will be submitted to FDA by November 30th, 2007.

[Slide.]

This is an outline of the PREPARE study, 733 patients with primary breast cancers greater than or equal to 2 cm were enrolled. The patients were first randomized to either a every 21-day chemotherapy regimen consisting of epirubicin, cyclophosphamide and paclitaxel, or to a dose dense and dose intense regimen consisting of epirubicin, paclitaxel, cyclophosphamide, methotrexate and 5-Fu.

Now, in each of those arms, patients were then randomized to an ESA versus transfusion support arm and, after the completion of neoadjuvant chemotherapy, patients received surgery.

The co-primary objectives of this trial were to compare the relapse-free and overall survival of the two chemotherapy arms. Now, among numerous secondary objectives, there was a comparison of relapse-free and overall survival of the ESA versus transfusion support arm.

Now, the target hemoglobin in this trial was 12.5 to 13 and this trial was identified at ODAC 2004 by Amgen as an ongoing trial that was capable of addressing safety concerns of ESAs and this trial accrued patients from June

2002 to March 2005.

[Slide.]

These are the results of the PREPARE trial based on an analysis of 733 patients with a median follow-up of three years. Now, the results are based on a full analysis data set that excluded ineligible patients but analyzed patients according to their randomized treatment group.

FDA was notified of this data in late November 2007. The survival rate of patients receiving ESAs was lower than patients receiving transfusion support with a hazard ratio of 1.42 and a 95 percent confidence interval of 0.93 to 2.18.

The 3-year relapse-free survival rate of patients receiving ESAs was lower than patients receiving transfusion support with a hazard ratio of 1.33 and a 95 percent confidence interval of 0.99 to 1.79.

[Slide.]

Now, this is a Kaplan-Meier plot of the relapse-free survival with the red representing the control arm and the blue representing the ESA arm.

[Slide.]

Moving on to overall survival, this is a Kaplan-

Meier plot of the overall survival, again red representing control and blue representing ESA.

[Slide.]

Now, we will discuss the GOG-191 trial in cervical cancer.

This trial enrolled 114 patients with Stage IIB to IVA cervical cancer. Patients in both arms received concurrent cisplatin and radiation therapy. Patients were randomized to receive other ESAs or transfusion support.

The primary endpoint of this trial was progress-free survival. Secondary endpoints of this trial were overall survival and local control. The target hemoglobin in this trial was 12 to 14. The accrual to this trial occurred between August 2001 and September 2003.

FDA was aware in 2004 that the trial was terminated early due to an increase in thrombovascular events in the ESA arm, and the incidence of thrombovascular events have previously been summarized in the FDA briefing document from ODAC 2004.

The trial had been designed to include 460 patients. But it was prematurely terminated at 114 patients. The survival results were not available in 2004

and FDA was notified about survival data in December 2007.

These are the results of the trial, 114 patients. The progression-free survival rate for patients receiving ESAs was lower in patients receiving transfusion support with a hazard ratio of 1.6 and a 95 percent confidence interval of 0.58 to 1.91.

The survival rate for patients receiving ESAs was lower than patients receiving transfusion support with a hazard ratio of 1.28 and a 95 percent confidence interval of 0.68 to 2.42.

The local and distant occurrence rates were higher in the ESA arm compared to control.

[Slide.]

I will now pause to summarize the results of the PREPARE and GOG-191 studies. The PREPARE study in breast cancer patients receiving neoadjuvant chemotherapy showed trends to decreased overall survival and relapse-free survival in patients on the ESA arm, and the GOG-191 study of cervical cancer patients receiving chemo-radiotherapy showed a trend to decreased overall survival in patients on the ESA arm.

[Slide.]

We will now discuss new analyses performed by FDA. The first topic will be achieved versus targeted hemoglobin. The second topic will be classifying studies by tumor histology with primary data that has been submitted to, and analyzed by, FDA.

We are going to start with the achieved versus targeted hemoglobin. The point to remember on the next slide is that the hemoglobin actually achieved in a clinical trial may not be the same as the ideal target hemoglobin.

[Slide.]

These are the 8 studies that we have seen in the previous slides. So, if you look at the middle column, the hemoglobin target, again, all the studies targeted a hemoglobin of greater than or equal to 12.

To better understand what a target hemoglobin means, let's take the target hemoglobin in the 103 trial, which I am going to highlight in yellow, with apologies to those of you in the back, but it is the last trial shown in the table, and the target hemoglobin in this trial was 12 to 13.

If a patients's hemoglobin was less than 12, ESAs were given. If a patient's hemoglobin was between 12 and

13, ESAs were dose reduced and, if a patient's hemoglobin was greater than 13, ESAs were withheld.

So the ideal maintenance range for a patient's hemoglobin was between 12 to 13 in the 103 trial. The hemoglobin target really means an ideal maintenance range for a patient's hemoglobin. But, in a clinical trial, individual patient's hemoglobins may not actually fall within the hemoglobin target or ideal maintenance range.

This is the concept of the achieved hemoglobin, which is illustrated in the third column of this table. The achieved hemoglobins are a compilation of the median hemoglobins of individual patients in the trial and the numbers in parentheses represent the first and third quartiles of hemoglobin.

Data on the achieved hemoglobin has been submitted to FDA on 7 out of 8 of these trials.

I have now highlighted two studies in yellow, the 161 and the 103 trials. As you can see, the median achieved hemoglobins in these trials was less than 12. I am now going to illustrate concrete examples from these two trials.

[Slide.]

This is Study 103, commonly referred to as the

"Anemia of Cancer" study. This study enrolled patients receiving neither chemotherapy nor myelosuppressive radiotherapy, which is an off-label ESA use. Now, the shaded area delineates the target hemoglobin in this trial, which was 12 to 13. The blue ovals indicate the median achieved hemoglobins by patient receiving ESAs over the weeks of the study, and the vertical bars through the ovals are the first and third quartiles of hemoglobin achieved.

So, what is illustrated here is that the median achieved hemoglobins in this trial were less than the ideal target hemoglobin and the median achieved hemoglobins in this trial are under 12.

[Slide.]

This is Study 161 commonly referred to as the "Lymphoid Malignancy Study." In contrast to the 103 study illustrated previously, this trial enrolled patients receiving chemotherapy, which is again the indicated label use for ESAs.

The shaded area delineates the target hemoglobin in this trial, which was 13 to 15. So, again in this trial, the median achieved hemoglobins were less than the ideal target hemoglobins and the median achieved hemoglobins in

this trial are under 12.

[Slide.]

Both the 161 and 103 trials had median achieved hemoglobins of less than 12, and both trials had a statistically significant worsening of overall survival in patients receiving ESAs, which leads to the question of is the upper range for the target hemoglobin of 12 safe.

So, the uncertain nature of the risk of ESAs at hemoglobins less than 12 have led us to include the following statement in the boxed warning. The following text are sections from the boxed warning approved in November of 2007.

"The risks of decreased overall survival and tumor progression have not been excluded when ESAs are dosed to target hemoglobins less than 12. To minimize these risks, as well as the risk of serious cardiovascular and thrombovascular events, use the lowest dose of ESAs needed to avoid red cell transfusions."

[Slide.]

Now, we will look at studies by tumor histology with primary data that have been submitted to, and analyzed by, FDA.

[Slide.]

The data from two small cell lung cancer studies have been submitted to, and analyzed by, FDA, and subset analyses have been performed on Study 980297 that included both small cell and non-small cell lung cancer.

The largest of these studies was Study 2001-0145, an adequately designed study intended to show the superiority of ESAs on survival with a hazard ratio for survival excluded more than a 12 percent increased risk of death.

[Slide.]

Now, in contrast, the following tumor types have had data submitted to FDA that either show trend to or have a statistically significant increased tumor promotion and/or decreased survival.

Starting with non-small cell lung cancer, the CAN 20 study in patients receiving neither chemotherapy nor radiotherapy demonstrated decreased survival in patients receiving ESAs.

In Study 980297, shown in the previous slide, again enrolled patients with both small cell and non-small cell lung cancer and subset analyses performed on this study

in non-small cell lung cancer have not shown a statistically significant survival difference.

Now, in breast cancer, the BEST study in metastatic breast cancer showed decreased survival.

In the BRAVE study, in patients with metastatic breast cancer, no statistically significant decrease in survival was observed.

Now, the major difference between the BEST and the BRAVE study was that the BRAVE study in all patients receiving any line of chemotherapy, while the BEST study in all patients receiving first line chemotherapy.

Now, the neoadjuvant setting, as previously discussed, the PREPARE study has shown trends to decreased overall and relapse-free survival.

Now, in head and neck cancer, both the ENHANCE and DAHANCA studies enrolled patients receiving radiotherapy. And both studies have shown evidence of worsened tumor control. The ENHANCE study showed decreased overall survival, while the DAHANCA study had a trend to decreased overall survival.

Now, in patients with a heterogeneous group of lymphoid malignancies, the 161 study demonstrated decreased

overall survival. As previously mentioned in cervical cancer, GOG-191 study showed a trend to decreased overall survival and, in patients with a heterogeneous group of non-myeloid malignancies not receiving chemotherapy or myelosuppressive radiotherapy, the 103 study demonstrated decreased overall survival.

[Slide.]

Now, this slide illustrates the other major tumor types where the adverse effects of ESAs have not been adequately investigated in randomized, controlled trials with data submitted to, and analyzed by, FDA.

[Slide.]

We will now discuss events occurring after ODAC 2007 last May. We will examine the timeline of events--and we have seen this slide before. Again, marked are the months since May 2007.

In May 2007, after ODAC, a request for labeling revisions addressed recommendations from ODAC 2007 was sent by FDA to the sponsors. In May 2007, the Centers for Medicare and Medicaid Services proposed a National Coverage Decision on ESAs in oncology.

In June and August 2007, meetings occurred between

FDA and sponsor regarding modification of ongoing trials to increase the accrual rate and proposals for new trials were also discussed.

Additional meetings have also occurred regarding myelodysplastic syndrome and the erythropoietin receptor.

Now, in October and December 2007, clinical study reports and data sets were submitted on Study 2001-145 in small cell lung cancer. In October 2007, a MedGuide was requested by FDA. A MedGuide is a required sheet of information on a drug that must be provided to a patient.

In November 2007, as well as last Friday, revised labeling and a Dear Healthcare Provider letter were approved by FDA. As I previously stated, in late November and December 2007, the FDA was notified of adverse results from GOG-191 and PREPARE studies, and again clinical study reports and data were submitted on these studies and labeling updates were initiated.

Now, early January 2008, FDA issues a press release describing the results of GOG-191 and PREPARE studies. Finally, from December 2007 to February 2008, data sets on completed studies to support labeling and re-analysis were submitted, along with clinical study reports

and data sets on numerous other studies. We will be mentioning these other studies in subsequent slides.

[Slide.]

This is a summary of the National Coverage Decision by the Centers for Medicare and Medicaid Services proposed originally in May 2007.

The first ESA use is indicated when the hemoglobin is less than 10 prior to the initiation or maintenance of ESA treatment.

An ESA use is indicated when the hemoglobin continues to be less than 10 four weeks after the initiation of an ESA and the rise in hemoglobin is greater than 1.

Clinicians must submit the most recent hemoglobin levels at least as often as prior to each ESA claim for reimbursement.

ESAs must be stopped 8 weeks after the termination of chemotherapy and dose adjustment guidelines were supplied by the National Coverage Decision.

This is the boxed warning issued last Friday. This has previously been mentioned by the sponsor. The portions included in this slide include the relevant oncology section of the box.

ESAs decreased overall survival and/or time-to-tumor progression in clinical studies in breast, non-small cell lung, head and neck, lymphoid and cervical cancers when dosed to target hemoglobins greater than or equal to 12.

As I previously mentioned, the risk of decreased overall survival and tumor progression are not excluded when ESAs are dosed to target hemoglobins less than 12.

To minimize these risks and the risk of serious cardiovascular and thrombovascular events, use the lowest dose of ESAs needed to avoid red cell transfusions.

Use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy.

Discontinue ESAs following the completion of a chemotherapy course.

[Slide.]

To summarize the current data on the risk of ESAs in oncology, 6 studies showed statistically significant evidence of increased tumor promotion and/or decreased survival and the studies and the types of cancers are listed here again for your reference.

Two additional studies showed trends of increased tumor promotion and/or decreased survival. These are the

PREPARE and GOG-191 studies, with data presented to FDA after ODAC in May 2007.

[Slide.]

This presentation has offered an analyses on the risk of ESAs on trials that have observed increased risk, have been categorized by treatment type, by tumor type and by achieved or targeted hemoglobins.

The next four slides I will summarize these analyses.

Examples of increased risk have been observed across these factors, which would lead to the question of: Is there an oncology setting for ESAs that does not have an increased risk?

[Slide.]

In looking at trials of increased risk and categorizing them by treatment type, we have observed increased risk present in 4 studies in chemotherapy-induced anemia, which is again the labeled indication, 2 studies in patients receiving radiotherapy in off-label use, and 2 studies in patients receiving no chemotherapy, no myelosuppressive radiotherapy again in off-label use.

[Slide.]

In looking at trials with increasing risk, and now categorizing them by tumor types, a safety signal in survival was not observed in 3 trials in small cell lung cancer. The results in small cell lung cancer, an aggressive neuroendocrine tumor, are unlikely to be applicable to other tumor types, for example, epidermal tumors.

No data from randomized controlled trials has been submitted to, and analyzed by, FDA on the risk of ESAs in numerous other tumor types.

[Slide.]

These are the tumor types in which decreased overall survival and/or increased tumor promotion have been observed. The two studies in head and neck cancer, one study in metastatic breast cancer, one study in the neoadjuvant setting for breast cancer, one study in non-small cell lung cancer, one in lymphoid malignancies, one in cervical cancer and one in patients with a variety of non-myeloid malignancies.

[Slide.]

Now looking at the achieved versus targeted hemoglobins, no adequately designed studies have been

completed with a target hemoglobin less than 12.

In looking at trials with increased risk by achieved or targeted hemoglobin, we note that despite targeting a hemoglobin greater than or equal to 12, both the 103 and 161 trials achieved median hemoglobin of less than 12.

Now, in both of these trials, patients receiving ESAs had decreased survival. So, therefore, the safety of ESAs when used to target hemoglobins of less than 12 is not established.

[Slide.]

So, to conclude, ESAs or supportive care agents and therefore establishing safety is necessary.

The efficacy and the approval basis of ESAs in oncology is to reduce the proportion of cancer patients on chemotherapy receiving red blood cell transfusions.

Eight post-approval studies have provided evidence of decreased overall survival and/or decreased loco-regional control or relapse-free survival..

Numerous studies in both oncology and non-oncology settings have demonstrated an increased risk of thrombovascular events.

ESAs do not increase survival and may promote tumor growth.

Based on the 8 studies that we have mentioned, there should be a reconsideration of the risk:benefit ratio of ESAs in cancer patients.

Results from adequately designed ongoing or proposed studies will not be available for several years, and we will be discussing this further, as well.

[Slide.]

Now, we will discuss different risk evaluation and mitigation strategies for ESAs in the oncology indication.

The risk management proposals can be further divided into proposals for risk evaluation, which are strategies to further characterize risks including meta-analyses of completed trials and assessment of individual studies.

Proposals for risk mitigation are strategies that apply to the current use of ESAs.

[Slide.]

We will start with risk evaluation. In examining various meta-analyses in the literature and offered by the sponsors, meta-analysis remains a problematic technique to

definitively rule out risks of ESAs.

No completed oncology studies have definitively demonstrated superior overall or progression-free survival for an ESA-containing arm.

[Slide.]

Meta-analysis can obscure safety signals from individual studies. Meta-analyses results depend on the studies included where earlier meta-analyses have suggested statistical significance on survival favoring ESAs while later meta-analyses suggested statistical significance on survival favoring controls.

Cumulative and retrospective meta-analyses have issues on appropriate allocation of alpha, and meta-analyses include heterogeneous trials with variable quality, variable lengths of follow-up, variable target hemoglobins and heterogeneous tumor types.

[Slide.]

Now moving on to individual studies, we will now examine elements of optimal trial design to assess and exclude increased risk as recommended by the previous ODAC in 2004. We will also describe completed ongoing or proposed studies that nearly or completely meet these

recommendations.

[Slide.]

These were the major highlights of the 2004 ODAC recommendations regarding optimal trial design to exclude increased risk with ESAs.

First, trials be double-blind and placebo-controlled. The preferred primary endpoint be a survival endpoint. Trials be adequately powered to detect survival differences.

There should be a routine assessment for tumor progression. Trials should include a homogenous tumor type. The assessment of thrombovascular events should be a prospectively defined endpoint.

[Slide.]

These are studies that nearly or completely satisfy all of the ODAC 2004 major recommendations. They are divided into two categories. First, studies designed to detect and exclude an upper limit of risk.

The second category is studies designed to detect a superior outcome with ESAs.

Starting with the first category, EPO-ANE-3010 is a study in metastatic breast cancer but has had problems

with poor study accrual and is presently enrolling patients.

Study N93-004 is a study in small cell lung cancer. This study was prematurely terminated in July 2001 for slow accrual. We have previously presented the results of this study.

Finally, as presented by the sponsor, Study 2007-0782. This was proposed again by Amgen after ODAC 2007 and proposes to enroll patients with advanced breast, lung and colorectal cancer. This study has not yet been initiated.

Moving on to the second category, again, studies designed to detect a superior outcome with ESAs. Study 2001-0145 in small cell lung cancer. This finished accrual in July 2006, and we have previously presented the results of this study.

[Slide.]

Now, a very large amount of data has recently been submitted to FDA from numerous studies, some of which have been mentioned in the sponsor's presentation.

FDA had informed the sponsors prior to data submission that FDA would not be able to review this data prior to this ODAC. The clinical study reports have been received on 18 studies totaling over 35,600 pages, data sets

have been received on 30 studies.

The date of December 20, 2007, was selected by FDA as a cutoff date in order to prepare for this ODAC. Now, none of these submitted studies was specifically designed to detect and exclude increased risk of death.

[Slide.]

FDA is aware that some of these studies do not report a statistically significant increased risk of tumor promotion and/or decreased survival. FDA reminds the Committee that the absence of evidence of increased risk in studies that are not designed to detect and exclude increased risk does not mean that there is definitive evidence that such risks are not present.

[Slide.]

Now we will move on to risk mitigation, which are strategies that apply to the current use of ESAs.

[Slide.]

Apart from labeling changes, these are other proposals for risk mitigation. We will start with the sponsor's proposals, which include various forms of physician education including dissemination of relevant published literature and labeling, Dear Healthcare Provider

letter on ESAs, a revised letter was approved by FDA last Friday, preparing a Frequently Asked Question document regarding ESA use, National Coverage Decision by CMS, and the outcome of three different ODACs, unrestricted educational support for independent continuing medical education training, education of members of the company speaker bureau, and providing materials on ESA safety issues at scientific booths at major biomedical meetings.

Moving on, cancer patient advocacy group communications. At FDA's request, a Medication Guide has been drafted by the sponsor and we are currently collaborating on this.

An assessment of risk communication to patients and providers. Finally, labeling changes, as I stated, a revised label was approved by FDA last Friday.

[Slide.]

Now, FDA is concerned that the sponsor's proposals may not be sufficient to mitigate current risks. FDA requests that the Committee consider the following additional steps:

One strategy for risk mitigation that the Committee may consider is the removal of the indication for

chemotherapy-induced anemia.

[Slide.]

If the indication for chemotherapy-induced anemia were to remain in the label, FDA asks the Committee to consider whether the following additional labeling changes are appropriate to minimize risk to patients:

To first restrict the current indication to specific cancer types for safety has been adequately assessed, which at the current time includes small cell lung cancer.

Sampling labeling could state the following: "ESA is indicated for the treatment of chemotherapy-induced anemia in patients with small cell lung cancer receiving myelosuppressive chemotherapy."

[Slide.]

Now, the Committee may consider restricting the indication to use in patients who may not be cured, for example, patients with locally advanced or metastatic cancer.

Sample labeling could state the following:

"ESA is indicated for the treatment of chemotherapy-induced anemia in patients with locally

advanced or metastatic cancer receiving myelosuppressive chemotherapy."

[Slide.]

Next, the Committee may consider stating that ESAs are not indicated for patients receiving neoadjuvant and/or adjuvant treatment.

Sample labeling could state the following:

"ESA is indicated for treatment of chemotherapy-induced anemia in patients with locally advanced or metastatic cancer receiving myelosuppressive chemotherapy. ESA is not indicated for use in patients receiving neoadjuvant and/or adjuvant chemotherapy."

[Slide.]

Now, the Committee may also consider stating that ESAs are not indicated for patients in clinical settings where harmful effects have been demonstrated in at least two studies, for example, in breast and/or head and neck cancers.

Sample labeling could state the following:

"ESA is indicated for treatment of chemotherapy-induced anemia in certain patients with cancer receiving myelosuppressive chemotherapy. ESA is not indicated for use

in patients with breast or head and neck cancer."

[Slide.]

Finally, based on currently available data, the Committee may specify a hemoglobin level at which the initiation of ESAs is appropriate assuming a patient is asymptomatic and has no comorbid conditions.

[Slide.]

Finally, other proposals for risk mitigation from FDA are as follows:

First, require an informed consent between the patient and physician describing the risks and benefits of ESAs and red cell transfusions.

A similar process has been done with other drugs. But FDA's experience with this tool is limited and this process can be difficult to monitor and enforce.

Another proposal is for a restricted distribution system. Examples of a restricted distribution system includes existing systems in place for thalidomide, lenalidomide and Isotretinoin.

Such a system could restrict ESA prescribing to providers who agree to educate patients on the risk and benefit of ESAs and verify a patient's hemoglobins and use

ESAs according to the label.

ESA distribution would be limited to inpatient and outpatient pharmacies that only accept prescriptions from these enrolled providers. Clearly, developing such a system would be a complex process.

That concludes my presentation. I will now turn it over to Dr. Mortimer.

DR. MORTIMER: At this time the Committee will have the opportunity to ask questions of the sponsor and the FDA.

Dr. Perry.

Questions to the Presenters

DR. PERRY: My question is to the FDA. You might want to stay there at the microphone.

If you go to your Slide No. 29, the summary of the two studies PREPARE and GOG-191. I was taught--and I need your help here, I am only a simple clinician--I was taught that when confidence intervals pass 1, that you are not to rely upon the information.

So the confidence intervals here in the first one are 0.93 to 2.18. I wouldn't consider that statistically significant. Is that correct?

DR. JUNEJA: I have to admit I am mostly a clinician, as well.

Dr. Rothmann, if you want to answer that question better than I can? I have my own answer, but Dr. Rothmann I think probably has a better answer.

DR. ROTHMANN: That is correct. And we haven't said that it is statistically significant, and it says on the slide there, "Trend to."

DR. PERRY: Yes, I know. There is a careful attempt here to say trends at times. And then there is a generalization that says we shouldn't use these agents in neoadjuvant breast cancer based on this particular study, because it shows decreased survival rather than pointing out what I think is more correct, that shows a trend toward decreased survival that is not statistically significant.

If I can go down to the GOG-191 study, it seems to me that has the same.

DR. ROTHMANN: That is correct. And I think the numbers speak for themselves.

DR. PERRY: Okay. Can we go to Slide 33? You made a point about achieved hemoglobin levels. But it seems to me that the DAHANCA study about which a great deal is

said, and it seemingly shows decreased survival, that we don't have the data for the target hemoglobin achieved, and for the CAN 20 study we have insufficient data.

So do I infer from there that we have an incomplete data set and shouldn't make any comments or conclusions based on an incomplete data set?

DR. JUNEJA: I will start with the DAHANCA study. We do not have data submitted to FDA on the DAHANCA study, and I am sure the sponsor can comment further on that.

Now with the CAN 20 study and the submitted data, on the achieved hemoglobin, unfortunately, our statistical reviewers may be able to speak further, there was not-- again, the study had 66 or 70 patients. I always get mixed up as to the exact number. But the submitted data on the achieved hemoglobin in this trial was not sufficient to draw any even conclusions about the median or the quartiles, and I will turn that over to statistical reviewers if they want to say anything more about CAN 20.

DR. ROTHMANN: I am told that that study did not have hemoglobin level data. This is a study that had 70 patients and which the median survival in the experimental arm was 2 months and, in the control arm, 4 months.

DR. PERRY: My point is as you may be gathering, we are making a great deal about studies that don't have statistical significance. In previous ODAC meetings when a sponsor has been asked to provide data in favor of approving a new drug, we have very strongly declined their attempts to prove a point when all we have seen are trends and not statistically significant evidence.

DR. JUNEJA: Well, again, I will have to let the numbers here speak for themselves. Again, with regard to this table, as I said, data has been submitted on 7 out of 8 of these studies with regard to the achieved hemoglobin.

The 8th study again was data not submitted for achieved hemoglobin is the DAHANCA study.

DR. PERRY: It looks to me like you had 6 out of 8 if you count the same way I count. If you don't have DAHANCA and CAN 20, that is 2 out of 8.

DR. JUNEJA: I understand. Again, CAN 20, data has been submitted to us. But there are not a sufficient number of hemoglobin levels from this study for us to draw a conclusion from it.

DR. MORTIMER: I would just like to remind the committee that this is a supportive care drug. So, unlike

other agents that we are asked to discuss, this is a supportive care drug that has not actually demonstrated a benefit in decreasing fatigue but clearly does raise hemoglobin levels. So I don't think this is really analogous to many of the other drugs.

DR. PERRY: A point taken, Madam Chairman. But I also want to make sure that everybody is tried by the same judge and the same jury.

DR. MORTIMER: Thank you.

DR. KEEGAN: I think you are correct in your interpretation of the information, but a couple of points. The first is that we felt that these were important public health issues to bring to the attention as soon as we had information that might bear in mind the totality of the data in breast cancer seems to at least be consistent, if not all equally statistically significant.

The other is that the level of evidence and the weight that we put on an efficacy claim is different from the weight of evidence that we apply to safety information and that we use a somewhat different standard in determining when a risk is present, and that we do not hold that to the same level of statistical significance as we do for

promotional labeling claims.

DR. MORTIMER: Thank you, Dr. Keegan.

Dr. Harrington.

DR. HARRINGTON: You both answered the answer that I was going to give Dr. Perry quite well. I guess I would just add to that, that in addition to whether or not a confidence interval covers one, the range of values in the confidence interval are important in deciding whether or not one is able or willing to tolerate risk to a certain degree.

These confidence intervals are quite wide but they do show that, for instance, a doubling in the hazard are not inconsistent with the data in the PREPARE study, an increase of more than 75 percent in relapse-free survival.

I agree that it is very, very difficult to interpret it in instances where we have a supportive care drug. And we are not looking for absolute proof of danger here. But some measure of the evidence which must be weighed against benefit.

DR. MORTIMER: Thank you.

Ms. Schiff.

MS. SCHIFF: My question is directed to Amgen and J&J. What criteria did you use to come up with starting

dosing at 10 and bring it to 12? Why didn't you, for example, just pick 9 to 11? Is it just arbitrary?

DR. LILLIE: In answer to the last part of your question, no, it isn't just arbitrary, and if I could have slide on, please.

[Slide.]

There is a continuous relationship between hemoglobins and transfusion. There is no clear-cut point but here we have data showing the baseline hemoglobins in a number of our Phase 3 placebo-controlled studies on which registration was based.

You see here the absolute risks of transfusion are lowest when hemoglobins are highest, however, the benefit is preserved even at an initiation of 10 and below. And we have taken 10 at this point where there is still clear benefit from reduction of transfusions for patients. But this will reduce exposure to ESAs in this population.

Of note, these data are based not purely on initiation. But, of course, all of these studies had targets which were higher, which allowed patients to rise on initiation in order to maintain that hemoglobin and avoid transfusions.

If we look at the benefits of ESAs from transfusions--but we can also look at symptomatic relief, as well--those benefits clearly do not increase when one goes beyond 12.

On that basis of avoiding transfusions and ensuring that patients who can benefit do benefit, having a target and an initiation at the same level is really not practical in clinical practice.

You have to be able to allow for patient and hemoglobin measurement variability as you maintain a patient within that range and that is how we have come to 10 to 12. It maximizes benefits and it avoids exposure in patients who are unlikely to require transfusions but still ensures that those patients who are treated do indeed avoid the risks of transfusions.

DR. MORTIMER: Dr. Curt.

DR. CURT: A question for the sponsors. I am wondering if either sponsor is doing work in biomarkers to predict the 30 percent of patients who will respond to Epo. That would help you refine your safety profile and certainly reassure payers.

DR. LILLIE: The question is one that is indeed

one we have looked at in great depth, and we have a large database of patients who you seem to look at this in. The problem is having done extensive analysis back on these, we have not managed to identify factors that would serve as biomarkers for response.

There have been proposals. I am sure you will be as familiar with those as I am. For instance, the baseline hemoglobin is a gross predictor of response but is not a very accurate one and the patients who are below 10 will respond, patients who are above 10 will respond. So there are gross predictors but they are not helpful in terms of directly identifying the patients who are going to respond.

Likewise, iron indices have been looked at, at some length but again none of those have provided sufficient discrimination in research to date to reliably allow us to look at those parameters in terms of risk prediction of response.

So we have looked in great detail at hemoglobin parameters, at other subparameters of red cell indices, such as the mean red cell hemoglobins and others that may change early in responders.

Those are promising approaches. They are areas we

are still looking at. But at the moment there are not a definitive set of markers with which we can predict response without actually trying the drug in patients first.

DR. HAIT: Also, in direct response to the question, we are in discussions with NIH and NCI about these kinds of things and we can certainly take it up. And, in addition, we have engaged with an academic group in Cambridge to talk about the most powerful proteomic analysis they may come up with. So we are very interested in this, as well.

DR. MORTIMER: Dr. Redman.

DR. REDMAN: This is to the FDA, again on Slide 34 and 35. You made a conclusion that I want to question, because these are two studies where they were trying to achieve a target hemoglobin. You said since they didn't achieve a target hemoglobin of 12, that there is some question of whether that 12 value is valid or not.

I would put down that I think this could also support the sponsor's feeling that if you try to push in somebody not responding to an ESA, that it is a bad prognostic factor in that patient population itself.

So I don't think this data could be used to say

maybe 12 is even in question as a time point or an endpoint.

The other question I had, which is sort of interesting, Slide 48, when you presented the small cell data, you put a conclusion or a question there, and I want to know what it is based on, that the results in small cell lung cancer is unlikely to be applicable to other tumor types.

What is the difference in the host of somebody who has breast cancer, lung cancer, non-small cell lung cancer, or somebody with small cell lung cancer? I don't know what that is and, if somebody does, I would like to know what it is.

One other caveat, just because these are public meetings, the term tumor progression should not be used. The connotation of that term is severe.

You have maybe decreased risk of local control or decreased control of a tumor type that may be host related. But the study to do tumor progression, which is going to be, you know, ESA treatment versus best supportive care and doing actually tumor measurements is probably never going to be done and I just have an aversion to that term tumor progression.

DR. KEEGAN: With regards to your comment on the small cell lung cancer conclusion, in part that is driven by some observations. And there are differences of opinion among everyone including the sponsors and ourselves about the data on EPO receptors. But there has been some evidence to suggest that if erythropoietin receptors are important in mediating these adverse effects, that small cell lung cancer may not be a good model for other tumor types.

That is the primary reason, however, we probably also would not directly extrapolate from one tumor type of all of them given the differences in the findings.

With regards to the hemoglobin level, you are correct that it may be somewhat of an over-extrapolation. We were trying to do the best with what available data we had. As you have heard, there has been no study, and there is no ongoing study, which is using the upper ceiling, looking at ceilings other than 12 as modified since the Advisory Committee.

So I think that the only data we are going to get is many years away. So we were trying to tease through the data to look at this.

It is possible that there are other explanations

and somewhere in that 35,000 pages worth of documents we are hoping we get some more information. But we haven't gotten to it so we wanted to give you what was available and what we have looked at, at this point in time.

DR. MORTIMER: Dr. Wilson.

DR. WILSON: My comment is for the sponsors. You have mentioned that one of the endpoints or one of the markers you were planning on looking at is whether or not there are EPO receptors on the actual tumor cells.

Yet, there may be an effect of EPO on the micro-environment, which of course could impact the tumor cell in a very positive way. There are markers that could be looked at in terms of chemokines, cytokines within the blood and, specifically, have you considered looking at effects on angiogenesis?

This is a target area that has shown effectiveness with some targeted agents, and in fact, if EPO did increase angiogenesis, this could possibly be a cause for some of these possible findings.

DR. EISENBERG: I would like to ask Dr. Glen Begley from Amgen to respond.

DR. BEGLEY: Thank you very much for the question.

This is an area that has been of great interest to us and we have explored extensively.

Could I have the slide on, please.

[Slide.]

The question of whether or not EPO is able to stimulate endothelial cells is one that has been, as I said, of great interest to us, and the experiment that you see in front of you here is using the industry-accepted standard model for neovascularization.

On the top panel on the left you can see a rat cornea into which has been implanted a plug. This is the negative control soaked in bovine serum albumen. In the middle panel, you can see a similar plug soaked with vascular endothelial growth factor and you can see the ingrowth of new vessels from the limbus in the cornea.

On the panel on the right you can see a comparable experiment using erythropoietin in this case and the inability of erythropoietin to stimulate the ingrowth of new endothelial cells with new vessels.

That is quantitated below by a blinded investigator and is using concentrations of the EPO up to 100,000 times greater than we are able to achieve

clinically.

DR. WILSON: May I follow up? I mean I think it is very nice that you have done this. But there are severe limitations on models like this in human samples. Have you measured VEGF levels and other indices that could be associated with increased angiogenesis?

DR. BEGLEY: We don't have that data specifically. What we have done is take tumor samples from patients and we have laser-microdissected the stroma from the tumor samples. And then we have looked at the level of messenger RNA expression in those laser-microdissected samples and shown that there is no increased messenger RNA expression either in the tumor, nor in the endothelial cells about that which we see in normal tissues.

DR. WILSON: Have you done that for whole lymph node biopsies or whole tumor biopsies without doing microdissection?

DR. BEGLEY: Slide up, please.

[Slide.]

This slide refers to the laser-microdissection that I mentioned to you, the head and neck samples on the left, and published data on the right, looking at whole

tumor samples comparing tumor samples from patients with head and neck tumors compared with normal tissue from the head and neck region.

We have done similar studies that kind of get to the question you are asking, as well, where we have taken tumor samples and separated them using flow cytometry to get individual single cell preparations of the tumor cells and then we have used highly sensitive PhosFlow assays. So we have now looked at something like 16 phosphorylated proteins within the tumor samples.

Slide up, please.

[Slide.]

These are now individual tumor cells. And we have looked at, for example, PhosFlow AKT plus a number of other PhosFlow proteins.

This slide shows PhosFlow AKT on the right panel. We have looked at 10 primary tumor samples here, so this is an early analysis. They are ongoing but you can see, for example, breast, ovarian, colon tissue, and the circled area shows the inability of erythropoietin in this situation we are using 300 units/ml to stimulate PhosFlow AKT, although in the same tumor sample immediately to the left you can see

the IGF, AGF, HGF are able to stimulate PhosFlow AKT.

As I have indicated, we have looked at a total of 16 signal, intracellular signaling molecules, and been unable to see stimulation by EPO of the tumor cells. But all of the control samples and experiments have performed as we would have expected.

These are ongoing studies and we hope to be able to amplify the number of different tumor samples we have looked at.

DR. MORTIMER: Thank you. The company is to be applauded at trying to get to the basic science basis of this signal that we have seen.

I have a question for the company regarding the BRAVE study and also the GELA study. In the BRAVE study, which has already been published--and this was advanced breast cancer--there was no difference in overall survival between the patients who received erythropoietin or darbepoetin and those in the control arm.

In the design of the study, it was mentioned that transferrins less than 22 percent, 22 in the control arm, that those patients were allowed to get ESAs. It is very difficult in the publication to figure out actually how many

patients in the control arm actually got ESAs. But it is stated that the median transferrin level is 22 so I would presume it was a significant number of individuals and may, in fact, offset that this was really a placebo-controlled trial.

DR. BOWERS: So the BRAVE study is available to us only by way of the same publication, Dr. Mortimer, that it is available to you. It is a study that was conducted in Europe and sponsored by Hoffman-La Roche. The survival results of the study have already been presented by FDA this morning.

If I could have the slide on.

[Slide.]

Just to present the Kaplan-Meier for overall survival from the study. It treated women with metastatic breast cancer receiving first- or second-line chemotherapy. This is data from the publication with a hazard ratio of 1.07 at a confidence interval that includes 1. But I am unable to address the very specifics of your question.

DR. MORTIMER: I guess the same problem arises in the GELA study where you are going to allow ESAs in individuals whose hemoglobins are less than 12, which means

the placebo arm is going to be also heavily using ESAs.

DR. LILLIE: As I said, that was a decision by the GELA group in France. There is a standard of care there and ESAs are accepted as that, and they felt it difficult to conduct a controlled experiment with no access to ESAs.

The threshold for that is 9 g/dl, and we understand that approximately 15 percent of patients will be exposed to ESAs in that study.

DR. MORTIMER: Dr. Harrington.

DR. HARRINGTON: Two questions. One, it seems as though even the most--well, it seems as though both the sponsor and the FDA have talked about a labeling that really directs the treatment towards preventing transfusions.

So I am wondering why there is so little data on the adverse outcomes of transfusions in the previous trials where people have been randomized to a placebo versus the agent and presumably been transfused.

What we heard I think during the presentation that while there are global data, there are data overall about transfusion risks. There seem to be none from these trials, so that is the first question. That one I think is probably for the sponsor.

The second is a little bit analogous to Mike Perry's question in the sense that I am just a naive statistician on this one. But it seems to me that the proposed randomized trial, the one that is going forward, which has the randomization arm in the agent, in the active agent to include dosing to a target to start at 12 and to a target of 13 is pretty distant from the labeling, which says it is unsafe--could be unsafe if you get above 10.

So I am just wondering whether that trial, unless I have misunderstood, the design is viable.

DR. LILLIE: I would be very happy to clear up that misunderstanding.

DR. HARRINGTON: Thank you.

DR. LILLIE: The initiation at the moment would be below 11 with a ceiling of 12, so there is no--which would be consistent with the current label. We would always need to discuss with the Agency if we do move the initiation to 10. Slide on, please.

[Slide.]

Here, you can see again the intent here is to use the agent according to label with a ceiling of 12. There is of course, currently not a specified initiation. We would

obviously like to discuss the initiation level and have submitted proposals to the Agency on this meeting, so this study should be consistent with the labeled use.

Also, I could clarify that 3010 has been amended to be consistent again with the current label and has a ceiling of 12 also.

DR. HARRINGTON: My error. I was probably looking at the wrong slide.

On the transfusion risks or adverse outcomes for patients who were transfused on these randomized trials, what do we have?

DR. LILLIE: I think the point that was being made by the Agency, if I understood correctly, is that those have not been specifically sought in studies.

Adverse events in transfusions are well recognized and on that basis, investigators are often unlikely to report those during the standard adverse event reporting in the study, because the agent under study is, of course, the ESA, not the transfusion, and that really results in a bias in the terms of reporting that we might see in adverse events.

One of the things that we are going to do in the

new study is to provide a page of the report form which will directly address whether investigators feel that adverse events are being caused by the transfusion as opposed to the ESA, although again that would of course be hard to determine when both are being used simultaneously in some patients in a blinded fashion.

So we are attempting to do that in the new study. It has been hard to disentangle that in the prior studies that have been done, and, of course, there really is no literature on the randomized use of transfusions versus nothing at all. That literature just doesn't exist, so, of course, there is no database for us to rely on in that respect.

DR. MORTIMER: Thank you.

DR. TENDLER: If I could just add to Tom's comments, many of the concerns that we have had about blood transfusions in terms of transmitting infectious risks including unknown infectious pathogens, again, would be more long term effects that would not be necessarily picked up in these studies.

DR. MORTIMER: Thank you.

Dr. Link.

DR. LINK: I just had a follow-up question about the proposed study while you had that slide up there. Are you going to give us perhaps a timeline for that trial, the 6,000-patient study? When would it start, sort of ballpark, how long would accrual go on, when would we have meaningful results of that to make a decision.

I guess sort of a follow-up question, in view of what has already been on the label, what is the likelihood that you will actually be able to succeed in accruing patients?

DR. LILLIE: Slide on, please.

[Slide.]

Just to refer back to the schema, here, we are anticipating that this will take an accrual period of five years although as I stated, we are actively looking at feasibility now.

You raised the very real question of the feasibility of doing such a large placebo-controlled study. We have looked at this in some detail and, as I said, one of the ways that we are addressing this is firstly making this a global study.

Secondly, we are allowing the inclusion of broader

chemotherapy regimens, which we don't believe will impair the ability of the study to answer the important questions but will improve patient accrual. So it's a step we have taken in 3010.

There is a 2:1 randomization in favor of the darbepoetin arm so that patients entering the study do have a reasonable expectation of receiving benefit from ESA in terms of not receiving transfusions. We are putting the full weight of the companies behind this study in order to try and get this done as quickly as is possible.

There will, of course, also be data safety monitoring, who will formally check the harm at specified numbers of events in each tumor type as we go along. So there will be some indication earlier on in the completion of the study as to whether there is harm with these agents in this non-inferiority study design.

The challenges that you raise really reflect the tension between designing a study which is ideal in terms of the factors that we put up from both the Agency and ourselves, and those are clearly the factors that are ideal in designing a study to answer these questions and, if you want a study that is robustly designed to do that, then,

this is absolutely the correct design. But the implication of that is a large study.

There are other approaches, such as a simple survival study in more heterogeneous tumor types that could be accrued faster but would not be able to directly address things such as progression because those complicate and make the study more difficult to accrue. So there are other options that we would be very happy to discuss with the Committee or the FDA that might allow more timely completion of a large study, simple survival study looking at mortality, but that clearly would not answer some of the other questions that are rightly being raised.

DR. LINK: When is this going to launch? There is five years of accrual.

DR. LILLIE: We have a protocol that we have already discussed with the FDA on a number of occasions over the last year. We would wish to submit this to a special protocol assessment. I think that is the most sensible thing to do for both the sponsor and the FDA to ensure that we agree on the premises of the study. That does have a timeline associated with it and we would have to wait for that to complete.

Assuming that that went smoothly, we would hope to be seeing the start of the study towards the end of this year with the start-up time that is inevitable in terms of setting up such a large study.

DR. BOWERS: If I may add a point about Study 3010 that Johnson & Johnson is conducting. I am Peter Bowers from Johnson & Johnson. That study will complete enrollment in the 2010 time frame.

DR. MORTIMER: Thank you.

Dr. Kramer.

DR. KRAMER: I have three questions for the sponsors that I would like to ask one at a time.

The first has to do with the risk minimization strategy. The question is given that this drug is used for other indications, as we know, how do you propose to actually implement the limited distribution just to the physicians that agree to participate in the RiskMAP plan?

DR. THOMAS: Thank you for the question. This is the area where we need to spend the most time in terms of trying to get control of the distribution to that population. Our proposal is to target distribution via the actual provider side, so down at the hospital or at the

community center level, and so making that side the gatekeeper for prescription.

It clearly would be very difficult in the retail pharmacy situation to discriminate between distribution that was occurring for nephrology versus oncology.

It is one of the reasons, though, that while we remain committed to doing whatever is required to be successful, we need to be pragmatic about this and actually make sure that we can, in fact, put in place a meaningful distribution program.

I would say, however, that bringing in place auditing and prescribe a checklist will allow us to check that, in fact, patients have been prescribed the drug for the appropriate indication, claims databases.

Most of the payers require hemoglobin data, will give us a firm control on whether the actual prescription also meets the eligibility criteria. But we agree that, in fact, restricted distribution programs have multiple indications and the large volumes of patients in nephrology will be extremely difficult to enforce.

DR. KRAMER: So, essentially, it would be mostly retrospective auditing of the prospective prevention.

DR. THOMAS: What we would do is we would require the physician to fax in the eligibility criteria and also fax in the agreement. But you are correct, to assess that it has been done appropriately we would need to go to the patient record and audit that.

DR. KRAMER: The second question I have--this is the first ODAC that I have attended for this drug, although I did attend the September hearing, and I am really struck at the very protracted timeline for an assessment of safety.

In that regard, I was really struck by the sponsor's table in the packet we received, that listed the studies that the sponsor identified as being applicable to safety.

One of the things that struck me, I would like to ask the sponsor about, is that of the randomized trials of epoetin alfa, there were 15 trials that were listed as relevant to safety, and 12 of those 15 trials were completed enrollment between 2001 and 2003. Yet those trials are either now just being submitted in February or so of 2008 or have not yet had data submitted.

I would like to understand that delay.

DR. CORNFELD: Thank you for the question. I am

Mark Cornfeld. I am the regulatory leader for Procrit.

Could I have the slide on, please.

[Slide.]

This is the table of informative epoetin alfa studies which we shared with both the May 2004 ODAC and the May 2007 ODAC. The question did arise at the last ODAC and it was intended to point out that these studies, while they were recognized as important, the concerns were that they had not been submitted. And that was entirely due to the fact that the patients were still in follow-up and the studies were still ongoing.

So I am very pleased to be able to give an update today that according to the timeline which we shared with you last May, all of these studies have now been submitted on schedule and, in fact, in the case of the Mobus study, slightly ahead of schedule.

If I could have Slide 48 also.

[Slide.]

FDA referred to the large amounts of additional data and we acknowledge that there has been quite a lot that has been sent in, in the last several weeks. The studies that we just showed are the bottom half of the table--so the

additional data were the first of the studies that are in top half and they include the GOG-191, which was mentioned.

The point that we are trying to make is that these were all referenced in the FDA briefing book. And we have provided synopses in the past, we have been providing time tables most recently in August of last year and January of this year and, actually as an action item from the 2004 ODAC, we have been providing regular safety updates on several of these studies including the Mobus and the Blohmer studies.

DR. KRAMER: I had one last question.

DR. MORTIMER: Go ahead.

DR. KRAMER: Although it wasn't addressed in either the sponsor or the FDA presentation, in the materials that we received, and frankly, it might have been from the materials we were submitted in advance of the public comment period, there was mention to physician incentives being in place for prescription of these drugs, and I really don't know what those are and would like to know if the sponsor could describe that.

DR. OFFMAN: Thank you for the question. Yes, the FDA briefing book does mention as part of our risk

management, a concern about physician incentives and the desire for us to address them.

Slide on, please.

[Slide.]

The decision by oncologists to prescribe ESAs is based on clinical factors and medical judgment and we do have prescription data to support that ESAs are used appropriately in oncology patients.

There is a long-standing method in oncology for the coverage of physician-administered drugs. It is known as the buy-and-bill model. Doctors purchase these products and then later receive reimbursement from third party payers in government agencies.

This system is used widely in the United States for hundreds of drugs, largely oncology, and include the ESAs.

The sponsors are fully prepared to work with government agencies and third party payers as part of our risk management, as well as patient and provider groups to develop appropriate reimbursement policies that address the issues that have been raised by the FDA in their briefing book and the issues raised by others regarding perceived

physician incentives.

DR. MORTIMER: Thank you.

DR. KEEGAN: Could we follow up on one of the questions that was asked, the question before that, and some of our concerns about the timely submission?

DR. MORTIMER: Go ahead.

DR. JUNEJA: Could we back a backup Slide No. 12, please, shown.

[Slide.]

This is just with regard to this Mobus study in adjuvant breast cancer that has been mentioned by the sponsor.

So this was the slide presented at ODAC 2004 by Johnson & Johnson. This is basically a cut and paste of this slide. This again identifies the ongoing randomized trial for epoetin--not for darbepoetin, for epoetin--and, on this slide in ODAC 2004, the Mobus study was not identified, so I am not clear. Maybe the sponsor could clarify where that information is coming from.

DR. BOWERS: Certainly, I will be glad to clarify. I am Dr. Peter Bowers from Johnson & Johnson. Indeed, the Mobus study was not identified on this slide presented at

the 2004 ODAC but it was identified to the FDA in the first update on the studies that was provided subsequent to the May 2004 ODAC meeting towards the end of 2004. It is referenced clearly as an additional study that we had identified.

Of interest, it is conducted by the German Cooperative Group HEO in Germany.

DR. MORTIMER: Dr. Perry.

DR. PERRY: I would like to ask both the sponsors again, I think that the previous speaker's answer was correct but not complete. I didn't hear the word "bundling" used or explained.

It is my impression that discount prices are given when you buy several of the sponsor's products at one time. If you buy Aranesp and Neulasta at the same time, that you get a better rate, which therefore influences, particularly in private practice, the rate at which you might prescribe those drugs.

Is that an erroneous impression?

DR. OFFMAN: I think just to follow up on my previous slides, if you can call up the slide.

[Slide.]

The first point I think that is very important for everyone to recognize is that when prescription data are evaluated in the United States in the oncology setting, there currently does not appear to be over-utilization of ESAs. In fact, if incentives were present and responsible for over-utilization of ESAs in oncology, you would expect to see a number of things.

First, you might expect that large amounts of ESAs were being used to achieve higher hemoglobin levels. But, in fact, that is not the case. Fewer than 5 percent of all ESA administrations occur when hemoglobins are greater than 12.

Secondly, you might assume that you would see high doses of erythropoietic agents being used in clinical practice and, indeed, this isn't the case. The mean weekly dose of Aranesp, for example, is approximately 20 percent less than the labeled dose.

You also might expect to see that almost all patients with chemotherapy-induced anemia would be treated with ESAs if incentives were influencing utilization. In fact, that is also not the case. Up to 30 percent of patients in the oncology setting undergoing chemotherapy,

who have hemoglobins less than 11, are not receiving therapy with ESAs.

Finally, if incentives were playing an important role, you would note differences in ESA patterns of care among different systems with financial structures, such as staff model HMOs where they had salaried clinicians as opposed to contracted or traditional managed care organizations. Indeed, research shows that the patterns of care in the utilization of ESAs is quite similar in these two different settings.

In general, when we look closely and interrogate the prescription data, we see in the United States prior to 2007 and in the current state quite appropriate use of ESAs.

DR. PERRY: Which doesn't answer my question.

[Laughter.]

DR. PERRY: Maybe you ought to be on Dancing with the Stars or something. You have tap danced around the question. Is there bundling, are there rebates, yes or no?

DR. OFFMAN: Yes, well, in the current system--

[Laughter.]

DR. OFFMAN: Yes, there are. In the current system, as the Government has set out Medicare Part B

reimbursement, it is paid on what they call an average selling price. What that means is that the Government reimburses providers based on an average of the price that the purchasers pay.

Market competition and price competition in the United States does take the form of rebates and discounts. And, of course, those are perfectly legal, and they do result in tremendous savings to Government payers but they have, in fact, fueled the perception.

DR. PERRY: We are not debating that. All I want to ask is a simple question. Were there rebates and were there bundling? And the answer to both those questions, if I am correct, is yes. Is that correct?

DR. OFFMAN: There are rebates and discounts being provided, and Amgen does have a contract that uses the portfolio of products.

DR. PERRY: Can you say the word yes?

DR. OFFMAN: Yes.

DR. PERRY: Yes twice. Thank you.

DR. MORTIMER: Dr. Kramer, that answers your question?

DR. KRAMER: Yes.

DR. MORTIMER: Ms. Schiff.

MS. SCHIFF: I think from a patient perspective, we want to know as soon as possible at what level, if any, these drugs are safe. Therefore, I would suggest that we do the trials at lower beginning and end targets, because if we have questions about whether it is going to work between 10 and 12, at least if we start low, we won't have to wait another 8 years, you know, to then do one step lower.

Why don't we go in the opposite direction and look at whether 8 to 10 or something is safe and then, if we establish that, then go on to the next one instead of taking the chance that there might be negative findings, and then we would have to wait 16 years to know.

It seems like that you have always gone from the other direction. Why don't we start from when transfusions are really given and see what happens and not increase the overuse of the drug. The lower you go, the less you increase the overuse of the drug.

Then, just finally, I mean there was, on the question of whether there has always been appropriate use, I mean since the new label, half the amount has been used as before the new label, so there must have been some overuse.

DR. MORTIMER: I would just like to ask a question of the company just as a point of clarification, because again there is a little bit of dancing about within label use and it has repeatedly been said in this forum and in the press that when these agents are used within label indications there is no evidence of harm. But, as the FDA pointed out, there really are no studies that have actually tested this to show evidence of harm.

I just want to make sure the company agrees with that.

DR. BOWERS: Dr. Peter Bowers from Johnson & Johnson. Thanks, Dr. Mortimer.

In regard to the label and the label target hemoglobins, indeed, the comment is correct. But, of course, we must recognize that the label has been evolving fairly rapidly over the last several months and years.

If I could have this G-22 slide on, please.

[Slide.]

However, we have been able to look at the body of evidence that is available to us from a large number of studies and when we classify those studies into two general buckets, studies that used lower hemoglobin targets where

the intent of the study was to correct anemia and thereby reduce transfusion utilization, when we conduct a meta-analysis, a pooled analysis of that low target group of studies, we see that the hazard ratio for survival, the point estimate is 0.98 with a confidence interval that spans 1, as I think you can see at the bottom of this slide, which is the collection of low hemoglobin target studies.

If I could have Slide ST23, please.

[Slide.]

In contrast to the results from the collection of low target hemoglobin studies, we have results from our high target hemoglobin studies and these have used higher targets. Generally, the endpoints of these studies have been to evaluate survival.

They have not been particularly designed to focus on transfusion reduction and, when we pool the results from the high target group of study, we see a point estimate that now shifts to the other side of 1, 1.08 favoring the placebo or control treatment, the 95 percent confidence interval runs from 0.98 to 1.19.

DR. MORTIMER: Dr. Pazdur, you wish to comment?

DR. PAZDUR: I had a question. I wanted to go

over and get some guidance or some clarification I should say on your proposed label changes with the initiation of ESAs at a hemoglobin less than or equal to 10 g/dl.

Is this an attempt to bring you into some type of similarity to the CMS National Coverage Decision and do you see the CMS National Coverage Decision being consistent with now the proposals that you are making?

DR. EISENBERG: I will address that. I think the answer to the question is no. We believe the initiation level less than 10 as is now also reflected in the label that will be implemented in Europe based on the data that Dr. Lillie showed you, is a conservative range, I think to the question that was raised regarding when you should consider an ESA versus transfusion from a patient perspective. I think it is a very important question.

We believe most clinicians in practice consider transfusion when the hemoglobin drops below 10, and as I think you frame quite nicely, in the otherwise healthy patient. We recognize there may be decisions made when someone has comorbidities that might lead to a different decision.

But we think it is a conservative approach. The

difference with the National Coverage Decision and the European label, for example, is that we believe that the use of ESAs, if they are--again, this would answer the question that was raised around how they should be used--if they are to be effective in avoiding transfusion and reducing exposure, we need to base that recommendation on pharmacology.

If someone's hemoglobin rises above 10, because they are a good responder, every piece of data we have suggests that patient, in fact, will avoid transfusion and have a good outcome. To wait until they drop below 10 to meet a target that then you now would provide ESAs again, we don't believe really is appropriate use from a pharmacologic perspective.

We do recognize that it does need to be a conservative decision and we reflected that in the updates as I have indicated, both in the EU and the U.S.

DR. PAZDUR: In the current label, it states that the dose should be the lowest dose to avoid transfusion. So are you trying to say, then, that really you need a hemoglobin greater than 10 to avoid transfusions, is that your point?

DR. EISENBERG: I think the data that Dr. Lillie showed, in fact, as you know, we also submitted at the end of last year, following the recommendation from ODAC last year, that we consider the appropriate initiation level.

Our data actually were best when, in the clinical studies, the initiation was less than 11, and that was provided from the randomized data. We believe, as we have said, that to have an abundance of caution around this, that the lowest dose to avoid transfusion should be targeting the lower end of that range so initiation less than 10 is a titratable drug.

Obviously, if someone responds and has a good response and is avoiding transfusion, keeping them to the low end, we don't advocate nor believe that it's appropriate the patient should be targeted to higher levels than that necessary to avoid transfusion.

DR. PAZDUR: Give us some guidance here. Where do you think the drug should be dosed to?

DR. EISENBERG: I think the dosing--and we didn't perhaps go through this explicitly--but I think dosing really falls into two categories in general, and we can provide specific dosing information for each product.

Initiation less than 10, if the patient is a good responder, the dose that achieved that response should be minimized to the dose that is necessary to avoid transfusion.

If the patient has responded, let's say for argument's sake they are 10.5, it takes several weeks to see a response, one could even envision lowering the dose. It depends on the agent how you might do that. But reducing the dose to maintain it in the lower range between 10 and 11, we think that would avoid transfusion.

If it's a poor responder, they didn't respond and exceed the dose of 10, in that circumstance, we believe that it would be appropriate to have one more try essentially depending on the product. It takes a period of time depending on the pharmacology of each agent to assess response but, certainly, if there is no response after 8 weeks to stop providing the ESA, it is unlikely to be of benefit.

So our goal I think should be conservative management.

Slide up for a moment.

[Slide.]

I don't want to belabor the point but I think, if

you look at those poor responders who don't get above 10, this is the high risk group, we don't believe we should be providing additional dosing to them. And these are data that are real data to give you a sense from the clinical trials. This is with darbepoetin alfa. But there are similar data for epoetin alfa, and both Johnson & Johnson and Amgen feel we can provide appropriate guidance in this regard.

Does that answer your question, Dr. Pazdur? Hopefully, that is clear to the committee. It does not answer your question?

DR. PAZDUR: I just would like some clarification. You are going to initiate it at a hemoglobin of less than or equal to 10. Where do you see the target of using this going to?

DR. EISENBERG: I think if the decision was made that a patient would need a transfusion because their hemoglobin was drifting down below 10, the clinician makes that decision, then, it would argue to me that that decision, at least in my experience, would have been based on--I provide ESAs, but I certainly transfuse patients--that, as their hemoglobin is falling back towards that 10

number, I would be rethinking transfusion.

So what I am suggesting, I think what we feel is appropriate, that if they responded, they are in that 10 to 11 range, you use the lowest dose to maintain them in that 10 to 11 range.

There are going to be some patients in whom the response might be quite brisk and they may go above 11 for argument's sake, we would feel that the dose should be reduced and that you should use the lowest dose to avoid transfusion and that transfusion trigger, at least based on our information, generally from most clinicians is when a patient is approaching the lower end of the range, the 10.

I think we can certainly provide label guidance that would be quite explicit in that regard and reduce exposure to patients who are appropriate for transfusion avoidance.

DR. HAIT: I would just like to add, Dr. Pazdur, that these patients often are continuing to get chemotherapy and it is very difficult to begin as it is falling below 10 and then stop and evaluate as it is going above 10, do we get another cycle of chemotherapy. So there is also a practical clinical matter.

DR. EISENBERG: Have we answered your question?

DR. PAZDUR: Yes.

DR. MORTIMER: We have eight burning questions here. Do any of these questions relate to the hemoglobin level? Yes, go ahead.

DR. LESAR: Yes, it is a question related to that. Has there been any attempt to evaluate dose response--that is, exposure to ESAs and response across studies--and/or the dose given and the response achieved; that is, it was quite informative when we were looking at the ESAs in chronic renal failure.

My other question somewhat related to that is do you have data on how often the drug is used in non-responders, or continue to be used in non-responders?

DR. LILLIE: Thank you. Slide up, please.

[Slide.]

In the oncology section, as, in fact, is also seen in nephrology section, an inverse correlation between achieved hemoglobin and dose. Again, that is not surprising, it is a confounded association.

We have explored a number of different doses also--not on this slide--and we see that these are titratable

drugs and each patient needs to be dealt with individually by the treating clinician.

Again, one of our aims with the label is to provide enough latitude for the patient and the physician to make informed decisions about how to use these drugs without exposing to harm.

Also, we have looked at acute hemoglobins and outcomes. Again, these are confounded. But associations are that these are, in fact, patients who exceed the safety limit of 12 in studies which were done prior to that limit being involved.

You can see here that actually for overall survival, the trends are not in favor of achieving those high hemoglobins and we accept that those are confounded

But really our basis of saying let's not keep treating non-responders when they are not getting benefit in terms of avoiding transfusion really are based on these observations. So they are pragmatic clinical observations that we believe patients who aren't responding. Dr. Eisenberg showed the graph; these patients are getting transfusion rates in the 60 to 70 percent range. Therefore, we believe that, after a trial of therapy, it is worthwhile

stopping and not exposing those patients.

We don't have data on how frequently patients who are non-responders continue to be dosed. We don't have data that tells us that.

DR. MORTIMER: Dr. Richardson.

DR. RICHARDSON: I would like to kind of get at some of the same issues. It seems to me that the safety signals seem to be strongest in those studies where the target hemoglobin levels were highest.

I think the thing that troubles me, and I suspect troubles a lot of the folks on the panel, is just the question of whether we are looking at a dose-response effect. That dose-response effect may be different across various tumors types.

Are there data on the dose of ESAs used in these higher target hemoglobin studies versus those used in studies aimed at lower hemoglobin targets, either total dose of ESA exposure, or dose over time, do you have those numbers?

DR. LILLIE: I am not sure that we do have all of those numbers. What we see, however, in cumulative dose, is that there is not an absolute relationship between dose

administered and, in fact, we have done studies which have randomized patients between a higher dose approach and a lower dose approach.

These were colloquially known as front loading studies, and I believe we have a slide that looks at the hazard ratios between these higher dose approaches and lower dose approaches which do not show any difference in survival or outcomes between the high dose approaches and the low dose approaches.

DR. RICHARDSON: Some of these dose calculations are going to be confounded by the fact that you are looking at dose in units per week as opposed to--

DR. LILLIE: We have looked at it both cumulatively and to attempt to address the question I think you are raising. I have done it by average weekly doses to try and normalize the length of time the patients stay on the study and really that is the foundation of--whilst we don't see an overall association with just a higher dose strategy for front loading in our cases.

When we look at the patients who don't respond, those are the patients who do get the highest doses and those are also the patients who have the worst outcomes.

So, there is some evidence around a dose association. But we don't see it in the studies where we have randomized between a high dose strategy and a low dose strategy although Johnson & Johnson may also have further data from their high target studies.

DR. BERLIN: Thanks. Jesse Berlin from Johnson & Johnson.

If I could have ST-13.

[Slide.]

This doesn't directly address the question in terms of a randomized study but, when we look within the BEST study, which is one of our studies that has shown the strongest signal, we do see this phenomenon, the same kind of phenomenon that Dr. Lillie is describing--that is, that the mean doses--and these are admittedly retrospective looks, but when you look at patients who survived versus patients who died--these are weekly doses I think--the mean weekly doses are much higher in the patients who died than those who lived.

Could I have ST-3, please.

[Slide.]

A similar kind of point I think comes out of this

issue of hyporesponders. I will move to another slide that will I think highlight the point. We have used a slightly different definition from Amgen.

When we define three categories of response, increasers, who have an increase in the first four weeks of treatment of half a gram of hemoglobin or more, decreasers who do decrease by half a gram or more, and then this stable group, who are the in-between group.

Then, we look at hazard ratios starting from that four-week time point. So this is a landmark analysis, again admittedly exploratory. But we do see this phenomenon that the patients who decrease versus those who are stable have an elevated hazard ratio.

Could we go to ST-4.

[Slide.]

This is the same classification that Dr. Bowers presented a few minutes ago, looking at studies that go beyond anemia correction. So these are the sort of high target studies. And now repeating the same kind of analysis, but restricted to these high target studies, you see this hazard ratio goes up to 1.5, statistically significant now.

So, the suggestion here is that again it is these high target studies where the dose is being pushed are where we see the signal.

If we could just see ST-5.

[Slide.]

Again, these are now the studies that are the lower target studies. When we repeat this analysis, this is the complement of the group we just looked at, again looking at decreasers versus stable. The hazard ratio now is basically 1.

So, again, it is consistent and admittedly exploratory post hoc, but consistent with this idea that the trouble arises in the hyporesponders in these studies that are targeting higher hemoglobins.

DR. MORTIMER: Clearly, this would have to be shown in a prospective study to be legitimate.

DR. BERLIN: Absolutely. The whole issue of management of hyporesponders has not been studied in the randomized trial.

DR. RICHARDSON: But the question I was asking really has to do with how much ESA were these patients exposed to in the stronger signal studies compared to those

where the signals are weaker, where the targets--you don't have that. Okay.

DR. MORTIMER: Dr. Redman.

DR. REDMAN: This is sort of along the same lines, not using mortality but using thrombotic events. Do you have suggestive evidence that is related to dose, it is related to the hemoglobin responder versus non-responder?

DR. BOWERS: If I could have Slide TV-3, please.

[Slide.]

Just to reiterate, I think a point that Dr. Lillie made very clearly during his presentation, is that there is, of course, confounding between these several elements, dose response and underlying health status of the patients. And so it gets quite complicated to try and specifically look at just one of these variables in this complex milieu.

But in any event, remembering that background, we again have looked at the rates of thrombotic vascular events in our studies, classified by this low hemoglobin target anemia correction setting versus the high hemoglobin target setting where typically doses were escalated to try and elevate or maintain hemoglobins in the higher range.

This panel of percents from this group of studies

indicates the frequency of clinically relevant thrombotic vascular events that were reported as adverse events by the investigators during the course of the study.

As you see looking at the panel of numbers, the column of numbers on the right, the frequency of TVEs in the epoetin alfa exposed patient ranges from zero in some of the smaller, shorter studies to as high as 10 percent in a study of patients receiving cisplatin-based chemotherapy.

That is the low target setting. If I could have Slide TV4, please.

[Slide.]

In contrast to those frequencies of thrombotic vascular events seen in those low hemoglobin target studies, this panel of results displays the frequency that we have observed in high target studies.

As you see, there is a substantial increase in the overall frequency of thrombotic vascular events, clinically relevant thrombotic vascular events, DVTs, pulmonary emboli, those kinds of clinically important events ranging from zero percent and again in smaller, shorter studies to as high as 31 percent in a small cell lung cancer study, which also happened to have the highest hemoglobin target 14 to 16.

Just to add to this, in that same study, we amended the protocol during the course of the study based on the frequency of adverse events to bring the hemoglobin target down to 12 to 14 and, following that amendment, there was a substantial reduction in the frequency of thrombotic vascular events.

I could show you the slide if you are interested.

DR. MORTIMER: We are kind of running out of time.

Dr. Day.

DR. DAY: I have two brief questions concerning the risk mitigation plan. First of all, I am pleased to learn that the Medication Guide has been approved as of last Friday. I noted quite a few problems with the previous patient information sheets and, hopefully, those have been resolved.

Concerning the Medication Guide in the briefing material, there was quite a bit of presentation about monitoring of the Medication Guide, which is good, however, I noted that this monitoring was about asking patients whether they received the Medication Guide, number one, and number two, whether they remember having a conversation with their physician about it.

I didn't see anything about comprehension testing. If you get it and you remember getting it, and you remember talking about it but don't remember anything about the information, then, that is a lot of activity that could be wasted.

So, for the sponsor or perhaps in discussion with Dr. Kawalski at FDA, are there any plans to add some comprehension testing questions?

DR. THOMAS: Adrian Thomas for the sponsor.

Slide up, please.

[Slide.]

We didn't go into a lot of detail during the presentation. This is an area that we are rapidly evolving. We fully agree with you and, in fact, in terms of our monitoring, we will be certainly looking at the frequency that that event has actually occurred, on the compliance side but also the impact of the education.

We have a look at the patient education, it was in the middle range, it will actually be, not just monitoring, a discussion occurring, but actually whether the information was transmitted.

We are looking at a variety of different media to

do this. We are considering whether this will be something that would be web based, CD-ROM, paper, video, we will certainly look first before deploying that, to partner absolutely with the efficacy groups and patient groups, and also with FDA. But that is a critical part, is to communicate the risk, not just do the activity.

DR. DAY: And for the physicians?

DR. THOMAS: And for the physicians also.

DR. DAY: Question No. 2 concerning direct consumer promotion. This morning we heard we do not intend to use broadcast DTC. Does that mean that the print ads for DTC will continue those in the magazines?

DR. THOMAS: We propose to focus our communication efforts around educating regarding the risk and the benefit. We specified broadcast DTC. There are other promotional tools that you have raised. We will be evaluating the utility of those tools specifically to communicate the risk and the benefit, not for promotion.

DR. MORTIMER: Thank you.

Dr. Murgo.

DR. MURGO: The sponsor needs a break, so I have a question for the FDA and it is related to risk management.

In the briefing document, the briefing document refers to some tools. One of the tools is limits on advertising and promotion. There are a number of mechanisms that could be applied and it has to do with restrictions in advertising, promotion, et cetera, et cetera.

I am a little puzzled by the comment in here that these are not FDA enforceable. For the exception perhaps of restrictions on physician incentives, I don't quite understand why the restrictions on advertising promotion is not FDA enforceable.

DR. JENKINS: Can you repeat the question?

DR. MURGO: Is that because I said it unclearly, John, or because you didn't hear me?

DR. JENKINS: Because I just stepped back into the room.

DR. MURGO: Okay. My question has to do with clarifying one of the comments that is made in the briefing document on page 22, that has to do with risk management proposals. One proposal limits advertising and promotion and it indicates that this tool is not FDA enforceable.

I am a little puzzled by that, because maybe perhaps with the exception of restriction on physician

incentives, it seems to me these other tools, the other mechanisms for applying this tool should be enforceable by the FDA.

DR. JENKINS: I am going to be brave and try to answer that question because I am not an attorney and I don't represent all of the Agency's views on advertising and promotion.

Clearly, there are First Amendment issues that become important when we start dealing with advertising and restrictions on advertising. Our general approach to advertising, as I understand it, is to make sure that the advertising is not false or misleading.

So we review the advertising to those standards. There is very little ability that I am aware of for FDA to say you cannot advertise. There are some new provisions in the FDA Amendments Act of 2007 that relate to advertising.

I am not fully familiar with those, but I don't believe those include an ability for us to prohibit advertising. It does relate to some situations where we can require presubmission for our review of the advertising before it's utilized. But again I think the standard remains that it not be false or misleading.

So, if a company voluntarily agrees to not do DTC advertising, that is something they have voluntarily agreed not to do. I don't think we have the authority to tell them they cannot do direct to consumer advertising.

DR. MURGO: No, but you should have the authority to restrict content.

DR. JENKINS: Again, Tony, the standard always has to be is it false or misleading and is it fairly balanced, does it fairly present the benefit information balanced by the risk information.

That is the same standard we always apply to advertising review. If you are suggesting that we could mandate inclusion of certain items, I don't know if we have that authority. We could certainly suggest inclusion of certain information. But again I am not an attorney.

This is a very difficult area for me to be trying to answer your question because of the legal issues, the constitutional issues or restriction of speech.

DR. MORTIMER: Dr. Day, and then I think we are going to have to break for lunch here.

DR. DAY: I believe that when there is a black box warning, that that information needs to be provided within

the DTC item whether it is broadcast or print.

DR. JENKINS: Again, that goes to providing fair balance of presenting the risk and the benefits in the advertising.

DR. DAY: Exactly. So ads can be withdrawn if they don't meet that requirement.

DR. JENKINS: Well, there can be enforcement action taken against the manufacturer if the advertising is false or misleading. It doesn't mean that the product is withdrawn. There could be enforcement action about the advertising piece itself.

DR. MORTIMER: Thank you. We are going to take a one-hour break. So we will be back here at 1 o'clock. We will finish up with the remaining questions. Thank you.

[Whereupon, at 12:00 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. MORTIMER: Let's get started on the Open Public Hearing. Thank you.

Open Public Hearing

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of

your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their considerations of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

DR. MORTIMER: Each of our speakers has three minutes to speak and after three minutes just know that the microphone will be silenced. We have 16 individuals who are going to be speaking today.

We are going to begin with Robert Erwin, who is the president of the Marti Nelson Cancer Foundation.

MR. ERWIN: Thank you. The Marti Nelson Cancer Foundation is an all-volunteer nonprofit organization. Neither the foundation nor I have received funding from any of the companies involved in ESA manufacturing or sales. I am also on the board of C3.

After reviewing much of the recently published papers on ESA use in cancer patients, including the recent Lancet editorial and the JAMA meta-analysis, the Marti Nelson Cancer Foundation and our advisors remain gravely concerned about the continued use of ESAs for cancer chemotherapy patients as we provide advice to people whose individual life or death is not a question of statistics.

That said, the Foundation is also ambivalent about what conclusion to draw from the totality of the data. Oversimplification of complex issues will not lead to good decisions. We are concerned that if the use of ESAs in oncology is eliminated entirely, we will deprive some patients of important benefit.

However, without further restrictions on the use of ESAs, we are very concerned that some patients will unnecessarily suffer life-threatening thrombotic events or tumor growth causing them to die sooner than patients who do

not receive ESAs.

Therefore, many of my colleagues and I are reserving judgment for now on this very important issue and looking to this committee to answer the most important question before us today, should the companies continue to marked ESAs in oncology during this time of uncertainty about the safety of their use in cancer patients.

If the decision is to maintain an oncology indication, then, there is another important problem with the marketing of ESAs that FDA and its ODAC advisors cannot solve alone, that is, we need personal financial equipoise on the part of physicians.

We strongly believe that personal profit should never be a factor in a physician's treatment of a patient. How much money can be made from choosing one drug versus another, or one dose, or duration of treatment versus another should not be part of the workup or treatment plan.

The current system has led to distrust that is bad for both patients and dedicated physicians. Misplaced financial incentives have no place in the compassionate and evidence-based practice of medicine.

Potential overuse of ESAs is only the tip of the

iceberg. We call upon manufacturers, professional societies and associations, CMS, the FDA and Congress, if necessary, to eliminate perverse incentives from the practice of medicine.

I don't have time to elaborate on this, but I think all of you know what I am talking about.

Thank you for the opportunity to address you.

DR. MORTIMER: Charles Bennett, Northwestern University.

DR. BENNETT: Thank you. I am Charles Bennett. I have no conflicts of interest. I am principal investigator for the Radar Group. We take no money from hospitals, universities, medical schools, philanthropists and drug companies.

The Radar Group, there was a question in the FDA briefing about meta-analyses. We just highlight in here that Radar published meta-analyses. We published one on thalidomide and lenalidomide in 2006 in JAMA. That paper was submitted through a Citizen's Petition to the FDA in 2005, was accepted by the FDA for part of a revision to the package insert so meta-analysis at that time on a safety base work was accepted.

We identify here two other meta-analyses included in a recent JAMA. As you see in the bottom ones, we also have published smaller analyses with ranging from 16 to 136, and journals ranging from JAMA to New England Journal of Medicine.

The updated meta-analysis that we present here is based on the data that came out in the last couple of weeks. We now have 52 studies. The hazard ratio remains significant at 1.09. The p-value and the confidence interval Mike Perry doesn't include one.

The next slide.

On the hazard ratio of 1.57 for VTE, which is the same as it was before in the JAMA article again updated.

Now, with the basic science at the NCI meeting, we didn't hear this morning, but I thought it was very important--at the December meeting, I think there is a manuscript about what happened at the basic science meeting. Mike Li, Steven Li presented this material for us there and published it in the JAMA paper.

It makes a big point in here that, in fact, there is no basic science at all to show that if there is a safety concern, it would actually be related all to the hemoglobin

level.

What we think here is if you really want to do a meta-analysis, you should really focus on disease, on studies where the focus is on survival, disease-free survival, progression-free survival, tumor progression and, if you put all of those studies into one meta-analysis, the hazard ratio is 1.18, twice as high about as we had published in JAMA. You can see it does not include 1.

If you look at multiple disease studies versus single disease studies, the single disease studies, as you identified this morning in the materials, was 1.14, again showing that there is a significant signal.

If you look at studies that terminated early, the hazard ratio is 1.32, again statistically significant. If we do a multiple meta-regression analysis here, which includes both diseases, multiple versus single, as well as primary outcomes, the only fact that is significant in a meta-regression is, in fact, the studies were survival, disease-free survival, progression-free survival was the primary outcome. And you can see the multiple meta-analysis. It is 1.29 or so.

The basic science findings, it was important to

see. We have done a meta-analysis of systematic review. If you look at the issues of EPO-R, we found in the literature 239 articles, 52 articles show EPO-R. Some things, as mentioned by company and other people are positive, some are negative.

One of the points we would like to mention is the reason why meta-analyses are confusing is very few meta-analyses have lots of studies with primary or secondary outcome, primary outcome being survival.

As you see here, as the number went up, which is our JAMA article, and finally put out in the analysis I showed you today, the signal was very clear.

Thank you very much.

DR. MORTIMER: Thank you, Dr. Bennett.

Cara Tenenbaum from the Ovarian Cancer National Alliance.

MS. TENENBAUM: Hi. Thank you. The Ovarian Cancer National Alliance does receive funding from the manufacturers of these drugs.

I am left after all the data that was presented today with some questions. First, I want to say that patients express a need for ESAs, not only to reduce

transfusions but to continue timely treatment, and quality of life should not be totally discounted when making these decisions. However, ovarian cancer patients have no data on which to rely.

None of the data presented or the proposed studies include ovarian cancer patients. These patients have multiple recurrences, more than 70 percent of ovarian cancer patients will have at least one recurrence and numerous rounds of platinum-based therapy.

Also, the targeted safe hemoglobin levels seem to be a moving target. A few weeks ago it was definitely, definitely 12. Today, I am hearing 10. I am not really hearing a clarity about the safety data.

I am not sure if I am to assume that ESAs are safe until or unless a study proves them dangerous, or if I am supposed to advise patients to be wary until ESAs are proven safe and then how are patients supposed to know.

As I leave here today, I don't know what my take-away message is for my patients; should I tell them to take ESAs, they make them feel better and, until we know they are dangerous, go ahead? Or are we supposed to urge caution until we know that they are dangerous?

Also, I want to mention the patient brochure. I was really surprised to hear about that. A lot of the patient advocacy groups that are here testifying asked for that brochure and none of us have seen it. So I would like to see that before it is released and, if possible, comment on it.

I want to thank you all for your time and attention to this matter. For ovarian cancer patients and for all cancer patients, drug safety has to be priority. I hope that today that you can all provide us with clear guidelines on safe use of ESAs.

Thank you.

DR. MORTIMER: Thank you.

Francis Motley from the Disability Advocacy.

MS. MOTLEY: I have no financial interest in any of the companies, either the competitors or the presenters here today. I have been a patient advocate interacting with FDA since Commissioner Kessler called for advocates in his reign. I represent applicants for Medicaid, Medicare and disability applicants.

Third party payor treatment restrictions are economic decisions. FDA indications and notices provide

them a leaping point, not an endpoint.

Medicare mandated restrictions on ESA's administration for patients who have clinically significant complaints attributable to anemia of chemotherapy, are facing a return to the era of transfusions, the complications of transfusions and a return to delayed cycles with reduced dosing of chemotherapy. Outcomes will be poorer.

Catastrophically ill cancer patients in the '70s and early '80s had no recourse but to seek disability because the treatments had such devastating effects on their ability to maintain employment and the prognosis was much more guarded.

With the development of supportive drugs such as ESAs, patients have been able to stay as productive members of society, working, caring for their families, even campaigning with their spouses as they run for President, all while receiving chemotherapy.

Their chemotherapy cycles are consistently of higher dosages, consistently more on cycle, and they are compressed into the shortest time period. So we are ending up with our cycle compression and dose intensification.

Those that are covered by Medicare and Medicaid are generally our most economically devastated patients. They are being restricted in their ESAs and their outcomes are going to be dramatically reduced.

We are going to see increased disability claimants all because of an economic issue that Dr. Straub has used your indications to increase.

DR. MORTIMER: Thank you.

Michael Kolodziej from New York Oncology and Hematology.

DR. KOLODZIEJ: Yes, I have no direct financial interest in this although I have in good conscience prescribed ESAs to my patients.

I am a private practitioner in Upstate New York. I would like to thank you for the opportunity to address the committee. I also thank them for being thoughtful and deliberate in this complex matter.

I also represent the U.S. Oncology Physician Network because I am the chairman of their P & D Committee. There are 1,200 of us and we take care of a lot of patients. And we are really very, very committed to giving our patients the best care, the safest care and respecting the

evidence.

We took actions within our committee regarding ESAs that antedated any activity by CMS or FDA or anybody else. Two years ago, three years ago, when there was an issue of counterfeiting, we were upfront with our e-pedigree program, so we know that our drugs are not counterfeit.

We implemented an evidence-based treatment pathway a year before the FDA meeting last year, that was completely in agreement with the ASH ASCO guidelines.

When there was a hint that anemia of cancer posed a risk, we stopped using the drug immediately and we implemented a patient education informed consent document last November. So we are a little ahead of the curve.

I am all about patient safety, but let's be a little bit honest about the data. There are really only four studies of chemotherapy-induced anemia, two irradiation and two anemia of cancer, so we are not using those drugs in that indication. So I am not sure whether that is a relevant area to focus our interest.

We have bandied about the prompts with the studies that are out there. We all are in agreement that they are not the way the drugs are used. That is true.