsored trial in small-cell lung cancer, and 213 patients of the anticipated 600 patients have been accrued. That's placebo-controlled.

The next trial is the AGO trial that I talked about. That's a neoadjuvant breast cancer trial being conducted by the German Gynecologic Oncology Study Group. That's a study with an anticipated enrollment of around 700 patients, a little more than that, of whom 400 patients have already been accrued. I indicated that that interim analysis, which will include pathology endpoints, will be looked at by the Data Monitoring

and Safety Committee in approximately five or six weeks.

The third study is a study by the Western German Study Group, and they'll be studying adjuvant breast cancer patients, and that trial has just started accrual.

The fourth study, the GELA Study, is a study in aggressive non-Hodgkin's lymphoma--oh, there it is. Thank you. I was doing this by memory. This is so much easier, actually. The GELA group is studying patients with non-Hodgkin's lymphoma randomized to either dose stance or standard chemotherapy plus or minus Aranesp or no epoetin.

And then the final study is being conducted by the Danish Head and Neck Cancer Study Group. You've heard already this afternoon from Dr. Overgaard about the rationale for that study and the fact I've indicated here that 260 of the 600 patients have been already accrued, with a safety interim analysis already completed and the study continuing.

DR. DeLAP: If we can just quickly come back to the slide from Dr. George's presentation.

DR. M. GEORGE: Thank you. This is a slide I showed you earlier in four separate tumor types where we have ongoing or completed clinical trials where a tumor-relevant endpoint is the endpoint.

We have many other trials, some very, very large, including thousands of patients, in tumor types like breast cancer, adjuvant breast cancer, or Hodgkin's disease. Those trials enrolled 1,000 patients, but are not geared toward survival but assessing correcting anemia and quality of life. So I'm not going to present any of those trials, but the list very, very lengthy.

In the tumor type, where we have relevant endpoints are head and neck cancer. The (?) of the seven(?) trials has enrolled, is completed, has enrolled 301 patients, is currently under follow-up, and the primary endpoint is disease-free survival at two years. We will have those data very, very shortly.

The RTOG study is a study in patients also receiving radiation therapy for advanced head and neck cancer. The study started with radiation therapy alone, then was amended to include chemotherapy also.

As mentioned earlier in Dr. Bowers' presentation, the study was stopped to accrual because of the increased incidence of TVE. And when the Data Safety Monitoring Board of the study reviewed the interim data, they thought that in their trial there was no possibility of showing a benefit. Those patients are in follow-up, and we will have the data shortly

In non-small-cell lung cancer, there is a pretty large study in Germany called GER-22, which is planned to enroll 612 patients. Current enrollment is around 250 patients, and the study is ongoing. The last Data Safety Monitoring Board meeting was a few weeks ago, and the trial is still ongoing. The patients received chemotherapy first, followed, after three cycles of chemotherapy, by radiation therapy. The patients who have locally

advanced Stage III untreated non-small-cell lung cancer--

DR. CHESON: We're going to need to limit the details on this, because the point was: Do we need more than one trial? And it's quite obvious from both of these slides that we already have many, many trials going on.

DR. M. GEORGE: And we're proposing a large trial on top of all those trials.

DR. CHESON: Thank you.

DR. KEEGAN: Dr. Martino, just to clarify the sequence of events, as we became aware of this data, we contacted the companies to determine what studies they had available or planned that might speak to this question. But the purpose of this committee is to comment on the qualities of such trials that you think should be incorporated to provide convincing data. So that if, in fact, although they have many trials that are in the works or ongoing, if you find that they are lacking critical elements, we would like to hear that so that we can negotiate with the companies the

appropriate trial to get the data. So that if you see that there are critical elements missing, that's really why we need to talk about this. They may have studies going, they weren't intended for the purpose we are here to discuss today, but they may fit the bill. If they don't, we would like you to say so.

DR. CHESON: Clearly, we haven't seen the protocols, but based on what we've seen in the way of presentations, there are quite a number of studies for which the primary endpoint are those that the FDA is looking for. They are accruing patients, and so from my perspective hopefully at least several of these out of the very large number will be addressing the important issues that have brought us here today.

First will be Dr. Redman.

DR. REDMAN: I agree with Dr. Cheson. The studies are ongoing. In order to analyze a study based on one slide is next to impossible. It lacks a lot of information. But I think looking at the companies that are doing those trials and the

investigators that are doing them, I certainly don't have a problem with what's been going on.

DR. CHESON: If you'd like us to look at some of these protocols with you and make sure they have the appropriate elements, we'd be glad to do that in our advisory capacity.

DR. WEISS: I'm just wondering if--Dr. Martino started this discussion earlier on about the issue of whether or not you should study a population--everybody agrees, I think, that a homogeneous population is important, but whether you should try to address the issue if you have a target hemoglobin of sort of the standard range that's in the label, which is approximately 12 or so, versus a strategy of pushing to the higher hemoglobins. It seems like there's some diversity of opinion around the table about what are the important questions or how the study is to be designed, what should be the strategy in terms of the targets. And just looking at the slides that Dr. Parkinson presented where they summarized on the slides what the targets were, there were a

number of them that basically strove for a target of about 14. Obviously, it's a little bit different, I guess, if you're talking about men versus women and what trials. But, in general, you're talking about 14 except for the one Danish trial which would be achieving a target of 15 or pushing to try to, I guess, taper or stop the dose if the hemoglobin goes to 15.

We didn't really hear from Dr. George about what the targets where in those numbers of different ongoing trials. So I'm just wondering if those--except that the one that they're proposing to do in breast cancer, which is actually designed to target a hemoglobin that actually is at the recommended label of hemoglobin, which is about 12 or so.

So I'm just wondering--I mean, it seems like there's a smattering of many different trials and many different tumor types, some looking at a target of one versus a higher target. There's sort of a whole hodgepodge of things, but is there a particular issue with respect to target that--I

guess I'd like to hear from the committee whether or not there's a particular target that we should really be asking the companies to look at in terms of the strategy in terms of trying to assess benefits and risks.

DR. CHESON: Dr. Parkinson, a quick answer.

DR. PARKINSON: Just one quick clarification, for the five trials our target of 13, okay? Hemoglobin, withheld if above that at 14. That's European label, so that's guidelines in Europe. The fifth trial is the Danish trial. Just a clarification.

DR. THOMAS: As a further point of clarification, we have amended all ongoing protocols in this area to reduce the target hemoglobin levels to a uniform level, and our view would be that to do one at a higher level is to do a study on TVE, not on benefits in terms of tumor responses.

DR. WEISS: I guess it goes back to something that Dr. Martino raised earlier, which is

that many of these studies, with the exception of just a few minor ones, are actually now tapered down to looking at outcomes within the recommended label target. Whether or not that--you know, whether or not you have comments about that, because I know you raised that issue earlier, whether that's something that should actually be on the table to consider. If there are no issues at those targets, is it appropriate to try to push to higher targets to evaluate potentially other benefits in terms of better survival and other outcomes?

DR. CHESON: Dr. George was next.

DR. GEORGE: Well, my comments weren't directly related to that.

DR. CHESON: We want to finish this first.

Do you have a comment related to this?

DR. CARPENTER: It would seem at least logical to me to approach the question about tumor benefit or risk at the levels currently targeted now. If we then find either some beneficial effect or at least exclude a detrimental effect, that

would leave the table open to go to a separate study that compares two levels. But it seems to me that if we try to answer the two questions at the same time, we're going to get numbers problems. We're going to get problems with speed of accrual that are going to make it harder to get a timely answer to the first question.

DR. CHESON: I agree with you. It's my feeling that we would first like to have our level of comfort at the indicated dose of the drug that it was safe and efficacious. If there are questions, such as the head and neck study we've heard about, of higher doses, then those are investigational doses that can be explored separately. But I'd be willing to hear from my colleagues if they disagree or agree.

Dr. Reaman?

DR. REAMAN: I absolutely agree, and I think if we're going to be looking at safety at the currently recommended indication, then we really ought to consider excluding those trials in which there is a target higher than what is the indicated

target in the package insert.

DR. CHESON: Any other comments on this particular point?

[No response.]

DR. CHESON: Then we go to Dr. George.

DR. GEORGE: Well, the point I was going to make was in reference to these issues of the design. And it has to do with making sure that what we're really trying to do is eliminate a detrimental effect of some magnitude, I think. And that can be done in studies; even when it's some kind of superiority design, you can still make sure you're looking at things that--because some of the trials that even were presented showed--they were presented as if there was no difference. But, in fact, if you look at things just as simple as the confidence intervals on certain things like hazard ratios, they didn't exclude something that might have been pretty detrimental, even though the curves were superimposable and looked exactly the same. That's the problem with these non-inferiority kinds of designs.

But I think we have to keep that in mind, that that's really what we're after here. I mean, if it works, great. But what we're trying to do is make sure it's not something bad.

DR. CHESON: Ms. Mayer?

MS. MAYER: Perhaps I missed one of the trials, but the BEST Trial was done in first-line metastatic breast cancer. The proposed two breast cancer trials I believe are both adjuvant trials.

My question is: Is there a concern that you might not in adjuvant trials capture the same effect that appeared perhaps in the metastatic trial?

DR. M. GEORGE: If I may try to answer your question, the proposed trial is not a trial in adjuvant breast cancer, but it's to treat patients who have metastatic disease. There are some major differences between the BEST Trial and the proposed trial. The first one is the patients are anemic at entry. The second is how we are going to assess endpoint. The third one is the duration of therapy with erythropoietin. In the BEST Trial, the

duration of therapy was one year targeting high hemoglobin level.

DR. CHESON: Thank you.

Dr. Taylor?

DR. TAYLOR: I want to support the idea that we are looking at more than one tumor because I don't think we do know exactly why people may do worse. I don't think we have an etiology or a mechanism for which the erythropoietin product may be adversely affecting people. So I think that looking at different populations is not a bad idea.

The other reason is that extrapolations are already made in that a lot of women receiving adjuvant chemotherapy are on erythropoietin products, and we need to know is it just the fact that a woman has metastatic disease, is sicker, and has other predisposing factors, or is it erythropoietin?

DR. CHESON: Okay. Well, that question has answered itself in that we have so many trials going on in so many diseases.

Dr. Bauer?

DR. BAUER: I think there's a fairly narrow margin here, especially from the safety. I think the clear thread is that, you know, you drive hematocrits up higher and you get more thrombogenicity. And so I think, you know, the trials, I guess, we're all talking better built in with hemoglobin limits which are lower than those that might have been desired, say in some of the radiotherapy trials to improve oxygenation, especially when you're talking about trials where you're entering people who will probably have normal hematocrits who would normally not be candidates for erythropoietic growth factor. Your margin in terms of driving up hematocrit is not all that great.

But I think in response to the query, I think you have to have clear limits in terms of keeping hemoglobin either below 14 or certainly target 13 and stop, or something, for patient safety, for protection, because you just don't want hematocrits to go uncontrollably high.

DR. CHESON: Okay. So, to summarize the

answer to this question, there really is no need to summarize this because we already have multiple trials going on. And if you have concerns about the specifics of the trials, I'm sure you have the protocols, and if you need some of us to go over them in our particular areas of expertise, I'm sure my colleagues would be glad to do that.

The next point I think we discussed a little bit earlier, but maybe not conclusively, and that is, the FDA has recommended that trials be conducted in primary tumors where the EPO-R status, whether it be expression, ligand, affinity, and functionality of malignant cells in tumor vasculature is known.

That's going to be tough. I think we heard some very eloquent information this morning that, A, it's going to be difficult and, B, it may not be totally relevant, but I'm opening the floor to additional discussion as to whether this is--it's a nice idea, but is it doable in a variety of circumstances? Feasibility, technicality, and is it really relevant? Dr. Doroshow?

DR. DOROSHOW: Yes, I think that although I'm usually a proponent of obtaining fresh frozen materials for correlative studies, I think that this is not feasible other than in the neoadjuvant setting. I think the trials are of such size that at most you will get a very small fraction that will be potentially not reflective of the outcomes you're trying to study. That's even irrespective of the elegant data that we were presented with earlier about lack of relevance.

DR. CHESON: Okay. So does anybody else want to comment on--could you please identify yourself?

DR. ROSENBERG: Yes, I'm Amy Rosenberg, the Director of the Division of Therapeutic Proteins. And while I agree I think it would be difficult to characterize these receptors, especially functionally, I don't think it's impossible. Techniques of laser capture and micro-dissection and protein arrays that can assess via antibodies--antibody arrays, phosphorylated proteins, are available. I think rather than

conclude that it's impossible, perhaps it would be instructive to find out whether using more novel, new techniques, it's possible to look at this. Because, otherwise, we're not going to know anything about the biology. We're not going to know--you get a clinical result; you're not going to know how to correlate that with functional effects, especially for tumor activity.

So I think it's actually a critical point. I think we'll learn very little except a clinical outcome if we don't try and pursue it. And I think there are ways to pursue it, and I think that those should be looked into.

DR. CHESON: My concern is that these are multicenter and perhaps multinational studies where--I guess our colleague who is the expert over there might want to comment again about whether there are enough reference laboratories that could do these or the samples could be shipped in, what the feasibility is for shipped samples versus on-site samples, et cetera, et cetera.

DR. LODISH: Well, as I tried to indicate

in my earlier presentation, we're at a level of research rather than a robotized, commercialized assay that could be done reproducibly. I think things like laser capture to isolate tumor cells, arrays at an ultra-micro-level clearly are the wave of the future, but they're not practical now. And certainly in a clinical setting I couldn't advocate for them at all. And--well, let's end it there. Ten years from now, we may revisit the system.

DR. CHESON: Thank you.

DR. DeLAP: A comment?

DR. CHESON: Okay.

DR. LEVINE: Mark Levine, McMaster. The proposed trial is in women with metastatic breast cancer. It's very difficult to get fresh tissue in those patients. If there's chest wall disease and so on, it's possible, but our experience, many of us in the room, of doing trials in metastatic breast cancer, it's not like adjuvant. It's not early-stage breast cancer. So I don't think it's feasible.

DR. CHESON: I think the only setting

where it may be possible is in a very limited single institution or maybe a couple of institutions who are part of the large cooperative arrangement doing it on a very pilot, very experimental basis as an exploratory issue. But to do it as part of this sort of trial, with these sorts of trials, and which diseases would you do them in, again, if you talk about micro arrays and those things, they're going to differ from disease to disease, stage to stage. If you look at lymphomas, even within histology of multiple different array patterns, I'm not sure that we are quite there yet.

Dr. Keegan, did you want to say something?

DR. KEEGAN: I think that the sentiment behind this question was really one of generalizability. If we do a study and we see a negative outcome, an adverse outcome, do we generalize it to all tumors? Similarly, if we see no evidence of an effect, do we generalize it? And this was one attempt to try and look at possible mechanisms by which this might be affecting it.

If there's agreement that it can't be done in the clinical trials due to lack of technology, I think we have left open the possibility of trying at least to characterize different tumor types through tissue banks or other means so that we can put the results of different trials in context, particularly if we get answers that are not consistent between different tumor types. I think that was our concern also in terms of how one chooses to select the tumor types to begin with.

DR. CHESON: I think this is an excellent target for FDA-directed funded research.

[Laughter.]

DR. CHESON: Dr. Brawley?

DR. BRAWLEY: You know, I was wondering, are we going to start doing a number of biopsies on perhaps thousands of patients that are unnecessary? If you have to go get the tissue, you know, for clinical reasons, that's one thing. But to just do the biopsy for the purposes of doing the biopsy for science, that's another issue beyond the logistics of how the tissue is going to be handled, you know,

minus 70 or liquid nitrogen and so forth, and the transport and logistical issues. I think we have to worry about that ethical issue.

DR. CHESON: Well, a lot of those questions, such as transport, et cetera, can be done on non-human tumor samples.

DR. BRAWLEY: Right.

DR. CHESON: But, for example, doing biopsies, the CLGB is going to be conducting a lymphoma trial looking at micro arrays and diffuse large B-cell lymphoma prospectively, and it will require needle biopsies of patients who have already been biopsied. And we expect it's going to hamper accrual because a lot of people won't want to be re-biopsied, but to some the information will be of sufficient importance that it may be of interest and whatever.

Dr. Feldman?

DR. FELDMAN: Yes, I'd like to separate out the issue of feasibility with that of relevance, and I agree that it probably is not a very feasible thing to do, whether it's in a

clinical trial or samples shipped to research laboratories.

But I would disagree with those who think that this may not be relevant, and I think it would be very important, whether it be by FDA-directed research or some other preclinical way, to find out the precise relevance of these EPO receptors on tumors.

DR. CHESON: Absolutely. We're not disagreeing with that.

DR. FELDMAN: Particularly in those tissues where normal tissue does not have EPO receptor and tumor does, which includes the breast.

DR. CHESON: We agree that is a scientific question of importance. It's just the feasibility in a large-scale trial that we were considering at the moment.

Dr. George?

DR. GEORGE: Just to follow up on something Dr. Keegan said, just a warning. I predict that you will get results that are going to be hard to interpret. They're not going to be

entirely consistent. So it may be how you think about this ahead of time. It may be a good time to do that, how you're going to put all this together.

DR. WEISS: We'll come back to you at this committee when those results are all there.

DR. CHESON: We will look forward to it.

[Laughter.]

DR. KEEGAN: I think to go to your point and to correct something that you said, Dr. Cheson, in fact, we have only begun to look at this information, and we have not even reviewed the protocols because most of these were actually not company-sponsored trials. We really haven't gotten to that yet. So we have not--I mean, this is very timely advice for us in looking and giving guidance and the necessity for getting additional information. So we will look at it with an eye to getting inconsistent results across products, across trials, and try and build into that, and we may need to come back to you on some of those issues.

DR. CHESON: Now would be a good time to

get the protocols to ensure the consistency, so that you get the answer, and you find out in five years that someone didn't do what needed to be done.

Who was over there? Dr. Bauer?

DR. BAUER: To reiterate a theme here, you know, that any results that are obtained in one tumor type I think are -- [microphone off] -- it's not generic anemia. This is something that's tumor-specific, potentially treatment-specific, given the design of the trials, chemotherapy in some and radiation in others--I'm sorry--will be lack of generalizability from one tumor to another.

DR. CHESON: I think we have many, many of the important tumor types included here, so we will get generalized information. So that's our sense on this particular question. Do we need to summarize it any more, or have we got it? Okay.

The next one, clinical conditions comprising thrombotic and cardiovascular events vary from study to study. What are those specific events that are clinically important?

I think we kind of all agreed on most of them--didn't we?--that were in the protocols. There was one where Dr. Luksenburg excised chest pain, and a number of us were discussing this, and we were wondering if you had actually gone into the study data to find out what that chest pain really was and whether it might not have been really relevant to the trial, and not before these were just tossed out.

DR. LUKSENBURG: I don't think we have that specificity of attribution, just as chest pain.

DR. CHESON: Okay. So it's kind of hard to arbitrarily just yank them all.

Dr. Keegan, did you have something?

DR. KEEGAN: That's what I was going to say. That's actually the problem with a lot of safety data that we collect, that if you don't target in advance what you want, you get things that are coded in ways that make it difficult to determine what it is you're looking at. In the particular study that Harvey was alluding to, that

was actually in lung cancer. And so we thought it would be particularly difficult there to determine what the chest pain was attributed to. But what we need are specific items to make sure that we're capturing the relevant and important--

DR. CHESON: Now, in--I forget which of the two partners here had a slide of eligibility and toxicity and listing what were considered cardiovascular problems. If someone would just put it up here real quick so we can say yea or nay and come to agreement?

DR. DeLAP: I think we can do that. I think alternatively we could--we have Dr. Mark Levine with us, and he could speak to what's necessary or--well, okay. This is a broad definition. Obviously, there are a lot of subcategories that feed into these major categories. But there are venous and arterial, so there are deep venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial infarction, cerebral vascular accident.

I think what I'd come back to, though, is

what I think Dr. Keegan was saying, that if we're going to study this, we need to study these as endpoints rather than as serious AEs, such as kind of get collected in a study. So I was just going to ask Dr. Levine if he had any comments about how we should do this as study endpoints.

DR. LEVINE: I'll just be brief. I think the agency--and Ken Bauer well knows that in the thrombosis trials that the agency looks at, there are standard definitions for objectively documented pulmonary embolus, deep vein thrombosis; on the arterial side, myocardial infarction and stroke. They're well defined in the literature, and that's what should be defined prospectively, and I think that would advance the field much more than just looking at AE forms.

DR. CHESON: Now, are you suggesting that there be some sort of ongoing screening for these events or that there just be a heightened awareness of their clinical presence?

DR. DeLAP: I think that we're agreeing that this is an issue that needs further research,

and I think that there needs to be structured research in future protocols so that we're all talking about the same thing and we're actually assessing these in a precise way so that we can get answers and actually start making comparisons across trials and those kinds of things.

DR. CHESON: Dr. Bauer?

DR. BAUER: It's pretty clear. We're talking about symptomatic endpoints. We're not talking about routine screening. So we're talking about clinically symptomatic relevant events, which are different for other FDA-approved indications for prophylaxis. We're talking about patients who present--

DR. CHESON: So you will miss things, but they're probably not clinically relevant.

DR. BAUER: Well, the important thing is that the symptomatic events then be objectively documented by appropriate radiographic studies, and that's what sometimes is lacking in AEs, that patients are--if they're suspected of having a thrombotic event that they're objectively diagnosed

by appropriate imaging studies, and that's what we really need.

DR. CARPENTER: And the other thing that will turn out to be important is to ask--since these are going to be symptomatic things, to ask at prespecified intervals so that if there are differences which might occur, they can be picked up regularly. We won't bias the ascertainment.

DR. CHESON: And I think we need to also have careful histories for pre-existing conditions and that these things be evaluated such as with--I'm surprised you didn't say that--looking for hypo-coagulable conditions, the factor deficiencies and what have you, protein deficiencies.

DR. KEEGAN: Are you suggesting that as eligibility criteria, Dr. Cheson?

DR. CHESON: No. I'm suggesting that you take a careful history as part of the entrance onto the study, that we know whether there is a family history or personal history of prior DVTs, cardiovascular disease, et cetera.

DR. KEEGAN: Right. But in the absence of specifically developed case report forms, I think the likelihood of getting good, quality data on that might be difficult. I'm not sure if the ongoing--I mean, remember, we're playing catch-up here--these ongoing trials are specifically capturing that information.

DR. CHESON: Just a suggestion.

Dr. Reaman?

DR. REAMAN: I was going to actually ask how--I certainly applaud the use of these as study endpoints instead of just AE findings. But how is that going to impact on the ongoing trials that are actually going to be used to answer these questions. Are there plans to amend studies looking at these at study endpoints?

DR. PARKINSON: Just a couple of comments.

First is we've generally not used these as endpoints but, rather, as prespecified points of interest, and that's probably a good way to go, as I think you just suggested, Dr. Keegan.

With respect to the ongoing trials, we're

very much interested in the committee's recommendations in this regard. Clearly, they need to be followed--they need to be followed as prespecified points of--pieces--what do you call that? Events of interest. I was thinking of points of light there for a second.

But one of the things, I think, that might be very interesting--and I'd ask the committee for their advice--is about using common prespecified events of interest to allow comparability in different clinical trial settings, because clearly this is complicated. We have analyzed thrombotic events every which way but loose since these trials were--not published, but the results became available. And so you find an association which is rather weak with the use of epoetins. The highest association is a history of prior thrombotic event.

Another association, which is independent, relates to performance status. We've never excluded patients with prior thrombotic event from our trials. That may not always be the case. So there are a number of parameters and a number of

collection parameters that would be nice to be standardized in the interest of trying to get closer, as we all I think are interested in here today, closer to the real answers.

DR. DeLAP: If I could just add, we've started to collect that kind of information in our latest clinical trials, you know, more prospectively, but obviously it will be very helpful, as Dr. Parkinson says, if we have a uniform way of doing it so that we can, you know, compare notes, as it were, and get meaningful interpretations in multiple trials.

DR. CHESON: Thank you.

Getting just to the last--yes?

DR. WEISS: Just a real quick clarification. So you talked about getting a good, careful history, family history, prior histories, et cetera, maybe detecting undisclosed hypo-coagulability states. Are people thinking, though, something that Dr. Parkinson alluded to, that those people should be excluded from trials or just carefully document it so you can try to

evaluate what their risks are relative to other populations and trials?

DR. PARKINSON: You know, I think we're all interested in real-world answers because these drugs are really used, generally. Because we have not excluded patients with prior thrombotic events, our rates actually reflect real-world use of the drug in patients even with a prior history of thrombotic event.

That would be our feeling, but we'd be interested in the committee's discussion on this.

DR. CHESON: I'm all for the real world.

[Laughter.]

DR. CHESON: I knew you'd like that.

Have you all gotten from the committee what you need on this particular question?

DR. KEEGAN: I think we've gone a long way. I just would ask if Dr. Bauer would comment a little bit on the type of documentation that you would like for these sorts of events so that while we're still in the public forum here you could comment on how these should be documented for

purposes of data collection.

DR. BAUER: You know, for the five entities that Mark Levine put up, there's strict criteria, be it, you know, CT, angiography, or ultrasound for a leg DVT and stroke and so forth, and myocardial infarction, standard criteria. So I think that suffices.

Let me just go back to this issue of screening regarding eligibility. I think it should be simple, and the strongest issue you'd want to know about is really personal history of prior thrombosis. And I guess at a minimum for this kind of trial, I guess I would be uneasy about enrolling people with prior history of thrombosis in this trial as the only real exclusion, other than a known thrombophilic disorder. I'm not advocating it by any which way routine screening. But the issue, I think, of enrolling people who have had documented prior thrombosis, you know, I think is an issue for the FDA and trial design, since I gather they are allowing people to enroll who have had prior thrombosis.

DR. PARKINSON: We didn't actively seek to enroll them. Let me make that clear.

[Laughter.]

DR. PARKINSON: We did not exclude them, and we recorded that information, which is why we can present to you do our analysis of this. And that is, I think, what we would advocate.

DR. CHESON: But the other issue is that patients with cancer are already at the increased risk of thrombotic events.

DR. PARKINSON: TE-25--oh, sorry.

DR. CHESON: What?

DR. PARKINSON: That analysis is actually quite interesting. This is the pooled oncology trials analysis looking at this potential interaction between this history of prior thrombotic event and treatment. It's interesting. I'll leave it to you to interpret.

DR. DeLAP: Our data also says that the biggest predictor of whether a patient is going to have a thrombotic episode on the trial is if they had one before, both in the placebo group and in

the treatment group. And, in fact, the other thing I would just add is that in looking at the different subsets of numbers of risk factors for thrombotic events, it looks like there is some added risk with erythropoietic therapy at any given baseline risk. But it's not something that gets profoundly worse at the higher baseline risk. So I wouldn't--you know, I think it's better, as was said before, to include as broad a population of patients as you can and see what the answer is. And the data that we have suggests that you can actually enroll patients with a fairly significant underlying risk of thrombotic events, and you may see some additional risk, but it doesn't look like it's a profound additional risk on top of the underlying risk.

DR. CHESON: Dr. Bauer?

DR. BAUER: I dare say, with the consent form pretty prominently in, you know, risk of thrombosis is one of the adverse effects, in the real world you're going to get very few of these people into these trials.

DR. CHESON: I think that gets to the last question, and that is, Should we have special trials risk for high risk and low risk? And I think that would be a difficult set of trials to do because they all become at high risk when they have cancer; it's just that some are higher than others.

And I'll repeat my question of the agency. Are there any other issues that we have not addressed to your satisfaction this morning?

DR. KEEGAN: I just want to make a comment about an issue that was raised that I don't think was fully resolved, and that was the concern about looking at impact on overall survival because of the difficulties with interpretation of data following completion of the treatment. And I would like to make it clear that our feeling is that there may be difficulties in interpretation, but we don't think that that difficulty should preclude our attempts to determine if there are survival impacts. So that while progression-free survival is an important endpoint to look at, we should also attempt to address the question on survival.

DR. CHESON: I agree. Whereas progression-free survival to many of us is the preferred primary endpoint in this setting, the trials should be powered to adequately detect survival differences as well as secondary endpoints.

Are there any--overall survival, right--additional comments from the committee? I see two hands up. Ladies first. Dr. Taylor?

DR. TAYLOR: Well, I would agree, you have to look at overall survival, because I still go back that we don't know what the mechanism is for erythropoietin effect on survival. And to just look at progression-free survival is not going to answer that question. And, yes, there will be difficulties, but we have to know what that is.

DR. CHESON: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I believe that these studies are a real challenge. They are difficult conduct and difficult to interpret at the end. And one additional factor that we haven't mentioned is the use of concomitant medications which might be

anti-coagulant or pro-coagulant in nature.

And, again, we haven't seen the protocols, as you have said, but I would assume that the sponsors are collecting data on concomitant medication because it's fairly standard. However, it's important also to understand that the severity of an adverse event is also going to be impacted by how rapidly therapy is instituted, what kind of therapy, and then the duration of that event is also impacted by those considerations.

So it's just additional data that needs to be collected in order to make sense of the results at the end.

DR. CHESON: Very good point.

Any other comments or questions?

[No response.]

DR. CHESON: If not, I would like to thank the sponsors for their excellent presentations, carefully prepared, full of interesting data, and to my colleagues in the agency and on the panel for a very lively, interactive, and hopefully productive discussion.

DR. WEISS: We second that. Thank you for all your input.

DR. CHESON: We'll be back here at 12--make it 1 o'clock. We'll give an extra five minutes. Thank you.

[Luncheon recess.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. KELSEN: Good afternoon. My name is David Kelsen, and I'm a former member of ODAC, and I've been asked to serve as Acting Chairman this afternoon. And I'd like to welcome you this afternoon to a session which will discuss endpoints for colorectal cancer, regulatory approval.

Before we begin the session, I'd like to ask the members of the committee to introduce themselves, and we'll start with Dr. Grillo-Lopez.

DR. GRILLO-LOPEZ: I'm Antonio Grillo-Lopez. I am a hematologist/oncologist with the Neoplastic and Autoimmune Diseases Research Institute.

MS. ROACH Nancy Roach from the Marti Nelson Cancer Foundation, and I'm the patient rep for this session.

DR. SARGENT: Dan Sargent, biostatistician from the Mayo Clinic.

DR. O'CONNELL: Michael O'Connell, medical oncologist and Director of Allegheny Cancer Center

and Associate Chair of the NSABP.

DR. BRAWLEY: Otis Brawley. I'm a medical oncologist and epidemiologist from Emory University.

DR. MARTINO: Silvana Martino, medical oncology, from the John Wayne Cancer Institute.

DR. TAYLOR: Sarah Taylor, medical oncology, palliative care, University of Kansas.

DR. REAMAN: Gregory Reaman, pediatric oncologist, the George Washington University and Children's National Medical Center.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan.

MS. CLIFFORD: Johanna Clifford, FDA, Executive Secretary to this meeting.

DR. CHESON: Bruce Cheson, Georgetown University, Lombardi Comprehensive Cancer Center.

DR. GEORGE: Stephen George, Biostatistics, Duke University.

MS. HAYLOCK: Pamela Haylock, oncology nurse, and I'm the consumer representative.

DR. CARPENTER: John Carpenter, medical

oncologist, University of Alabama at Birmingham.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist, M.D. Anderson Cancer Center in Houston.

DR. DuBROW: Ronnie DuBrow. I'm a radiologist at M.D. Anderson Cancer Center in Houston also.

DR. IBRAHIM: Amna Ibrahim, medical officer, Division of Oncology Drug Products.

DR. HIRSCHFELD: Steven Hirschfeld, pediatric oncologist, Center for Biologics, FDA.

DR. WILLIAMS: Grant Williams, Deputy Director, Division of Oncology Drug Products.

DR. KEEGAN: Patricia Keegan, Division Director, Oncology Biologic Products.

DR. PAZDUR: Richard Pazdur, Division Director, Oncology Drug Products, FDA.

DR. KELSEN: Thank you. I'll ask Ms. Clifford to read a statement about conflict of interest.

MS. CLIFFORD: Thank you. The following announcement addresses conflict of interest issues with respect to this meeting and is made a part of

the record to preclude even the appearance of impropriety at this meeting.

The topics to be discussed this afternoon will not focus on any particular product or company but, rather, may affect all manufacturers of products to treat colorectal cancer. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their own or their employer's financial interests. All participants have been screened for interests in the products and companies that could be affected by today's discussions.

In accordance with 18 U.S.C, Section 208(b)(3), the Food and Drug Administration has granted waivers to Dr. David Kelsen and Dr. Daniel Sargent because it has determined that the need for their services outweighs the potential for a conflict of interest. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr.

Antonio Grillo-Lopez, Chairman, Neoplastic and Autoimmune Diseases Research Institute, is participating in this meeting as an industry representative, acting on behalf of regulated industry.

In the event the discussions involve products or firms not on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. KELSEN: Thank you. We'll open this afternoon's session with opening remarks from Dr. Pazdur.

DR. PAZDUR: I have to take a look at the audience, and I noticed that it's really dropped

down in attendance, and perhaps it reflects the departure of the stock analysts since we're not talking about any product-specific application here.

I began the comments on Monday, and the presentation that I'm going to give I think is very similar to what I gave in my introductory remarks before we discussed the two drugs on Monday. And I just want to go over some of these points because I think that these points are germane not only to the discussions that we had on Monday, but also are germane to a discussion on colorectal cancer endpoints, and these are recurring themes over and over and over again.

The agency is open. That's why we're having this discussion with you. We want transparency of process. We want to make sure that the endpoints that we select and discuss with our regulated industry are ones that really measure the true efficacy of the drug, are really going to give us a determination of why we should approve a drug.

As you are all aware of, we have

traditionally held to the standard of the demonstration of a survival advantage for the approval, the regular approval of a drug in the first-line setting, and also in the adjuvant setting of colorectal carcinoma. And as I mentioned and we discussed throughout these proceedings, we've looked at survival as an unambiguous endpoint. It's measured on a daily basis. We feel that given an accepted safety profile that it is the ultimate in clinical benefit.

But, nevertheless, as I stated in my opening comments on Monday, we realized that there can be shortcomings of a survival analysis, depending on what setting one is looking at. Obviously, survival analysis requires large numbers of patients. This may or may not be a problem in colorectal carcinoma. Obviously, it's not as big a problem in colorectal carcinoma as it would be, for example, in hairy cell leukemia or in lymphoma.

There are problems perhaps with long patient follow-ups, which generally is not that big

of a problem in metastatic colorectal carcinoma, but with improvements in survival, fortunately, we are seeing that patients with colorectal carcinoma live longer.

Perhaps one of the areas that we're most concerned about is this issue of crossover, and crossover can go two ways, and we've seen this in discussions of applications. Obviously, it can obscure a survival advantage in a randomized study, but if there is an unequal crossover going in one direction, it may actually provide you the suggestion, at least of an erroneous conclusion based on survival.

So, by all means, all of our endpoints that we have are far from perfect, and I think people have addressed this throughout the day. We're here to get your consensus and your feeling on where we should go with our discussion with industry in the future.

I think when we talk about the specifics here, let's go over endpoints, and I think issues that we need to focus on--and we will be focusing

on these during the presentations, but also in the discussion. When we take a look at the adjuvant setting and look at disease-free survival, I think we have important questions that we must address. If we accept this as a regulatory endpoint, are we saying that disease-free survival is a surrogate for survival, overall survival? Is it reasonably a likely surrogate for overall survival? And those are the key words for accelerated approval. Is it a surrogate for an improved life because one delays the uncertainties of the diagnosis of cancer being made in an adjuvant setting at the time of relapse? So there are issues here that I think we need to address when we talk about disease-free survival.

When we talk about in the advanced disease setting, when we're talking about time to progression or progression-free survival, again, are we saying it is a surrogate for survival or is it a really true endpoint of clinical meaningfulness in itself? And those are some of the questions that we will be posing to you.

In the two applications that we saw

yesterday, especially with the first, I think there were important questions that we discussed regarding the rigor of measurement of a time to event endpoint such as progression-free survival. One has to account for missing visits, asymmetry of follow-ups. What is the role of an external radiology committee vis-a-vis the response or the progression determination, I should say, of the actual investigators that are seeing these patients? And could this vary from disease to disease? For example, in colon cancer where most of the progression is picked up on CT scan, are investigators' determinations in a randomized study which might balance out clinical findings of progression really going to be that important when we have a discussion of what is the role of a radiology committee?

We've had a tendency for recent applications--and you've seen these because they've come to you--to be asked to make decisions on the basis of one trial. Should we require a greater degree of statistical significance if we take a

look at one trial versus two trials? I'll let you know as a caveat that there are many divisions in the FDA that do look at a higher degree of statistical persuasiveness when they examine one trial. If we move away from survival, would this be especially important to require a higher degree of statistical significance?

As we had in our discussion of the morning application on Monday, what is the value of a small increment in progression? How does one define that as one enters the trial prospectively with the company?

So these are just some of the questions that I want to pose to you. Here, again, our whole purpose in looking at this is a degree of transparency. We're open. We want to make sure that we're giving the correct advice to patients. I always say there are sins of omission and sins of commission when we're in drug development and making regulatory decisions. Many times the marketplace itself will address a bad drug that's out there. People simply won't use it. However,

if drugs don't get out there, the marketplace and market forces cannot answer that question. And, obviously, there is always a degree of balance. What we're looking for, however, when we have an ODAC meeting such as this is what is the rigor, what is the science that would go into making these decisions.

Thank you very much.

DR. KELSEN: Thank you, Dr. Pazdur.

I'll ask Dr. Ibrahim now to discuss regulatory background and past approvals.

DR. IBRAHIM: Good afternoon. I will be discussing the regulatory background and past FDA approvals in colorectal cancer.

First, the presentation outline will be as follows: I will discuss a background of regulatory requirements for drug approval, endpoints for regular and accelerated approval, agents approved for adjuvant, first-line, and recurrent therapy of colorectal cancer, and endpoints used for them will be presented. I will review briefly the major trials that led to drug approval, first for drugs

for adjuvant therapy and then for first-line and second-line therapy. Finally, I will conclude with the endpoints that have supported approval of drugs for colorectal cancer in these three treatment settings.

Drug approval requires adequate and well-controlled studies demonstrating that the drug is safe and is effective for the approved indication. The safety requirement comes from the Federal Food, Drug, and Cosmetic Act of 1938. The efficacy requirement is from a 1962 amendment to the Act.

There are two routes to a new drug approval. The traditional route is a regular approval. Sometimes it is referred to as full approval. It requires the demonstration of clinical benefit or an effect on an established surrogate for clinical benefit. Clinical benefit is usually considered to be tangible benefit of obvious worth to the patient, such as prolongation of survival or relief of pain.

Sometimes FDA has accepted surrogates as

the basis for regular approval, usually after much clinical experience with the surrogate and widespread acceptance by patients and physicians. Examples are lowering blood pressure and lowering cholesterol. On occasion, these assumptions of obvious benefit have been proven wrong, such as the benefit of suppressing some arrhythmias.

Another mode of approval is accelerated approval, approval which can be based on a surrogate endpoint considered to be reasonably likely to predict clinical benefit. I will discuss accelerated approval in a later slide.

One of the central questions we address at the end of Phase II meetings is: How many trials are needed for approval? The usual answer is more than one, and this is based on the definition of substantial evidence of effectiveness in the amended Food, Drug, and Cosmetic Act and the fact that the word "trials" is plural in that definition. Reasons for needing additional evidence are the possibility of unrecognized trial bias and also just chance alone.

However, FDA has recognized that sometimes results from a single trial may suffice. Although approvals based on a single trial have been granted on occasion for many years, this practice was written into law by the FDA Modernization Act, or FDAMA, in 1997. The possible use of only one trial was also detailed in the FDA Effectiveness Guidance, finalized in 1998. As worded in that guidance, a single trial may suffice, but generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival and a confirmatory study would have been difficult to conduct on ethical grounds.

Regular approval requires evidence of clinical benefit or improvement in an established surrogate of benefit. In oncology, survival is obviously the gold standard for clinical benefit. But the FDA has accepted other endpoints for cancer drug approval.

In the 1970s, FDA usually approved cancer

drugs based on objective response rates. In the early 1980s, after discussion with ODAC, FDA determined that response rate was generally not sufficient evidence for approval. Given the toxicity of cancer drugs, approval needed evidence of improvement in survival or in a patient's quality of life. Example: improved physical functioning or improved tumor-related symptoms.

There have been recent examples of endpoints that were accepted as established surrogates of clinical benefit in specific cancer settings. These endpoints supported regular approval. Disease-free survival has been accepted as an adequate endpoint in the setting of adjuvant treatment of breast cancer based on the belief that a large proportion of the recurrence were symptomatic.

Durable complete response was considered an acceptable endpoint in testicular cancer and acute leukemia because the untreated conditions were quickly lethal, or even in some chronic leukemias and lymphomas when it was clear that

remission would lead to less infection, bleeding, and blood product support.

Even with solid tumors, the FDA has suggested that tumor response may sometimes support approval, but that this judgment needs also to consider additional evidence such as response duration, relief of tumor-related symptoms, and drug toxicity.

As discussed in the following sections, response rate with adequate response duration has sometimes supported either regular approval or accelerated approval, especially in patients with heavily pre-treated or refractory disease, and especially with less toxic therapies, such as hormone treatment of breast cancer.

Recently, the Division of Oncology Drug Products evaluated the basis of approvals since 1990 for drugs in our division. As shown on this slide, survival was the approval endpoint in the minority of approvals: 73 percent of all approvals were not based on survival, and if you exclude accelerated approvals, 67 percent of approvals were

not based on survival.

Let's turn to accelerated approval. This slide lists the major issues. The accelerated approval regulations are for diseases that are serious or life-threatening, where the new drug appears to provide benefit over available therapy. The key point for our consideration is that accelerated approval can be granted on the basis of a surrogate endpoint that is reasonably like to predict clinical benefit.

After accelerated approval, the applicant is required to perform a post-marketing study to demonstrate that the treatment with the drug is indeed associated with clinical benefit. If the post-marketing study fails to demonstrate clinical benefit or if the applicant does not show due diligence in conducting the required study, the regulations describe a process for rapidly removing the drug from the market.

The approved agents in the table are listed according to the treatment setting with the drugs for adjuvant use in the left column, for

first-line use in the middle column, and those for the recurring cancer in the column on the right. I will present them to you in chronological order.

5FU was the first drug approved for colon cancer in 1962. We will not discuss this further since 5FU approval predated the era of controlled clinical trials in oncology.

After a long gap, levamisole was approved in combination with 5FU in 1990 for adjuvant use. Although reports in the literature have been described regarding results supporting the use of 5FU Leucovorin for adjuvant therapy, the FDA has not received an NDA submission supporting this indication. Leucovorin was approved in 1991 in combination with 5FU for first-line therapy.

Irinotecan initially received accelerated approval for recurrent colorectal cancer in 1996, followed by a regular approval for the same indication. Subsequently, in 2000 it was approved for first-line use.

Capecitabine is the only agent approved for first-line setting based on non-inferiority

analysis.

Oxaliplatin in combination with 5FU/leucovorin received an accelerated approval for recurrent colorectal cancer, which was converted to a regular approval, and then it was also approved for first-line therapy earlier this year.

Bevacizumab and cetuximab in 2004 are the first biologic agents to have received approvals for first-line and recurrent colorectal cancer, respectively. The approval for bevacizumab was regular, and for cetuximab it was accelerated.

As you will see, survival was the endpoint supporting all regular approvals. Randomized trials demonstrating superiority led to all but one of the regular approvals. For one drug, capecitabine, non-inferiority in overall survival supported regular approval. Three drugs received accelerated approval in previously treated populations. Two were supported by a response rate in single-arm trials and one by a response rate and time to tumor progression superiority shown in interim analysis of a randomized trial.

Now, agents for adjuvant therapy.

Levamisole was approved in combination with 5FU in 1990 based on the results of two trials. After surgery, patients were randomized to no further therapy, levamisole alone, or 5FU plus levamisole. Levamisole plus 5FU demonstrated a reduction in death rate by about 30 percent. The follow-up period was two to five years for these studies. Although the contribution of levamisole to this regimen was not demonstrated in clinical trials, this was the first adjuvant regimen to show a survival benefit. And levamisole was approved based on these results.

Agents for first-line therapy.

The combination of 5FU/leucovorin was approved for treatment of advanced disease in 1991. Study 1 is a five-arm study, but for simplicity only three arms are shown in this table. A randomized study demonstrated improvement in response rate, time to tumor progression, and overall survival of high- or low-dose leucovorin combined with 5FU. These two arms of the study

were extended along with sequential methotrexate, 5FU/leucovorin arm from the same study. This is the study seen in the table. The results remain consistent with the initial study. Overall survival was about 12.5 months in the initial as well as the extension of the study.

In 2000, irinotecan was approved for first-line therapy following its initial accelerated approval for refractory colon cancer. Two randomized, multicenter trials compared infusion of 5FU/leucovorin plus or minus irinotecan in untreated patients. Each trial had over 300 patients and demonstrated an improvement in response rate, time to tumor progression, and overall survival.

These differences in survival were observed in spite of second-line therapy in a large number of patients on both arms, including crossover to irinotecan-containing regimens in the control arm.

Capecitabine is the only colon cancer drug approved based on non-inferiority analysis. The

combined survival data from two open-label, randomized trials of capecitabine versus 5FU/leucovorin formed the basis of approval. Sufficient historical data existed to allow a reasonably precise estimate of the effect of 5FU/leucovorin on survival. The non-inferiority analysis showed that at least 50 percent of the 5FU/leucovorin effect was retained by capecitabine. This drug was approved for a restricted first-line indication, "for patients when treatment with thoropyrimidine(?) therapy alone is preferred."

One drug, oxaliplatin, and one biologic agent, bevacizumab, were approved for first-line use in colon cancer in 2004. In one randomized trial, a combination of oxaliplatin with 5FU/leucovorin, known as the FOLFOX4 regimen, demonstrated superiority in overall survival when compared with the control regimen of IFL. The study design was complicated, and there was an unequal crossover. Twenty-four percent of the patients in the IFL arm received oxaliplatin in their second-line therapy; whereas, only 8 percent

of patients in the oxaliplatin combination arm received irinotecan. An improved time to tumor progression supported the improved survival observed in the FOLFOX4 arm. Additionally, it could be inferred that oxaliplatin plus 5FU/leucovorin administered sequentially with IFL is better than irinotecan plus 5FU/leucovorin without oxaliplatin.

The safety and efficacy of bevacizumab in the initial treatment of patients with metastatic carcinoma of the colon and rectum were studied in two randomized, controlled clinical trials in combination with intravenous 5FU-based chemotherapy. The results of the larger trial with over 800 patients demonstrated a superiority in overall survival by about five months. In the smaller trial, a randomized, exploratory Phase II trial with just over 100 patients, statistical significance was observed only for progression-free survival in the 5FU/leucovorin plus 5 milligrams of bevacizumab. There was a trend for improved survival.

Agents for refractory cancer.

In 1996, irinotecan was the first chemotherapy agent since 5FU to receive approval for treatment of pretreated, advanced colorectal cancer. Three single-arm studies with response rate ranging from 14 to 21 percent and response duration of 5.8 months led to accelerated approval for second-line therapy. A survival benefits was subsequently demonstrated in two randomized trials shown in the next slide.

These randomized trials demonstrated superiority in survival by 2 to 2.5 months against best supportive care, and 5FU-based regimens led to regular approval in the second-line setting. Interestingly, these trials were not part of the original regulatory plan to convert the accelerated approval to regular approval. While the single-arm trials were being reviewed by FDA, these confirmatory trials were being conduct in Europe. The initial agreement between the sponsor and FDA was that the trials in the first-line setting were to provide initial proof of clinical benefit.

Oxaliplatin in combination with 5FU/leucovorin received accelerated approval based on improved response rate and time to tumor progression, shown at an interim analysis of a three-arm randomized trials. Patients in this trial had disease which progressed on or recurred within six months of treatment with the IFL regimen. The oxaliplatin combination arm had a response rate of 9 percent versus 0 to 1 percent in the single agent oxaliplatin arm and 5FU/leucovorin control. The time to tumor progression was increased by two to three months compared to the other two arms.

There were some important observations. Because of the inclusion of the single agent oxaliplatin arm, the contribution of 5FU/leucovorin to the combination regimen was shown definitively. It also demonstrated that oxaliplatin should not be used alone in the pretreated population. Follow-up of this study did not demonstrate a survival advantage for the oxaliplatin regimen.

Cetuximab used in combination with

irinotecan received accelerated approval in 2004 for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. An accelerated approval was also granted for cetuximab as a single agent for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

This regular approval is based on one two-armed randomized trial and two single-arm studies. The multicenter, randomized, controlled clinical trial was conducted in over 300 patients randomized to receive either cetuximab plus irinotecan or cetuximab monotherapy. Cetuximab plus irinotecan improved time to tumor progression by about 2.5 months compared to the single agent cetuximab.

In the single-arm trials, the overall response rate was 9 to 15 percent for single agent cetuximab and in combination with irinotecan. The median durations of response were approximately 6.5 to 4.2, respectively.

In summary, the FDA requirements for drug approval were reviewed, including the need for evidence from well-conducted, well-controlled clinical trials, or sometimes from a single trial plus confirmatory evidence; and regular approval which needs evidence showing clinical benefit or an accepted surrogate for clinical benefit; and accelerated approval which must show an advantage with respect to available therapy and may use an endpoint that is only reasonably likely to predict benefit. We reviewed the approval endpoints that FDA has accepted over the past several years.

I will conclude my presentation with this slide, which gives an overview of the basis of approval in colorectal cancer. Levamisole with 5FU is the only drug approved for adjuvant therapy after demonstration of superiority in survival. Five drugs are approved for first-line therapy, and they are 5FU, irinotecan, oxaliplatin, bevacizumab, and capecitabine. Superiority analysis for first (?) and non-inferiority for capecitabine for survival led to the approval. Irinotecan,

oxaliplatin, and cetuximab are the three drugs that have received accelerated approval for recurrent disease based on response rate and on time to tumor progression.

For irinotecan, clinical benefit, that is, survival, was demonstrated later in two randomized studies, leading to full approval in the recurrent disease setting. Oxaliplatin's accelerated approval was converted to a regular approval on the basis of a large randomized trial in previously untreated patients.

Thank you.

DR. KELSEN: Thank you. We're going to hold questions until after the two additional presentations, and I'll now ask Dr. O'Connell if he'll give his synopsis on the FDA Endpoints Workshop.

DR. O'CONNELL: Thanks very much, David.

My task today is to review for you the results of the workshop sponsored by the FDA and held on November 12th of last year. I had the privilege of co-chairing this meeting along with

Dr. Pazdur. Dr. Williams and Dr. Ibrahim also gave presentations. Dr. Kelsen was a panelist. Dr. Sargent also gave a presentation there.

The purpose of that workshop was to discuss both the positive and the negative aspects of various endpoints for approval of new drugs for colorectal cancer. Specifically, it was not reach a consensus or to give FDA any advice. That's the job of this committee today.

Secondly, we were to identify areas for further research that might help identify more effective endpoints for colorectal cancer drug approval.

And then third was to provide information to you so that you could give whatever recommendations you think appropriate to the FDA based upon this discussion.

The workshop consisted of a series of presentations, very similar to the one you just heard, regarding the regulatory background and the summary of previous approvals. There were five presentations given by different panelists at this

meeting, and I'll briefly summarize these presentations for you.

I said there was a very lively, interactive discussion between the speakers and the multidisciplinary panel. There certainly was a free range of expression of opinions on the various endpoints. And then we concluded with some discussion of questions that were posed by the FDA.

My goal in this presentation today is to give you a very brief capsule summary of the presentations and the main points of discussion without going through a litany of all of the discussions that occurred over that six-hour period.

The focus is really to provide some information regarding new endpoints for regulatory approval of drugs for colorectal cancer and, in particular, there are three endpoints that are of particular interest that I'll emphasize during my presentation: time to progression as a regulatory endpoint for first-line metastatic colorectal cancer; three-year disease-free survival as an

endpoint for regulatory approval in the colon adjuvant situation; and three-year local control as an endpoint in rectal cancer adjuvant studies.

So let's briefly go through the presentations. One of these presentations was given by Dr. Charles Blanke from the University of Oregon. His topic was the use of biomarkers or quality of life as regulatory endpoints for patients with colorectal cancer. There was a fair amount of discussion regarding the use of the carcino-embryonic antigen, or CEA, and it was the point of view of the speaker and the panel that it really wasn't possible to consistently predict clinical benefit based on fluctuations of CEA.

Further, the ASCO guidelines do not recommend other biomarkers for colorectal cancer, including the variety of molecular markers that have more recently been described in the literature.

Dr. Blanke then went on to discuss the pros and cons of quality-of-life analysis in colorectal cancer patients. Of course, he pointed

out that there are multiple methodologic issues involved with quality-of-life measurements, problems with missing data, problems with perhaps not asking the correct question in the quality-of-life questionnaire or instrument that's pertinent to the particular disease process under question.

He pointed out that it really isn't know whether there are significant changes in quality-of-life parameters in regimens known to be effective in colorectal cancer and also pointed out you really can't discriminate between safety and efficacy based on quality-of-life endpoints.

Perhaps one of the most important issues was that many patients with metastatic colorectal really don't have significant tumor-related symptoms. They don't have severe pain. They don't have a significant decrease in performance status. Many of these patients are asymptomatic or have minimal symptoms, questioning the use of resources in measuring this parameter in a population that frequently does not demonstrate significant

symptoms.

Dr. Blanke then went on to discuss the clinical benefit response, which, of course, was used as a regulatory endpoint for approval of drugs in pancreatic cancer where most patients with pancreatic cancer do have pain, do have significant reduction in their performance status, and frequently have significant weight loss. Again, the issue with metastatic colorectal cancer, these parameters are frequently not present.

Further, those three specific symptoms do not really adequately encompass the variety of symptoms that patients with metastatic colorectal cancer might experience related to bowel obstruction, the development of ascites, liver dysfunction and so on.

And, again, this type of clinical benefit response was felt perhaps to be of most benefit in patients that were likely to be very symptomatic, which would include patients with rectal cancer to a much greater degree since patients with rectal cancer frequently experience local tumor recurrence

which can result in severe pain, ureteral obstruction, and other clinical problems.

Dr. Meg Mooney from the National Cancer Institute then provided a discussion of endpoints for neoadjuvant and adjuvant therapy of rectal cancer. Here, in contradistinction to colon cancer, the failures are frequently very symptomatic, and there's a higher proportion of locoregional failures as a component of the failures in patients undergoing potentially curative surgery. In fact, one of the panel members was very precise in stating that local tumor control at three years is an appropriate endpoint for full approval, and there were several other members of the panel that had the same point of view and no dissent.

Pathologic complete response engendered more discussion. If you have a patient receiving preoperative radiation and chemotherapy, one measure of efficacy is to determine whether in the resected specimen there's any histologic evidence of residual tumor. And although it was felt to

definitely relate to biological activity, there were quality control issues raised: evaluation of the radium margin(?), quality control issues in determining whether or not there truly was microscopic residual disease. So the general feeling there was that pathologic complete response might be premature as a regulatory endpoint at this point.

Colostomy-free survival is the endpoint in the management of anal carcinoma, the clinically relevant endpoint, and, in fact, would also apply to a certain subset of patients with rectal cancer, but only to patients that have very low-lying tumors. And so for patients with colon cancer or for rectal cancer above the very distal several centimeters, this was not felt to be a helpful endpoint in colorectal cancer.

Dr. Tom Fleming from the University of Washington then gave a very articulate and, in fact, I would say, impassioned presentation regarding surrogate endpoints and non-inferiority trials. He pointed out, as you've already heard,

that primary endpoints for drug regulation need to be sensitive, measurable, and clinically relevant, with the accepted endpoints or measures of clinical benefit being improvement in survival or decrease in tumor-related symptoms.

He then went on to discuss surrogate endpoints, pointed out that biological activity might be reflected in a surrogate endpoint, but that might not establish clinical benefit for patients. He gave a couple of examples from the cardiovascular literature where flecainide and other agents were used as antiarrhythmics and can prevent ventricular tachycardia. The surrogate endpoint was improved but, unfortunately, was associated with a high risk of sudden death and so that the overall benefit of these agents was abrogated by the delayed and unexpected toxic effects.

He stated that meta-analyses were really required to adequately validate a surrogate endpoint. That is, even if you had had a study or two where there was a significant association

between a surrogate--progression-free survival, for example, and survival--that you really needed to have a cadre of studies to evaluate that relationship in several different venues to be certain that the surrogate was truly predicting clinical benefit. And he pointed out that such surrogate markers that are adequately validated are distinctly rare in clinical medicine, but I believe it was Dr. Williams that pointed out that the FDA has granted approval using surrogate endpoints that haven't been formally validated, and we saw some examples just a few moment ago in Dr. Ibrahim's presentation.

Tom then went on to discuss non-inferiority trials, and I won't belabor this point except to say that there are very important methodological factors that need to be taken into consideration, that it's not enough for the curves to overlap, you need to be certain that you're not allowing a significant decrease in therapeutic effect in these non-inferiority trials. And there was some lack of enthusiasm in general on the part

of the panelists that these studies might not truly move the field forward. And the main area of interest for non-inferiority trials is if there was a treatment that was substantially less toxic than the current standard.

Then we move on to the last two presentations, which focused on time to tumor progression and disease-free survival for the adjuvant situation, respectively. This presentation was given by Dr. Langdon Miller. He discussed clinical benefit or the time to tumor progression as a clinical benefit endpoint for first-line metastatic colorectal cancer. And Dr. Miller took the point of view of making a very strong case for time to tumor progression.

He pointed out that in colorectal cancer now, in contradistinction to years gone by, we have multiple therapies that do have benefit in this disease and that it has, therefore, become more difficult to assess the impact on survival because of these effectiveness therapies that can have an impact on second-line treatment. Second-line

treatment can be effective and thereby obscure the relationship between the initial treatment and the ultimate survival of the patient.

He argued against the use of symptomatic progression or time to symptom progression because these patients frequently aren't symptomatic to start out with. It's very subjective and difficult to measure.

He stated from his point of view that time to tumor progression should be a valid endpoint for full approval in first-line colorectal cancer because this endpoint directly evaluates changes in the disease burden, that is, regression of tumor or lack of progression of tumor; correlates with other outcomes and, in particular, survival, and I'll show you some data on this point in just a moment. It has the big advantage that it's not confounded by subsequent therapies. Second-line treatment won't affect the time to tumor progression, and he made that point that it offers utility as an endpoint in non-inferiority trials because the sample sizes that would be required would be much

smaller.

He made the point that the endpoint can be objectively quantified, reviewed, and audited by external panels; if you're doing radiographic procedures to document the lack of progression at a particular point in time, offered clear interpretation, straightforward analysis, and certainly would conserve patient resources and hasten drug development.

The data that he presented correlating time to tumor progression and survival in first-line metastatic colorectal came from two clinical trials involving 1,000 patients treated with irinotecan-based chemotherapy. And so he had primary patient data for these 1,000 patients and found a very strong correlation between time to tumor progression and overall survival among these 1,000 patients. A Cox analysis was performed, plugging in all of the important prognostic discriminants, and time to tumor progression was still strongly associated with survival.

Secondly, in the questioning session, we

asked whether any meta-analyses had been done of this surrogate endpoint, and the response was that one meta-analysis has been performed involving the published summary results of 29 trials involving some 13,000 patients, where there was, again, a highly significant correlation between time to tumor progression and survival, but this was not with the primary individual patient data.

This presentation generated a lot of discussion among the panelists. There was some concern expressed that there really needs to be a very objective and reliable methodology for assessing time to tumor progression. It's not nearly as definitive as patient survival. But it was felt that with modern radiologic techniques and external review committees and properly written protocols, that particular barrier could be addressed.

There was a lot of discussion regarding whether time to tumor progression reflects clinical benefit in its own right per se, and here I'd say that there was a big disagreement. There was not

consensus on the part of the panel.

For example, if a patient is asymptomatic and has metastatic disease, his time to tumor progression is perhaps prolonged by a month or two, but he experiences very severe toxicity as a result of the chemotherapy, and the overall survival is not really changed. How much of a benefit is that to the patient? And there was, therefore, not a consensus on that particular point.

Is time to tumor progression reasonably likely to predict clinical benefit based upon the association between TTP and survival? I think the majority of the panel would feel that would be the case, but also that a more complete gestalt regarding the patient and the clinical circumstance need to be taken into consideration. We heard that comment earlier today. We're interested in the response rate, the survival, the toxicity pattern, in addition to time to tumor progression to really make an overall assessment of the benefit of the treatment for the patient.

Then, finally, Dr. Dan Sargent, who is

here today, gave a preliminary analysis of the correlation between three-year disease-free survival and overall survival as endpoints in evaluating adjuvant therapy for colon cancer. Dan presented the results involving some 12 prospectively randomized, Phase II clinical trials in patients with resectable colon cancer. There are some 38 treatment arms involved in these 12 trials and more than 10,000 patients involved. And he did have primary data.

The preliminary conclusions of this presentation showed a rather striking correlation between three-year disease-free survival and five-year overall survival. The event rates, that is, the number of relapses in three years or the number of deaths within five years, was virtually identical so that whether you used one endpoint or the other, this did not have a significant impact on the sample size. He found that three-year disease-free survival may slightly overestimate differences in five-year overall survival, particularly in the experimental arms of these

randomized trials. And there were three of the studies where there was a statistically significant difference in three-year disease-free survival at borderline p values, in the range of 0.03 to 0.04, but no significant difference in five-year overall survival. But the point was made that some of these trials were not adequately powered to detect differences in overall survival. And it was also pointed out, I believe by Dr. Fleming, that this was not a formally validated surrogate.

So Dan presented those results as a work in progress and in just a moment will be presenting an update of this analysis where he's done considerable additional work since that time.

There was discussion among the panel as to whether three-year disease-free survival represented clinical benefit per se in its own right, and there were a number of individuals there that felt this was the case, independent of survival effect.

I guess I would express a personal concern that survival also would need to be evaluated in

these studies to be certain that there wasn't a delayed adverse impact on survival that wouldn't be seen until some delayed point in time, so you wouldn't want to trade a significant benefit in three-year disease-free survival for a significant decrement in long-term survival. And it was also pointed out that disease-free survival is used for full approval in breast cancer adjuvant therapy. Why not in colon cancer?

And so, then, to conclude, we bring these questions for your consideration today. Should the following endpoints be recommended to the FDA for new drugs in colorectal cancer? And if so, should they be for full or for accelerated approval?

In the colon adjuvant setting, is three-year disease-free survival an appropriate regulatory endpoint? There was considerable feeling expressed at the workshop that this would be the case.

For first-line metastatic colorectal cancer, is time to tumor progression or progression-free survival an appropriate endpoint?

And there was considerable feeling that it was reasonably likely to correlate with clinical benefit.

And in the rectal adjuvant setting, should three-year local control, preventing the devastating symptoms from local tumor recurrence be a regulatory endpoint for new drugs being studied in the rectal adjuvant setting?

Thank you very much.

DR. KELSEN: Thank you, Mike.

I think this is a very good time to go to Dan Sargent and hear the update on his analysis.

DR. SARGENT: Thank you very much. I appreciate the opportunity to present updated data today from a meta-analysis exploring the question of disease-free versus overall survival as an endpoint for adjuvant colon cancer studies.

In the setting of colon cancer, it is clear to impact and improve the chance of cure, we must decrease the rate of relapse. Eighty-five percent of deaths within eight years of diagnosis are following a recurrence of the cancer, so

recurrent colon cancer is certainly the primary cause of death in patients who are initially thought to be able to be surgically cured.

In addition, due to the devastating consequences of recurrence of disease, prolonging a patient's time without disease certainly should have beneficial impacts on their quality of life.

This led us to explore the following hypothesis: that disease-free survival assessed after three years is an appropriate endpoint to replace overall survival in adjuvant colon cancer trials. The benefits of such a change would be clear. This would allow the more rapid completion and the reporting of clinical trials and, if it held true, would allow promising agents to benefit patients more quickly.

In order to assess this question, we have gathered data from multiple large, randomized trials. We have individual patient data from every trial, and the analyses started out, at least, simple, comparing disease-free survival and overall survival for study arms.

We've chosen landmark time points of three years for disease-free survival and five years as an endpoint for overall survival, and you'll see why.

In addition to looking on an arm-by-arm basis, we have looked within trials, looking at the difference between the control arm and the experimental arm of each trial to determine if differences that are present on one endpoint are translated over into the other endpoint. We feel that the most important comparison is the comparison of hazard ratio. That is, what is the hazard ratio between a control and experimental arm for disease-free survival? What is the hazard ratio comparing control to experimental arms for overall survival?

To make sure everyone is clear, we used the following definitions: Overall survival is the time from randomization to death due to any cause. Disease-free survival is the time from randomization to the first occurrence of either a recurrent event or death. And we do note that

second primaries were not included as events in our disease-free survival. Having said that, the rate of second primaries is very low, and including them has almost no impact on these analyses.

With respect to the validation of surrogate endpoints, many methods have been proposed, and there is no agreed-upon standard of practice in the statistical community. Therefore, we have chosen to examine multiple approaches ranging from simple to complex.

The simple approach is to use a weighted linear regression of one endpoint on the other, weighting by the sample size of that trial.

Another approach--and I will explain each of these approaches as I present them--is the Prentice and Freedman approach looking at a quantity known as the proportion explained. Two other sets of authors--Begg and Leung, and Burzykowski and colleagues--have proposed other methods in Journal of Royal Statistical Society recently, and I will explain those as they are presented.

On this slide, the trials that are included in the analysis are listed. We see that they range from first accrual in 1977 all the way down to 1994, so we do span a considerable amount of time. Many of these trials had surgery-alone control arms, but some of the later trials had 5FU-based treatments in all arms. Sample size ranged from approximately 250 up to about 2,200; total sample size, close to 13,000 patients, and a total of 33 different treatment arms.

Among those 33 arms, there were nine that were surgery-alone control arms and 24 that were considered active treatments in that they were 5FU-based.

The median follow-up on these patients is eight years, and we have complete data to five years on 93 percent of patients. And there was some inconsistency among these studies in long-term follow-up, and, therefore, we have censored all analyses at eight years because that was consistent follow-up through eight years in these studies.

Just looking at the patient

characteristics, we can see that most of the patients were between the ages of 50 and 70. About 15 percent were over the age of 70, so consistent with the age distribution on clinical trials, but probably skewed younger than the distribution in the overall population.

We had about a 50/50 split on gender; 20 percent or so were treated with surgery alone, and the majority of patients, 62 percent, were Stage III. Stage I patients were included in one single trial.

Turning to some data, here we've got the recurrence rate by six-month intervals from the date of randomization. If we add up adjacent number of figures, we get recurrence rates by year. So we can see that in the first year following randomization, approximately 10.5 percent of patients recur; in the second year, it's actually the highest recurrence rates; adding these numbers, you get 12.5 percent; and about 7 percent in the third year. After that, the rate of recurrence falls off rather steeply.

So, really, the dominant force in recurrent disease happens in the first three years following randomization.

We then looked at the time from occurrence to death, and consistent with data that we've known for a long time on advanced colon cancer, we have a median time from occurrence to death of about a year. And so patients that recur by three years very likely will have died by five years.

We then looked at the rate of agreement on a per patient basis for these two endpoints. So what's shown here--and notice the scale does not go to zero; it's magnified to show additional detail--is the concordance rate between a disease-free survival endpoint at x years, where x ranges from one up to five, and the overall status at five years.

So what does this mean? If we look at the three-year time point, we see approximately 90 percent agreement between your disease-free survival status at three years and your overall survival status at five years. And we can see that

this curve climbs for the first year or two following randomization, but that it really plateaus at about the three-year time point.

So that suggested that three years is an appropriate time point to look, and here shown graphically is the simple rate of disease-free survival at three years compared to overall survival at five years. And, again, notice that these scales are magnified to show additional detail. They do not go from zero to one. If they did, you'd just see this little crowd in the middle. So we blew them up.

Spearman correlation is 0.89, R-squared from our regression is 0.86, both measures indicating significant concordance between these two effects.

Our regression equation result was that overall survival is, in essence, zero plus one times three-year disease-free survival. Looking at the p values, we see that the intercept is not significantly different from zero. The slope is significantly different from zero, but it's not

significantly different from one. And so statistically we cannot reject the simple equation that five-year overall survival equals three-year disease-free survival.

Within each of the study arms, 33 different study arms, the largest difference in absolute numbers was 6 percent between disease-free survival and overall survival. In 27 of the 33 arms, the difference between these two endpoints was 3 percent or smaller.

So the first set of conclusions is that on a patient-by-patient basis, three years does seem a reasonable time point to look. The recurrence rate is higher in the first three years and then falls off. The survival following recurrence is about a year. And the per patient concordance reaches its peak at about three years and then plateaus. And on an arm-by-arm basis, three-year disease-free survival from regression modeling is an excellent predictor of five-year overall survival.

Perhaps more importantly, we're interested in the question of: Does a comparison of study

arms using disease-free survival reach the same conclusion as if we used overall survival? Because that's what we really want to know: Does a new treatment do better than an old treatment?

In order to do this, we attempted to actually mimic the conduct of the clinical trial because at three years of minimum follow-up--some patients have been on the study for longer than that. Studies take two or three years to accrue, and so three years after the last patient is registered, some patients will have been followed for four years or five years. And so because we had the individual patient data, we attempted to replicate the analysis that would have been completed at the three- and five-year time points to try to answer the question: What if we did the analysis at the time that the analysis would have been done, not retrospectively?

We also have started to perform analyses at three years median follow-up as opposed to minimum follow-up, and the conclusions we're reaching are very similar on those endpoints. But

that is not a completed work.

Perhaps the most important slide, at least in my opinion, this plots the hazard ratios comparing control arm to the experimental arm in each study. On the x axis is the disease-free survival hazard ratio compared to the overall survival hazard ratio. We see a very tight concordance. Again, we have a Spearman rank correlation of 89 percent, and the R-squared from our regression is 0.87, indicating a tight and consistent relationship between hazard ratios for disease-free and overall survival.

The regression equation is that the overall survival hazard ratio is 0.09 plus 93 percent times the disease-free survival hazard ratio. If we look at the parameter estimates, we will again see the intercept is not significantly different from zero. The slope is significantly different from zero, but not significantly different from one. So, again, we cannot reject that the hazard ratio for overall survival equals the hazard ratio for disease-free survival.

To translate this into some real numbers, I have the panel on the right, where what's given is suppose we see a hazard ratio for disease-free survival of 0.6. What does that suggest for a hazard ratio for overall survival? And the translation is 0.65, and it ranges across the values of disease-free survival hazard ratios that we might see. And what we see is the regression equation suggests a slight attenuation of hazard ratios from the disease-free survival to the overall survival towards one. But it's a slight attenuation, on the order of about 10 to 15 percent. And I'll describe this grade in more detail.

For the statisticians in the audience, now I get to have some fun, if that's your idea of fun.

Looking at some formal measures of surrogacy, the proportion explained was proposed by Freedman in 1992 as follow-up work to work by Prentice in 1989. In essence, this approach fits two Cox regression survival models--one without the surrogate endpoint included, one with the surrogate

endpoint included.

If the surrogate is truly related to the outcome of interest, the surrogate should explain most of the variability in that model. And so what they propose to do is look at the proportion of treatment effect explained by the surrogate, and if the surrogate explains close to 100 percent of the variability, if they presume the surrogate, that would imply that it is a good surrogate.

This measure has been criticized by several authors for many reasons, one of which is that it's not actually a true proportion and it's not bounded between zero and one. Nonetheless, this is probably the most common method used, and so we fit that to this data set.

Here are the results from the two models. Looking first without disease-free survival as an endpoint, as a surrogate in the model for overall survival, this is the log hazard ratio indicating a very significant benefit for treatment when disease-free survival is not included a parameter in the model. When disease-free survival is

included as a parameter in the model, the p value becomes non-significant, indicating that the disease-free survival is explaining almost all of the variability in the endpoint.

When you calculate the proportion, you actually come up with 138 percent, validating the criticism of this measure that it's not a true proportion. Nonetheless, this does imply that disease-free survival may be a good surrogate for overall survival.

A more sophisticated approach was recommended by Burzykowski and colleagues in 2001, where they fit a bivariate copula survivor model, which, in essence, fits the survival model using--examines the effect of a set of covariates on both endpoints of interest. And if the effect of the covariates on both endpoints is similar, that suggests that the two endpoints themselves are similar. And so they defined two measures, a trial level R-squared to look at the concordance between endpoints on a trial-by-trial level, and an individual level to look at the per patient

concordance. And values close to one for both measures indicate surrogacy.

The results applied to this data set have an R-squared value of 0.85, confidence interval of 0.72 to 0.99, and at an individual level we have a concordance measure of 0.9.

How to interpret these results. In the paper that Burzykowski and colleagues published, they had an example from ovarian cancer, and they actually had values of R-squared and TAO very close to these values in their example. And their conclusion was that it seems plausible to conclude that this is a valid surrogate given the values that we see here.

This is a graphical representation of that method looking at the impact on disease-free survival time compared to the impact on overall survival time. These are log hazard ratios. The size of the circle is proportional to the sample size of the trial. Again, we see high, tight concordance between the two measures using this sophisticated model.

Finally, an approach I really tend to prefer, Begg and Leung gave a very simple measure. The validity of a surrogate endpoint should be judged by the probability that the trial results based on the surrogate endpoint alone are concordant with the trial results that would be obtained if the true endpoint were observed and used. Simple, straightforward, do they give the same conclusion? Who needs fancy statistics?

Of 18 total within-trial comparisons, we compared the two arms using the endpoint of disease-free survival, using the endpoint of overall survival, log rank testing. Straightforward, as simple as we can get.

Of the 18, 16 gave the same conclusion regardless of which endpoint you used. Eleven trials had no difference between the two arms for either endpoint; five had significant differences between arms for both endpoints.

There were two trials that were significant only for disease-free survival, but both of these had p values of 0.03, so only

marginal significance for disease-free survival.

That is shown graphically on this slide where for each of the 18 trials we have plotted in yellow the disease-free survival estimate and confidence interval, and in blue the overall survival confidence interval and estimate. And as you go in sets of two, you'll notice how similar within a trial the confidence interval and the estimates are for these two endpoints.

If you look more closely, you will see that most of the time the blue dot is a little closer to one than the yellow dot. What does that mean? It means that we have a slight attenuation of the effect, that the hazard ratio for disease-free survival is a little bit farther away from one than the hazard ratio for overall survival. But, again, this attenuation is very slight, and that's consistent as you go down the plot.

Focusing on two trials in particular, one of the comparison within the trial, NSABPC-04, and the other was an NCCTG trial from 1978, these were

the two trials where the disease-free survival hazard ratio, confidence interval, you can see that it excluded one, and it was significant. And for the overall survival, it included one, thus was not significant. And that's the same here. But you can see in both cases the disease-free survival hazard ratio got very close to one, and the overall survival hazard ratio hardly excluded one. So the results are really consistent with each other, and what we ran into was just a little bore edge effect there.

So the second set of conclusions. As an endpoint for comparison, the hazard ratio for disease-free survival is an excellent predictor of the hazard ratio for the overall survival with a slight attenuation. Marginally significant improvements in disease-free survival may not translate into overall survival. The formal measures that we have assessed do suggest surrogacy is appropriate for these two endpoints.

How to translate this into something that can be helpful and useful to the practicing

clinician--at least I hope. Let's suppose in a trial of 2,000 patients we observed a disease-free survival hazard ratio of 0.8. Using our model, you can translate this into a predicted hazard ratio for overall survival of 0.84. So we see that slight attenuation.

In addition, we can compute a 95-percent predicted interval for the hazard ratio for overall survival. In this case, it would go very 0.77 to 0.91. So in this case of a trial of 2,000, if you observe 0.8, you're 95-percent prediction interval for overall survival would exclude one.

We can do this not only for a value of 0.8, but we can do it for any observed value of disease-free survival and calculate bounds like this. Now, of course, that depends on the sample size from your trial. This example used 2,000 patients. If we instead use 1,000 patients--and these red lines are a little bit hard to see, but we can see that the lines fall outside the lines for 1,000. They get wider. The prediction interval is wider. And if you have a trial for

3,000 patients, the blue bands get narrower. So based on the sample size, we can see how sure we can be about our prediction.

Now, suppose we want to be sure--and I apologize, these red lines show up much better on my screen than they do here. Maybe I'll just go to the yellow line. Okay.

Suppose that we want to ensure that our overall survival hazard ratio--that the prediction interval for our overall survival hazard ratio excludes one. What we can do is go across the line and come down, and notice that if our observed disease-free survival hazard ratio is less than 0.90, our predicted interval for our overall survival hazard ratio will exclude one. And, also, for the case of 3,000, you can just calibrate it as you see fit.

In order to test the validity of this model, we have performed leave-one-out cross-validation. What does that mean? It means of the 18 comparisons, we took one out at a time, fit the model to the 17 that remained, used the

data from those 17 to predict what happens in the trial that we did not include in our model, and then see if the model based on the 17 predicts well on the one that we did not include their data.

Shown here in the blue dots are the predicted hazard ratio for overall survival based on disease-free survival. In the red are the actual results. And we can see that for 17 of the 18 trials, the actual result fell with the 95-percent prediction intervals. This is exactly what we would expect. If we have 18 and we're computing 95-percent confidence intervals, one of them should fall outside. Here it is. It fell outside, but just by a little bit. Also notice that sometimes the actual, which are the red, are above the blues; sometimes they're below the blues. So this indicates that the model is calibrated well and is predicting accurately.

Turning to a few points for discussion, we did have individual patient data from all of our trials. All of these trials used 5FU-based regimens. They did includes a mixture of Stage III

and Stage II patients. Our preliminary work suggests that the concordance is somewhat stronger for Stage III than it is for Stage II. That's not surprising because recurrences would happen more quickly in Stage III than in Stage II. But we're doing further analyses on that point, but we do feel that for trials similar to those that were included here, which included a mixture of Stage II and Stage III, these results should be relevant.

I think open for discussion is issues about how relevant this is to the current practice. For example, we now have more advanced--more effective therapies available in the advanced disease setting. We've improved the median survival from 12 months to 18 to 20 months. Having said that, most people who recur by year three still die by year five.

In addition, we have improved methods for detection of occurrence with improved imaging techniques, so perhaps recurrences are being detected earlier in a more curative state.

I think it's also open for discussion what

about non-cytotoxic or targeted agents. Perhaps instead of preventing a recurrence, perhaps just delay a recurrence. And if such agents are available, the concordance between these endpoints could decrease. Or maybe we just need to look at different time points.

Conclusions are that for the studies we've examined, disease-free survival is an excellent predictor of overall survival. It meets most formal definitions of surrogacy. There is a modest attenuation of treatment effect between these two endpoints on the order of 10 to 15 percent. And the model allows prediction of the benefit on overall survival based on what we observe for disease-free survival.

I close by acknowledging my many collaborators from around the world on this project and put in a plug. This is still not the final analysis that will be done. We have recently in the last few weeks gained data from three additional large trials. It will be included in the analysis to be presented at ASCO in June of

this year, and I did want to note that I did receive permission from ASCO to present this material at this meeting today.

Thank you very much.

DR. KELSEN: Thank you, Dr. Sargent.

So at this point we'll open the floor for questions to any of the four presenters, questions from the panel.

DR. GEORGE: You started off giving a nice presentation of why three-year disease-free survival, how it relates to five-year overall survival, and then you seemed to kind of drop that as you got further into it, talking about hazard ratios, which I assume were based on estimates from the whole data, not just restricted to three years and five years. Is that true?

DR. SARGENT: No, they were--the hazard ratios for disease-free survival were calculated using only the data from the first three years.

DR. GEORGE: And despite your elegant arguments for why that seems to work well, why would you not use all the data? Is this just a

pragmatic thing that you want to be able to predict it earlier?

DR. SARGENT: The question was not so much from an academic standpoint as it was--we have to--we took a pragmatic approach. We have to do an analysis at a certain time point. You analyze a trial, and the question is when can we analyze a trial. And really, the goal is: Can we analyze a trial more quickly?

And so if we're able to analyze a trial earlier and reach the same conclusions if we analyzed it later, that was something that we sought to show.

DR. GEORGE: But the thing that's still puzzling me about this is the three-year disease-free survival is sort of--it's like a per patient analysis, is it not? That is, you're really looking at, on each patient, whether--what's the chance of making it to the three years disease-free survival. It's not three years calendar time from the time you start the study, because they're two different things.

DR. SARGENT: That is correct. For the first set of analyses, which were on the per patient basis, it was to establish is three years a reasonable time point to look within a patient. Then we turned our attention to what happens when you actually analyze the trial, and you have to analyze the trial at a certain time point, and we chose what if we analyzed the trial at the three-year time point using data from all the patients, and if the patient had four years because they were entered earlier, taking advantage of that data.

So the first set of analyses was really to establish that three years is a sensible time point to look on a per patient basis, and then that was supported then later by is three years a sensible time point to look on a per trial basis.

DR. KELSEN: Dr. Brawley?

DR. BRAWLEY: Dr. Sargent, I want to congratulate you. I just sat through a statistics lecture, and I actually think I understand it. Maybe I need a head CT.

[Laughter.]

DR. BRAWLEY: The question is: You make a very strong argument for use of disease-free survival as a surrogate for overall survival when using anti-neoplastic agents. Can you speculate on how well this model would translate if we were to start looking at things like growth factor inhibitors, where instead of looking at disease-free survival we would be looking at things like progression-free survival?

DR. SARGENT: I really don't feel comfortable extrapolating beyond the range of the data and the trials that we included in the analysis. Thank you.

DR. KELSEN: Dr. Redman?

DR. REDMAN: Something along similar lines to that. With the model that you have set up, if we now go out five years from now--and I don't know what's going to be happening, but if we now know that the median survival for advanced or recurrent colorectal cancer goes out to 24 or 30 months, do you think this model will still hold? Or the other

question also is if we then push the time to relapse out with therapies.

DR. SARGENT: Regarding the first question, I think the model will be less sensitive to that because the magnitude--the advances that have been made in advanced colorectal cancer are wonderful. In absolute magnitude, they're still modest. And so if we increased the median survival from one year to two years, the reality is everyone who recurs year one, everyone who recurs year two, and most of the people who still recur in year three will still have an unfortunate outcome of death by year five. And so I think we need to have a pretty profound impact on survival in the advanced disease setting to translate into this model.

Having said that, it may be that we have to look at a later time point, and I think we have the opportunity with the collaboration that we've established and the data that we have, we've already been pledged to have data from some of the new trials when they become available. I think, of

course, the challenge is the five-year data is not available from those trials.

With respect to the second question, I think that's more up in the air. I think if recurrences are simply delayed as opposed to prevented, then I--and recurrences start happening more frequently out in the fourth year and the fifth year, then I think that could have some pretty serious consequences to the validity of this model, and it would need to be assessed again for those different agents.

I think Ross Prentice in his seminal work on this topic has made the point that a surrogate is really relevant and related to the treatments that are being used, and if treatments are used that have different mechanisms of action or influence the endpoints in different ways, then the surrogate endpoint that had been previously validated may not be considered valid anymore and would need to be re-validated for that new set of agents.

DR. KELSEN: Dr. Martino?

DR. MARTINO: Two questions, I think both to Dr. Sargent, but the rest of you may chime in.

First of all, I'm not sure that I now understand when you say three years, what we're counting from. So explain that to me first.

DR. SARGENT: Okay. We've done two sets of analysis. One is on a per patient basis, and that is three years from the date that they are enrolled in the trial

DR. MARTINO: Okay.

DR. SARGENT: The second set of analysis is on the trial-by-trial basis, and that is doing an analysis--presuming that we perform our primary analysis at the time point three years after the first--excuse me, after the last patient is enrolled. So we have three years minimum follow-up on all patients, but some patients may have four years, some patients may have five years, because they entered the trial earlier.

DR. MARTINO: And so which of those are you advising to this group? That's what I'm not clear on.

DR. SARGENT: Okay. I think what's relevant primarily for this group--I'm not advising anybody. I'm just presenting data. But I think from this committee's perspective, if I was sitting on the committee, you see data presented by a sponsor that compares two trials arms--a control arm and an experimental arm--and that's an analysis that's done with a specific endpoint at a specific time point. And I would suggest, based on this data, that for the type of agents that have been explored in this analysis, an analysis that's presented on disease-free survival three years following the entry of the last patient on study is an excellent predictor of an analysis that may be subsequently presented to this committee at a time point five years after the last patient is entered and on an endpoint of overall survival.

DR. MARTINO: Now, the other way that I've seen this type of data presented, predominantly in breast cancer, is that one actually specifies how many events you want to see, and then when those have occurred, you use that as the time point at

which you compare two arms. I need your thoughts on that way of doing things.

DR. SARGENT: Okay. That's an excellent point.

The time points are all related to the minimum duration of follow-up, and what this, in essence, presumes, if I was a sponsor organizing a trial, I would design my trial and design my hypothesis tests so that the number of events necessary to provide my power became available at the time we projected the last patient would have been followed for three years. And so this is all presuming that we have enough events to power our trial appropriately.

DR. MARTINO: Okay. And that gets me to my final question. As has happened in breast cancer in the adjuvant setting, I anticipate a similar behavior will occur in colon cancer, which is that as you have a few more agents that appear to work in the metastatic setting, you now to start to ask adjuvant questions in patients with lesser and lesser disease. And so presumably now a

three-year endpoint, however one defines that three-year, might encompass most of the recurrences. But as you start to look at lesser and lesser disease, that three-year won't quite be the same. You may have to wait for five years for patients with little disease to recur for you to then capture 80 percent or whatever percent of them you want.

So if I'm understanding that correctly, then whatever decision is made today may be less applicable with the passage of time, and that time might be even two years from now.

Do you understand my question? Am I making sense?

DR. SARGENT: Yes, absolutely. So to comment on that, I think that the results that I've presented today are relevant to trials that would be conducted with a similar patient population as were included in these trials. And these trials included a mixture of Stage II and Stage III patients. It was actually quite consistent, about a 60/40 to 50/50 split between Stage II and Stage

III's. I think in a study of just Stage II patients, these particular data may be less relevant. However, we have individual patient data. We are performing the analyses in just the Stage II patients and in just the Stage III patients to see if the concordance is as strong in each group. And as I stated, our preliminary results are that the concordance is stronger in the Stage III patients than it is in the Stage II patients. But having said that, if a trial has about this mix of patients, I think these results would hold valid.

DR. KELSEN: Ms. Roach?

MS. ROACH: First of all, I saw this presentation in November, and it was fascinating to see the work that was done since then. So thank you.

I have two questions, and both of them are pretty straightforward. If and when someone comes forward with a proposal for a trial for, say, Avastin and a 5FU-based regime for Stage III patients to delay and/or prevent recurrence, then

are you saying that this--they might be able to think about disease-free survival, but really, overall survival would need to be the endpoint on that because of the use of a biologic.

DR. SARGENT: Well, I think I have a comment and a response.

The comment is that I think it's up for this committee to decide two questions. One is: Is disease-free survival a surrogate for overall survival? But I think the other question is: Is disease-free survival an important endpoint on its own regard, irregardless of its relationship with overall survival?

And so if this committee feels that disease-free survival is an important endpoint on its own, then I think the question becomes less relevant.

With respect to, though, if the endpoint of disease-free survival is only felt to be valid due to its surrogacy or due to its relationship with five-year overall survival, then I do not believe this data would provide a support for that

surrogacy to hold with this different class of agents.

MS. ROACH: Okay. And then my second question is: Can you keep this going? You've started something really (?) here, and so how do you keep it so that in ten years it's not completely useless?

DR. SARGENT: Well, we've already established collaborations with many investigators, including the new trials that have been done with irinotecan and oxaliplatin in the adjuvant setting. Both of those investigative groups have agreed to participate in this analysis, and so we'll be able to update our analysis there. And at that time, that's all that there is out there. The biologics are just entering the adjuvant trials, and so it will be, you know, eight years really until that data is available, presuming they accrue for three years and have five years additional follow-up.

So I think that those questions are very relevant; however, I don't anticipate this committee would be seeing any such data for quite

some time.

DR. KELSEN: Dr. Brawley had a follow-up question.

DR. BRAWLEY: Yes, part of which has been answered. Dr. Sargent would you agree with the point that the correlation between disease-free survival and overall survival is a much tighter correlation than, say, as you apply years to it, especially when you look at the stage issue?

What I'm trying to say, in short, in as few words as possible, is as stage goes down, maybe disease-free survival needs to go up. But it can still maintain a good correlation with overall survival.

DR. SARGENT: I think that there are two factors that relate to that. One is, as the stage goes down, the time to recurrence probably goes up. The second is that, as the stage goes down, fewer of the deaths are due to the cancer and more are due to other causes. And so I think, A, the time point may differ for earlier-stage cancers, that we may have to look at three or four or five years

because recurrences are later. And, second, my expectation--and I don't have data to support this--is that the attenuation of the effect may be larger due to a greater proportion of deaths due to competing causes.

DR. KELSEN: It may be as stage goes down that it's not time to recurrence changes; absolute cure rate is higher, and the model for breast cancer may not be 100-percent valid. And so time to a non-cancer-related event may be much more of an issue.

Other questions? Yes, Dr. Rodriguez?

DR. RODRIGUEZ: I know that we were focusing on the analysis of correlation of disease-free survival with overall survival, but I also noticed that, you know, this covers a wide range of time frame for the studies. And I noticed that the design of the studies keeps shifting from initially the control arm being surgery only, now to arms using 5FU. So are you seeing a trend in this meta-analysis for longer disease-free survival, even as the complexity of the adjuvant

treatments increases? Is that true or not?

DR. SARGENT: Well, we have--two responses to that, I guess.

First is that we have explored the validity of the relationship over time. And has the relationship between disease-free survival and overall survival changed over time? The answer to that one is no. That has been very consistent. And, in fact, if you so desired, I could go and show that on a slide, the slide of the hazard ratios--maybe I don't have that. I think I do have that slide in there, actually.

But related to your specific question, I think, is have we seen over time the absolute benefit, and we've actually tried to stay away from such an analysis because that involves comparisons of non-randomized arms to each other. Nonetheless, that is something that we have observed, that the survival rates for either disease-free or overall survival from the trials performed in the early 1980s compared to the trials that have become mature in the late 1990s, though the overall

survival and disease-free survival rates certainly have improved over time, is that due to better treatments? Is that due to better staging? Is that due to better supportive care? Is that due to better surgery? We don't know. And so we have stayed away, actually, from making those sorts of comparisons of absolute treatment effects over time--excuse me, of absolute survivals over time. What we've focused on is the treatment effect over time, and is the treatment effect, comparing the treatment arm to the control arm, consistent--which it is.

I hope that answered the question. Thank you.

DR. KELSEN: Dr. Cheson?

DR. CHESON: To ask a somewhat naive question falling under the category of "we should be so lucky," but if we were to develop a much more effective treatment for relapsed patients, how would that impact on this? And how do you take into account the fact that this new therapy may have some sort of interaction with the initial

therapy, either positive or negative? Meaning it's going to work if you had x, but it's not going to work if you had y.

DR. SARGENT: Well, I think it is important to note that if we could triple the survival following recurrence, I think that would have an impact. I think, you know, in terms of the time points we're looking at, we're looking at a two-year window between the three-year time point and the five-year time point.

Once we start pushing the median survival following occurrence out past that two-year window, then I think it could really have a bigger impact on these results. We haven't seen that yet. Hopefully we will.

With respect to interaction between the treatment they received first and the treatment they received subsequently, we only have data on patients who were treated with a 5FU-based sort of thing initially. And I guess I really can't speculate as to if patients are treated with some other sort of agent up front.

DR. KELSEN: I have a question for FDA, for Dr. Ibrahim, related to using other tumors as a model. In breast cancer, three-year disease-free survival is recognized for approval of a new agent in the adjuvant setting as opposed to colon cancer, talking about today, and I think that you said it was because breast cancer recurrences were symptomatic. Does that apply to both hormonal therapy as well as cytotoxic therapy? And is it correct that the rationale for using three-year disease-free survival in breast cancer was based on the fact that women would be more likely to be symptomatic from a recurrence than, say, a man or a woman who has colon cancer? And is that still true with modern imaging today?

DR. IBRAHIM: I'm not sure I can answer that question. Maybe Rick or Grant--

DR. PAZDUR: Our opinion regarding breast cancer, which occurred many, many, many years ago, was based on the fact that it was believed that these recurrences were symptomatic. Okay? Whether one wants to believe that now or not believe it

with introductions of other imaging, closer follow-up of patients, et cetera, is open to discussion.

I don't know how much relevance that has here because I would see that the vast majority of recurrences from colorectal carcinoma, especially as our follow-up of patients and our radiographic imaging becomes better and more intense, that most of these recurrences are not symptomatic. So it's a little bit different situation. I don't necessarily think we have to rely on that it's occurred many years ago. I wouldn't use that as any regulatory precedent that we use that basis, because I don't even know if it would hold at this time. Perhaps Silvana would like to comment on recurrences and symptoms.

DR. MARTINO: Well, a couple of thoughts, Rick, because this is one of my issues as well. My impression is that sometimes the FDA has accepted three-year disease-free events, but for the most part, we tend to pilot things to five years, not to three, when we do, you know, large, intergroup sort

of trials. So I'm not sure that three years is where you've given most of the approvals in breast cancer. I believe it is closer to five. Number one. Okay?

But relative--so that's that. Okay.

Relative to patients becoming symptomatic, I don't think that that biology has changed. When a patient with breast cancer recurs, she generally is symptomatic, because often what drives the x-rays that you are going to do are, in fact, symptoms. Very rarely is it something else.

I don't understand the biology of colon cancer well enough--because this is what's going through my mind, is I keep hearing several of you who deal with colon cancer using this expression that they're asymptomatic. And I'm assuming what that means is they've got something in the liver, for the most part, and it's not causing them a new problem, though I'm not sure how you figured it out that they had it in the first place. But there must be some time point where they do become symptomatic, and one of the things I need to

personally understand as I think about disease-free survival as a valuable endpoint onto its own, exclusive of survival, is if you do have this asymptomatic colon in a recurrent patient, is there some time span when you can say, well, within a year most of them are going to be symptomatic, anyway? Is there such an understanding biologically?

DR. KELSEN: Dr. O'Connell and I will both address that. I think Dan pointed out, first of all, that the time to death from recurrence prior to newer agents is about a year.

DR. MARTINO: But it's not time to death I'm interested in--

DR. O'CONNELL: It's time to symptomatic progression, and there have been studies done in patients with known metastatic colorectal cancer who were asymptomatic at the point of beginning the observations, and this was worked on by Dr. Moertel. The median time to progression is about five months, and 80 percent of patients were symptomatic within one year. But the median was

five months.

DR. MARTINO: So there is a reasonable correlation there that if you recur within that year, 80 percent will be symptomatic.

DR. O'CONNELL: Yes.

DR. MARTINO: So to me--and this becomes the issue in terms of is overall survival the only objective that we should be aiming for, because it strikes me that if symptoms follow reliably to that degree, that disease-free-ness is important.

DR. O'CONNELL: Yes.

DR. MARTINO: And is important all by itself. The other is wonderful, but it doesn't obviate that there's value in being disease-free because you will become symptomatic within a reasonable short period of time.

DR. O'CONNELL: I agree.

DR. KELSEN: Ms. Roach?

MS. ROACH: I have a follow-up question on that. What is the typical timeline, in your judgment, between symptomatic progression--the development of symptoms and then death?

DR. KELSEN: I think Dr. O'Connell commented on this. There are several trials, not a large number of randomized studies of no treatment versus immediate treatment, which gave the symptoms, the Nordic trial and several others, and the time frames were exactly what Mike said.

DR. O'CONNELL: Actually, Dr. Miller presented some data at a workshop as well that if one looked at the point in time from progression, with advanced metastatic disease progressing, to the time of death, it's about eight months, and with salvage therapy out to 11 months or so. So, again, there's a period of several months from the time of developing symptoms until death. And I guess it wasn't precisely symptomatic progression that Langdon was talking about. It was any progression. The median time was eight months from the detection of any progression from metastatic disease, whether symptomatic or not, and death. And so presumably it would be shorter than that if it was asymptomatic progression, coming back to about the five- to six-month range again.

DR. KELSEN: Dr. Hirschfeld, you had a question?

DR. HIRSCHFELD: I have a question for Dr. Sargent, and I, too, want to congratulate you on the initiative of this very intriguing analysis. Several of our colleagues around the table have pointed out the potential limitations of the analysis with regard to types of therapy, types of products. We're particularly interested in immunotherapies, among others. But we haven't yet discussed alterations in how one measures progression, and there have been a lot of developments in looking at PET scans and other types of imaging techniques, as well as other potential techniques.

So to maintain the interest and to follow Ms. Roach's suggestion of having this as an ongoing project, what other types of analyses then would you entertain or explore to look at disease-free survival and overall survival, other than your landmark analyses, which has been pointed out is a shifting target already?

DR. SARGENT: Well, I think the trials that were conducted and included in this analysis were conducted in, for the most part, the pre-PET era and had very protocolized follow-up. And so I guess what further analysis would we conduct, I think we would want to look now--once we look at some new trials--at the method of assessment of the recurrence and is it true that, say, PET-detected recurrences are as highly correlated with survival as non--as physically detected or x-ray or CT. I think the new trials actually provide much richer data sets than many of these older trials that collected very much bare-bones sort of approaches. And so I do think there will be a number of additional pieces of information that we can look at.

With respect to immunotherapies in particular, I guess the jury is still out, and we have to get some actual data on five-year assessment with those therapies.

DR. KELSEN: Dr. Pazdur?

DR. PAZDUR: I think, you know, several

people have brought up, well, what if our evaluation techniques change? What if the drugs change? God knows. Okay?

As a discussion here, I think we have to point out where we are now. Obviously, we can always reassess where we're going to and what changes will be impacted. But I kind of want to direct the attention and the flow of the discussion, because we have a lot of material to cover here, toward what we have at hand. We could always talk about what will be a new improvement in ten years or five years, what will be the role of PET scanning, what will be the role of this and that. That will impact--then we as a regulatory agency have to make that decision.

I'll just parenthetically add that, even though we are allured by new mechanisms of actions of drugs, many times, at least in the advanced disease, we've seen very consistent effects on established endpoints--Avastin, for example, having a consistent effect on our ways of measuring anti-tumor activities or response rate improvement

and improvement in time to progression or improvement in survival.

So even though drugs may have a different mechanism of action--and, granted, it's in the advanced disease--they still may ultimately express their effect on more conventional endpoints. But here, again, I think our time is somewhat limited here, and we could go off and hypothesize in multiple different directions. But we're here, we're working in 2004, and let's keep the discussion to that and move forward.

DR. KELSEN: Any other questions of the panel? Dr. Brawley?

DR. BRAWLEY: In follow-up to what Dr. Pazdur just said, because there are some points that I had, if you look back over the last 30 years, you've got a number of trials as technology has changed over time. Lead-time bias has been introduced with each introduction of each new technology. Even within CT scan generations, we've increased lead-time bias.

The randomization and the fact that the

trial is all being done at the same time has always sort of equalized that, and the one thing that we can do, Rick, is look backward and we can see that the development of CT scan, the introduction of MRI and so far the introduction of PET scan has not really changed disease-free survival as a good correlate for overall survival.

DR. KELSEN: Any other questions from the panel or from FDA?

[No response.]

DR. KELSEN: If not, we'll then go to the open public hearing portion, and there is one speaker, I believe Mr. Carroll. Before we have Mr. Carroll's comments, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Board, the FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral

statement to advise the committee of any financial relationship that you may have with any company or any group that's likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or group's payment of your travel, lodging, or other expenses. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MR. CARROLL: Thank you, Mr. Chairman, and good afternoon to the committee. My name is Kevin Carroll, and I'm employed by AstraZeneca in the role of global statistical leader for oncology, based over in the U.K. What I'd like to do for the next ten minutes or so is to share with you some thoughts and some data that I believe are relevant to your discussions with respect to the use of progression as an endpoint in colorectal cancer

studies.

My time is limited, and I do hope you'll forgive me if I rush through these slides a little.

In response to the workshop in November and the calls to look at progression and survival data in the first-line setting, we at AstraZeneca did look at our experience in this area with Tomudex, and we found that the data that we have in that clinical trial and program support progression-free survival in the first-line setting as a true surrogate for survival.

Furthermore, we undertook a brief review of the emerging mixture in this area and found that the observation made in our Tomudex program was generally supported by the literature.

Furthermore, as we saw yesterday, there were considerable concerns about using progression-free survival in terms of issues relating to the timing of the event and potential introduction of bias. As we move through these next few slides, I hope to share with you an alternative analysis being an event count analysis,

which I believe provides a simple alternative to the analysis of PFS time and avoids the kinds of concerns that we have seen yesterday.

Lastly, we maintain that progression is a meaningful endpoint in and of itself in first-line colorectal cancer and, given the complexity of crossover and the increasing number of available effective therapies, should be employed as the primary endpoint in the first-line setting, which is a view that is common with views expressed in the literature.

In the mid-1990s, AstraZeneca sponsored a program of three Phase III randomized trials of Tomudex versus 5FU in the first-line treatment of advanced colorectal cancer. On this next slide, I briefly show you the results of these trials, primarily to indicate that there is a treatment effect on both progression-free survival and overall survival in these trials. And, therefore, in the same way as we've just seen, we can formally assess whether there's any evidence of surrogacy in this setting in this data set.

When we do that, we find indeed that there is evidence based on these data that PFS is a true surrogate for survival in this setting. As has been mentioned before and also a has been discussed in the committee in the past, progression is not a matter of correlation--sorry, surrogacy is not a matter of correlation. What we're trying to establish is whether the effect of treatment on the endpoint of interest--in this case survival--is mediated through an effect on an earlier endpoint. In simple terms, this means that if we were to do an analysis of survival and we adjusted for the early effects of progression, would the treatment effect on survival vanish? And, indeed, if we do that analysis on this data set, what we find is that a survival analysis adjusting for progression-free survival is no longer significant, and that suggests that progression is indeed a surrogate, at least in this data set.

Furthermore, there are more sophisticated means of assessing surrogacy, and I think we've just seen some of those touched on. And if we

apply these more up-to-date techniques, we're able to predict the effect of a 5FU-like treatment on survival given its effect on progression. And I think there's a mistake in your slides--in your handout, and what we find in the Tomudex data is that if progression was increased by, say, 50 percent, we would expect survival to be increased by around 29 percent, with a confidence interval as shown. And I think such predictions are going to be useful if we're thinking about using progression in the first-line setting.

The positive association between the effect of treatment on survival and the effect of treatment on progression-free survival is displayed in this figure, which is very similar to the one that you've just seen. And this is using the methodology published by Buyse and Molenberg recently.

What we see here, the circles are actually regions in the trial program, in fact, distinct countries that participated in the Tomudex trial program. And what we see is there is a significant

correlation between the effects of treatment on PFS and the effects on overall survival. And that further supports the surrogacy of progression-free survival in this setting.

Of course, the little bit of data I've shown you on Tomudex in response to comments made in the workshop is really only one small piece of data, and I think we clearly have to look at all the available data in order to place this information into context. And I just placed on this slide the recently emerging and published information in the first-line setting where I think you can see that there are large effects on progression-free survival across a number of trials which generally, but not always, are translating into survival benefits. Clearly, the interpretation of these data is made complex by crossover issues, by maturity issues, and follow-up issues. But, nevertheless, I think you might agree that these data tend to support progression as an endpoint in this setting.

Very similar to the previous presentation,

what we really need to do here is to apply a meta-analytic approach to all the available first-line data in order to truly establish once and for all the relationship between progression and survival in this setting, and that would be something that AstraZeneca would very much support as a willing participant.

Now, moving on briefly to talk a little bit about issues in using progression--and we saw a number of issues debated yesterday, and this slide, in fact, was also used yesterday, where clearly progression-free survival time is not known with complete certainty, and that can lead to overestimation and bias, and this is of great concern.

The key question in my mind is: What can you do about that? And I think there are a number of very complicated, sophisticated ways of trying to deal with complicated sensory mechanisms and a number of assumptions for the timing of event, and I'm not sure that any of those methodologies are really satisfactory.

One simple approach that might be considered, I think, is as an alternative, or at least in support of PFS time analyses, that we actually compare treatments on the basis of an overall event count over the trial follow-up period. This is an idea which is actually very similar to the single time point approach that I think was discussed both in the workshop in November and also in the Advisory Committee in December. And I'll show you a quick example of that in a moment.

Essentially, if you were to employ an event count analysis, the benefit that you would have is that you would be comparing treatments free from concerns about the timing of the event, which was at least one of the issues yesterday. The treatment effect--the difference between treatments could be described usefully in terms of the relative risk of progression over the follow-up period, and, furthermore, it's relatively straightforward to show that if you use this alternative endpoint, there's relatively little

loss in statistical power. And, in fact, in circumstances where the treatment effect is delayed so the Kaplan-Meier doesn't open at the beginning but opens at some later time point, it's actually more powerful than the regular way we look at data today. And, therefore, I would think that this kind of event count analysis should at least be considered as a supportive analysis when looking at analyses of progression-free survival time because it provides reassurance with respect to a lack of bias and provides reassurance that perhaps conclusions on PFS time are robust.

As I promised, I think it's helpful just to illustrate this endpoint with an example, and this slide is rather complicated so I'll just take a moment to explain what's going on here.

What we can do is we could take a regular Kaplan-Meier curve and we can break the follow-up axis along the bottom as shown on this slide here. The blue circles on this slide represent the hazard ratio derived from the regular analysis of PFS time, and the red circle represents an analysis of

an event count, ignoring the time to progression and getting around some of those problems we talked about yesterday.

So if we consider the first three months of the Kaplan-Meier curve--sorry, the first six weeks of the Kaplan-Meier curve, what we see is that whether we do an analysis of PFS time in a regular way or whether we do a simplified analysis of the events that occurred over that period of time, you get essentially the same answer.

If we extend the follow-up period to a 12-week follow-up and then do a PFS time on the first 12 weeks and get the hazard ratio--and we plot that in blue--we can also calculate the relative risk just on the numbers of events. And, again, you can see that the two analyses are very similar and so on through follow-up.

What this rather complex slide shows you is that there is really no difference between the outcomes achieved when you use a PFS analysis and a simplified event count analysis in this trial. That suggests that the PFS conclusions reached

here, at least, are robust. There is no bias introduced because we see results that are supported by a simpler analysis of event count. And I think, therefore, this provides some reassurance that we can employ simpler methods of the data analysis and collection in first-line colorectal trials and others when looking at PFS.

In summary, then, I would just close by saying that AstraZeneca's Phase III program data on Tomudex provide evidence to support PFS as a true surrogate for first-line colorectal cancer. The recent literature I think is supportive of that observation, that improvements in PFS are generally followed by improvements in survival. Furthermore, there are always concerns using progression-free survival, and I think we can consider an event count analysis as at least as supportive analysis if not a direct replacement for the regular analysis of PFS time when concerns exist about the imputation of times and also asymmetric follow-up. And, of course, an event count analysis can accommodate and get around the issues of asymmetric

follow-up.

Finally, I would just say that, irrespective of whether we ever formally and convincingly establish surrogacy between PFS and survival using rigorous statistical methodology in the first-line setting, we would maintain that progression-free survival is a clinically meaningful endpoint in and of itself. And given the issues of crossover and an increasing number of therapies available as second-line treatments, PFS should be employed as a primary endpoint in clinical trials in the first-line setting.

Thank you for your time and attention.

DR. KELSEN: Thank you, Mr. Carroll.

We have time for one question. Dr. O'Connell?

DR. O'CONNELL: Yes, I just wanted to make a comment that at the workshop the one point for further research that emanated from that meeting was exactly what you just suggested to do. In fact, a formal meta-analysis from the cooperative groups in the United States to determine the

association between progression-free survival or time to progression and overall survival to have a more broad view than the two or three or now four studies that have been discussed so far.

DR. KELSEN: Thank you, Dr. O'Connell.

At this point, we're going to take a--do you have a question, Rick?

DR. PAZDUR: I have one. AstraZeneca did three trials with--and I don't think you mentioned the results. What we're obviously interested in is: Does time to progression, if you measure it, predict for survival, subsequent survival? And of those three trials that were using time to progression, how did that correlate with survival in those individual studies? If you take--I think it was like O11, O12, I forgot the actual numbers. I don't know the data specifically--

MR. CARROLL: Yes, I'm very happy to talk to individual trial results. I think it's a very good question. I did flash up a slide very briefly, but time was short so I went straight past it.

What we have, there were three trials, each of about the same size, and what you find is that in two of those trials you can individually apply the formal Prentice criteria for surrogacy, and in two of those trials we see that about half of the effect on survival is explained by the effect on progression-free survival, which is very consistent with putting all the data together, which is what I've shown on this slide.

So the individual trials support the overall result in terms of surrogacy, and if we apply--the other methodology that could be applied is the Buyse-Molenberg that we've seen before where we try and predict the effect on survival given the effect on progression. And that methodology can be applied to two trials because one of the trials showed a very small effect and, therefore, it was kind of difficult to apply that methodology. But in the two trials where we could apply this alternative methodology, again, we saw that there was a correlation, a significant correlation between the effect on progression and effect on

survival. So the overall results I've run through quickly are supported by the individual trial data. And, in fact, we will be publishing this material with the--

DR. PAZDUR: So what you're saying, if you took all three of those trials, in two of them if we made a decision does PFS correlate with survival and improvement in survival, we would have been correct in two of those trials. There was an improvement in PFS. And then subsequently in that trial, it was correlated with a positive effect on survival. That was present in two trials, and then in the third one it was not. Is that what you're saying?

MR. CARROLL: No. I'm saying that there's one trial where individually you can't apply--the criteria we've talked about today require special conditions to be in place for significant effects and endpoints. So you couldn't, strictly speaking, apply the criteria to some trials, so we don't know. But the two trials we could apply the criteria, we could predict survival given the

progression effects.

DR. PAZDUR: Okay. Thank you.

DR. KELSEN: If there are no further questions, we're going to take a ten-minute break. We'll reconvene at 3:20.

[Recess.]

DR. KELSEN: Okay. Before we start, Dr. Pazdur wants to make a few comments.

DR. PAZDUR: In my introductory comments, I forgot to make a very important comment, and that deals with the process that we're going through looking at the endpoints. And I'd like to express the agency's personal gratitude to both ASCO, the American Society of Clinical Oncology, and AECR for their efforts in assisting us with the various workshops we've had. They've done a terrific job. The people involved have been excellent in coordinating multitudes of activities that go into these workshops.

So, again, I wanted to bring that up, and I was remiss in not doing so. Thank you.

DR. KELSEN: Thank you, Dr. Pazdur.

If we can turn to the questions of the committee: In December, the committee discussed the issue of disease-free survival as a general matter dealing with many tumors. And what the agency would like us to talk about today is limited to colon cancer, not discussing other tumors.

I think everyone has had a chance to read the questions to the committee. I'd like to go to Question No. 1. I'll read Question No. 1, and then we'll open it for discussion.

Question 1: For colon cancer drugs, could an increase in disease-free survival compared to standard therapy represent clinical benefit and be an adequate basis for regular drug approval?

We'll open that now for discussion.

DR. PAZDUR: One point that I'd like to bring up is obviously we are assuming that there is a sufficient magnitude of effect, obviously if the magnitude comes into being and is the data quality appropriate, et cetera, assume that that's a given. We realize that that's a given.

DR. KELSEN: And assume that it's either a

very large adequate trial or trials.

Discussion from the committee? Dr. George?

DR. GEORGE: I'll start. I think the answer is yes, based on what I've heard and know, but it's what we know today with the current therapies and the current modalities for detection and so forth, all those caveats. But that's all we have to go on. I think the future may hold something different, but so I'd say certainly the answer is yes here.

DR. KELSEN: Dr. Brawley?

DR. BRAWLEY: I think the answer is yes, and I'd actually also propose thinking about something that would be a little perhaps innovative. You could give a tentative approval or some type of approval based on disease-free survival, and then that same cohort or the same study population could ultimately be studied to get overall survival later on.

During the period of time between the initial approval for disease-free survival, you

could actually--people in the United States could actually use this drug, and then there would be a secondary review at the time the overall survival data was available.

DR. KELSEN: Dr. George?

DR. GEORGE: I think, though, what you're talking about there sounds more like accelerated approval. What this is talking about is disease-free survival as a clinical benefit itself, which would be regular approval, unless you're proposing to change--

DR. PAZDUR: Correct. To follow up on Otis' answer, basically, we normally would take a look at mature survival data, with the caveat that we're very interested, as Mike pointed out, that there isn't any decrement in survival. That's an important point, and we've done this with multiple applications outside of this area.

DR. KELSEN: Yes, Steve?

DR. GEORGE: I don't want to keep jumping in here, but that's sort of Question 1(d), I think. Could we--

DR. KELSEN: Yes, we'll get to--

DR. GEORGE: Do you want to wait to come to that?

DR. KELSEN: What we're going to do is we're going to discuss and vote on the big print, on the big question of regular approval. And then depending on the vote of the committee, we'll then look at the subcategories (a), (b), (c), and (d) as they apply.

Ms. Roach?

MS. ROACH: My answer is yes, but, as long as the novel treatments coming down the pike, the work that's done--that's been done to show the relationship is continued to keep showing that relationship and the clarity of the relationship.

DR. KELSEN: Thank you.

Dr. O'Connell?

DR. O'CONNELL: Just to clarify what Dr. Pazdur said, a regular approval for three-year disease-free survival would entail examination of the five-year survival to be certain that there wasn't some delayed detriment, and that it wouldn't

be necessary to look at simply accelerated approval at three years to assure that survival would be subsequently examined. Is that right?

DR. PAZDUR: We would negotiate with the sponsor to look at that. That would be part of the agreement.

DR. KEEGAN: Actually, I'm concerned that you don't confuse a required committee to collect the data with an agreement. Regular approval would be completed upon the three-year disease-free survival data. So you may or may not get the five-year data. We would ask for it, and it could be an agreed-upon commitment. But we wouldn't have the same ability to withdraw an approval based on failure to complete that commitment, for instance, which may be a distinction without--

DR. BRAWLEY: Yes, I'm accepting reality. I was at the beginning of my comment expressing what I wish the law would allow. I understand the law does not allow that.

DR. KELSEN: Dr. Williams?

DR. WILLIAMS: I'm hearing a little bit of

confusion of comments. Dr. Martino earlier mentioned the concept that there might be symptomatic recurrences and, therefore, disease-free survival itself was a clinical benefit, I would guess regardless of the time or the setting, et cetera, that delaying that suffering was the endpoint. But I'm also hearing comments that, well, as long as things don't change, et cetera, which would suggest that it primarily is the surrogacy for survival that's driving you.

So I don't know if you want to clarify whether--that if you beat the best thing out there with regard to disease-free survival in any realm and would that be clinical benefit, or would it only be tied to this particular set of analyses that have to do with surrogacy for survival?

DR. O'CONNELL: From my point of view, there would be clinical benefit associated with an improvement in three-year disease-free survival per se, not as a surrogate. But I would also want to know what the long-term outcome is going to be to

be certain there wasn't some unexpected deleterious effect on overall survival.

DR. WILLIAMS: But you're not requiring that it fulfill the presumed surrogacy--

DR. O'CONNELL: Correct.

DR. WILLIAMS: --just that you don't have a bad outcome.

DR. O'CONNELL: Correct.

DR. HIRSCHFELD: I'm sorry. A clarification. I think the question is disease-free survival without a specific landmark analysis attached to it, and it's not three-year disease-free survival or some other prespecified--I think that's--

DR. KELSEN: That is correct.

DR. HIRSCHFELD: --the point we're seeking advice on.

DR. KELSEN: Correct. That's number (a).

Dr. Rodriguez?

DR. RODRIGUEZ: I just had--I guess it's for clarification. If indeed for whatever reason subsequently it was found that this combination or

this drug did cause unexpected mortality, I assume the same process would follow through as is done with, for example, the cardiac drugs that were found to cause premature death?

DR. KELSEN: Dr. Pazdur?

DR. PAZDUR: For any approval, yes, if there is an unexpected toxicity associated, we would review that, bring it back to this committee, and the drug could be withdrawn, that indication.

DR. KELSEN: Dr. Taylor?

[No response.]

DR. KELSEN: Other questions for discussion?

[No response.]

DR. KELSEN: Okay. So I will read the question again, and then we will vote on this question. And I've been asked to make sure everybody pauses a little bit after the person before them so they can get all the votes down correctly.

So we're voting on the following question: For colon cancer drugs, could an increase in

disease-free survival--not yet defined--compared to standard therapy represent clinical benefit and be an adequate basis for regular drug approval?

MS. ROACH: Yes.

DR. SARGENT: Yes.

DR. O'CONNELL: Yes.

DR. BRAWLEY: Yes.

DR. MARTINO: Yes.

DR. TAYLOR: Yes.

DR. REAMAN: Yes.

DR. REDMAN: Yes.

DR. KELSEN: Yes.

DR. CHESON: Yes.

DR. GEORGE: Yes.

MS. HAYLOCK: Yes.

DR. CARPENTER: Yes.

DR. RODRIGUEZ: Yes.

DR. DuBROW: Yes.

DR. KELSEN: That sounds unanimous to me.

So the recommendation of the committee is that disease-free survival be considered for standard--as a clinical benefit for full approval.

And now I'll ask for brief discussion and comment, if any, for 1(a), which for the audience asks the question--guidance for the duration at which that time point should be. Should that time point be three-year disease-free survival or five-year disease-free survival or presumably some other point in between?

DR. PAZDUR: And just to follow up on Grant's question so we are clear on this, what this unanimous vote is saying is that you all feel that this is of benefit in itself.

DR. KELSEN: Three-year versus five-year. Comments? Discussion? Dr. Carpenter?

DR. CARPENTER: I think everything we've heard rather careful and extensive study on is three-year, and the lack of information, well-documented information and careful study on the other endpoint, it would seem the most sensible to use the one that's been the best studied now and leave it open to alternative durations.

DR. KELSEN: Dr. George?

DR. GEORGE: My comment on this is that

three years, I think, seems reasonable as it exists now, but it's a three-year minimum follow-up, I think is what we're talking about, because the accrual period could vary widely, and we're talking about a minimum of three-year follow-up on each subject, or at least enough follow-up on enough patients for three years to have a reliable answer.

So I think there's some fuzziness here in whether we want to be looking at three-year--a real three-year disease-free survival or we just want enough follow-up on all patients so we're reasonably sure to have captured a--gotten a reliable answer to the question we're trying to ask, and that three years was based on primarily because that's where the action was, so to speak, that's where the events were occurring.

So I don't particularly--I'm not particularly sold on the idea of looking at--say when you end up looking at this one point in time, three-year disease-free survival.

DR. KELSEN: Dr. Williams?

DR. WILLIAMS: Again, I think it depends

on what we're talking about. The reason that you would pick three years--certainly we've seen a lot of good comparisons to survival. But if you take the philosophical attitude that it's benefit, it would seem less important for that. But, of course, it is near the plateau and perhaps if you'd like to get away from, you know, where most of the action has occurred--I mean, do you have any feelings regarding--out of the context of surrogacy, why three years?

DR. GEORGE: You're asking me? No, I think as with any disease, you'd want to be sure that you have gotten to a point where you're reasonably sure that most of the events have occurred. If you do it too early, you're liable to fool yourself. So you want to go out far enough.

Now, that could change with time, with therapies or improvements or such, but that's why I say I don't like sticking with the--I don't like just saying three years versus five years. I think it should be more dependent on--I mean, if you enter everybody--suppose you had a trial that

accrual was so rapid that everybody entered on the first day. Then in three years, you'll have most of the events. But if you have another trial that takes years to accrue, you're going to have those early patients who will have some information, but not the later ones. And so you want to go far enough so you have enough information to make the analysis an appropriate one.

DR. PAZDUR: I have a question for Dan and for Mike, NSABP and NCCTG. When you're doing an adjuvant study, you're follow-up, your initial analysis, your three-year analysis which you normally do, would it be three years following the last patient, or is it a median of three years follow-up? Because, remember, we're getting most of our data now on many of these adjuvant protocols from the cooperative groups, and I need to know their understanding on this point.

DR. SARGENT: I'll answer first, Mike. It's actually an event-driven analysis as opposed to a time-driven analysis. But our general policy, within NCCTG, at least, is to base our estimation

of when that would occur based on a projected event rate and accrual rate to project that analysis to occur at about three years after the close of enrollment. And so it's really event-driven as opposed to time-driven, and I'd just like to make that point to emphasize what Dr. George indicated, that I think it's very important to note that my analysis that has been conducted did not just look at the single time point of three years. It used all the data from the patients up until a time point three years after the close of randomization. It used hazard ratio and logrank tests. It did not look at a specific rate at a specific time point.

T5A DR. O'CONNELL: The NSABP trials are also event-driven, and so there are several interim analyses and final analysis after a given proportion or a certain number of events occur, same as the NCCTG.

DR. KELSEN: Dr. Martino?

DR. MARTINO: I just want to underscore the importance of these last few statements that were made, because we've been throwing around this

three-year thing as if we all knew what it meant, and there really are at least three possible things that I understand it could mean. I'm sure the statisticians have more. And so this becomes--you know, understanding what we mean by this to me is very crucial. You know, recognizing that some of these things are, in fact, driven by the inter-group relationships, but there are drug companies now who also run their own adjuvant trials.

And so unless you have a clear understanding, I could see me sitting here with someone saying, yeah, but to us, three years didn't--wasn't event-driven but, rather, was three years from some date.

So we need to be very clear that we're unanimous on this.

DR. KELSEN: I was actually going to ask if you wanted to reformulate the question for us or just leave it in this general sense back to you of three-year disease-free survival.

DR. WILLIAMS: I think we understand.

DR. KELSEN: Dr. Taylor?

DR. TAYLOR: I just wanted to say what she was saying. It can't be just three years from the start. You have to make a definition.

DR. KELSEN: Any other discussion?

DR. SARGENT: The data that I presented is three years minimum follow-up on each patient. Now, having said that, this is an ongoing analysis, and we've started to look at three-year median follow-up, and the initial results look very promising with three-year median. But a member of the audience during the break said, well, what about two years? What about some other time? And so I think that's still a question for ongoing investigation, but the data that we've looked at so far does support the three-year minimum follow-up time point and consider all data available up until that time point.

DR. WILLIAMS: And I think you've made a good case that three years is when you're approaching the plateau of the curve, and that seems like a reasonable basis. So we're hearing

three-year minimum as your recommendation at this point in time.

DR. KELSEN: Yes, do you need us to vote on this, or are you satisfied with the tenor of the discussion?

DR. PAZDUR: We're satisfied.

DR. KELSEN: Okay. If there's no further discussion about that, (b) and (c) sort of are answered since we voted in favor of regular approval as representing clinical benefit. Would the agency like us to discuss (d) for guidance.

DR. PAZDUR: Yes.

DR. KELSEN: So I will briefly read (d). I will summarize 1(d) for the panel.

Consider a study in which there is a statistically significant difference in disease-free survival, but after adequate follow-up there's no evidence of a survival effect, there is no survival trend in favor of the experimental arm. Would increased disease-free survival alone be adequate for approval in this setting? If so, discuss the nature of the clinical benefit from the

increased disease-free survival when there's no survival benefit. That is, the study's presented and disease-free survival is clearly improved, but you look at the curves and it doesn't look like survival is going anywhere.

Discussion? Dr. Martino?

DR. MARTINO: Well, I think we actually have discussed this, and I think the point that was made originally was that we felt that in and of its own this would be a valuable clinical endpoint. The only caveat is if there had been a bad survival outcome, in which case, you know, you have recourse to how you handle that. But it would not--but other than that, I think we've answered your question. Haven't we?

DR. PAZDUR: I think you've answered it, but what we're looking for is a little bit of clarification why. Because there are some of perhaps a more conservative element that would say, you know, if you're just saying that you're sparing people toxicity of chemotherapy for advanced disease, or you're treating a far larger portion of

people with chemotherapy in the adjuvant setting. So why specifically in your clinical judgment do you think an improvement in disease-free survival is important?

DR. MARTINO: Well, what you all have reminded at least me of today is that when a person recurs, you can sort of anticipate that within some months--and those months aren't many--that, in fact, they will be symptomatic. And so for me, that is good enough. I'm quite satisfied that preventing symptoms is valuable.

DR. KELSEN: Dr. George?

DR. GEORGE: To follow up on that a little bit, two points. One is the clinical benefit is in, number one, that progression follows fairly shortly; and, number two, there's something we haven't discussed, I think, in that there's a psychological aspect that I'm willing to sort of accept, that if someone says if you delay progression it's a good thing, sort of face validity, almost, which I'm willing to accept that. Of course, I wouldn't be willing to accept it quite

as readily if there weren't this knowledge that there are symptoms coming soon after.

Now, here's the problem with the survival thing, though, that I don't know--I think we have to really think this through. If you do have regular approval for disease-free survival and then continue to follow for survival, there's at least a theoretical possibility that some new agent would have some weird mechanism of action that could have a nice effect on disease-free survival and have some longer-term deleterious effect on survival through some mechanism that we don't know about.

Now, in a particular study if you were to look at that, what might happen? You might approve it based on disease-free survival, and you say, well, as long--you gave the example of having, say, no effect on survival. But that implies, if you had no effect on survival, that you're really not ruling out an actual decrement in survival. I mean, you could actually have survival look better, not be significantly better. By usual statistical things, approaches, you would say, well, you really

haven't ruled out a slight negative effect. And if you had, say, the two survival curves lying flat on top of each other, you haven't ruled out probably a pretty big decrement. This has to do with the same kinds of arguments that are made in non-inferiority kinds of studies.

But that could put you in a quandary. I mean, you could say--especially it would put you in a quandary if survival starts looking a little worse. I mean, it may not be worse, but it's--you really are worried that maybe what we've done here is approve something that looked good in disease-free survival and, in fact, overall survival could actually be worse, despite all our work in looking at this as a clinical benefit in itself and as a surrogate. So that's a worry?

DR. PAZDUR: I realize you're worried, and we would be looking at this, and I think most sponsors would be following patients for survival. Why? Well, obviously, if they have a survival benefit, they'd want to make that survival claim.

Now, the question that I have which we

asked for a first-line setting, but is really germane here, if we moved away from survival as a primary endpoint of a trial when we discuss these to a disease-free survival, what should the studies be powered for? Because that is a question. And, remember, if we don't ask a survival question and have under-powered trials, we have the potential of never knowing that we have, you know, affected survival, which would be very deleterious, I think, to the field of oncology in general, not to really have an accurate depiction of what our therapies really give patients.

We would be happy to have a primary endpoint of disease-free survival and perhaps a secondary endpoint where the trial would be powered. Obviously, it would have more patients, a trial powered for survival. Am I correct on that?

DR. SARGENT: Well, the event rates for disease-free survival after three years of follow-up and for overall survival after five years of follow-up are virtually identical.

DR. PAZDUR: So they're not different.

DR. SARGENT: So the power--the sample size should be the same.

Now, recognizing that if the trial follows the pattern of these, there is that slight attenuation of the impact. And so if the question is do we need adequate power to detect the slightly attenuated effect, then you may need a somewhat larger trial for overall survival, but not by very much. We're talking about the order of 10 percent, and the suggestion that I gave, I think, in November was that if you did power it for disease-free survival at, say, a hazard ratio of 1.4, you might consider powering it for--overpowering it a little bit for, say, 1.35, which would then give you the power to detect overall survival at 1.4, assuming a slight attenuation.

DR. PAZDUR: But we could, to allay Dr. George's fear, in the formal statistical analysis plan require an analysis and data submission as part of the move away from survival, looking at it as a secondary endpoint. And obviously you would

have to win on overall survival as you--I mean, you would have to win on disease-free survival to look at overall survival. But one would think one would do that anyway, you know, the natural history of the disease.

DR. KELSEN: Dr. Williams?

DR. WILLIAMS: I think embedded in this question is the concern about what should you expect to see with regard to the survival hazard at the time you do this minimum three years' follow-up. And I don't know. Certainly things do change over time, also, with treatments that may have an effect on survival. So I don't know if we should be expecting to see a trend in survival, if it's going to occur, at the time you would do this analysis. Do you have any idea? Should you be expecting a trend in survival?

DR. SARGENT: At the three-year time point?

DR. WILLIAMS: Yes.

DR. SARGENT: I wouldn't count on it. We haven't looked at that issue specifically, but the

rate of death at follow-up time does not have that sharp spike. People continue actually to die at a pretty uniform rate over the first five years, and we know that because we've tested the validity of some of the statistical models. For example, an exponential survival model fits very well for overall survival, which in essence assumes that your risk of death each year is constant over time. An exponential survival model does not fit for disease-free survival because there's this sharp spike in recurrences earlier that falls off later.

So I think to answer the question, none of the data that we have analyzed would suggest that there should be a clear, significant benefit for overall survival at the three-year point just because there is one in disease-free survival.

DR. WILLIAMS: And I wonder, do some of the earlier studies that were using no treatment or just surgery, might they have seen a little more of an early survival effect, you know, than the later studies that include an active adjuvant arm--I mean, the control as an adjuvant arm?

DR. SARGENT: I'm trying to make sure I understand the question. Could you rephrase the question?

DR. WILLIAMS: Well, would you--when there was not an active adjuvant--active control arm, would you have seen a survival effect earlier, perhaps, you know, so you would have seen a survival trend earlier than you would now where the active control arm has an adjuvant active control?

DR. SARGENT: It's actually been pretty consistent over time that if the curves separate, they separate relatively early and continue with the separation, and that's been consistent both in the early trials and in the later trials that we've looked at.

DR. KELSEN: Steve?

DR. HIRSCHFELD: In addition to a decrement in survival, there's also interest in and certainly we have intentions to follow other events which could be catastrophic, like second malignancies, and these have shown up in some circumstances or some delayed neurologic

impairment.

DR. KELSEN: Right, and with new biologics it may be not five years, it may be seven years. It could be some other time.

Have you had enough discussion and guidance from us and we don't need to vote on that?

DR. PAZDUR: Yes.

DR. KELSEN: Okay. So at this point we have voted in favor of accepting disease-free survival as representing clinical benefit and approval, regular approval, and we'll move to the next question, Question No. 2, which I'll read, which now deals with advanced patients, presumably Stage IV patients. When a surrogate endpoint for clinical benefit is needed in advanced colon cancer, would the preferred surrogate endpoint be progression-free survival or time to progression? Discuss progression-free and TTP in the first-line treatment setting first.

Discussion from the committee. Dr. Sargent?

DR. SARGENT: My point I guess would be

that I don't think either TTP or PFS has been validated as a surrogate endpoint in this setting.

DR. KELSEN: Other comments? Steve?

DR. GEORGE: We should probably have a clear-cut definition of a difference in these two endpoints. I had a question about this before.

DR. WILLIAMS: Primarily the deaths are included in progression-free survival.

DR. GEORGE: Right. That's the difference, and the question--that makes the question about the time to progression where you could have deaths without progression. There is still a question of how those are handled. This is sort of a technical point, maybe, but, you know, it's a competing risk kind of problem.

DR. WILLIAMS: The point that Tom Fleming at the workshop was that his belief was that the clinical benefit endpoint should include deaths because obviously it's a very important outcome.

Of course, there are those who believe that the more pure tumor endpoint is time to progression. If you're trying to measure tumor

effect, that would be it. So, you know, there are two different views on this.

DR. KELSEN: Dr. O'Connell?

DR. O'CONNELL: I guess I would argue in favor of including death in the parameter to be assessed for a couple of reasons: one, if a patient dies and you don't have any information about the cause of death, these patients all have proven metastatic disease and there's a higher likelihood that cancer contributed to that patient's mortality in the advanced disease setting.

And, secondly, if the patient dies because of toxicity related to the treatment, that's awfully important to know from a clinical standpoint.

DR. KELSEN: Dr. Redman?

DR. REDMAN: I tend to agree with that. I think including all deaths because sometimes we don't know what the relationship is between the treatment that we administer and a comorbid condition that exists in this population.

DR. KELSEN: Can I ask the agency to comment on this? The question is asking, if we chose between these two alternatives as surrogates, the current regulatory stance is a survival improvement. So is this question asking--

DR. WILLIAMS: Those are, you know, the next questions. But as we go forward in our next questions, are they going to be PFS or TTP? Then you can answer the heavy questions.

DR. KELSEN: All right. Let's discuss the light question first.

Dr. George?

DR. GEORGE: Well, I'll go back to that definitional issue, and I think it's the progression-free survival that should be used for reasons both because all these things we don't know about the deaths that nominally don't occur with recurrence, but also just from a technical point of view, it gets more difficult to do those kinds of analyses. They're not as simple. And so I think for both those reasons I would prefer the progression-free survival.

DR. KELSEN: Ms. Roach?

MS. ROACH: One of the things that came up very clearly in the discussion yesterday were the problems with using either kind of progression endpoint as a surrogate endpoint or a real endpoint, such as how to deal with new lesions and validating the progression of non-measurable disease. How--can you formalize that process?

DR. WILLIAMS: Yes. We definitely are working on that, and we're going to be working on the guidance and have internal work on it, and we're going to certainly have some external discussion and comments. So we certainly think it needs a lot more work.

DR. PAZDUR: I'd like to amplify that point. I think that's an excellent point, Nancy, because that was, you know, a major problem with some of the applications that we have seen.

I think oncology in general has relegated this progression-free survival kind of to this nebulous area where one doesn't address and approach this with rigor. I think we've outlined

some of the problems with it that will need to be put forward, not only in a guidance but in a plan, prospective plan that the company writes, which may be different from one drug to another here. I think there's pros and cons of how to handle this. But it has to be prospectively managed--interval between assessments, what to do if somebody misses a visit, how to handle the independent radiology committee that is looking at this data versus what the investigator brings forward. One cannot, after somebody has taken a look at the data, decide, well, I'll go with the investigator or I'll go with the independent review committee. Obviously this inflates error rates.

In colon cancer, we may want to look just at the radiology review since most people don't have physical findings to that degree and in a randomized study they'd balance out.

But this needs to have attention. We're talking internally about how to review the x-rays, how many of these x-rays to look at. We are not, obviously, going to look at 10,000 x-rays at the

FDA. We're going to be auditing x-rays in that regard.

The issue is one of--and I'm glad Dr. DuBrow is here--including radiologists as investigators, and I think that needs to be done because it has to be--these reports that we get have to have a uniform meaning to them. We can't just get these vague reports that the radiologists give out--"There is a suggestion of a soft-tissue mass. Clinical correlation is indicated."

I think there's going to have to be identification of a radiologist at each site, adequate resources directed toward that individual, measurements of the lesions prospectively by that given radiologist.

DR. KELSEN: Dr. DuBrow?

DR. DuBROW: Can I just add one thing? That is, in your original conception of the protocol that you've built into it radiographic techniques that allow you to compare one study with another so that the exact same technique is used each time on the same type of scanner with the same

type of intravenous contrast, et cetera. Otherwise, these studies become impossible to compare.

DR. KELSEN: Dr. Taylor?

DR. TAYLOR: I'm going to have to have a very specific definition of what progression is going to be because I think that can be very vague as well. It makes a study a much more difficult study for those of us who may be in Kansas and who their patient comes in from Winfield to Kansas City with their scans, and it's easier to always do it in Winfield. That's a big deal for some patients, and you may end up scanning them that day emergently, and you're comparing other scans. It makes it more difficult in many ways for the investigator.

DR. PAZDUR: To follow up on--remember, this criteria that we used were meant for response criteria, not progression criteria, also, and so we really need to revisit the whole area.

DR. TAYLOR: You have to define that.

DR. KELSEN: Dr. Redman?

DR. REDMAN: I can't avoid a political statement. So you're in favor of reinstituting the funding budget to the cooperative groups up to the level that was approved?

[Laughter.]

DR. PAZDUR: I love all cooperative groups.

DR. KELSEN: Other discussion?

[No response.]

DR. KELSEN: Would you like us to vote on this point for you?

DR. PAZDUR: Yes.

DR. KELSEN: So I'm going to phrase the question as follows: When a surrogate endpoint for clinical benefit is needed in advanced colon cancer, the preferred endpoint is progression-free survival. Yes means yes, and no would mean that you don't accept that.

MS. ROACH: Does yes mean yes with all the caveats we've put in there?

DR. KELSEN: Yes always means yes with all the caveats.

MS. ROACH: Yes.
DR. SARGENT: Yes.
DR. O'CONNELL: Yes.
DR. BRAWLEY: Yes.
DR. MARTINO: Yes.
DR. TAYLOR: Yes, but I would like to see it validated in some way.
DR. REAMAN: Yes.
DR. REDMAN: Yes for PFS.
DR. KELSEN: Yes.
DR. CHESON: Yes.
DR. GEORGE: Yes.
MS. HAYLOCK: Yes.
DR. CARPENTER: Yes.
DR. RODRIGUEZ: Yes.
DR. DuBROW: Yes.
DR. KELSEN: Two unanimous votes.
So we will now go to--we're now recommending PFS as the surrogate, and now the question--Dr. Pazdur?
DR. PAZDUR: Before we get into Question No. 3, I kind of want to lay out where our

discussions in the agency have gone, looking at moving away from survival, because I think it's important for people to realize that this has undergone extensive discussion in the agency for years. Okay? And we can't just look at this as, you know, one day we got up and we just think PFS is better than survival.

And when you're discussing these questions--and I think this is particularly germane in colorectal carcinoma as we have more and more agents available--the results of the oxaliplatin first-line trial I think is a good example of this--is the effect of--confounding effects of therapies.

In essence, when we began our discussion on Monday, which many of you weren't here, we laid out some principles that one reason or several reasons to move away from survival might be some disadvantages. These would include crossover or confounding effects of other therapies, if there was a particularly long follow-up in the natural history of the disease, for example, in indolent

lymphomas or carcinoids where it would be almost impossible to look at survival data in a meaningfully expedited fashion; and, thirdly, the large numbers of patients that are frequently required.

But we have to have a reason of why we're moving away. It can't just be we wake up one day and, okay, we have a new committee here, the committee five years ago or ten years ago voted on survival, and now that there's new members here.

So I'd like to hear some discussion of why in this particular disease setting--and perhaps I've already laid it out for you--is the reason.

DR. KELSEN: Okay. So we'll open that for discussion. Dr. O'Connell?

DR. O'CONNELL: I think you did lay out the--

DR. PAZDUR: Not to lead you.

[Laughter.]

DR. O'CONNELL: Well, you don't have to lead very hard because that's exactly what I think. It's interesting that the treatment of colorectal

cancer is migrating--is becoming much more similar to the treatment of breast cancer over the years. And many of the issues that we as GI oncologists never had to face before, we're suddenly confronted with. And with the multiple alternative drugs that are now available, it makes it very difficult to use survival as a primary endpoint to evaluate the initial treatment because of the effectiveness of salvage therapy. I think that's the main reason to consider progression-free survival as a valid regulatory endpoint.

It's not so much to shrink the sample size or decrease the cost of doing clinical trials or necessarily to make them more efficient. It will achieve all of those effects, but the real reason, I think, is that we now have to contend with--and it's a very good thing to contend with--the effectiveness of salvage therapy.

DR. KELSEN: Other comments from the committee? Dr. George?

DR. GEORGE: To follow up on that, Mike, are you saying then that progression-free survival

is a clinical benefit? Because I think we don't have the evidence for the surrogacy issue. But is it a clinical benefit in the same way just by simply delaying progression that is somehow in itself a benefit?

DR. O'CONNELL: It's a much more controversial point, I think, than with disease-free survival in the adjuvant situation, because here these patients all have metastatic disease, advanced, incurable malignant disease, by definition in going into the study. There's not the psychological benefit or psychological detriment of realizing that you have a recurrence in the adjuvant situation. You know that you have incurable malignant disease as you go into these treatments. So you don't have that psychological impact in the advanced disease setting.

And if one looks at a one- or two- or three-month extension of progression-free survival but pays the price of a 25- or 50-percent rate of grade 3 and 4 toxicity, how much clinical benefit has really accrued to the patient? And so I'm less

convinced that progression-free survival is of clinical benefit in its own right. I think that it is reasonably predictive of survival. I don't think that the data is nearly as robust for progression-free survival as it is for disease-free survival in the adjuvant situation. But the AstraZeneca data that we heard today, the two trials that Dr. Miller presented, and a meta-analysis that was referred to, all suggested that progression-free survival did have some correlation or surrogacy to overall survival.

Now, Dr. Sargent may have some additional information that might tend to go a bit against that argument, and perhaps he should share another meta-analysis that I wasn't aware of.

DR. SARGENT: I think the data is actually relatively consistent on this point, and that is that there is a moderate correlation between PFS or TTP and overall survival. The data that was presented today had a proportion explained of about 50 percent. Previous analyses have also shown about a 50-percent proportion explained. Some

relationship--I think it is actually pretty well established that it's not a surrogate marker in this case. I think further analyses are probably required, but there certainly, from my opinion, is not evidence of formal surrogacy in this case.

DR. PAZDUR: Could I make a point or ask you a question? This was done from a retrospective--a meta-analysis, I take it, your statements?

DR. SARGENT: There is a publication by Burzykowski and colleagues in 2001, Journal of Royal Statistical Society Series C, that actually did explore this exact point. It was a limited analysis, and they actually concluded that there is no evidence to support formal surrogacy of disease--actually, I believe that was TTP and overall survival. Not to say they didn't consider that there was a relationship. There is a relationship, there is a correlation, but it does not meet formal surrogacy criteria.

DR. PAZDUR: The issue that I wanted to bring up is if it was a meta-analysis done on

earlier trials, remember the magnitude of the effect has a great deal to do with the relationship between the surrogate endpoint and the eventual outcome. If we took a look at response rates, for example, in colon cancer, the response rates in the 5FU era were 15 percent, with 5FU-leucovorin, and now we're approaching 45, 50 percent in some trials. Again, partial responses.

Would you take a look at--do you think that that could have had some influence on it?

DR. SARGENT: Absolutely. I think you can only--a surrogate is only as--can only be as strong as the effect is. And if there's a modest effect, then the surrogate can only do so much. So I guess my point is that with respect to 5FU-based treatments where the analyses have really been conducted, the multi-study analyses, they haven't demonstrated it. It indeed become stronger with respect to the new regimens, but those analyses just haven't been conducted at this time point.

DR. KELSEN: Ms. Roach?

MS. ROACH: I have a question for Dr.

Hirschfeld or Dr. Keegan. Along this line, as the new--and I know I'm not supposed to talk about the stuff coming down the pike, but there are some things in the pipeline that seem fairly close to coming to FDA for evaluation. And they are much less toxic, or at least that's my impression. And one of the things that--one of the issues that comes up with treatment on a consistent basis is as you're dealing with people who are progressing, you don't want to put them in--I'm sorry. It's been a long day for everybody. You don't want to expose them to a toxic therapy, but if the therapy isn't toxic, does that change the whole endpoint discussion? Does that change the framing of the discussion?

DR. KEEGAN: I would say that for some of the biologic products where there's been a perception that they have a relatively modest toxicity profile more in the range which is observed with hormonal therapy, that that has been taken into account in that the presumption is, as for many of the hormonal therapies, rightly or

wrongly, that there isn't really a lot of treatment-related toxic deaths, which was part of the feeling behind the need to assess survival for the more toxic anti-neoplastic therapies.

I think my concern is that we started with the presumption that biologics might not be very toxic, and I think what we're seeing is that what they really have is a very different toxicity profile. For instance, we don't see traditional cytopenias and alopecia, but we see other things. And that I think we don't have a lot of experience weighing into whether or not that could ultimately have a very negative effect both on, you know, quality of life or even survival if they could do that. I think that that's one of the concerns.

I think the other is that I'm a little leery of going--I understand what Dr. Sargent said about the fact that we've got a lot of data with anti-neoplastics and we don't have a lot of data with the biologics yet to know if the same predictability, the same relationships are going to hold.

So I think we're looking at two changing fields at the same time, and it's a little hard to, on the one hand, say, well, I'm sure that all the efficacy relationships will hold but the toxicity issues won't really apply, they shouldn't come into play here.

I would rather consider if we were going to treat them in a similar fashion, treat them kind of similar across the board, by and large, and not make a presumption before we have the data that, in fact, they might have the same kind of survival impact or toxicity concerns that some of the more traditional products--or at least not with as little information as we have.

DR. HIRSCHFELD: I'd like to respond also. I think the biggest driver in terms of the attractiveness of the therapy is not the anticipated toxicity, but it's the effect size. And I think with the evolution of small molecules as well as the biologics and immunotherapies, we will always evaluate the toxicity versus the benefit in making decisions. And presumably the benefit would

always outweigh whatever toxic events or adverse events may occur. But what drives the field forward is the effect size, and there we will have to see as these data come in. And then we can go back to Dr. Sargent and ask him for a new analysis.

MS. ROACH: I have kind of a follow-up on that or just a comment real briefly. I think this discussion shows how complex this issue is, and I think that transparency of process and product is critically important to bring people along as we're dealing with all of these different shifts in the landscape. And I would urge FDA to be more forthcoming during reviews and approvals. For example, posting the material, the briefing material for ODAC is great. That still leaves an awful lot of products where that kind of material isn't posted. And I think that that's the kind of thing that will help bring the community along and help them understand why you all are choosing to do what you do.

DR. HIRSCHFELD: All approved products have--just a point of information, all approved

products have the reviews posted now on the Internet. The only reviews that are not available publicly are for those products which are not approved at the time they're submitted.

DR. KELSEN: Dr. Taylor?

DR. TAYLOR: I want to go back to the fact that we haven't validated this. I'm a little bit uncomfortable in that I understand the problems with survival and I'm very accepting that we don't have good ways of determining these things. But we've kind of thrown out response rate for various reasons, partially because we don't think it necessarily correlates with survival, and now we're going to be willing to accept what I would have defined as stable disease on a number of Phase II trials in that patients aren't progressing, they have very stable disease. And I think we do have to validate whether that truly means something.

I'm also less willing to say it is a clinical benefit as I see a lot of people in the palliative care setting who are not progressing but have very miserable lives. And you can have a very

stable disease and have lots of symptoms, and I'm not sure that it--I just really hope that we can find a way to validate this or find some other means.

DR. PAZDUR: Let me address that issue. You know, when we're talking about stable disease, we're usually talking about a single-arm trial. Here we would be requiring a randomized study with a robust finding in this, and I think that's other areas that we might want to discuss, how robust, how real that finding is.

Remember from my previous comments, we have to first figure out if it's real, and then the robustness of this and its relationship to toxicity comes into play here, to get back to one of the points Nancy was addressing.

The other issue that--you know, we are fixated on this correlation between survival and PFS, but remember, one of the other issues that has been promulgated by the agency is not only is the effect of a drug could be manifested by an improvement in the quantity of life, but also in

the quality of one's life. And I'm not talking about quality-of-life tools here. I'm talking about if people would consider this a relatively established surrogate if one had an improvement in progression-free survival or an improvement in one's quality of life, perhaps even when they're in that progression-free survival zone.

DR. TAYLOR: I think that's harder to define, though, and it certainly in a group is a much harder thing to define, because as you work with people and talk with them, there are some who are willing to trade coming to the doctor and taking chemotherapy and others who are not. So I think it's a much more difficult--I'm not sure it's your perfect answer.

DR. WILLIAMS: I just want to make the observation, I think Dr. O'Connell suggested that at first recurrence, most patients are asymptomatic; but then they subsequently progress and are symptomatic. So I would guess that at least in the first-line setting, most of those stable disease patients would not be predominantly

symptomatic until they progressed again. That I'm just reading into your earlier comment, Dr. O'Connell.

DR. TAYLOR: I think it depends on when they get to go on the study and when they decide and whether their doctor told them to wait until they were symptomatic to take treatment.

DR. KELSEN: Dr. O'Connell?

DR. O'CONNELL: I wonder if I can ask Dan to comment on the data that was presented at the workshop where there were 1,000 patients treated with irinotecan-based combination chemotherapy, where there was a substantial difference in treatment effect, about 50-percent objective response rates with the irinotecan combination treatments compared to the controls.

In those patients that received the irinotecan-based treatments, time to tumor progression--not progression-free survival in that analysis but time to tumor progression was highly correlated with overall survival, even when corrected for various prognostic discriminants

within a Cox covariate model. It's not a formal test of surrogacy, but does that data convince you or make you think that time to tumor progression would be a reasonable predictor of survival?

DR. SARGENT: It's part of the puzzle, but two trials looking at a single agent I don't think are sufficient evidence, at least to convince me.

DR. KELSEN: Other discussion from the committee?

[No response.]

DR. KELSEN: So a minute ago, if we had to choose a surrogate, we favored PFS. But the question we're being asked now is a different question, so I'll read this again before we vote on it.

For approval of drugs for first-line therapy of advanced colon cancer, presumably Stage IV, could PFS/TTP, understanding our previous discussion, benefit of a new drug compared to a standard first-line regimen comparitor on justify regular or full drug approval? And then the agency has got a small comment: Assume the standard

control arm has a known small survival benefit.

So we're now being asked to vote upon, unless we have further discussion, the issue of whether we would recommend regular drug approval. I don't know whether we'll then discuss it would have a role in accelerated approval or whatever.

Other discussion before we go to a vote?

[No response.]

DR. KELSEN: Okay. If not, Ms. Roach?

MS. ROACH: Can you start over there this time?

[Laughter.]

DR. KELSEN: Sure. Dr. DuBrow?

DR. DuBROW: Yes.

DR. RODRIGUEZ: Since I've gotten less convinced as I've heard later comments, I think my answer is no.

DR. KELSEN: John?

DR. CARPENTER: I'm going to abstain on this. I'm not sure.

DR. KELSEN: Okay.

MS. HAYLOCK: Yes.

DR. GEORGE: No.
DR. CHESON: Yes.
DR. KELSEN: Yes.
DR. REDMAN: Yes, as long as we get to the answers of four.
DR. REAMAN: Yes.
DR. TAYLOR: No.
DR. BRAWLEY: Yes.
DR. O'CONNELL: Yes.
DR. SARGENT: No.
MS. ROACH: No, not until we have all of the above.
DR. PAZDUR: A relatively mixed vote, I take it.
DR. KELSEN: It's an eight to five vote.
DR. PAZDUR: Eight to five. Okay. Let me throw out this suggestion for you. How about we're in a situation where we have a reason--we have an improvement in progression-free survival or time to progression, and the survival advantage is not demonstrated; however, there is convincing evidence that there has been crossover of therapies that

could explain why we're not seeing a survival advantage. Should we accept in that situation the effect on the "surrogate" of time to progression? And this is a real live example of many years ago.

DR. KELSEN: Yes, it certainly is. Open for discussion. There's a confounding variable that may have affected survival.

DR. PAZDUR: You can postulate a reason why you have not demonstrated a survival effect, for example, confounding of the survival analysis by crossover.

DR. BRAWLEY: But, Rick, by the same token, a placebo would do the same thing.

DR. PAZDUR: No, I'm talking about if you have a known--you know, if you have, say, a standard therapy or some--you know, not a placebo-controlled trial we're talking about. I'm talking about if you have a reason to deviate from your suggestion here, would there--let me ask it in another way. Is there any situation where you might deviate from this suggestion?

DR. SARGENT: I would deviate if two

circumstances were present: A, we have substantial evidence of differential crossover; and, B, there is a trend in survival in the appropriate direction. It may not be significant, but at least it's consistent with the PFS results.

DR. PAZDUR: Just to clarify, I realize you answered the question in the affirmative. For those who felt negatively about it, okay? And that's who I'm addressing this question to. Would there be--

DR. KELSEN: I think it's appropriate--

DR. PAZDUR: --sensitivity to not being so dogmatic as saying, no, I will only accept survival in those people.

DR. KELSEN: And this further discussion is appropriate because, clearly, the magnitude of the vote indicated how big the unease is and how controversial this point might be.

Is there any other discussion? Yes, Dr. George?

5B DR. GEORGE: I think my unease about it was because, unlike disease-free survival in the

adjuvant setting, progression-free survival I don't think has been established in the same way as the surrogate, nor is it obvious to me that it's the same--has inherently something in it that's a clinical benefit all by itself.

Now, with respect to the crossover issue, I've made this point before, but no one seems to listen, but I'll say it again just for a general point. That is, I think this falls into the example of something where you would like to get the answer to something but you can't get it; that is, you say I have this new treatment and I'm going to compare it to the standard. I'd really like to know whether it prolongs survival, but I'm giving this very early in the disease. I have all these other things that are liable to be given at some point for some reasons that I can't control. And all I can do is I'm doing this randomized study, and I'll observe what happens.

My point about this is that is the answer; that is, even--no matter what you try to do to try to explain it, the answer is if I start off trying

to give these two treatments, in the current setting with the available therapies and the real-world situation, this therapy did not prolong survival. Now, you can give reasons; it may be because of crossover, may be because of other therapies that were given. The answer is still the same. It didn't prolong survival.

So that's when you would definitely like to have something that could give you some answer that, like progression-free survival might tell you something biologically and say, all right, something's going on here with this therapy. But in the real-world setting, it doesn't prolong the survival. So that's the answer with survival. So if I'm stuck with survival--

DR. PAZDUR: Would you buy, for example, progression-free survival in that situation, or in any situation, to reasonably likely predict clinical--

DR. GEORGE: Yes, that's what I was going to get to. I think that it's like an accelerated approval kind of thing. I don't know if you may

want to talk about that.

DR. PAZDUR: Let me give you the scenario here so I think you people could understand the real-world situation that we face frequently. Obviously, people develop drugs and they are highly touted to be very effective therapies, and there's great interest on the part of patients to receive these therapies before they are approved. Many times we're requested both in the first-line setting, and even more advanced disease setting, that at the time of progression people will get a perceived effective therapy even though it hasn't been approved. And, therefore, we can get into problems when we have a survival analysis because, you know, both the groups of patients that are randomized eventually will get the drug.

We saw that, for example, in the third-line setting with oxaliplatin where the vast majority of patients entered on the trial in the third-line setting, I'm talking about, got the drug. More, I think, for the more advanced disease setting, the later disease--

DR. KELSEN: Since this is now a more pressing issue, let me just look at Question 4, as you wrap it into your discussion, because now that we've indicated by a split vote that PFS/TTP might be an acceptable standard for regular drug approval, the agency wants to know a little bit more, wants to know--does that mean they have to have a big difference between these groups? Could we discuss the magnitude of that difference?

We frequently are talking about trial and trials, so could the committee comment on point 4? Dr. Redman?

DR. REDMAN: Yes, just for those that voted no, I mean, is it an absolute, or is it a degree? If you have a randomized trial, drug A versus drug B, in a metastatic setting and the progression-free survival of the standard is two and the progression-free survival is ten months, and yet it's going to take another three years to find an overall survival advantage, is it an absolute no, you won't accept that? Or is it just a degree? Because I think that is what 4 is

asking. I mean, nobody's going to say, gee, there's a three-week progression-free survival, you know.

DR. KELSEN: Well, I think the agency is asking that question. That's exactly the question that--

[Simultaneous conversation.]

DR. REDMAN: I think that's dependent on the drug and its side effects, and I think that's what clinical medicine is. You can't make a cutoff and say, gee, you know, if it's one month, six weeks, you know, if we're going to do bone marrow transplant, you're going to be in the hospital for four weeks to get a four-week progression-free survival, I mean--

DR. PAZDUR: --asking the question because I want to get some degree of flexibility here on where people stand, because people see these votes and obviously can come down and say, well, ODAC said this; therefore, you must adhere to this. And I'm just wondering if we could have more discussion on people's flexibility on this point.

DR. KELSEN: So could we have comments--

DR. PAZDUR: Maybe magnitude of difference.

DR. KELSEN: Yes. Dr. Taylor, then Dr. Cheson.

DR. TAYLOR: I think that, as Bruce has said, I think you have to individualize it. I certainly wouldn't--I could be flexible if I saw a dramatic difference between it. But I think that we are choosing something that we haven't done before, and we have to be very cautious. And certainly some of the drugs we looked at yesterday, they would have had a--it had been on the market, and I don't think that would have been appropriate.

DR. KELSEN: Dr. Reaman and then Dr. Cheson.

DR. REAMAN: I would be flexible also, although I voted affirmative. But I think in general, the magnitude would have to be very significant.

DR. PAZDUR: You're not talking statistical significance.

DR. REAMAN: Clinically significant, not statistically.

DR. CHESON: I think it's not only quantity but it's quality, and one of the discussions yesterday we were talking about was there some change in performance status, was there some change in symptoms. And there's a difference between two months of good life and two months of, as Sarah was talking about before, really poor quality of life. So I think you have to be flexible and individualize somewhat both on the duration and what that duration means to the patients. And for those sorts of studies, you should encourage them to obtain that other information such as functionality--not necessarily formal fact quality of life and those sorts of things, although it's not a bad idea, but to get other measurements that would support it.

DR. PAZDUR: One of the things as we asked in--perhaps--I don't know if you want to comment about it, we would ask or we have been asking--in discussing about this, asking for the trials to be

powered for survival, obviously, and to look at that issue also.

DR. KELSEN: Dr. Carpenter?

DR. CARPENTER: It might be helpful if we just said that I think most of us would be looking in terms of months as opposed to days and weeks.

DR. O'CONNELL: Yes.

DR. CARPENTER: As far as an increase, if you were to give an order of magnitude. Then if you're talking about months, the other things that would be critically important would be the things that Dr. Cheson mentioned.

DR. KELSEN: Dr. Reaman?

DR. REAMAN: I'm just going to follow up on Dr. Cheson's comment, and, Rick, I think you mentioned that you were going to be preparing a guidance to industry, and I think it would be very important to include as part of that the suggestion, if not the requirement, to do formal quality-of-life questions or to address those issues.

DR. KELSEN: Ms. Roach?

MS. ROACH: My mom would love it if I was a doctor.

I think the problem with black-and-white answers on all this, while I understand you'd like certainty, is that there's always a degree of judgment. And so I think looking at it in terms of where we want to get and did we get there is maybe more helpful. So the orders of magnitude that you all are talking about are right by my perspective.

I also think that in terms of the evidentiary requirements, there is a ton of really interesting and intriguing imaging things coming down the pike, with volumetric measures and activity and things like that. And I think if we could use some of what we do here to validate the technology as well as validate the drug, it would be helpful to everyone.

And I also want to put in a plug for putting the funding back to the cooperative groups.

DR. KELSEN: So if I could summarize, what I think we've heard is that the committee was for and has added guidance about it being but a

substantial difference in PFS/TTP, and the magnitude of the evidence would be quite convincing.

Do you want us to discuss 5 as well or--okay. So I'll go to the last point on the agenda, which is: If one accepts PFS/TTP, what, if any, survival evidence should be needed? And the agency specifically wants to know whether the studies should be powered to rule out a negative impact on survival and whether or not they should be, on the converse, powered to look for a realistic improvement in survival. So if one accepted TTP or PFS. Dan, if you want to make a comment, or Steve?

DR. SARGENT: Well, my comment with respect to 5(b) is a three-month improvement in TTP that might translate into a three-month improvement in overall survival are very different elements. And requiring a trial, given the answer to No. 3 was yes, requiring a trial to be powered for overall survival may indeed be prohibitive given a modest benefit that may be expected in overall

survival.

DR. WILLIAMS: I think this was written considering a very realistic setting, whereas the competitor drug out there does have a survival advantage of two years. And I think, you know--two months, I'm sorry. Right. So in that setting, I mean, you have to think about would you or would you not be ruling out that you were inferior to the other drug.

DR. SARGENT: I think 5(a) is very reasonable. To rule out a decrement is very different than having power to demonstrate an improvement. And so I think my opinion on 5(a) is yes; 5(b) is probably no.

DR. KELSEN: Dr. George?

DR. GEORGE: When I first saw 5(a), I interpreted it a little differently. I thought you were looking at some non-inferiority trial which would--I would have said no because it's huge. But to rule out a specific decrement, I think it's a good idea to look for that to make sure that it's not done and to have that prespecified is a good

idea.

For (b), I'm a little less sure. It depends on the--you know, I guess the realistic improvement, I don't know what that means exactly, but--

DR. PAZDUR: Well, even now, obviously, when we ask for powers to be--the trials to be powered, there is a guesstimation of an effect. One of the reasons why we are interested in this is obviously we are facing increasing numbers of single trials that are coming to us, and sometimes trials that are underpowered, which leaves everybody in a quagmire of what to do with these trials. Do we have a real treatment effect? A fear that if we go to a time to progression or progression-free survival that would require a fewer number of patients, we'll see a gradual decrease in the size of patients numbers that are being entered on trials.

Again, if we never ask a survival question and power for some type of survival improvement, okay--and remember, we're asking for a robust

finding in time to progression which would probably translate into a smaller survival effect. One should be able to see that.

DR. GEORGE: What I was suggesting in this setting, it would be not necessarily to power to detect realistic improvement, as you've stated it here, but to design the study appropriately based on the time to progression and then look at--then address the issue carefully of what that means, what kind of things you could pick up with respect to survival, and when you could pick them up, and make sure that--I mean, I'm just saying this in sort of a subjective way. You'd have to just assess whether that seems reasonable, in other words, not do it in the usual way you design a study where you say I'm trying to pick up this kind of difference, but just say in this setting I can pick up this sort of difference at this time during the analysis. You know, giving plots, in other words, instead of just picking a point and saying I have a specified power at this alternative.

DR. WILLIAMS: I have to say I interpreted

the question a little bit differently. I actually helped to write it. But to rule out a survival decrement, I mean, one interpretation could be there's another drug out here with a two-month benefit and maybe I'm being compared to it. I want to make sure I haven't lost some of that. So that could be not very different from a non-inferiority study; whereas, (b), you know, somebody can always make some idea of how much survival you might be detecting. So I'm not sure--do you have any guidance on (a) what we should be looking for? We've got a little progression advantage, perhaps substantial, compared to a drug that has a two-month increase in survival. Do we need in any way to rule out we're losing that, or we just presume that we're not since we're--

DR. KELSEN: One of your problems would be because, as I think Mike said before--he had to leave--with more and more new agents coming down the line, where are you going to see where you lost the survival? I mean, how will you do that? And that's what I was wondering, because you'll now

have a first-line therapy, a second-line. We're talking about a third-line therapy. You know, we might get like breast cancer and have fourth-line and fifth-line therapies. And so where was it lost in this off-protocol, presumably, list of agents that the patient got? And I'm not sure procedurally how you'll be able to identify that quite so easily, but I'd be interested in how it statistically could be approached.

DR. GEORGE: This could be a real problem if you're looking at it the way you just expressed, as some kind of non-inferiority. It would be a real problem in doing the studies. And I think that's not what you want to do because that's--you know, they would be huge trials to answer--I mean, to not really address the really important questions in this area.

So I think you have to do something kind of pragmatic, is what I'm thinking here, that you would specify in the design something about what you're going to be looking for. But you don't design the study to be definitively sure that

you're not more than some small decrement below the control.

DR. WILLIAMS: So you're suggesting some kind of--basically a safety type decrement, in other words, I can rule out that, you know, I've induced some sort of survival decrement.

DR. KELSEN: I think one of the problems, you know, in this, since we're talking about a disease, in this disease, not like small-cell lung cancer, for example, if the patients who enter the first-line study are really almost asymptomatic or to a large amount asymptomatic, you have this window. So it's not--if you don't get them into remission on the first regimen you won't have time to get to that second regimen. And so it would be really hard for you to look, I think, for that you lost two months somewhere in there, but you'll have hopefully more than one shot with currently available therapy.

I'm sorry. Ms. Roach, you had a question? Oh, Dan?

DR. SARGENT: I think my proposal would be

somewhat of a confidence interval-based approach where we may not see an advantage for overall survival, but we have a sufficient sample size to estimate our confidence interval around our estimated effect on overall survival that does exclude a decrement in survival. So hopefully the hazard ratio, you know, may not be significant, but at least is in the right direction and the confidence interval is tight enough that we're sure that it's not indeed a decrement.

DR. WILLIAMS: And I guess the $100 question is: What is the size of that decrement?

DR. SARGENT: I think it's relevant to what the improvement was compared to the previous standard.

DR. KELSEN: Have we been able to answer the questions that the agency posed? Are there any other questions that you'd like us to discuss or any other points you'd like us to discuss today?

DR. PAZDUR: We did have the rectal cancer question, and I don't know if that is something people would entertain at this time, whether a

difference with rectal recurrence would signify clinical benefit. And we're talking about probably adjuncts to radiation therapy, that type of a situation.

DR. KELSEN: And just to refresh people's memory, when Dr. O'Connell gave his presentation, you might remember that he said the third point from the workshop, in addition to what we've covered today, was a recommendation that at three-year disease-free survival--sorry, three-year freedom from local failure in rectal cancer was a very meritorious thing to have because of the symptoms, and the agency I think is asking for guidance and what's the view of the committee in view of that.

DR. CARPENTER: That's regularly associated with symptoms, and it seems to be--that seems to be easier because clear delay or avoidance of major symptoms is just going to be a benefit, it seems to me.

DR. KELSEN: Yes, the issue they'd face is, you know, how you validate that they failed

locally but that's an imaging--doing careful imaging question.

DR. CARPENTER: That's definable.

DR. KELSEN: Yes, that's definable.

DR. CARPENTER: You could make some criteria of how you're going to do that.

DR. KELSEN: Is there any other discussion about that?

[No response.]

DR. KELSEN: Because we're making a broad recommendation in a few minutes. But it sounds like there's support for the workshop's conclusion that this is an important issue for the agency to consider as a different way of approving an agent.

Any other issues you would like us to discuss?

DR. PAZDUR: Not that I am aware of. I'm cognizant of the short discussion on this. We would bring it back to the committee or for external discussions with our consultants before we'd make any final agreements regarding the latter point, because I realize we haven't had sufficient

discussion on that. And plus many of the members have already left.

DR. KELSEN: If that's the case and there's no further discussion, I want to thank the members of the committee for their participation today, also for the opportunity to chair the session. Thank you very much.

[Whereupon, at 4:44 p.m., the meeting was concluded.]

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