sequellae: fatigue, decreased energy, and activity reductions."

This was the dosing regimen. It was a mixed population, nonmyeloid tumor types receiving non-platinum chemo. Interestingly, the baseline hemoglobin was less than or equal to 10.5, so very much in line with current standards. It did allow entry for patients with a hemoglobin up to 12, if they in fact had more than a 1.5 per gram per deciliter decrease in hemoglobin.

The primary endpoint was transfusion reduction, but secondary endpoints were prespecified and included, as I said, the patient report outcomes instruments that are well known to the oncology community, the FACT-N and the CLASS and the SF-36. Survival was collected in long-term followup.

The next slide, slide up.

(Staff complies.)

DR. ZUKIWSKI: In terms of the primary endpoint, there was a significant reduction transfusion requirement. Although the study wasn't powered for survival, there was a trend after a median followup of

26 months favoring the EPO treated patient.

Again, I think it is very informative in a study where the baseline hemoglobin levels were very much in line with current label guidelines. The hemoglobin level achieved was approximately 12.1. The thrombotic incidence was relatively low and similar in both treatment groups, and adverse events were comparable between treatment groups.

Next slide, slide up, please.

(Staff complies.)

DR. ZUKIWSKI: Again, here are the individual FACT and subscales. I present all three because there is a consistent benefit in both the general subscale, the subscale measuring fatigue and the subscale measuring anemia, showing that in EPO-treated patients there is a significant improvement in all three scores as compared to the placebo patients in which as you see all three scores decline. It is really this difference that we are measuring here that significant improvement for all three subscales of the FACT-N.

Next slide please, slide up.

(Staff complies.)

DR. ZUKIWSKI: Beyond the FACT-N instrument, which was used to measure patient report outcomes, this is the cancer linear analog scale, which as you can see here is also showing a consistent benefit for the three scales that are measured within this patient report outcome instrument, specifically, energy level, ability to do activities, and overall quality of life -- all part of the CLASS instrument for patient report outcomes and also showing the consistent benefit, showing a significant improvement in these three subscales for EPO-treated patients as compared to control.

We can go to QA8, please. Slide up.

(Staff complies.)

DR. ZUKIWSKI: In addition to INT-10, there are four other prospective randomized control studies of epoetin alfa with at least a hundred subjects per study. All four have demonstrated improved patient report outcomes in the EPO group as compared to controlled.

Now, not all of these are placebo-controlled, so I do want to emphasize that, but they nevertheless are randomized trials and three of which, one of which being the INT-10 study which I just mentioned, reached

statistical significance. All of them use similar patient report outcomes instruments.

CHAIRPERSON ECKHARDT: Can I ask you a question? Were any of these submitted as part of the registration package to the FDA?

DR. ZUKIWSKI: For the original labeling?

CHAIRPERSON ECKHARDT: Mm-hmm.

DR. ZUKIWSKI: No, one of them was, the Able study. Actually, why don't we go to QA-14.

CHAIRPERSON ECKHARDT: Dr. Pazdur.

DR. KEEGAN: I can say that INT-10, which was conducted with Eprex not Procrit, was not submitted to the FDA in support of quality of life claims.

DR. ZUKIWSKI: Okay. That is correct.

You can go to QA-11, please. Slide up.

(Staff complies.)

DR. ALBAIN: Was there a reason why it was not, if I may ask?

DR. ZUKIWSKI: We actually did have a discussion with the Agency in April 2000 Type C meeting to discuss the suitability of INT-10 being able to meet a labeled claim for epoetin alfa and the discussion was

around the methodology of the instrument, how the instrument was developed.

In that context, there were some limitations that were raised with the validity of these instruments being acceptable for supporting labeling claims.

DR. KEEGAN: I would also add that the design which allowed a heterogeneous population to be enrolled likely was also a concern for the FDA at that time.

CHAIRPERSON ECKHARDT: Okay.

DR. ZUKIWSKI: I do want to just make one more comment around the patient report outcomes and the ESA effect.

If we can bring up Slide QA-9, please. Slide up.

(Staff complies.)

DR. ZUKIWSKI: In addition to the individual patient-level data from studies, there are two meta-analysis groups that have specifically looked at patient-reported outcomes and included both of them, both the Cochrane meta-analysis as well as the AHRQ despite the fact of citing limitations, again, with the instruments.

Both, as you see, have concluded that for the Cochrane, an overall positive effect on health-related patient report outcomes from ESAs, that seems unlikely to be due to chance, and the AHRQ results which state that the results favor ESA treatment over control, but again stating that there is insufficient evidence for definitive conclusions.

I also would like to add that based on similar data, both the EORTC and the Canadian Cancer Anemia Development Guidelines, so two independent groups that develop guidelines for treating cancer-related anemia have both concluded that epoetin alfa produces significant and clinically relevant improvements in quality of life of patients with cancer.

CHAIRPERSON ECKHARDT: Thank you. We will move on.

Dr. Murgo, I know you had a question a while back.

DR. MURGO: Thank you. Actually, I have a question for Dr. Baynes regarding Study 103, in particular, the baseline characteristics. I refer to Company Slide C-53.

(PowerPoint presentation in progress.)

DR. MURGO: What I notice in addition to the baseline characteristics of the prior chemotherapy and gender, there being differences, the difference in the sample size in the placebo group versus the darbepoetin alfa group. In my opinion, a striking difference, 470 in the placebo group and 515 in the darbepoetin group.

One question, is there an explanation for why there is this imbalance? Two, are there any data -- I'm assuming that this is not the randomized population but the population that received treatment, and if that's the case, is there information about the patients who actually were randomized but did not receive treatment?

DR. BAYNES: Thank you for the question. Yes, indeed the study design was such that in fact all of these patients are randomized, but the randomization algorithm called for once a certain number of transfusions had actually occurred in the study.

The randomization changed from one to one to nine to one, so it was a prespecified alteration in randomization at the time of hitting a specific transfusion trigger point.

DR. MURGO: That was prospectively?

DR. BAYNES: That was prospectively defined, yes, sir.

CHAIRPERSON ECKHARDT: Thank you.

Dr. Martino.

DR. MARTINO: Two questions, if I may, one to the FDA. I want to get back to Dr. Albain's question on the quality of life issue. Why is it that we do not have quality of life as one of the approved values of this therapy? Is it simply that nothing has been brought forth? Is there argument related to the instruments used? Or, what is the issue there? And then I would like to ask another question, please.

DR. KEEGAN: The reason, it had to do with presentation of the data, the study design. We would like to see a randomized, placebo-controlled trial in a homogeneous population where patients have the same disease, the same stage of disease, and the same type of therapy.

We don't think that we can interpret it in a heterogenous population such as what is in INT-10. We also do have some concerns about the instruments, but I

would say that our concerns with the types of data that we have seen was more than just a concern with the instrument.

DR. MARTINO: Thank you.

The other question is to Amgen and to J&J. Part of my problem in thinking through all of this is that there really are too many studies and they become very jumbled in the mind. I am primarily struggling with the following.

If there is an issue that we are decreasing survival, what studies are there actually where survival was the primary -- not secondary, not tertiary, not tenth -- the primary endpoint that met actually accrual and for which we have data? That's what I want to hear. Is there such a study? Is there more than one? The hodgepodge of things that are presented to make our jobs much more complex and nearly impossible.

DR. KEEGAN: If you would like an answer from FDA, our understanding is the only such trial was the BEST trial in breast cancer where the primary endpoint was 12-month overall survival rates.

DR. BAYNES: I believe the 145 Study meets

those criteria as well as a prespecified survival study.

DR. KEEGAN: Yes, we would agree it was a co-primary endpoint of 145.

DR. MARTINO: Can I then assume that in both trials the driving force to the end number of patients randomized was in fact survival for both of those?

DR. PERLMUTTER: Yes, that's correct. But keep in mind that the 145 Study was designed to show superiority. That was the essence of the study. Based on prior results that suggested that one would get a superior result in that sense, and so was BEST.

DR. MARTINO: Okay. Don't leave.

(General laughter.)

DR. MARTINO: All right. Then, what I'm hearing is that both from the FDA and from the pharmaceutical companies is that, in fact, we have two trials that meet those requirements; okay. Would you then for me summarize the results of those on one and only one endpoint, which is survival?

DR. PERLMUTTER: Right. The 145 Study was, as we say, a study in small-cell lung cancer that was designed to look at a primary endpoint of survival, and

the result of that study was neutral as we previously described and those data have been made available to the FDA. Synopses have been posted.

The BEST Study, and I'll just slide up, you can see the diagram again for overall survival for the 145 Study. I think it is extremely reassuring that the darbepoetin alfa arm and placebo arm are overlapping in this way. The BEST study was a study that has other features to it, and I would like Dr. Bowers to come and describe that.

DR. BRAWLEY: An inferiority trial or a survival trial, what was the hypothesis of 145?

DR. PERLMUTTER: I'm sorry, Dr. Brawley. The hypothesis is that treatment with darbepoetin alfa would actually achieve a superior result. It was designed to show superiority with respect to survival.

DR. BRAWLEY: Am I correct you didn't show that?

DR. PERLMUTTER: It did not show superiority, that's correct.

DR. BRAWLEY: Is it fair then to say that it did not show a decrease in survival?

DR. PERLMUTTER: Well, that brings up an interesting question, which I would like to have addressed from a statistical point of view, because this came up in our discussion, and perhaps we should go to that now.

Jesse I wonder, Dr. Berlin, if you would come and address the statistical issue, and Dr. Snappen as well? Maybe we could have Dr. Snappen first from a statistical perspective. I think that would be helpful at this point.

DR. SNAPPEN: Okay. Once again, as stated, the 145 trial was designed as a superiority trial. It was designed to detect a true hazard ratio of .75 with 90 percent power.

As was stated earlier, as you heard, the fact that a trial designed to show superiority fails to show superiority does not mean that that trial has shown non-inferiority.

However, after the trial is complete, there is no difference in how you would conduct or analyze a superiority trial versus a noninferiority trial. In both cases, you would look at the final confidence

interval that is observed and compare the upper bound of the confidence interval to some limit that you would consider to be a worrisome limit.

In this case, for the 145 results, the upper bound of the confidence interval was a hazard ratio of 1.11, and so we can say just as if this had come from a noninferiority trial, it's excluded with 95 percent confidence an increased risk of more than 11 percent.

DR. BRAWLEY: You really believe that?

(General laughter.)

DR. SNAPPEN: Yeah. There is no difference in how a superiority and noninferiority trial would be analyzed. The confidence interval has the same meaning in both cases.

We have a non-inferiority expert from the University of North Carolina, Professor Gary Koch, who I think might have some additional comment to make on that.

DR. KOCH: Yes, it's Gary Koch, University of North Carolina. As you heard, the study was designed as a superiority study with 90 percent power to address a hazard ratio of .75.

The same size it has would have been comparable to the sample size you would have needed had you designed a noninferiority study to rule out a hazard ratio of 1.33 in order to demonstrate similarity if the true hazard ratio was one.

It is well known in terms of multiple testing that you can always test noninferiority first against some bound, and if you are successful for it, you can keep testing against progressively lower bounds and ultimately do a test of superiority against a hazard ratio of one.

The study could have specified that it would originally address noninferiority with a hazard ratio of 1.33 because it would have had 90 percent power to have addressed that if, indeed, there was no difference between the arms.

Then, given that it showed noninferiority at 1.33, it could then test a bound of 1.32 and then 1.31 and then 1.30 and keep on going until you got to 1.11. After that point, it would stop.

All of that testing can be done at the .05 level or, more accurately, the one-sided 025 level

because it is a closed testing procedure. The mathematics of closed-testing procedure basically says that when you consider the intersections of all of those hypotheses you more or less can proceed from one to the next one at the one-sided 025 level.

Now, the fact of the matter is they did not actually write that into the protocol. The comments that I am giving represent what they could have written into the protocol and what they had actual power to do and an analysis procedure that would have been totally rigorous and could have been in the protocol.

You have to balance what was hypothetically possible and within the scope of the study design against the reality of how the study actually was designed and what the analysis showed.

DR. ECKHARDT: All right. Dr. Rothman.

DR. ROTHMAN: Yes, thanks.

Just some comments. First, we had no discussions with Amgen with regards to appropriate noninferiority margin for the study, and also study conduct and the ramifications of study conduct for a superiority trial or noninferiority trial are different.

Study conduct that tend to make both arms look similar decreases the chance to show superiority but increases the chance to show noninferiority, and we have not in any way been able to evaluate at present the study conduct of this trial.

CHAIRPERSON ECKHARDT: All right. Thank you.

DR. KOCH: You have the data and you can do the analysis, but, again, the comment is a hypothetical comment. What the study showed, as Dr. Snappen indicated as well as in the core presentation, is the upper bound of the confidence interval is 1.11.

You will be able to do your own robustness analyses to identify how durable that is and then will be able to make your own judgment as to the interpretation of the study.

CHAIRPERSON ECKHARDT: All right. Let's move on.

Ms. Schiff.

DR. MARTINO: Madam Chairman, I'm sorry, but my question was not answered in total. We got detoured into details of the first trial and I appreciate the discussion. They were about to present to me the BEST

trial results.

DR. BOWERS: Thank you. I'm Dr. Peter Bowers from Johnson & Johnson. I would like to have the slide on, please.

(PowerPoint presentation in progress.)

DR. BOWERS: This is just a brief review of the BEST study, EPO-INT-76 conducted outside the United States by the company using Eprex in a patient population of women with metastatic breast cancer receiving first-line chemotherapy.

Epoetin alfa, Eprex, was administered or placebo once a week at a dose of 40,000 units, starting when the hemoglobin dropped below 13 and targeting a hemoglobin range of 12 to 14. As you recognize, that is a hemoglobin range that is outside the current label. It is above the current label limit of a limit of 12.

The primary endpoint of the study was 12 months survival, and objective measures of tumor response or disease progression were not specified in the protocol or the study. It was a large, simple study conducted with an endpoint of survival in mind.

The study was discontinued at the

recommendation of the DSMV reviewing the data for the study, and at the patient of discontinuation 88 percent of the subjects enrolled had completed a full 12 months of the study therapy or had been withdrawn. The last patient in the study had completed approximately nine months of study drug therapy.

May I have the next slide on, please?

(Staff complies.)

DR. BOWERS: These are the Kaplan-Meier plots from the INT-76 Study. Blue represents the epoetin alfa group. Grey represents the placebo group.

As you can see, there is a difference at the 12-month survival point. Primary endpoint is indicated by the dashed vertical line. A hundred and fifteen subjects, women, in the placebo group had died at that point whereas 148 women in the EPO-treated group had died. The hazard ratio for the 12 months survival was 1.37, favoring the placebo group patients.

May I have the next slide on, please.

(Staff complies.)

DR. BOWERS: We continued the follow the subjects who had been enrolled in INT-76 until 75

percent of all subjects enrolled had succumbed to their disease. This is the survival curve for the long-term followup, indicating that although the curves had separated and reached early and reached a maximal separation by four months after study drug treatment had commenced, they then continued parallel on to approximately 12 months where they started to converge. From that point forward, they are essentially superimposable.

May I have the next slide, please? Slide on.

(Staff complies.)

DR. BOWERS: This is the slide of time-to-disease progression. As I mentioned, although the protocol did not specify a set schedule of objective radiographic assessments of tumor, we were able to collect investigator-assessed or recorded disease progression.

As you see again, the placebo group is in gray; the Eprex, epoetin alfa, group is represented in the aqua color. In this particular Kaplan-Meier plot, those two curves are superimposable with a hazard ratio of .97 and a confidence interval that includes unity. I

would like to refer to Slide 38 --

CHAIRPERSON ECKHARDT: Before you move on, there was a question on the previous slide by Dr. Mortimer.

DR. MORTIMER: Yes. I'm just curious, when did people stop their EPO? I mean, we see the curve converge. Were they off their EPO by that point?

DR. BOWERS: Per-protocol EPO was to be continued for the full 12 months of the duration of the study.

DR. MORTIMER: The curves, then, converged after people stopped their EPO? Am I interpreting that correctly?

DR. BOWERS: Yes.

DR. MORTIMER: Okay.

DR. MARTINO: Do we have any insight as to the causes of death of these patients?

DR. BOWERS: We do.

May I have the Slide BC-7, please? Slide on.

(Staff complies.)

DR. BOWERS: We looked at the causes of death of the patients who had died at the four-month time

period because that was the point in time at which the curves had separated maximally and the data were minimally confounded by patients being withdrawn from the study crossing over to other therapies, and so forth.

As you see in the top panel of numbers, these are the investigator-attributed causes of deaths, this top panel here (indicating). We also performed a retrospective blinded chart review of all deaths that occurred of patients during the first four months of the study, and there was also that retrospective blinded chart review which was conducted by an independent, outside group of oncologists, represented in the lower panel of numbers.

As you see, investigators attributed more deaths to disease progression in the first four months in the epoetin alfa group patients with some imbalance also seen in thrombotic-vascular event deaths.

However, in the independent blinded chart review, the independent oncologists, who as I say were blinded to treatment assignment, assessed more deaths as being due to thrombotic-vascular event than had been

recorded on the case report form.

I might just note that the setup of the case report form was such that there was a checkbox next to "cause of death, disease progression" that could checked.

There was a category for "other." The investigator could check "other," but then would need to write in the specific proximate cause of death, and so we wonder if that perhaps introduced some bias into the ascertainment of the cause of death.

DR. MORTIMER: Do you know what the hemoglobin levels were for those individuals? I mean, the argument is that the higher the hemoglobin, the greater the problem. Were those thromboembolic complications in individuals with high hemoglobins, in fact?

DR. BOWERS: If I could just have a moment.

(Pause.)

DR. BOWERS: Slide IT-16 please.

(Staff complies.)

DR. BOWERS: It gives, displays, the mean hemoglobin levels of the patients who died in each group in Study INT-76. In general, the hemoglobin levels of

the epoetin-alfa-treated patients who died were lower, this is time in weeks across the "X" axis, were lower than the hemoglobin levels achieved in the patients who lived in this study. We see a similar pattern in the placebo group patients; the hemoglobin levels were lower in the patients who died.

DR. MORTIMER: But for the thrombotic--?

(Simultaneous discussion.)

DR. LINK: This includes all causes of death or just the thrombotic causes of death?

DR. BOWERS: This is everybody who died in the study.

DR. LINK: How about just the thrombotic?

DR. BOWERS: The number of thrombotic events in the study is relatively small and doesn't allow us to conclude definitively that hemoglobins were higher or lower in the patients who died of thrombotic causes in INT-76.

DR. LINKS: These are just means, then?

DR. BOWERS: These are means of everybody.

CHAIRPERSON ECKHARDT: All right. Thank you.

Any other questions, Dr. Martino?

DR. MARTINO: (Moving head from side to side.)

CHAIRPERSON ECKHARDT: Okay. We've got sort of a list going here. Ms. Schiff had a question.

MS. SCHIFF: Given the fact that we knew way back in 1992 that there was a hypothetical risk of tumor promotion and then it was discovered that there was a higher risk of TVEs, I can't understand -- this is addressed both to the FDA and to Amgen and J&J -- why there were no studies done and now why there is only one, the J&E, that is done according to the label.

DR. PERLMUTTER: Well, I think it is important to keep in mind that the label of course has changed over time, so when we look at it now the studies are not done according to the label, but the label has also changed over time.

I also think it is very important to place all of this in the appropriate historical context. I tried to do that. Keep in mind that the potential concerns with regard to thrombovascular events have been known for a long time, and that has remained very stable for a long time.

We have done a great deal of work to try and address the issue of whether or not there is any effect of epoetins on tumor progression in a whole variety of different settings.

Now, we have had the opportunity to review those data with you from the clinical setting, and of course we also have a very, very deep analysis in a preclinical environment showing that epoetins do not stimulate tumor progression.

We feel that we have been enormously proactive in trying to address these issues both preclinically and clinically and would be happy to step through the totality of that dataset with you.

Again, I would point out that with respect to tumor progression, looking in the chemotherapy-induced anemia indication we do not have data that suggests that tumor progression is an issue as a result of epoetin treatment, we simply don't.

MS. SCHIFF: You don't have data that it is, either.

DR. PERLMUTTER: Well, it's extremely difficult for us to prove a negative. You know, I would

point out that if you look at, for example, the small-cell lung cancer, Study 145, in which both survival and progression are superimposable, you can argue, "Well, gee, that's not the right tumor type in which to look."

Frankly, you know, tumor type after tumor type we have the same kinds of results. There is no data to support the view that EPO receptors are signaling in those tumors.

We don't have any signal that suggests that there is an effect on tumor progression in that setting. In chemotherapy-induced anemia, we don't have a signal, we don't.

MS. SCHIFF: Do you have it in other settings?

DR. PERLMUTTER: The only settings in which tumor progression has been an issue has been in the head and neck cancer setting with radiotherapy assessed as locoregional control clinically, and there are a variety of reasons to be concerned about those results. We would be happy to step through that with you as well, if you would like to see that.

MS. SCHIFF: Well, does anyone else want to

see it?

DR. PERLMUTTER: If anybody wants to see it, we would love to step through the analysis.

CHAIRPERSON ECKHARDT: It was presented earlier.

MS. SCHIFF: Okay.

CHAIRPERSON ECKHARDT: Dr. Brawley.

DR. BRAWLEY: Dr. Perlmutter and Dr. Baynes, my great concern is that we have seen a small-cell lung cancer trial that, I'll grant you, wasn't done through what I would consider the orthodox statistics, but suggests that the drug does not stimulate small-cell lung cancer.

We then have the head and neck cancer studies, some of which we have seen the data, some of which we haven't. I'm concerned that this compound is a stimulant, a "tumor fertilizer," for epidermal tumors.

I'm interested in squamous-cell cancer of the lung as well as squamous-cell cancer of the head and neck. I'm also interested in adenocarcinoma of the lung, since we have seen adenocarcinoma breast data. What data do you have to assure me that this is not

Miracle-Gro® for cancer?

DR. PERLMUTTER: That's a question we love to take on. There are two kinds of data that I would like to present to you, if I could. The first is the totality of preclinical data with respect to EPO, EPO receptors, and the second is clinical data in those settings. Is that acceptable?

(No verbal response.)

DR. PERLMUTTER: Okay. First of all, to bring up the preclinical data, if I could have Dr. Begley join us here, and he will briefly review the preclinical data. Dr. Begley is the head of our basic research group in oncology.

CHAIRPERSON ECKHARDT: May I ask that you make this brief. We've got a lot more questions.

Thank you.

DR. BEGLEY: Can I address the issue of the data relating that the EPO receptor is expressed in human cancers? Is that the most relevant?

DR. BRAWLEY: Well, I'm interested in, I'm interested mostly in clinical data.

DR. PERLMUTTER: Well, if you want to just see

the clinical data, we can do that for you. I don't want to take up your time.

DR. BEGLEY: Can I have three slides? Slide on, please.

(Staff complies.)

CHAIRPERSON ECKHARDT: Yes, I would prefer that we focus on the clinical data. The preclinical data I think is fairly well outlined in the information provided.

DR. PERLMUTTER: In the briefing book, okay. With that in mind, then, if I could have Dr. Baynes review the data that exists in the setting of epithelial tumors, and particularly lung cancer.

DR. BAYNES: I would like to, first, quickly remind everyone that the original approval for darbepoetin was actually based upon a study conducted in lung cancer. It was actually a mixture of small-cell and non-small-cell.

Indeed, slide on, please. Back one, back one slide, yes. Slide on.

(Staff complies.)

DR. BAYNES: Indeed, this was the approval

data, which in fact was not mentioned in the FDA presentation, but primary data in fact are on hand as well as followup data. They were a part, the followup data were a part of the long-term extension trial at the time of the extended-dose file.

What we see, in fact, is that the survival curves are in fact separating. In fact, the Nussbaum overall appears to do slightly better. This is actually what led us to go and study small-cell lung cancer in the setting of the 145 Trial.

If I could move now to the solid-tumor weight of evidence. We have a significant body of clinical trial data which have indeed looked at various solid tumors. Particularly, I wanted to show this because it will speak to the epithelial component.

Slide on, please.

(Staff complies.)

DR. BAYNES: Here we see a number of different randomized control clinical trials that have addressed in the CIA setting a number of solid tumors. I point out here a number, firstly, of breast cancer trials. Here we see the APRO study, the MEBA study, the Leyland-

Jones study. In addition, we have lung cancer trials in here, the Vansteenkiste trial, which we have spoken to. I believe Dunphy's trial was a lung cancer trial.

In the head and neck setting, I would also like to mention in the radiation setting that while we have seen the signal with the Henke trial, which I think is worth discussing then, because that is a very confounded trial. The DAHANCA trial I will remind you we have not seen any data yet, so we are really working off hypothetical data there.

There actually are two clinical trials in the head and neck setting that actually did not show the significance. Actually, when you look a the weight of evidence in randomized controlled trials, it is not clear that there is a signal in fact in any of the epithelial tumors.

CHAIRPERSON ECKHARDT: All right.

DR. BRAWLEY: One real quick followup, hopefully quick. How come much of the data from those trials haven't been turned over to the FDA and most of the stuff that the FDA said that they received is summary data?

DR. BAYNES: Well, I think we all recognize clinical trial work happens in many different arenas. For example, a large numbers of cooperative group studies are done that don't get submitted to the FDA. Investigators do clinical trials that are randomized in high-quality which don't get turned over to the FDA.

There is clearly a sort of evidence base here that is more than just what the FDA has in its possession. We have turned over all primary data that we have. But suffice it to say, there is a much larger body of clinical trial data, which in fact most of you around the table participate in.

CHAIRPERSON ECKHARDT: All right. Dr. Perry

DR. PAZDUR: Gail, I would like to answer that question or that response, because I really think that this really deserves an answer from the FDA on this.

I really think that there were, especially after the 2004 meeting, considerable controversy regarding the safety of this drug which led obviously to that 2004 meeting.

The sponsor really has an obligation. These are not just studies that were out there being done by

investigators, no, the two sponsors of these companies in 2004 did present these as trials that were supposed to answer the questions that were posed by the Committee to demonstrate the safety of these drugs.

In subsequent conferences with the company, they told us that, "Well, we really don't have necessarily access to the data on the studies." I really think if these studies were being done to answer the questions, they really have the obligation really to work with the investigators prospectively after the 2004 meeting to provide us with all of the data.

CHAIRPERSON ECKHARDT: Thank you.

Dr. Perry.

DR. PERRY: In the FDA's presentation about the studies, there were a lot of comments that the studies were not prospectively designed to pick up all the thromboembolic phenomenon. I would like to get the FDA's ideas of what an ideal design to pick up all these events would be.

It seems to me that clinically we pick up the venous thrombosis. We are aware if somebody has a heart attack or a stroke. Are we talking about doing Doppler

monitoring studies on people looking for occult DVTs every three months? Are we talking about angiograms for pulmonary emboli on asymptomatic patients every six months?

I look at the list of things that are included under TVEs. They include up to 20 things including cardiomyopathy in some studies. I would like some definition of what you think is important and how the companies or anybody else designing a study should prospectively look for them.

DR. JUNEJA: Let me start with the study in cancer patients, which I have referred to a lot, EPO-ANE-310, which is that large breast cancer trial that was proposed at ODAC 2004, the one that has had significant difficulties in accrual.

Now, that study specifically asked patients for clinical signs and symptoms related to thrombovascular events on a regular schedule, and that has not been a component of these other cancer studies that I presented today.

Now, if you want to talk about non-cancer patients, the spine study, which was the study in

perioperative patients getting major elective spinal surgery, again, the primary endpoint was to look for the incidence of DVTs. That study routinely did perform postoperative Doppler on patients after their surgery.

DR. PERRY: That study has very little credibility with me. If you do spine surgery on somebody and don't put them on prophylactic coagulants, it doesn't seem to me that that would be exactly a standard of practice. I mean, most people who get orthopaedic surgery get some kind of anticoagulant.

DR. KEEGAN: This population was, in fact, selected because they are not routinely anticoagulated. We are not talking about hip replacement.

DR. PERRY: Otis is correcting me over here. I stand corrected by my senior.

(General laughter.)

CHAIRPERSON ECKHARDT: All right. Let's move on. We still have some other questions.

Dr. Redmond.

DR. REDMOND: It's been asked and answered.

CHAIRPERSON ECKHARDT: Okay. Dr. Harrington or Haylock -- sorry, Ms. Haylock.

MS. HAYLOCK: The comments this morning about the inpatient or ICU population that was included in some of the studies versus community-based and ambulatory patients highlights the, hmm, heterogeneity of the population.

I'm wondering among patients that we might routinely or that we might expect to have a long-term survival, for example, relatively early-stage breast cancer patients who get pretty aggressive Myelosuppressive therapy, what might be the morbidities and cause of death in that kind of a population?

Then, I guess along with that, are there some early signs and symptoms of people getting into trouble that patients might address by some more aggressive patient education or more information that helps them make truly informed decisions about whether or not to undergo this kind of therapy?

DR. PERLMUTTER: I think you asked important questions, and thank you very much for that about clinical judgment. I would like to ask Dr. Glaspy please to come and talk from his perspective in terms of managing patients in exactly that kind of circumstance

with respect to ESAs and transfusions.

DR. GLASPY: First of all, I think the ICU comments this morning were related to the transfusion talk. They were talking about transfusions to different targets in ICU patients. Those weren't ESA-directed talks.

In terms of transfusions, I think we heard an excellent review. I don't have too much to add to the risk of transfusions. I don't think any of us think they are innocuous. We're glad they went down in risk, but there are problems with them. First of all, they are a very temporary fix.

In our patient populations, patients are repeatedly transfused. The average transfusion per patient in our trials has been 2.7 units per transfused patient, so that adds up to a fair amount of transfusions.

As Jeff talked about this morning, we are transfusing them in part for symptoms, often not for simply a hemoglobin trigger, and so they are bouncing up and down into that symptom range. That is not an optimal place to be if there are safe ways to be

someplace else. There is that potential negative impact on cancer outcomes.

Slide on. Next slide, next slide. Is that it? There you go. Slide on.

(PowerPoint presentation in progress.)

DR. GLASPY: Okay. You heard a little bit this morning about the potential negative effects on cancer outcomes that the transfusion person talked about. This is the data I think he was referring to.

This comes from a Cochrane analysis of studies that were done in the perioperative period for cancer surgery, specifically focused on colon cancer surgery in most of the trials, that suggest that the more transfusion that one gets in association with the initial cancer surgery, the more likely you are to have a bad outcome of that cancer.

I don't think we should put too much of an emphasis on this. It is a theoretical issue. Because the bloodier cancers, the ones that require more transfusions, are probably worse to begin with.

But it contributes to a concern on the part of us clinicians that we don't have proof that transfusions

don't decrease the cancer outcomes as well. It contributes to our fear of transfusions and our patients' fear of transfusions.

The other thing I would like to talk about came up in some of the public address here, and that had to do with the impact of changing our practices in the management of cancer patients.

I want to speak only to the appropriate use. If there is inappropriate use going on that is driven by reimbursement, that is a bad thing. I am not here to defend that. I wish it would go away. If it's happening, it's terrible.

By the same token, I think the best person to make a decision is a patient who is fully informed and that patient's doctor. I think that that autonomy has worked well for the majority of oncologist who are all trying to do a good thing.

That said, now talking about if we were to change our practices, we don't have a largesse of blood available as a country. About 8 to 9 percent of outpatient surgeries get cancelled in this country because blood isn't available and they have to be

rescheduled.

According to the Red Cross, the country works on a margin of about 600,000 units of blood, and that's the wiggle room we have to go between high-demand and low-demand periods.

There are 450,000 patients receiving ESAs in this country. If they prevent transfusions in half of the people who are going to be transfused and it's 2.7 transfusions on average per patient, eliminating ESA use in oncology could consume a big chunk of that margin that we're working on.

I mean, the math you can do all kinds of different ways. I don't want to draw any firm conclusions, but the magnitudes of what wiggle room we have in the blood supply and what we are saving through ESAs in oncology is of similar magnitude.

CHAIRPERSON ECKHARDT: All right. Thank you.

We still have quite a few questions to get through, so I would like for both the questioner and the target person answering the question to try to make comments brief.

I have Dr. Harrington next on my list.

DR. HARRINGTON: Thank you.

I have three questions about areas where there seems to be still some disagreement between the FDA and the presenting sponsors about existing data. Let me list them off and then people can tackle them, some are for the company and some are for FDA.

The first is the point/counterpoint about the provision of primary data for which the FDA only has only summary data right now. I think the immediacy of our action may well depend upon how long it is going to take to get those primary data to the FDA, so I would like to hear a little bit from the companies about barriers and when they expect to get that data to the FDA.

The second is about the meta-analysis. We saw very different looking forest plots here, one from the FDA and one from the company. The FDA's reviewer stated, quite rightly, that the quality of a meta-analysis depends crucially on what studies are included and what are excluded.

What I would like to hear a little bit more detail from the FDA is what important studies do they

think are excluded from the forest plot shown by the company?

Then, finally, there is for me this mysterious DAHANCA study in Denmark for which the companies seem to think the data are not out there and not reliable. The FDA has actual P values and hazard ratios. I would like someone to fill in the gap for me there and let me know where is that data, how reliable is it, and is it in the public domain yet.

DR. PERLMUTTER: Okay. We would like to begin by emphasizing our attention to the diligence obligations that we took on in 2004 and then we will in the process talk about the DAHANCA data which was part of that diligence. Dr. Baynes is going to go through all of these things for you.

DR. HARRINGTON: But briefly I would imagine; right?

(No verbal response.)

DR. BAYNES: Slide up, please.

(PowerPoint presentation in progress.)

DR. BAYNES: In terms of the Amgen postmarketing commitment, we see here the expected

volume of data come in and essentially when studies complete. These are the times during which we believe that in fact we will be able to provide these primary data sources to the FDA.

Slide, please.

(Staff complies.)

DR. BAYNES: If I could move then to the DAHANCA trial, essentially the trial, as I indicated, was stopped for futility. Preliminary, interim result set was communicated.

Essentially, the exact verbiage on the webpage says "Approximately 10 percent in three locoregional progression" and then gives a fairly precise P value "also, notes no significant difference in overall survival." The principal investigator cautions against overinterpretation.

Next slide, please. Slide on.

(Staff complies.)

DR. BAYNES: This is, in fact, verbatim from what Dr. Overgaard had sent to us and which we have forwarded to the FDA. I'm going to read this for you. He says:

"We are a bit concerned about the data being overinterpreted. That is why we are reluctant to present any further information until it has been properly collected from all 522 patients.

"I will warn about concluding more than we have done, namely, that it was not likely that if the trial if completed would come out in favor of Aranesp no more, no less.

"We are now in the process of doing this additional collection and so far have not seen any data which are in disagreement with this conclusion. This also includes that we did not apparently see any excess deaths from lung cancer causes including cardiovascular events, despite the high hemoglobin levels accepted in the study.

"I do in principal think that it is too early to declare DAHANCA-10 study negative in the sense that Aranesp will cause a decrease survival in patients as mentioned. We just conclude that the likelihood that will become positive is very small, so please do not interpret the study beyond that."

Then, if I could perhaps just go to the

ongoing Pharmacovigilance Program. Slide on.

(Staff complies.)

DR. BAYNES: These are the components of the Pharmacovigilant Program the were presented at the '04 ODAC, recognized by '04 ODAC, and actually agreed to by the FDA. This became a post-marketing commitment in 2006.

The 145 data Amgen -- well, first, the study was prosecuted with due vigor. It was, in fact, completed on the 22d of February, and primary data are in the hands of the FDA along with a study report.

The GELA study, I have indicated the interim has been presented, and we are expecting data delivery on schedule. The PREPARE study, likewise. The study in adjuvant breast cancer from the ARA 03 group, expecting interim data at ASCO this year, data delivery on track. In fact, DAHANCA we have spoken about already.

In terms of the post-marketing commitment which was agreed to by FDA, indeed the protocols have been reviewed by FDA, and indeed the statistical analysis plans from the cooperative groups in these later four cases that have been reviewed by the FDA are

currently on track. In fact, due diligence has been fully executed around the post-marketing commitment.

CHAIRPERSON ECKHARDT: All right. Dr. Richardson.

DR. KEEGAN: Wait.

CHAIRPERSON ECKHARDT: Dr. Keegan.

DR. ROTHMAN: Let me respond to I guess what was asked of us. First, how do we get that information about DAHANCA? We were given a study report that for both locoregional control and overall survival, there is on randomization.

We gave the number of events, the total number of events, and the P values. The total number of events and the P values were used to work back and get the log hazard ratio and the standard error. That's how the hazard ratio and the confidence interval were determined for the DAHANCA.

As far as studies not in Amgen's meta-analysis, we note that the DAHANCA study isn't there and the CAN-20 study is not there. We probably would need a little more time to figure out exactly what studies are or aren't included because I think we are using some

different names for different studies.

DR. PERLMUTTER: Was the question, I'm sorry, how do these different meta-analyses differ? Oh, I'm sorry.

DR. HARRINGTON: No, but I think I'm getting my answer. The question was what important studies were left out of your meta-analysis. I heard there were two that are relatively recently completed.

DR. ROTHMAN: Yeah, DAHANCA is also left out.

DR. PERLMUTTER: Right, for which we don't have the data. But all of the CIA studies are included in our meta-analysis.

CHAIRPERSON ECKHARDT: All right. Dr. Richardson.

DR. ROTHMAN: Well, I guess I'm reminded to sort of add -- my apologies -- I mean, we do think some of the studies included do no have adequate followup. They are not necessarily, perhaps, influential on the final meta-analysis result.

For example, O'Shaughnessy just has her one event and we sort of study deaths -- as are some of the studies here, too -- not that they would contribute much

to the result of the ending meta-analysis. They weren't studies that had long-term followup, so we wouldn't have included them in any meta-analysis.

CHAIRPERSON ECKHARDT: All right. Dr. Richardson.

DR. RICHARDSON: I have a couple of questions that relate I guess to study design and study rationale. We heard this morning a little bit about oxygen extraction and oxygen dissociation curves. As far as I know, those curves have not changed since darbepoetin came on the scene.

I wonder, first of all, if there is any information with respect to oxygenation and tissue levels in patients who are given these kinds of drugs? Is there any evidence that these ESAs have any effect on these levels at hemoglobin levels above the 10 to 12 range?

Secondly, I guess, and this relates to a term that Dr. Baynes used, this was his description of the 145 study as a "hyperoxygenation" study and extensive stage small-cell lung cancer.

I'm wondering if there was some interaction

that you postulate between hemoglobin levels and platinum and BP-16 or a topocyte that would provide a rationale for doing a study, or is this all based on that weight separation of curves in the small-cell lung cancer study, which I think was conducted in both limited- and extensive-stage disease and really had a fairly miserable survival at least certainly weighted toward the extensive stage cohort of that group?

Then I guess, finally, I'm just curious whether these were studies were written by the investigators, or were the authors of this from the company?

DR. PERLMUTTER: Let me begin by saying that there is no clinical data that is helpful in terms of thinking about oxygenation, but if we could have the previous slide up.

This is a slide that shows nonclinical models, the hemoglobin levels and median POT and tissue for a variety of different tumors that have been placed into such models.

I don't think that this data, frankly, is terribly helpful in terms of thinking about the issue of

how does the hemoglobin, achieved hemoglobin, relate to oxygenation of the tumor and whether that could in any way affect the growth process.

If these data were used as a means of trying to explore the observation that increasing hemoglobin like hyperbaric oxygen treatment could improve tumor kill, and an attempt was made to try and correlate those things. With respect to the non-small-cell lung cancer study, I will let Dr. Baynes speak to that and the design issues.

DR. RICHARDSON: Let me say one thing about the hyperbaric oxygen business. I mean, that was beaten to death years ago. People looked at not only hyperbaric oxygen but increasing fractions of oxygen in patients' high inspired oxygen concentrations without any benefit.

DR. PERLMUTTER: No, I appreciate that. I know that to be true.

DR. RICHARDSON: What is the rationale for doing this in a group of head and neck patients? If there is no interaction with the oxygen -- I mean, if you can't do anything with oxygen, if this does not have

any sort of interaction at a cellular level, I mean, if the ESA doesn't do that, what is the basis for doing the study?

MR. PERLMUTTER: We agree that the hyperoxic theory at this point has no support. We agree it has no support, and we don't see a rationale for such studies. Those are not studies that we feel are important to do.

DR. BAYNES: I think to Dr. Perlmutter's point, there has been a fairly extensive preclinical set of data that suggests that in fact hypoxia is a tumor-resistance factor.

The head and neck cancer arena I think has been spurred by an observational notion that, in fact, intratumoral oxygen content seem to show some correlation with outcome. I'm not an expert in head and neck cancer, but I understand that there are a body of data around this.

In fact, the two studies that you have identified, the Henke and the DAHANCA trials, were both initiated by oncology, radiation oncologists with a specific interest in this field, and that is what drove those particular trials.

DR. RICHARDSON: The rationale with the small-cell studies?

DR. BAYNES: Well, there are data to suggest that, in fact, intratumoral hypoxia is a resistance factor for both alkylating agents and for radiation therapy. There is a fairly significant body of preclinical data to suggest that.

CHAIRPERSON ECKHARDT: Okay. We still have some other questions. Dr. Albain, you had one?

DR. ALBAIN: Yes. What perhaps is troubling me the most here is the broad application of these agents to chemotherapy regimens that would not require blood transfusions, in other words, in particular in the adjuvant breast cancer arena where you would not normally transfuse the patient.

Thus, I'm asking to see in greater detail your adjuvant breast cancer data, in particular, the recent data shown in San Antonio, updated data. We haven't really had a chance to see that today.

DR. PERLMUTTER: Yes, I will let Dr. Bowers speak to that or Dr. Zukiwski.

DR. BOWERS: If I may take a little bit of

indulgence, could I go to Slide BI-3, please?

(PowerPoint presentation in progress.)

DR. BOWERS: I would just like to clarify one of the situations regarding the recording of some of the data.

Slide up, please.

(Staff complies.)

DR. BOWERS: All of the studies outlined in the FDA Table 9 were above the hemoglobin target of 12 grams per deciliter. The RTOG study and the CAN-20 study were both cooperative group trials, which by contrast we do not have access to the data in typical cooperative contracts until the data is published. We were able to get the data very recently.

The CAN-20 has been published in "The Journal of Clinical Oncology," and the RTOG study has been submitted for publication. The data is in-house, within Johnson & Johnson, at the present time. Unfortunately, we were not able to get it any time sooner.

The CAN-17 trial, which was a company-sponsored trial, a breast cancer trial, which did not demonstrate any safety signals, we have recently sent

the CSR to the FDA. Unfortunately, we only provided, or fortunately we did provide to the FDA in May of 2006 the full safety data.

If we could go to the next slide, please?

(Staff complies.)

DR. BOWERS: I believe that, Dr. Albain, the study that you are referring to is the Mobus trial. It was presented in San Antonio. We have that data and we can present that.

DR. ALBAIN: That, but that other data as well that has been alluded to, I would like to see a summary of all of the adjuvant breast data.

DR. PERLMUTTER: Dr. Bowers?

DR. BOWERS: Yes, we can come back to this, but let's address the breast cancer data for you first.

DR. ALBAIN: Adjuvant breast besides Mobus, in addition to Mobus.

DR. JOHNSON: I would like to summarize the information that we do have regarding adjuvant breast cancer studies in particular for you. Just to summarize very quickly, there are three other studies in breast cancer to which I could speak, two of them are in the

adjuvant setting and one of them, the BRAVE study, conducted with epoetin beta is a study conducted in women with metastatic breast cancer patients.

The two in adjuvant, with adjuvant, women in the adjuvant setting are studies conducted with epoetin alfa, Eprex, outside of the United States. There is one additional study that I don't have listed on this trial. It has also enrolled some women with adjuvant disease. I haven't included it because it is a study that was terminated early. There were no safety signals in that study, and I can speak very briefly to that study for you.

If I could have the next slide.

DR. MORTIMER: There is a I know Shaunghnessy trial that I realize was done for cognitive function, but you have shown it up as having a three-fold increased incidence of death, and it is just obviously a very wide confidence margin given the small number of patients, but those are all adjuvant breast cancer patients.

DR. ALBAIN: That's exactly what I'm trying to get at here. Thank you, Joan.

DR. JOHNSON: I don't believe the O'Shaughnessy study was a controlled study. The studies that I have here --

DR. ALBAIN: I wanted to see all your data in this adjuvant-like population be it Stage II data such as the cognitive function studies as well as, you know, leave out the metastatic study, just focus on the adjuvant studies.

DR. JOHNSON: I will be happy to present the studies that I have. I don't have the data from the O'Shaughnessy study with me, but of course I would be happy to make that available to the members of the Committee.

If we could run through CAN-17, I think it is BC-10?

(PowerPoint presentation in progress.)

DR. JOHNSON: EPO CAN-17 is a study conducted to evaluate quality of life within the adjuvant therapy setting for breast cancer. Primary endpoint is quality of life and the secondary endpoint included transfusions and overall survival.

Women were followed for two years in this

study. This was a randomized, open-label study. Eprex, epoetin alfa, versus no Eprex. Eighty percent of patients enrolled were treated in the adjuvant setting, 20 percent had metastatic disease and there needed to be a planned 12 additional myleotoxic chemotherapy at baseline.

As I mentioned, this is a beyond-anemia correction study. Women were randomized into the study when their hemoglobin fell below 12 and were treated to a target of between 12 and 14.

May I have the next slide, please.

(Staff complies.)

DR. JOHNSON: The quality-of-life results in the study were significantly in favor of the Eprex-treated women. As you will see in a moment, the study results are quite reminiscent of the INT-10 study quality-of-life results, the CLASS assessment support of the findings on the effect and anemia scale used to assess quality of life in the study.

There was an improvement in hemoglobin in the Eprex-treated patients for baseline to week 12. Transfusions were substantially reduced in epoetin-

alfa-treated women in this study. Among the metastatic subset, 74 patients, response rates were similar.

Safety, there was a slight increase in thrombotic vascular events. On study, mortality, 27 deaths in the Eprex-treated women; 28 deaths in the control group.

If I could have the next slide on, please?

DR. ALBAIN: Before you leave that slide, how about in the adjuvant subset in that trial?

DR. JOHNSON: I'll show you the Kaplan-Meier plots for the group.

The next slide on, please. The next slide, please.

(Staff complies.)

DR. JOHNSON: These are the quality-of-life results. We'll skip them. The next slide, please.

(Staff complies.)

DR. JOHNSON: This is the Kaplan-Meier plot for the entire cohort, the 354.

If I could have the next slide, please?

(Staff complies.)

DR. JOHNSON: This is the metastatic group.

If I could have the next slide, please?

(Staff complies.)

DR. JOHNSON: This is the Kaplan-Meier plot for the adjuvant. Of the 80 percent of patients who were treated in the adjuvant setting, 142 treated with Eprex, 138 were in the control group, 9 deaths in Eprex-treated patients and 6 deaths in the no-Eprex treated group. Point estimate for the hazard ratio is .88 and a confidence interval that includes unity.

The Mobus study, and we have data by kind agreement with Professor Volker Mobus. He is going to be presenting an update at ASCO. He has kindly shared his data with us for presentation here today.

If I could have the first slide on please from the Mobus study?

DR. ALBAIN: You alluded to ASCO data about to be shown for an error, I didn't quite get the name of that study, in three weeks or so. Do you have that data as well?

DR. JOHNSON: I do.

Slide BC-18, please?

(Staff complies.)

DR. JOHNSON: This is an investigator-sponsored study conducted in Germany by Professor Mobus. It is a study that evaluated dose-dense versus conventional chemotherapy. In the dose-dense arm, there was a second randomization to EPO, epoetin alfa, Eprex support versus no Eprex, an open-label randomization.

The population were women being treated in the adjuvant setting. They were at higher risk for recurrent disease with greater than four positive lymph nodes.

As I mentioned, the second randomization randomized the women in the study to Eprex versus no Eprex. This is also a beyond-correction of anemia study. It used epoetin alfa, Eprex, 150 units, 3 times per week. The target hemoglobin level was 12.5 to 13. The dose was withheld, if the hemoglobin level exceeded 14.

The next slide on, please. The next slide. Thanks. This is just a schema of the study design. The next slide up, please. Thank you.

(Staff complies.)

DR. JOHNSON: According to the protocol-

defined analyses in the epoetin alfa randomization group, two-year, disease-free survival was to be reported, transfusions, hemoglobin, and intramemory recurrence. All patients studied were followed for two-year, disease-free survival; five-year disease-free survival; and five-year overall survival.

The transfusion data has been reported previously in the San Antonio conference and the five-year overall, excuse me, the five-year disease-free survival and overall survival at a median followup of 62 months will be presented at ASCO. Data snapshot of data from the study was transferred to J&JPRD on April '07.

If I could have the next slide up, please?

(Staff complies.)

DR. JOHNSON: In October 2003, subjects with one or more thrombotic vascular events in the Eprex-treated group, the epoetin alfa group, 3 percent versus 1.7 percent in the control group. Remember, all of these patients are receiving dose-dense chemotherapy. This is the dose-dense group.

In the ASCO abstract currently provided to us, 658 women were randomized to the dose-dense arm; and in

that dose-dense arm in the second randomization, 333 women were randomized to Eprex.

The five-year disease-free survival is 72 percent in the Eprex-treated women and 71 percent in the control group, and the P value for the difference is 0.86, nonsignificant.

The mortality snapshot, as I mentioned, at the median followup is 62 months. Overall survival among epoetin-alfa-treated women, 81 percent versus 83 percent in the control group, again, a nonsignificant P value. Transfusions were significantly reduced in EPO and alfa-treated women.

May I have the next slide, please?

(Staff complies.)

DR. JOHNSON: This is the Kaplan-Meier for time to recurrence for the women randomized to Eprex or control. The bolded line is the epoetin alfa group; the unbolded line, the control group. As you see, these curves are essentially superimposable and the log-rank test if nonsignificant.

May I have the next slide on, please?

(Staff complies.)

DR. JOHNSON: Overall survival, again, and this is after a median followup of 62 months, a substantial length of time. The log-rank test is nonsignificant, P value .89.

DR. MARTINO: I'm sorry. Can I make a comment, Dr. Albain?

(No verbal response.)

DR. MARTINO: Realize that these are not studies designed to answer the specific question of survival.

DR. ALBAIN: This was a preplanned randomization to look at the EPO endpoint, was it not?

DR. JOHNSON: That's correct.

DR. MARTINO: But survival, I'm getting at the end number to this subrandomization.

DR. ALBAIN: It's very small. What was your endpoint? Was it a transfusion endpoint, or was it a survival endpoint in the EPO versus not?

DR. JOHNSON: If I could have BC-20 up?

(Staff complies.)

DR. JOHNSON: The protocol again for you, the protocol-defined analyses in the epoetin alfa group:

two-year disease-free survival, transfusions, median hemoglobin, and intramammary recurrence. We don't have any data on the later endpoint. For all patients in the study, two-year disease-free survival, five-year disease-free survival, and five years of overall survival.

DR. ALBAIN: At least with robust followup, your disease-free curves are superimposed right now in this ASCO updated, what you're showing?

DR. JOHNSON: Yes, that's correct. This is at a median followup of 62 months.

CHAIRPERSON ECKHARDT: Dr. Keegan, did you have a comment?

DR. KEEGAN: We wanted to comment and ask for some clarification about our understanding of the protocol, which is the patients are assessed for tumor status at baseline end of chemotherapy and annually thereafter. Is that correct?

DR. JOHNSON: Dr. Keegan, I would have to pull the details of the protocols of concern for you. If you have that document there, I would --

DR. KEEGAN: I do not have the protocols with

me.

DR. JOHNSON: I would be happy to check for you and could provide the answer shortly.

DR. JUNEJA: I would like to make a comment on that because I have reviewed all of these protocols. The Mobus study, again, the primary endpoint was looking at the dose-intense versus the every-three-week arm. It was not looking at EPO versus supportive care.

The second thing is in terms of the assessment of disease-progression, chest X-ray, upper-abdominal ultrasound were again used at the beginning of chemotherapy, end of chemotherapy, and annually.

CHAIRPERSON ECKHARDT: All right. Thank you.

Dr. Doroshow.

DR. DOROSHOW: I have a short question, and that is, I am interested to know from any of the sponsors whether any data exists with respect to any clinical outcome or adverse event that distinguishes actual hemoglobin levels versus targeted hemoglobin levels?

DR. PERLMUTTER: At this point I don't think that we can look at these data in terms of hemoglobin

level achieved in the cancer populations and derive an interpretable conclusion, so I will just give you the short answer, which is, I don't think that there is an interpretable conclusion there.

There is a trend that we've spoken about, which is that one sees that if you look at -- slide up, please -- hazard ratios for time-dependent covariates with hemoglobin greater than 13, you can see that the responders in general have a better result.

But, as I point out, that is confounded by the fact that it is very likely that responders have a more favorable prognosis for other reasons. I don't think we can answer that question.

CHAIRPERSON ECKHARDT: All right. Dr. Allegra, did you still have a question?

DR. ALLEGRA: Just a quick question about toxicities related to transfusions. We've talked a fair amount about ESA toxicities. Can you tell me how often did you see high-grade toxicities including, grade 5's, that could be attributed to transfusion in your larger studies, BEST, for example?

DR. PERLMUTTER: I don't believe that we have

that dataset for you. I apologize. I don't have toxicities defined by transfusion results, but we will dig into the data and find it and we will get back to you. I don't have that, I'm sorry.

CHAIRPERSON ECKHARDT: Dr. Krook.

DR. KROOK: A question to Dave Crawford, my fellow clinician. On C-19, I remember what you said, that you need to treat five patients to decrease transfusions on one person. If I play the oncologist game, that's a 20 percent response rate.

The second issue would be on C-24, which is hemoglobin associated with higher quality-of-life issues. We have gone from a hemoglobin of 7 to 14, and yet we have a 15 percent grade in quality-of-life improvement.

Now, my own impression is that this here looks at all the other factors, Dave, that are involved in chemotherapy-induced anemia. I don't know whether the FDA has something -- but with, again, higher hemoglobin, we've only improved it 15 percent. We can sit here and talk is that important or not.

DR. CRAWFORD: Right. Let me reexplain this

slide. First of all, this is a cross-sectional analysis looking at patient-reported outcome in terms of a linear analog scale and what their hemoglobins were at that time and just showing the general association between higher hemoglobins and higher quality of life.

Now, if you do this prospectively, you will see a similar trend, but this particular analysis was cross-sectional, and it just suggests that the magnitude of difference, the magnitude of difference between grades of hemoglobin are greater in this 10 to 12 range than they are found in this range.

This is the range where we transfuse people; this is the range where we restore hemoglobin and minimize signs and symptoms. The better data, though, to really look at these analyses and really from the randomized data that we have shown earlier is between placebo and treatment, so I think that's a better way to look at it. It's just that this cut point works very nicely with other triggers for transfusion, signs and symptoms, and even some old data.

We talked about what other old data there is around what a "hemoglobin cut point" was. It turns out

from data from Clement Finch back in the seventies when he looked for endogenous EPO levels in people as they were phlebotomized they began to increase when hemoglobin fell below 12. It's a convergence of a lot of data around that number.

DR. KROOK: I guess what I'm trying to say is that if this in chemotherapy-induced anemia, I mean, the quality of life has improved except we have not taken them to 90 percent, if that is where we are going to.

DR. CRAWFORD: Again, this is a scale. None of us are at 90 percent of the scale. Most of us might be a little bit higher. But if you look at patients at the start of treatment from studies we have done from initial therapy, they are around 55 to 60, if you look at the cancer patient, per se. We can improve quality of life around symptoms relevant to anemia, but we can't improve all quality of life that impacts a cancer patient in terms of their disease.

DR. KROOK: It appears that the two things we are using is transfusion and quality-of-life issues for the ESAs. Again, on the previous slide, C-19, if I heard you right, you said we gave five patients

erythropoietin-stimulating agents to decrease transfusions for one.

DR. CRAWFORD: Correct. What we are doing is we are reducing transfusions. We are reducing the signs and symptoms associated with those transfusions. Even those patients who are transfused, there are less signs and symptoms and therefore, hopefully, better quality of life at least around fatigue and related symptoms that would occur.

I'm not an expert in NTT analysis, but I believe that treating five patients to benefit one patient is a favorable profile for most drugs. Certainly, a 20 percent rate is a good number by other criteria, and I think most patients that avoid a transfusion this would be a useful number to talk to them about.

I don't know if anyone else wants to address that, NNT?

DR. BAYNES: Just to emphasize the point, there have been a number of pooled analyses and single analyses looking at the effect size of transfusion. If we could go to the pooled analyses of effect size for

transfusion --

CHAIRPERSON ECKHARDT: Can you be brief?

DR. BAYNES: Sure.

CHAIRPERSON ECKHARDT: We need to move on.

DR. BAYNES: Okay. Just in general terms, most chemotherapy, as you heard from Dr. Crawford, has 50 to 60 percent incidence of transfusion, and that's reduced to 20 to 25 percent. The effect size is actually close to 50 percent on average, 50 to 60 percent in terms of reduction of transfusion.

CHAIRPERSON ECKHARDT: All right. Thank you.

Dr. Martino had one last question.

DR. MARTINO: I think I'm getting the impression here that there may or may not be EPO receptors on tumors, and if they exist, it appears that the general sense is that they are not a way to stimulate a tumor.

My question relates to, do we not know that there are receptors on the endothelial cell; and if that statement is accurate, what do we know relative to angiogenesis? Because there are other mechanisms by which tumors grow other than direct stimulus to them.

DR. PERLMUTTER: We can answer that question in great detail.

CHAIRPERSON ECKHARDT: Ah, but please be brief.

(General laughter.)

DR. PERLMUTTER: Maybe I should just say that reagents to detect the EPO receptor do not exist that would be able to pick up those kinds of receptors.

First of all, the EPO receptors expressed at very low abundance on the surface. There are not satisfactory reagents despite a lot of effort that can selectively pick up the receptor, because the existing antibodies are both polyclonal and polyspecific, and that makes it impossible to detect them.

Thus far it has not been possible to isolate an EPO-derived effect on those endothelial cells. It is speculation at this point about whether or not there could be an effect.

You can find EPO receptor message in a variety of different contexts, that is, messenger RNA. In terms of EPO-receptor signaling, to spare you the technical detail, you can't find that.

CHAIRPERSON ECKHARDT: All right. I think what we are going to do is wrap up this part of the session.

Dr. Keegan, did you have a--?

DR. CHERNEY: Yes. This is Barry Cherney of the FDA. There is an extensive literature that EPO receptors are found on plenty of tumor types, breast included, and that they are functional in in vitro tests and some limited tissue, tumor tissue, where they look for signaling in STAT5 signaling and they see the signaling. There is an extensive body of literature that counteracts what you say.

DR. PERLMUTTER: I think, then, under those circumstances, we probably should go into it and talk about exactly how confounded that literature is. Shall we do that?

CHAIRPERSON ECKHARDT: No.

(General laughter.)

DR. PERLMUTTER: Because I think we can refute that pretty directly.

DR. CHERNEY: No, I think the --

(Simultaneous discussion.)

DR. PERLMUTTER: We can take that apart pretty dramatically.

CHAIRPERSON ECKHARDT: I would just say that it is controversial, and I don't think that we will be able to arrive at a solution at this meeting, but thanks for the input from both of you.

What I would like to do is to wrap up this part of the session. We will be taking a 10-minute break.

I wanted to sort of sum up some of the questions that have gone on, and that would be that I think many of us on the Committee had a lot of questions about trial design, specifically, some of the endpoints that were utilized, accessibility of data and many questions with regards to why exactly data hasn't been available to scrutinize.

Many of us I think have been confused about the quality of life and fatigue and some of the patient-reported outcomes data and exactly why that does not appear to have been part of the label. We understand that that was not sufficient at the time of registration.

You know, I think it is very interesting that the data would have not been available or at least to the level to reach those kinds of conclusions because many of us see marketing to be somewhat revolving around some of that patient-reported data.

I think the other thing that's interesting is that there is very little known about the dosing with regards to this agent. I really didn't hear a lot of discussion about why the doses utilized were quite a bit higher than those utilized on the label.

I think we have sort of revolved and discussed a lot of those issues, and I look forward to the next session where we will drill down to some of the questions. We will take a 10-minute break, and then come back.

(Recess.)

QUESTIONS TO THE ODAC AND ODAC DISCUSSION

CHAIRPERSON ECKHARDT: Okay. We are going the move on to the first of several questions that have been posed to the ODAC Committee. I will ask Dr. Pazdur to chime in whenever he feels like; okay.

Essentially, as you can see, this question has

to do with sort of the body of the discussion that we have had today with regards to update on the risks. Keeping in mind again that we are not talking about a regimen that actually prolongs quality of life, this is supportive care, and so we need to be thinking about the risks and benefits within that context.

Based upon what we have heard today, we have a couple of votes, the first of which is revolving around the current restrictions that were put into the black box warning. You have those actually attached to the list of questions.

I think what is important is to think about whether or not the ongoing marketing authorization needs to be contingent on these being changed. We will in a few minutes get to what types of changes could be considered in particular tumor types and others.

I think this first vote really just points or asks whether or not we do think that additional restrictions need to be put onto the label; and then, secondly, whether or not this also should be contingent on additional trials.

Now, the idea would not be to have an extreme

amount of detail regarding the trials, but whether or not indeed this should be another requirement. I will take any discussion that someone has about that.

Dr. Perry.

DR. PERRY: Yes. I have a problem with the statement of this particular issue. It is very true that the infectious complications of transfusions have been reduced, but none of the others have.

People still get iron overload. People still get immunologic reactions. They still get hyperkalemia. It still becomes increasingly difficult to transfuse patients over time.

It becomes difficult to keep lines patent. It becomes difficult to find compatible blood if you're in a small town and somebody has been multitransfused.

I think that just simply saying that the infectious rates of transfusions have been reduced over time is rather disingenuous. I think what you really want to say is transfusions are available. It's possible to avoid them with erythropoietin-stimulating factors.

What is the risk/benefit ratio between the two, not between just the risk of your getting West Nile

Valley fever or something similar? I think the way this is stated is most inappropriate. The risk of transfusions are far more than just infectious.

DR. PAZDUR: Fair enough.

CHAIRPERSON ECKHARDT: Actually, I wanted to make a comment. I agree as well. I think certainly there are appropriate times for transfusions, but I think the idea of sort of going back to the Dark Ages, so to speak, with regards to supportive care is a step backwards.

I think what we should be thinking about today are ways to manage the risks that we have heard about with regards to this very useful supportive care agent. I would really put it into that context rather than whether or not we use the drug versus transfusion.

Any other discussion?

DR. MARTINO: I have lots of problems with this whole experience today, but one of the problems that I have is that as I read the black box, it basically says that if you have cancer and you are being treated for it, that these agents are okay.

Yet, when I asked the question, are there

studies that were actually designed to look at survival and that finished accrual and for which there is data that deals with that as the specific and primary endpoint, the two groups that were brought forth, lung and breast cancer, somehow to me don't seem to be addressed by this black box warning.

I am kind of thinking probably the group for which there was the most information that there may be some dangers are those patients, yet I don't know that we have dealt with that -- certainly not to my personal satisfaction.

But I must say an overriding issue that I have with all of this stuff is that we're being presented with problems in patients who are "hypertreated." Okay? That is what I see as the real issue.

You are asking me to think about patients who were overtreated and then to make decisions as if we are now going to properly treat them, whatever the hell that is. I am not sure how to think through this whole issue.

CHAIRPERSON ECKHARDT: Well, I'll make a comment to that. I actually think what we are seeing,

which is not unlike when you take drugs and you dose escalate them to a certain point and you start seeing boundaries of toxicities and you see characteristics of toxicities that become worrisome, I think what we're seeing is that there are issues perhaps if you push the dose of this beyond what's recommended.

I agree with you the problem is in translating that to the current situation that is being used. But I think that was really one of the concerns is, are these safety signals, albeit at doses that are nonlabeled, are they messages that need to be further incorporated into the current utilization of the agent to really maximize safety until we can conduct the appropriate studies at the appropriate doses?

DR. MARTINO: But then that same issue applies to patients who aren't on chemotherapy. They were also treated beyond that magic level. How do we separate that group out?

DR. KEEGAN: Could I clarify?

(No verbal response.)

DR. KEEGAN: The target for the anemia of cancer of study was not higher than the current

labeling.

DR. MARTINO: Was it not thirteen?

DR. KEEGAN: They held the dose at 13, but the target was twelve.

DR. MARTINO: Well, nevertheless, if you allow people to be transfused beyond the usual levels, you see you are still getting to a point where you're making a judgment about appropriate therapy when it was slightly inappropriate. I'll grant you maybe only slightly inappropriate, but it still is the same basic concept.

DR. KEEGAN: Right. I guess I was just trying to draw a distinction between that and the studies that were looking at hemoglobins of 13, 14, 15 and maintaining it at those levels.

DR. MARTINO: If you look at the breast cancer, the BEST trial, wasn't their goal around thirteenish or so? I don't think that was 15 or 16, unless I'm not remembering correctly.

DR. KEEGAN: Twelve to fourteen.

DR. MARTINO: You know, again, those to me don't seem too different to me.

CHAIRPERSON ECKHARDT: Dr. Mortimer.

DR. MORTIMER: You know, I share Dr. Martino's concern about making decisions on the basis of overtreatment conceivably. But I guess, you know, in asking the sponsors could they correlate toxicity with hemoglobin levels, they could not give us that data.

They said thrombotic complications were more common when hemoglobin was high. The cause and effect of toxicity wasn't there, and so I don't feel that feel that uncomfortable about making a decision.

DR. MARTINO: I'm not sure that I'm convinced that they satisfied me in that answer. Yes, they gave an answer, that's correct.

(Simultaneous discussion.)

CHAIRPERSON ECKHARDT: Dr. Redman. I'm sorry.

DR. KEEGAN: I was going to say the other important point to remember about the anemia of cancer study is in fact it showed no transfusion benefit.

DR. REDMAN: Yes, I guess I just need clarification. I'm not sure what marketing offer means, number one. Number two, I get the sense that in the black box we're going to just keep adding it on to every

negative study or non-positive study that there is and keep warning physicians that there is no positive study.

It seems like it's taking care of in the fact that it is for chemotherapy-induced anemia for a target of 12 and it has not been proven to be effective in many other non-myeloid malignancies. It's not been proven to be of any other benefit.

DR. PAZDUR: Authorization obviously means the ability to sell the drug. The other issue here is do these isolated signals, even though they might be done in, okay, not the exact population of a higher hemoglobin, are these bothersome enough to start putting other restrictions here?

Because here again you don't have any ideal population here, but you have something here, something there, something there. Do we need to really bring a little more stringent behavior the how this drug is prescribed even within the label's indication?

DR. REDMAN: I guess along the same comment, and this is probably really an oversimplification of it, but it's a McDonald's cup of coffee warning label

"It's hot." I mean, you don't have positive data that suggests that it's of any benefit in the patient population to achieve a hemoglobin greater than 12, okay, and you can use it in somebody who is not receiving chemotherapy. You have negative or non-positive trials, but you have no positive trials, so you can't have a positive indication. I guess what I'm getting to is the next negative trial that comes out, if one is done by industry, do we add it on to the black box?

CHAIRPERSON ECKHARDT: You know, I think one thing we need to keep in mind is that many times the labeling and restrictions can also translate into reimbursement, so it does become an operational issue with regards to the patient population being targeted.

I think what we are trying to get out with this particular question is hearing what we have heard today, is there anything in addition? Do we need to start adding things?

Again, the question is for a supportive care agent, to what extent do we need to have proof to have safety signals that are reasonable to put into the black

box warning?

Ms. Schiff.

MS. SCHIFF: I still don't understand why or how it's been proved that it is safe under 12, especially if it's been found that there is not an increase in TVEs as the hemoglobin rises.

That means it's the same under 12 as it is above 12, if there's no difference. Why are we assuming the under 12 is safe at this point? I haven't seen the data for that. There is no data.

DR. REDMAN: It is in there that there is a risk of TVEs. I mean, it is in the product insert. Nobody is ignoring it, it's there.

CHAIRPERSON ECKHARDT: Dr. Albain.

DR. ALBAIN: I would like to come back to Dr. Pazdur's question. I guess for situations like adjuvant breast cancer therapy I am not yet reassured. I have no prospectively designed, noninferiority study that it will not adversely impact survival. So, yes, I would like to see that on a label. In similar situations like that, I would be interested in what my colleagues think.

CHAIRPERSON ECKHARDT: That's exactly what

we're getting at.

DR. BRAWLEY: One of the most important issues I think here is that most doctors and most patients think that this drug has been approved because it improves quality of life, it improves fatigue. I don't see that in the FDA indication; I see it on late-night television.

I mean, there is a lot of sort of sleight of hand here with how the drug is used, what the drug is used for, and I think that is a real problem, especially when one looks at -- I was struck by one of the comments earlier today that said let the doctors decide who gets the drug.

The problem is that doctors get about $1,200 for every dose that they give patients, so the doctors are not necessarily objective. They don't have to make that same objectivity statement that we have to sign or conflict of interest statement that our people who spoke here had to do today, and that's a real problem.

CHAIRPERSON ECKHARDT: I would actually like to ask Dr. Pazdur to make comment clarifying sort of. I think we have all been struggling today with the

advertising that we see versus the body of data that was presented to actually support the indication. Perhaps Dr. Pazdur can enlighten us as to that dichotomy.

DR. PAZDUR: Okay. Labeling claims, okay, advertising claims are supposed to be derived from product labeling, okay. Obviously, there is a great deal of concern that I have and I think most of the clinical review staff have about these advertisements that were made.

One has to remember that we as the review division at the FDA are not responsible for the enforcement. There is a high degree of enforcement discretion that is exercised in CBER by the acronym "APLB," which is their enforcement and advertising division as well -- I shouldn't say enforcement, but their advertising division as well as in CDER by DDMAC.

The FDA Chief Counsel Office obviously sets the tone for enforcement. We are looking into this whole issue of why these ads were allowed to go on. I think that the FDA is responsible for giving the American public as well as the review staff that sits here the reason why these ads were allowed to go on. I

really would like to thank the advocate community for bringing this up because I think the FDA really does need to address this issue.

Enforcement discretion can occur for many reasons and obviously there is a fine line between the rights of First Amendment speech and the protection of the American population from false and misleading advertisement.

That is an enforcement discretion that is handled by other parts of the Agency as well as the Office of Chief Counsel. I think that they need to give the American public a clear understanding of why these ads were allowed to continue.

CHAIRPERSON ECKHARDT: Thank you.

Any other discussion before we go ahead? Remember, this first vote is to add additional restrictions in the product labeling based upon what you've heard.

One more?

DR. HARRINGTON: One more. A question from a non-clinician to my clinical colleagues. I noticed in the slides about transfusion that the recommendations to

start transfusions seemed to be dropping down to lower and lower hemoglobin. Why twelve? What's the rationale for twelve with these agents when transfusions is getting down as low as 7 grams per deciliter?

CHAIRPERSON ECKHARDT: Now, we actually have that as another question.

DR. HARRINGTON: Oh, sorry.

(General laughter.)

DR. HARRINGTON: I didn't read ahead. All right, so let's go ahead and get started. Remember, that you need to state your name and your vote.

Oh, sorry. Another question?

DR. RICHARDSON: I would just like to respond to my colleague, Dr. Perry. I think when he talks about a lot of difficulties in transfusing people repetitively, certainly that is an issue in the myelodysplastic and Aplastic anemia population. I think everybody realizes that there is a critical need for these agents in that group.

I would like to remind you, though, if you look back at the discussion that Dr. Glaspy gave earlier, I think it was the mean number or median number

of units of blood per patient transfused was 2.7. 2.7 units of blood is a little more than one transfusion episode in that population, so keep that in perspective as well.

CHAIRPERSON ECKHARDT: Thank you.

A PARTICIPANT: (Inaudible, no microphone.)

DR. HARRINGTON: Okay. My mistake. I'm sorry.

CHAIRPERSON ECKHARDT: Okay. All right. We are starting with Dr. Murgo. Okay, make a comment and then you get to vote.

DR. MURGO: My comment has to do with we're talking about restriction, additional restrictions on the package insert. It seems like the focus is on the black box and the warning section.

DR. PAZDUR: We are asking specific questions afterwards, so please do not consider restricting to a black box warning, but we are asking specific questions obviously on starting hemoglobins, target hemoglobins, tumor types, et cetera.

(Simultaneous discussion.)

CHAIRPERSON ECKHARDT: Right. This is purely

a change.

MR. MURGO: No, but my comment is will this also include the labeled indication? The labeled indication for cancer patients is very loose.

DR. PAZDUR: Yes, it could.

CHAIRPERSON ECKHARDT: What's your vote?

DR. MURGO: My vote for Part A?

CHAIRPERSON ECKHARDT: We're voting A right now.

DR. MURGO: Okay. My vote is yes.

CHAIRPERSON ECKHARDT: Please state your name?

DR. MURGO: Anthony Murgo.

DR. KROOK: Jim Krook, yes.

DR. REDMAN: With the caveat I'm still not quite sure I understand 1(a), no.

DR. MARTINO: Yes, Martino.

DR. ALLEGRA: Allegra, yes.

DR. LINK: Link, yes.

MS. HAYLOCK: Haylock, yes.

DR. HARRINGTON: Harrington, yes.

DR. DOROSHOW: Doroshow, yes.

DR. MORTIMER: Mortimer, yes.

CHAIRPERSON ECKHARDT: Eckhardt, yes.

DR. RICHARDSON: Richardson, yes.

DR. PERRY: Perry, no.

MS. SCHIFF: Schiff, yes.

DR. BRAWLEY: Brawley, yes.

DR. ALBAIN: Albain, yes.

DR. STRONCEK: Stroncek, yes.

CHAIRPERSON ECKHARDT: All right. Thank you. Fifteen to two, yes.

The second part of this is based upon, and again it could also be in conjunction with (a), which we've just voted on, is with regards to additional trials. Dr. Pazdur, perhaps you can elaborate on how detailed you want? I mean, in my view if this is a question of should additional trials be run in order to continue with marketing authorization?

DR. PAZDUR: Correvt. Again, since we do have a question that as with our last question goes into a little more detail on questions, maybe if somebody could just give an area that they would like another trial in or some question that they feel is burning here that they need to have answered in a trial"

DR. MARTINO: Yeah, we have burning questions. The burning question is does this thing actually kill people in the doses that we think are reasonable and appropriate? I don't see anything that has approached an answer to that question.

I would actually put a stop to all of these trials that are using higher doses than the recommended doses, because I don't think they are going to add to our knowledge. They are going to continue to confuse us and waste patient resources. To me it is not a complex thing in terms of conceptualizing; it may be complex in terms of doing.

CHAIRPERSON ECKHARDT: Dr. Link.

DR. LINK: Is there somewhere you could manage getting the data from the trials that you have already done so that you can do that before we go on to new trials?

DR. PAZDUR: At the present time we could ask for post-marketing commitments. I cannot make a contingency on continued authorization of the drug based on getting this data at this present time.

CHAIRPERSON ECKHARDT: Other comments?

Discussion?

(No verbal response.)

CHAIRPERSON ECKHARDT: Again, I guess this question -- I'm sorry, Dr. Redman.

DR. REDMAN: I guess the question is, again, is this asking for additional trials for additional indications to add to the marketing information, or as it stands now are additional trials needed to support the current marketing?

DR. PAZDUR: Correct.

DR. LINK: Maybe I need a clarification. You authorized some trials that you were putatively going to get data from in order to continue this. If we say that you should do the next set of trials, how do we know that you are going to get the data from those trials?

DR. PAZDUR: This is one of the problems that we face in post-marketing commitments for the FDA. We can ask them to be perhaps submitted, review, and work with the sponsor to try to get these done in a timely fashion. There are limitations we have on these post-marketing commitments at the present time.

CHAIRPERSON ECKHARDT: Dr. Brawley.

(No verbal response.)

CHAIRPERSON ECKHARDT: Dr. Perry.

DR. PERRY: I would like to point out, to be fair to the sponsors, it's very difficult sometimes to accrue to these trials. If you were a patient being randomized to one of these trials, you would have to ask yourself, "Why do I want to be on one of these particular trials when I could get a placebo, if I believe in Procrit or Arnesp?" If I don't believe in them, why would I want to take the chance of getting one of them?"

I think the company, it is in their best interest to complete the trial. You see the breast cancer trial, which is going to be criticized by the FDA because too many different kinds of chemotherapy agents are being used, but in order to get the trial done, the sponsor had no choice but to do that.

They couldn't mandate just one chemotherapy program or they would never get patients on it. They are doing the best they can, and they can't accumulate patients on the trial. It is a difficult thing.

What we need is a large, simple trial without

too many very difficult endpoints. That's why I was asking you about what kind of endpoints do we want for thromboembolic events before.

If you make it too cumbersome, you can't sell it to the patients. If you tell the patients "You're going to have to come in every week and get an angiogram to see if you have an asymptomatic pulmonary embolist," that ain't gonna sell in Peoria or anyplace else.

It's a compromise between what is doable and what we want to have done. I have some sympathy for the sponsors. It's in their best interest to have them done. If they could put a little more money into it and get it done, I'm sure they would.

CHAIRPERSON ECKHARDT: Dr. Brawley.

DR. BRAWLEY: I'm not sure it's in the best interest of the sponsor to do the trial, but I would love to see a large, simple trial with a survival endpoint.

DR. PAZDUR: No homogenous disease?

CHAIRPERSON ECKHARDT: And how about more than one dose?

DR. BRAWLEY: Say it again. Say it again,

sir.

DR. PAZDUR: No homogenous disease? And, a disease?

DR. BRAWLEY: In a homogeneous, epidermoid disease.

DR. PERRY: What homongeous disease do you defined?

CHAIRPERSON ECKHARDT: What dose?

DR. BRAWLEY: Squamous-cell lung cell.

DR. PERRY: Okay.

DR. BRAWLEY: Squamous-cell of the head and neck.

DR. PERRY: Well, squamous-cell lung cancer in the United States is 33 percent of all the cancers, so you've got --

DR. BRAWLEY: Well, they are presenting data on small-cell lung cancer, which is half of that.

DR. PERRY: Yes, but that's a population that you could easily define. Sometimes all you get is non-small-cell lung cancer not further defined.

DR. BRAWLEY: I would buy that. That's better than what we've got right now.

DR. PERRY: You're an easy sell; okay.

(General laughter.)

CHAIRPERSON ECKHARDT: Any other discussion?

(No verbal response.)

CHAIRPERSON ECKHARDT: The vote formulated, then, will be to vote for or against additional studies that would need to be performed in order to continue with marketing authorization, with the idea that later on we will be discussing a little bit more about what those trials would look like; okay.

Dr. Albain -- oh, sorry, Stroncek.

DR. STRONCEK: STRONCEK, yes.

DR. ALBAIN: Albain, yes.

DR. BRAWLEY: Brawley, yes.

MS. SCHIFF: Schiff, yes.

DR. PERRY: Perry, yes.

DR. RICHARDSON: Richardson, yes.

CHAIRPERSON ECKHARDT: Eckhardt, yes.

DR. MORTIMER: Mortimer, yes.

DR. DOROSHOW: Doroshow, yes.

DR. HARRINGTON: Yes.

MS. HAYLOCK: Haylock, yes.

DR. LINK: Link, yes.

DR. ALLEGRA: Allegra, yes.

DR. MARTINO: Martino, yes.

DR. REDMAN: Redman, yes. They will never be done.

(General laughter.)

DR. KROOK: Krook, yes.

DR. MURGO: Murgo, yes.

CHAIRPERSON ECKHARDT: All right. That was 17 yes.

Okay. Well, moving right along, as we go down the list, then what we are really doing is drilling down a little bit with regards to the restrictions that we, for the most, voted for.

This next question really looks across the different types of trials that were performed and asks whether or not we would specifically indicated particular types of tumors that would be restricted to, you know, not receive treatment.

I think really probably of the ones that were presented that have the greatest safety signals are breast cancer. I think there is some controversy over