questions regarding the potential of ESAs to cause tumor promotion.

Again, the studies were already ongoing as of ODAC 2004. FDA did not have an opportunity to comment on the design of these trials prior to their initiation.

Now, this study in yellow that has just appeared EPO-ANE-3010 this was proposed at ODAC 2004 by Johnson & Johnson. This is a large breast cancer trial that has had significant difficulties in accrual. Now, these studies that have appeared in the bottom part of the screen in yellow, other studies of interest since ODAC 2004, these were not studies designed to look at the safety signals but were studies designed to explore additional indications for ESAs. Now we need to discuss consideration regarding trial design and data submission.

This slide contrasts the two different categories of trials that have been performed with ESAs in cancer patients. First, is the superiority trial. The purpose of this trial is to show an improved outcome in cancer patients receiving ESAs. This is based on the hypothesis that an

increased hemoglobin will improve outcome. Failure to show superior survival with ESAs does not exclude the possibility of decreased survival in a superiority trial. The second category of the trial is a non-inferiority trial. The purpose of this type of trial is to exclude increased risk. Two non-inferiority trials with ESAs in cancer patients was specifically designed to detect unacceptable risks. In the non-inferiority design, it is preferable to exclude increased risk. Highlighted here in yellow are the two non-inferiority studies whose primary endpoints are to look for safety signals. What I would like you to notice is that all of the empty boxes represent studies that were superiority studies that were designed to look for improved outcomes with ESAs and did not have primary endpoints to look for safety signals.

None of these superiority studies have demonstrated improved outcomes with ESAs. This slide addresses the issue of data submission in clinical trials. The first type of submission that FDA receives is called "primary data."

This is a database from a clinical trial that contains efficacy data; for example, survival and response rate data; safety data; for example, thrombovascular-event data; and all data captured on case report forms.

The FDA then independently analyzes the database and verifies results. Submission of primary data is preferable to submission of a summary result, which leads us to the second type of submission, the summary result.

This is a descriptive data that has been analyzed by investigators and submitted to FDA. Summary results may be in the form of a general abstract or a publication or maybe a report submitted to FDA.

FDA cannot perform independent analysis of summary results and cannot verify results. FDA cannot detect flaws in data from summary results.

These are the studies with primary dispute submitted to FDA. To the left of the central figure, the BEST and N93 studies. Since ODAC 2004, the anemia of cancer, lymphoid malignancy, non-myeloid cancer, and 145 Study. In 2001, 0145 is in orange italics because

the primary data have just been received and have not been analyzed.

The purpose of this slide is to show that since ODAC 2004 FDA has received primary data for analysis on only a minority of studies that have been completed. The studies in the empty boxes in the right-hand side of the slide were proposed at ODAC 2004 as studies that were capable of addressing safety issues surrounding ESAs.

The 11 empty boxes on the right-hand side represent these studies. Of these 11 empty boxes, 3 studies are ongoing, 8 studies have completed patient accrual but have not had primary safety and efficacy data in an analyzable format submitted to FDA.

The FDA has been informed through regular reports on the status of these studies and their data availability and has been assured that primary data was forthcoming.

Several of the studies on the right-hand side of this slide have been initiated by European investigator rather than Amgen or Johnson & Johnson and are not under IND. The time lines for primary data

submission from these studies is unclear.

Now we will examine the results of three studies on the left-hand side of the slide, which were again events prior to ODAC 2004. The ODAC convened in 2004 after FDA received primary data from 93004 and increased mortality was observed in the BEST AND ENHANCE studies. These were the primary contributing factors to convening ODAC, but there were other supportive factors which I will now be mentioning.

Our small-cell lung cancer trial, CAN-20, was terminated early due to increased thrombovascular events seen in other trials and increased mortality reported in the BEST and ENHANCE studies. Unplanned analysis suggested an increased mortality in the ESA arm.

Our head and neck cancer trial, RTOG 9903, was terminated early due to the publication of the ENHANCE trial also in head and neck cancer in 2003. An unplanned analysis demonstrated a nonsignificant trend to a decreased locoregional control and increased mortality in the ESA arm.

Despite the fact that the preliminary results on CAN-20 and RTOG 9903 were known in 2004, these trials

only have summary results available at the current time.

Now, four other randomized, controlled trials that were not shown on the roadmap slide were terminated early due to increased thrombovascular events. We will not discuss these four studies here because they were previously discussed in ODAC 2004. The first trial that we are going to talk about is Study N93, which was initiated after the original approval of epoetin in 1993 for chemotherapy-associated anemia. FDA was analyzing the primary data from this study prior to ODAC 2004.

The N93 trial was a trial in limited- and extensive-stage small-cell lung cancer. It enrolled 224 of a planned 400 patients and terminated early due to poor accrual.

Patients in both arms received standard chemotherapy and radiation and were randomized to Procrit versus placebo. This was a non-inferiority study with a primary endpoint of overall response rate, the secondary endpoint was overall survival, and target hemoglobin was above current and prior recommendations.

The study met its non-inferiority endpoint

between the two groups with respect to the endpoint of overall response rate. Median survival for the two groups is also listed. However, the study had several limitations with respect to detection of effects on overall response rate primary endpoint.

Overall response rate was determined without central review of images. Seventeen percent of patients had missing tumor response data.

Confirming overall response rate by repeat imaging was not required, and overall response is not a sensitive detection method for tumor promotion.

Response rate is used as an endpoint for chemo-protection agents but not necessarily used for agents that may cause tumor promotion.

Now we will move on to the BEST study. This was a breast cancer trial, and its primary data was being reviewed by FDA at the same time as Study N93 just mentioned.

The decreased survival in the ESA arm of the BEST study was a contributing factor to convening ODAC in 2004. The BEST trial enrolled 939 patients with metastatic disease. This is among the largest trials

that we will be looking at today.

The patients in both arms received chemotherapy, but the study did not stratify by the type of chemotherapy regiment. Patients were randomized to epoetin versus placebo. This was a superiority trial with a primary endpoint of 12 months overall survival.

The secondary endpoints were overall response rates and time to progression. The target hemoglobin was above current and prior recommendations.

This trial showed a significantly decreased 12-month survival in the eopetin arm. Increased mortality in shorter time to progression was seen in the first four months of the trial.

There were no significant differences in the secondary endpoint of overall response rate, but this trial had several limitations with respect to detection of effects on tumor promotion.

First, inadequate tumor assessments at baseline in 26 percent of placebo subjects and 29 percent of Eprex subjects; incomplete tumor assessment throughout the study in 28 percent of all patients; no reported set schedule for objective tumor assessments;

and incomplete assessment of all known metastatic lesions.

Now, the other study FDA was aware of prior to ODAC 2004 has shown both decreased survival and decreased local control with the ENHANCE study in head and neck cancer. Along with the BEST study, the ENHANCE study was a primary contributing factor to convening ODAC 2004.

The ENHANCE trial was a trial in locally advanced head and neck cancer patients. This trial enrolled 351 patients. Patients in both arms received radiation therapy, which is an off-label use. Patients were randomized to epoetin versus placebo. This was a superiority trial on its primary endpoint, locoregional progression-free survival.

The secondary endpoints were overall survival and locoregional control; the target hemoglobin was above current and prior recommendations; and patients were stratified by resection status.

These are the results of the ENHANCE trial. Epoetin data demonstrated a detrimental effect on all three endpoints of locoregional progression-free

survival, locoregional control, and overall survival.

Here is a summary of the three trials just mentioned. Study N93 in patients with small-cell lung cancer met its non-inferiority endpoint of overall response rates between the ESA and placebo arm.

The BEST study in Stage IV breast cancer showed worse survival for patients on the ESA arm. The ENHANCE study in head and neck cancer showed worse survival and worse locoregional control for patients on the ESA arm.

Now that we have examined the results of those three studies leading up to ODAC 2004, we will review the Committee's recommendations regarding the optimal design of future trials to address the concerns for increased risk of ESAs in cancer patients.

Again, this is where we are on our road map. These were the Committee's recommendations, again, regarding optimal trial design, that trials were double-blind and placebo-controlled and preferred primary endpoint be a survival endpoint.

The trials would be adequately powered to detect survival differences, trials would have a routine

assessment of tumor progression, trials have a homogeneous tumor type, and tumor biopsies to assess for erythropoietin receptors was optional.

These were deemed optional due to controversy regarding whether erythropoietin receptors are linked to tumor promotion and also to practical issues surrounding tumor biopsies in patients on clinical trials.

Studies conducted outside of the U.S. would be generalizable to the U.S. cancer population. The assessment of TVEs should be a prospectively defined endpoint.

Case report forms should be designed to capture clinically symptomatic TVEs, and TVEs should be assessed at prespecified intervals. Please keep these recommendations in mind as we go through the rest of this discussion.

At this point we will review data from recent trials since ODAC 2004. Again, highlighted here in yellow were the trials that Johnson & Johnson and Amgen identified at ODAC 2004 to assess safety risk.

With the 2004 recommendations in mind, we ask the question, have any ongoing or proposed trials

presented at ODAC 2004 or since ODAC 2004 fully met the Committee's recommendations? The answer, unfortunately, is no.

Now, two trials have come close. We will discuss these trials next. By "close," I mean they have met a number of ODAC 2004's recommendations, but neither of these trials have fully met all of the recommendations.

Now, other trial designs have not met several of ODAC's recommendations. Again, these are the two trials that have a close to ideal design and we will be discussing these next.

Starting with Study 145, the Amgen small-cell lung cancer study which has results recently released, this is a study that enrolled 596 patients with extensive-stage small-cell lung cancer. The patients in both arms received first-time chemotherapy. Patients were randomized to Aranesp versus placebo.

This was a superiority trial, for its co-primary endpoints, overall survival and a hemoglobin endpoint. The trial used an off-label Aranesp dose, so it is not clear if we can generalize the results of this

trial to the label dose.

The target hemoglobin was above current and prior recommendations. This trial had accrued patients from 2002 to 2006 and accrual was ongoing at the time of ODAC 2004.

These are the results of the trial based on summary results submitted last month. The trial failed to demonstrate superior overall survival. Again, failure to show a superior survival associated with ESAs does not exclude the possibility of decreased survival. These are the overall survival results and those increased incidents of TVEs in the Aranesp arm.

Limitation to this trial is as follows. Small-cell lung cancer are unlikely to be generalizable to other tumor types. Small-cell is an aggressive neuroendocrine tumor, and results in this trial may not apply to other tumor types, for example, epidermal tumors. Also, a literature search has revealed that small-cell lung cancer is not a tumor type that expresses the erythropoietin receptor.

This is the Johnson & Johnson breast cancer trial. This enrolls patients with metastatic breast

cancer. This has enrolled at least as of March 108 out of a planned 1,000 patients.

You have heard updates on the enrollments from Johnson & Johnson this morning. Patients in both arms received a variety of first-line chemotherapy regimens. Patients are randomized to either epoetin versus transfusion support as needed.

This is a noninferiority trial with a primary endpoint of progression-free survival. The secondary endpoint include overall response rate, time to progression, overall survival, thrombovascular event incidence, and response duration.

It is worthwhile noting that this is the only cancer trial using ESAs that has routine thrombovascular event assessment. Target hemoglobin in this trial is consistent with current recommendations. Again, the design of this trial was presented at the previous ODAC. The final protocol for this trial was submitted to FDA in December 2004, and accrual to this trial began in March 2006 and is currently ongoing.

These are the limitations to this trial. Now, when this trial was first presented at the previous

ODAC, the target accrual was 2,000 patients. The target accrual was then reduced to a thousand patients by the time the final protocol was submitted.

Now, FDA did not agree to the reduction in size, but Johnson & Johnson was concerned about slow enrollment and the changing standards of care with respect to chemotherapy over the course of the trial. By reducing the size of the trial, this reduces the power of the study to detect clinically meaningful differences.

A variety of chemotherapy regimens are used in this trial, the study is not stratified for this, and the trial is also open-label.

Now, accrual to this trial has been slow. Again, the final protocol was submitted December 2004; enrollment, again, March 2006; and, as of March 2007, 108 patients out of a target 1,000 were accrued.

Now, highlighted here in yellow are studies that have had decreased survival or increased tumor promotion. Again, let's empty out these boxes. Now, as we have already gone over, prior to ODAC 2004 these studies listed in yellow, the BEST and ENHANCE studies

FDA was aware of.

Now, let's talk about this study that just appeared in yellow, the CAN-20 Study, non-small-cell lung cancer, the upper, right-hand side of the slide. Prior to ODAC 2004, FDA was aware of this study.

We were aware that this suggested an increased mortality in the ESA arm, but it was unclear as to the magnitude or significance of the increased mortality. From published literature earlier this year, the FDA now is aware of the magnitude and significance of increased mortality.

Now, these three studies have just appeared in yellow. With regard to these three since ODAC 2004, the FDA is aware of three additional studies that have shown decreased survival and increased tumor promotion: in the Anemia of Cancer Study, the Lymphoid Malignancy Study, and the DAHANCA Study in head and neck cancer.

We have four studies in yellow: We have anemia of cancer, lymphoid malignancy, DAHANCA, and the CAN-20 studies. We will be discussing these studies next.

Now, this is the Anemia of Cancer Study. It

is also referred to as "Study 103." This trial was performed to support expanding the current label for Aranesp. This enrolled 989 patients with a variety of cancer who were not on chemotherapy or myelosuppressive radiation therapy.

This is among the largest trials of safety signals, and patients were randomized to Aranesp versus placebo. The primary endpoint was transfusion endpoint, and the secondary endpoint was overall survival.

The target hemoglobin was consistent with current recommendations, and the stratification factors are listed here. The trial could not assess the effects of ESAs on tumor promotion, given the variety of tumors that were included in this trial. The accrual to this trial from 2004 to 2006, summary results were presented in December 2006 and primary data submitted to FDA in March 2007.

The results of this trial were as follows based on FDA review or primary data. There was a significantly shorter survival in the Aranesp arm. The trial did not meet its primary endpoint, which was a transfusion endpoint. There were increased

thrombovascular events in the Aranesp arm.

Now, additionally, I would like to note that the indication of using ESAs for the treatment of the anemia of cancer, meaning for cancer patients not on chemotherapy, existed only outside of the U.S. Now, following the results of the Anemia of Cancer Study, Johnson & Johnson removed the anemia of cancer indication.

Next, we have the Lymphoid Malignancy Study which enrolled 344 patients with multiple myeloma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, Hodgkin's disease, and chronic lymphocytic leukemia.

Patients in both arms received a variety of chemotherapy regimens, and the trial was not stratified according to the type of chemotherapy received.

Patients were randomized to Aranesp versus placebo. The primary endpoint was a hemoglobin endpoint. The target hemoglobin above current and prior recommendations. Again, like the Anemia of Cancer Study, this trial could not assess the effects of ESAs on tumor promotion, given the variety of tumors included in this trial.

Accrual to this trial was between 2000 to 2001. The results of this trial were presented by Amgen at the previous ODAC. The results at that time did not show a difference in survival.

The updated primary data was submitted to FDA last month. Based on this updated primary data, there was worsened overall survival in the ESA arm, which we will see in the next slide.

The results of this trial are as follows. Based on FDA review of updated primary data, there was shorter overall survival in the Aranesp arm, and there were increased thrombovascular events in the Aranesp arm.

Now, the two studies we just talked about, again, Anemia of Cancer and Lymphoid Malignancy Study, we have received primary data on both of them. In the next two studies, we only have summary results available.

This is the DAHANCA Head/Neck Cancer Study. This enrolled 522 patients. The patients received definitive radiation treatment, which is an off-label indication. Patients were randomized versus transfusion

support.

This was a superiority trial with primary endpoint, locoregional control; and second endpoint were overall survival, local control, and disease-specific survival. Target hemoglobin was above current and prior recommendations.

This trial was presented at the previous ODAC, and accrual was from 2002 to 2006. The study was terminated early after unplanned, in-term analysis in October 2006 showed no evidence of potential benefit in the ESA arm.

These are the results of the trial. Again, based on summary results, there was worse than locoregional control in the Aranesp arm, and there was shorter overall survival in the Aranesp arm.

This is the CAN-20 Study in non-small-cell lung cancer. This trial enrolled 70 patients with non-small-cell lung cancer who were on palliative care, and this was an off-label indication.

Patients were randomized to epoetin or transfusion support. The trial is a superiority trial. Its primary endpoint, quality of life. Target

hemoglobin again above current and prior recommendations.

This trial was presented at the previous ODAC, and accrual was from 2001 to 2003. This trial was terminated early again to due to increased thrombovascular events seen in other trials and increased mortality reported in the BEST and ENHANCE trials. An unplanned analysis in this trial suggested an increased mortality in the ESA arm and a target accrual in this trial was for 300 patients.

These are the results of this trial published in "The Journal of Clinical Oncology" in March 2007. Again, we knew about the decreased survival in the ESA arm in ODAC 2004, but did not know the magnitude or significance of the difference at that time. There was shorter survival in the epoetin arm, and the incidence of thrombovascular events was not reported.

Let's pause here to summarize the results of the four studies that we have just talked about, showing decreased survival or increased tumor promotion.

The Anemia of Cancer Study studied a variety of tumor types, showed decreased survival in patients on

the ESA arm. This study is also referred to as the "103 Study."

The Lymphoid Malignancy Study, which studied a variety of lymphoid malignancies, showed decreased survival in patients on the ESA arms. This trial is also referred to as the "161 Study."

The DAHANCA Study in head and neck cancer demonstrated decreased locoregional control and a trend to decreased survival in patients on the ESA arm.

The CAN-20 Study in non-small-cell lung cancer showed decreased survival to patients on the ESA arm. Now we will review some common features of nine studies that have no reported safety signals but have significant design limitations.

One of these studies has had primary data submitted to FDA for independent analysis. Another study had primary data submitted, but the data is not analyzable. Seven of these nine studies have only had summary results submitted to FDA.

These are the nine studies mentioned in the previous slide, both in orange and yellow. Rather than going over each one of them, I would like to concentrate

on some common limitations that they have.

The significant design limitations of these trials may preclude detection of safety signals that may actually be present. If you look at the studies in orange italics, "ARA-03" and the "GELA" studies, these are studies that have finished patients accrual.

The studies listed in yellow -- I'm sorry, the studies listed in orange italics, again, "ARA-03" and the "GELA" studies, have not finished patient accrual. The studies listed in yellow have finished patient accrual.

The limitations to detect safety signals, shown here, do not necessarily apply to every single trial from the previous slide but are present in three or more trials in the previous slide.

First, an inadequate frequency or modality of radiologic assessments to evaluate tumor recurrence; inadequate radiologic assessments to rule out distant metastases at baseline or during surveillance; no systematic assessment of thrombovascular events; open-label; a target hemoglobin not consistent with current recommendations.

Four of the nine studies were consistent with prior recommendations, which again recommended holding the ESA when the hemoglobin reached 13, and an off-label ESA dosage and dose adjustment.

The primary data have not been submitted to FDA on trials that have finished enrollment except for the 232 Trial, which was a study in non-myeloid malignancies and involved heterogeneous cancer populations.

Again, these are the specific limitations to two of these studies, 232, which I just mentioned has a heterogeneous tumor type, and has survival data that is limited to five months of followup.

Now, the GELA diffuse large B-cell lymphoma trial did not have an ESA safety question as its primary endpoint and also used ESAs in the control group.

Currently, what answers can we expect from studies that are ongoing? There are three studies of twelve studies that were ongoing or proposed at ODAC 2004 that are continuing accrue patients. Only one of these studies, EPO-ANE-3010 is of adequate design, but has had significant difficulties in accruing patients.

Of note, the accrual target again is half of that proposed at ODAC 2004 and requested by FDA.

Now, this study highlighted in yellow are the three studies that are continuing patient accrual currently. Again, the only study that we consider of adequate design is EPO-ANE-3010. The arrow in GELA studies do not have an adequate design to address safety questions.

Now, the sponsors have presented several meta-analyses in their presentations and in their briefing document. Now, these may not meet a formal criteria for meta-analyses for several reasons.

First, they do not have a prespecified plan for analysis. Second, they did not include all studies. Third, they included either epoetin or Aranesp, and that referred the studies in the briefing document -- I'm sorry, it refers to the meta-analyses in the briefing document. Some included studies did not have adequate followup for survival. FDA does not believe meta-analysis is an appropriate method of examining safety data from ESA trials.

We will now review the issues surrounding

meta-analyses. Here is why meta-analyses is not an appropriate technique to examine safety signals. Meta-analyses can obscure safety signals from individuals studies.

Meta-analysis results depend on the studies included. Earlier meta-analyses have suggested statistical significance on overall survival favoring ESAs while later meta-analyses suggest statistical significance on overall survival favoring controls.

Accumulative meta-analyses and retrospective meata-analyses have issues on the appropriate allocation of alpha. Finally, meta-analyses include heterogeneous trials with variable quality, variable length of followup, variable target hemoglobin, and heterogenous tumor types.

In examining the collective evidence of the use of ESAs in cancer patients, six studies have demonstrated inferior overall survival, locoregional progression-free survival, or local regional control for an ESA-containing arm. Those studies that FDA has knowledge of have demonstrated superior overall survival or progression-free survival for an ESA-containing arm.

These are criteria for the studies that we have included in the forest plot on the next slide. FDA included studies that had adequate followup for overall survival. Amgen and Johnson & Johnson included some studies that did not have adequate followup for overall survival.

We included studies that used any ESA, including either epoetin or Aranesp, for Amgen and Johnson & Johnson again in the briefing document, performed separate summaries for Aranesp and epoetin.

We included only Phase III studies while Amgen and Johnson & Johnson included Phase I, II, and III studies. Phase I studies included ineffective ESA doses. Finally, FDA used hazard ratio in the Forest plot rather than odds ratios which we used in the Amgen briefing document. Hazard ratios consider the time to event or death while odds ratios do not.

This is the Forest plot which again contains studies that have adequate followup for overall survival. Please note that not all of the studies in this slide have been presented today. This is meant to be a summary slide and not a meta-analysis.

As usual, the Forest plot to the right of the red dash line, hazard ratio worse for ESAs; to the left of the red dash line, hazard ratio worse for controls.

If you will note, the four studies at the top that have hazard ratios to the left of 1.0, these studies have 95 percent confidence intervals that cross 1.0. These studies showed a nonsignificant trend to improve survival with ESAs.

What I would like you to note is that the majority of studies in this slide actually fall to the right of the red line. The bottom five stories have lower bounds of 95 percent confidence intervals that are to the right of 1.0, the red dash line, and these are studies that had a significantly worsened survival in the ESA arm.

Now, a few notes regarding the Forest plot. The search for studies having adequate followup begins with some initial basket of studies. Unless every study having adequate followup -- meaning, that meets the search criteria -- is found, meta-analyses results will be biased towards whatever criteria surrounding those studies in the initial basket.

When the timing of a meta-analyses or summary of studies is not prespecified, the results will be biased towards the event that triggers the timing of the analysis.

Finally, the distribution of patients and events across cancer types in the meta-analysis is not representative of the practice of using ESAs in oncology. For example, small-cell lung cancer is overrepresented in the meta-analysis compared to the practice of using an ESA in oncology.

Now that we have reviewed the data from several cancer trials, I would briefly like to mention three studies in patients without cancer that have shown increased risks.

This slides illustrates increased risk in chronic renal failure patients, illustrated by two studies, in the CHOIR and Normal Hematocrit Study. The CHOIR Study enrolled 1,432 patients and assigned patients to higher or lower hemoglobin. There was a worse outcome for the higher hemoglobin group.

The Normal Hematocrit Study enrolled 1,265 patients and assigned patients to a higher or lower

hematocrit. Again, there was a worse outcome for the higher hematocrit group.

Increased thrombovascular events have also recently been seen in the SPINE Study, which enrolled 681 patients undergoing major elective spinal surgery. The patients did not receive prophylactic anticoagulation. Patients were randomized to perioperative ESA versus transfusion support. The primary endpoint of this study was the incidence of DVT, "deep-venous thrombosis." This trial routinely monitored patients for DVT.

At the upper confidence interval there is a difference between DVT rates between the two groups. It was greater than 4 percent, which was the prespecified margin. The noninferiority of ESAs to placebo could not be established.

Now, illustrated on this slide are the ESA-specific triggers for recent FDA actions: in November 2006, the CHOIR Study in chronic renal failure; in December 2006, the DAHANCA Study in head and neck cancer; in January 2007, the Anemia of Cancer Study; in February 2007, the CAN-20 Study in non-small-cell lung

cancer; and April 2007, the Lymphoid Malignancy Study.

These are the communication activities taken by FDA due to these recent triggers. First, the black-box warning, which has already been referred to; second, revised prescribing information; public health advisory issuance; press releases; health care professional sheets; bed watch safety alerts; and email of those communications to healthcare and professional societies.

This is the black-box warning issued March 2007: Use the lowest dose of ESAs that will gradually increase the hemoglobin concentration to the lowest levels sufficient to avoid red-blood cell transfusion.

ESAs increase the risk for death and for serious cardiovascular events when administered to target a hemoglobin greater than 12. In cancer patients,

use of ESAs shortened time to progression in patients with advanced head and neck cancer on radiation treatment when the target hemoglobin is greater than 12 and shortened overall survival; increased death attributed to disease progression at four months in those with metastatic breast cancer receiving chemotherapy when administered

to targeted hemoglobin greater than 12; and increased the risk of death when administered to targeted hemoglobin greater than 12 in patients with active malignant disease receiving neither chemotherapy nor radiation treatment. Finally, in surgery patients an increased incidence of DVTs was documented in patients receiving ESAs who were not receiving anticoagulation. Antithrombotic prophylaxis should strongly be considered when ESAs are used to reduce allogeneic blood transfusions.

To summarize, the five studies show evidence of increased tumor promotion or decreased survival with an excessive target hemoglobin between 12 to 15.5. The studies are listed here, again: one breast, two head and neck, one in lymphoid malignancy, and one in non-small cell lung cancer.

One additional study has evidence of decreased survival with target hemoglobin consistent with prior labeling, meaning, a healing hemoglobin of less than 13 in Study 103. This study was conducted in a variety of tumor types.

A difference in overall survival was not observed in two trials with small-cell lung cancer, but, again, results in small-cell lung cancer are unlikely to be applicable to other tumor types, for example, epidermal tumors. Both trials used ESAs in excess of current or previous recommendations.

EPO-ANE, a breast cancer trial that is close to ideal in design and uses the U.S. labeled dose of epoetin alfa was proposed at ODAC 2004 and is capable of addressing tumor promotion risks of ESAs. This is the only trial that addresses thrombovascular events, risks, and this trial is not accruing.

Of the three studies that continued to accrue patients, only EPO-ANE-3010 is designed close to ideal. Twelve studies were presented at ODAC 2004 by Johnson & Johnson and Amgen as capable of addressing ESA tumor promotion risks.

Ten of these twelve studies are not adequately designed with respect to ODAC 2004's recommendations. The primary data from five completed epoetin studies with no reported safety signals have not been submitted to FDA and these studies finished accrual as long as six

years ago.

To conclude, the efficacy of ESAs is to reduce the proportion of patients on chemotherapy receiving red-blood cells transfusions. The post-approval studies have shown decreased overall survival, decreased locoregional control, and increased thrombovascular risks.

ESAs do not increase survival and may promote tumor growth. In the 14 years since the first ESA was approved in the cancer indications, infectious risk associated with red-blood cell transfusion have decreased and serious risk associated with ESAs including death, tumor progression, and increased thrombovascular events have emerged.

Based on the six studies that showed decreased survival or increased tumor promotion, FDA believes there should be a reconsideration of the risk-to-benefit ratio of ESAs in cancer patients.

Finally, no completed or ongoing trial has addressed safety issues of ESAs in cancer patients with chemotherapy-associated anemia using currently approved dosing regimens in a generalizable tumor type.

Thank you for your attention.

CHAIRPERSON ECKHARDT: Thank you.

Now we will proceed to have a break and reconvene in 15 minutes.

(Recess.)

OPEN PUBLIC HEARING

CHAIRPERSON ECKHARDT: We can go ahead and get started. I'm going to go ahead and read this statement.

[Technical difficulties, in progress]

Gathering and decision making to ensure such transparency at the opening 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 any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group'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 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.

Thank you.

MS. CLIFFORD: Thank you, Dr. Eckhardt.

The first speaker today is Bob Erwin from the Marti Nelson Cancer Foundation.

Again, I would ask everybody to take their seats, please. We are getting the meeting started again.

MR. ERWIN: Thank you. I am president of the Marti Nelson Cancer Foundation, a nonprofit all volunteer patient advocacy organization. I also serve as an unpaid member of the board of directors of C3, the "Colorectal Cancer Coalition," a nonprofit patient advocacy organization that has received unrestricted educational grants from a number of corporations

including Amgen. I have no personal financial or professional stake in any company that makes, sells, or uses ESA products.

I thank you for the opportunity to address this important meeting of ODAC as you deal with the complex task of sorting through some large and sometimes conflicting data sets.

My remarks today will focus on two important issues not covered in your briefing package, both of which relate to money and can lead to the selective use of facts to achieve financial objectives that may conflict with patient interests, and both of which do have an impact on clinical practice.

The first issue is the financially motivated denial of payment for effective products that can enhance life, in short, reimbursement policy. While there are new concerns about safety in the use of ESA products in some indications, I'm concerned about the rapid shift downward in their utilization that has already begun as a result of the FDA's issuance of the black-box warning.

Some of these changes are appropriate, but it

is very troubling to see changes in the use of ESAs that are reimbursement-driven rather than guided by professional judgment about what may be in the best interest of an individual patient.

I understand that the ODAC Panel and the FDA staff have no control over reimbursement issues. Nevertheless, government agencies must be at least cognizant of the effect that one agency's policy has on the other agency's policy.

The Centers for Medicare and Medicaid Services, "CMS," which reportedly spends more than $2 billion each year on Epogen alone quickly jumped on recent concerns about ESA safety.

As quoted in the cancer letter: "CMS will review the scientific evidence to determine the appropriate use of ESAs for multiple clinical indications."

This raises obvious questions. Does CMS have the clinical expertise to conduct such a review? Will CMS meet with the FDA renal and oncology clinical review staff? Will the public be allowed to participate in those meetings? Will the results be made available to

the public?

In addition to CMS, other insurers are rushing to make changes in their reimbursement policies that are based less on the clinical needs of patients and more on the needs of their financial bottom lines. For example, both WellPoint and United Health have announced significant changes in their payment policies.

An example of my concern that I know you will be addressing is, for example, how will the insurance industry use differences in label language that you might recommend. For example, a "hemaglobin target" versus a "hemaglobin maximum."

The second issue that I would like to address is the amount of money generated by ESAs which may be result in the financially motivated overpromotion and overuse of these drugs.

Most of the substantial revenues generated by ESA sales have come from the development and marketing of what appear to be good products; however, aggressive advertising has clearly played a role in the demand for these products.

I'm sure you've all seen the advertisement of

the grandfather who didn't have the energy to get his camera to photograph his grandchildren on the front porch.

The implication of that advertisement is that if only he had received a rather expensive shot of Procrit he would have been able to muster the useful energy to preserve that touching family moment for posterity. This and similar ads promote hope -- hope for health, hope for life.

In 1759, the English poet and essayist Samuel Johnson said, "Promise, large promise, is the sole of an advertisement."

Nearly a couple of centuries later John Crosby said, "the first law in advertising is to avoid the concrete promise and cultivate the delightfully vague."

When the targets of the advertising are sick and dying people or the physicians who treat them, I think we must all acknowledge the probability of harm. Did the grandfather ad promote realistic hope or merely false hope?

Were these ads really acceptable to the FDA staff who regulate direct-to-consumer advertising? Have

the necessary studies been conducted to convincingly establish that alleviating fatigue for cancer chemotherapy patients is a benefit delivered by ESAs?

Advertising should never be allowed to drive demand for pharmaceutical products beyond the limits of good science and good medicine. However, advertising alone doesn't account for the ramp up in some of the sales of ESA products.

Equally influential is the potential for substantial profits flowing to the individuals and organizations who directly benefit from treatment and dose decisions.

As outlined quite well yesterday on the front page of "The New York Times," because of the article and because of the limitations on time, I'm going to cut out some of what is in my written comments, but I would like to replace that with one quick story.

A friend of mine's mother had terminal cancer, terminal lung cancer. My friend recently told me a very worrisome story about her mother's experience with Procrit.

When the decision was made that her mother

could no longer endure further treatment, she was placed in a nursing home in a hospice program. Her mother's oncologist very quickly ordered and sent 20 doses of Procrit to the nursing home for that woman.

The market value of those 20 doses must have been, what, $20,000 or $30,000. My friend's mother lived two more weeks after she entered the nursing home and never received one dose of the Procrit. How much profit did the oncologist get from that $30,000 Procrit prescription? What was the point of that prescription?

I will let you answer those questions, but I might suggest that if profit went to physicians for enrolling patients in clinical trials, the enrollment might happen a lot faster.

Academic centers are not immune to this profit influence. One of the University of California Medical Centers operates a dialysis center run by a tenured, full professor who for many years now has operated under a deal with the university whereby he directs the substantial profits from that portion of the center's reimbursement that includes payment for ESA use to his own non-peer-reviewed research programs.

The environment that you are dealing with is complex. On the one hand is overpromotion and overuse, on the other hand are safety issues that may be manipulated to inappropriately restrict access.

I urge you to strike a balance on behalf of objectivity and evidence-based patient benefits. An example, I am very concerned that returning to the use of transfusions instead of ESAs is most cancer patients will do more harm than good despite the risks of ESAs.

The risks of blood transfusion are not trivial and the logistics of managing an upsurge in transfusions could have a very negative impact on many patients, not to mention the individual personal perspective of the burden on each patient of that procedure.

We would like to see ESAs used for the benefit of patients and used aggressively but only up to the objective boundaries of benefit and risk, and the FDA is charged with conducting the objective assessments necessary to achieve that goal.

Unfortunately, the FDA I currently under attack from many quarters. Many of these attacks are driven by self-interest, politics, and money. For

example, the Washington Legal Foundation and the editorial page of "The Wall Street Journal," perhaps motivated by an anti-government/anti-regulatory philosophy, appear to be running a campaign to allow biotech companies to profit from the sale of inadequately tested products.

These products may well be no more than toxic placebos sold at outrageous prices to desperate people. High-quality data and objective analysis are the best way to blunt these attacks.

I ask the sponsors to commit to more timely submission of all data to the FDA and to commit more financial resources to obtain missing data and better quality data.

I would like to leave you with some specific questions which I hope will be addressed in your deliberations after lunch. There are meta-analyses data that suggest a quality of life benefit in the use of ESAs.

Do these data provide sufficient evidence to guide clinical practice; if not, what additional studies are feasible that could be done to gather this evidence?

Is enough known about the characteristics of patients likely to be harmed by ESAs to eliminate use in at-risk patients or to guide doses to lower levels; if not, what additional studies could be conducted?

Clearly, new limitations on the promotion of ESAs to physicians and consumers seem appropriate. To eliminate promotion of false hope in favor of legitimate medical education, we urge FDA to exercise its strictest regulatory authority in this area.

I understand that this topic is not the subject of today's discussion. However, because of the impact on clinical practice of advertising and the influence of that advertising, I urge the Committee to spend some time today on this topic and perhaps request a future public airing on the topic of appropriate direct-to-consumer advertising by the pharmaceutical industry.

Finally, how can FDA and CMS work effectively together to determine appropriate reimbursement policy for ESAs so that there is not an overreaction to safety data resulting in denial of access when these products can really help individual people?

Thank you very much for your time and attention.

MS. CLIFFORD: Thank you, Mr. Erwin.

Our next speaker is Dr. Samuel Silver.

DR. SILVER: Good morning. My name is Samuel Silver. I am a hematologist/oncologist and professor of internal medicine at the University of Michigan.

I am here today as a counselor of the Executive Committee and Chair of the Reimbursement Subcommittee on behalf of the American Society of Hematology, "ASH."

ASH represents over 1,000 hematologists in the United States who are committed to the treatment of blood and blood-related diseases. I have no financial association with any pharmaceutical company and the American Society of Hematology has paid for my travel.

Of paramount importance to ASH is to ensure the highest degree of patient safety. We appreciate this opportunity to provide comments to ODAC on the appropriate use of ESAs in light of current scientific evidence.

It is important to protect against not only

the overuse of the drugs, but there under use and misuse as well. Consequently, ASH notes that ESAs help to reduce the need for transfusions, and thereby alleviate strain of the nation's blood supply.

Therefore, the impact on the blood supply should be taking into account when determining changes in the use of these products. ASH has amended written comments for the record.

Today, I would like to focus my remarks on the following issues: One, does the available data merit action for patients with hematologic malignancies; two, the appropriate length of time for a patient to be considered under the umbrella of chemotherapy treatment; three, evidence to support the use of ESAs in anemic patients with low-risk myelodysplasia; and, four, treatment recommendations.

Number one, does the available data merit action for patients with hematologic malignancies. The recent FDA black-box warning cautions clinicians that there is an increased risk of death when ESAs are administered to a target to target hemoglobin of 12 grams per deciliter in patients with active ligand

disease receiving neither chemotherapy nor radiation therapy.

This warning was based upon an unpublished, and we've heard this story discussed from Amgen, patients with the anemia of cancer, nonmyeloid, who were not receiving anticancer treatment.

Few of those patients had hematologic malignancies and none, as far as I could tell, had the myelodysplastic syndrome or myeloproliferative disorders.

Therefore, the present quality of data to extend this warning to patients with hematologic malignancies or MDS or MPD does not currently exist. ASH recommends that ESAs be continued to be used for treatment of anemic patients with hematologic malignancies not undergoing chemotherapy.

At the same time ASH recommends that Phase III studies be initiated to address these further studies as could be done under the CMS/CED process.

Number two, the appropriate length of time for a patient to be considered under the umbrella of chemotherapy treatment, regarding the appropriate use of

ESAs for patients with cancer-oriented conditions, ASH has commented that ESAs may be used as a treatment option for patients with chemotherapy-associated anemia.

ASH notes that a patient may continue to suffer from anemia for some time following completion of treatment and recommends that ESAs be continued for treatment of anemia for 90 days post-chemotherapy. If anemia persists beyond 90 days after completion of chemotherapy, it would be reasonable to reevaluate the anemia to determine if this continues to be a result of the chemotherapy. Further studies concerning this topic would be beneficial. Number three is evidence to support the use of ESAs in anemic patients with low-risk myelodysplasia. Regarding patients with hematologic malignancies not on chemotherapy, there is evidence to support that ESAs in patients with anemia associated with low-risk myeloma, that is, myelomas with blast counts less than 5 percent in the marrow, multiple studies from such groups as the Nordic Group, the Italian Cooperative Group, and a recent pooled analysis from the Cleveland Clinic, just to cite a few groups,

have demonstrated the effectiveness of ESAs to decrease the need for transfusions.

Here the transfusions are more chronic as compared to much of what we talked about earlier today. ASH also believes ESAs may be used as an appropriate treatment option for patients with the anemia of chronic inflammation. Patients with noncancer-oriented conditions are distinct from patients being treated for the anemia of cancer.

Finally, treatment recommendations, ASH submits the following treatment recommendations, ESAs should be started in appropriate clinical settings at a hemoglobin level at or below 10 grams per deciliter. I should note that 10 grams per deciliter is not a trigger and that global assessment of the patient is needed.

ASH notes, however, that there may be extenuating circumstances when treating patients with comorbidities such as cardiac or pulmonary disease that could justify the use of ESAs before the hemoglobin has decreased to 10.

The therapeutic goal should be a hemoglobicn level of no higher than 12 grams per deciliter and

recommends that the dose of ESA be modified in accordance with the recent FDA black-box warning when the hemoglobin approaches 12.

ESAs should not be continued after eight weeks in the absence of response, assuming appropriate dose increase has been attempted in low responders. A response is a rise in hemoglobin of 1 gram per deciliter or greater.

In conclusion, ASH is currently updating our evidence-based practice guidelines concerning the use of erythropoietin agents to include other ESAs and is willing to share this information as the draft becomes available later this summer.

The Society strongly believes additional high-quality clinical trials are needed to better understand the impact of ESAs on patients with hematologic malignancies or disease.

For example, experts in hematology have used ESAs to treat anemic patients with multiple myeloma, myeloproliferative diseases, non-Hodgkin's lymphoma, chronic lymphocytic and chronic lymphocytic leukemia in the absence of chemotherapy where ESAs have proven

effective.

However, current studies have small numbers of these patients. The study that was discussed today on hematologic malignancies such as lymphoma had a higher hemoglobin target. Appropriate studies need to occur to allow appropriate analysis. Larger studies are needed.

Thank you for this opportunity to share ASH's recommendations concerning appropriate use of ESAs. I would be happy to answer any questions you may have.

Thank you once again.

MS. CLIFFORD: Thank you, Dr. Silver.

Our next speaker is Dr. Steven Gore.

DR. GORE: Thank you. My name is Steven Gore. I am an associate professor of oncology in the Division of Hematologic Malignancies at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, but I'm here today representing the Myelodysplastic Syndromes Foundation. The MDS Foundation has paid for my travel down here from Baltimore. Well, I stayed overnight.

(General laughter.)

DR. GORE: I recently signed an agreement with J&J to consult on an upcoming randomized trial of an ESA

in patients with MDS, but I have no other financial relationships with any of the companies that manufacture ESAs.

The MDS Foundation, while applauding the FDA's current and ongoing attention to the efficacy and safety of ESAs with cancer patients, is very concerned that MDS patients are becoming collateral damage as reimbursement decisions are being made which are currently restricting the access to ESAs for patients with MDS when we believe they are safe and effective.

Myelodysplastic syndromes are a heterogenous group of clonal stem cell disorders whose symptoms are determined to a large extent by the refractory cytopenias, with refractory anemia being the most prominent symptom-producing cell deficit.

ESAs positively impact the quality of life survival and possibly decrease the progression to acute lukemias in this set of hematologic malignancies, which is currently estimated to potentially represent the most common form of adult hematologic malignancy.

Now, anemia has a very significant impact on MDS patients, causing chronic fatigue and decreased

quality of life. The medical risks of transfusions, which have already been mentioned including transfusion reactions, iron overload in this chronically transfused group of patients who may be receiving transfusions for many years, the ongoing risk of transmission of infectious agents and alloimmunization, which may make hematologic support of these patients difficult in the future, as well as significantly decreasing the productive time for these patients due to their time in the clinic, which may require weekly or every-other-week transfusions.

Now, oncology delivery and hematology delivery in the U.S. is no longer well-configured to accommodate transfusion in the outpatient department. In 2005, only 1 in 24 transfusions for oncology patients was given in the office setting, for a total of 17,000 outpatient transfusions versus 417,000 in-hospital transfusions.

There are logistical challenges. There are very significant demands on office staff, with typical transfusions requiring four or more hours, many office practices having no capability or facilities for accommodating these red-cell transfusions.

The lower rates of ESA use in MDS patients would potentially push thousands of MDS patients back into hospitals for transfusions. ESAs have been shown to be effective and safe in patients with MDS. They have been studied now in hundreds of patients for greater than 10 years.

Although it is quite clear that none of these trials or most of these trials certainly have not been placebo-controlled randomized trials and few of them have been randomized trials, there has been no evidence promulgated from this database to show an increased risk of thrombosis or death in this population.

A recent randomized trial against observation was performed in the Eastern Cooperative Oncology Group and presented in ASH recently. This study targeted 105 MDS patients who were randomized to receive supportive care versus high-dose erythropoietin, 150 units per kilo per day, which was increased after 4 months to 300 units per kilo per day if there was no response.

The erythroid response rate, which was well-defined in the study was 35 percent in the EPO arm versus 9 percent in supportive care. Moreover, in

supportive care patients who were subsequently crossed over to receiving erythropoietin because of increasing transfusion requirements, there was an erythroid response rate of 30 percent.

In terms of development of AML in the study, 3.6 percent of patients in the supportive-care arm developed AML while in the study whereas only zero percent of the EPO arm developed AML.

Much of the safety and efficacy data of erythropoietin in MDS patients has been promulgated in a series of trials done in Scandinavia under the direction of Eva Hellstrom Lindberg. They have recently reported a summary of their data in 129 patients followed for at least 45 months treated with EPO plus or minus G-CSF is frequently added to increase the sensitivity of the bone marrow to the effects of EPO, and G-CSF is not given in the setting to increase neutrifils.

Hemoglobin of 11.5, which was the targeted hemoglobin level of grams per deciliter has been achieved in 39 percent of these patients. Transfusion independence was achieved in approximately 30 percent of the transfusion-dependent patients with a median

duration of response of 23 months, providing very important quality of care -- quality of life to these patients with MDS. There was no negative impact on survival compared to matched historical controls.

There is now some data that ESAs may affect improved survival in subsets of MDS patients. Comparison of these Nordic patients treated with EPO plus G-CSF to a supportive-care cohort patients treated in Pavia, Italy, included 176 transfusion-dependent patients and 187 untransfused patients whose hemoglobin was less than 10 grams per deciliter.

In this study patients, which was shown in ASH I believe, with a low transfusion need less than two units of red cells per month, survival appeared superior in the treated group of a hazard ratio of .57 and a significant P value.

Next, week there is going to be an international symposium on NDS held in Florence, Italy, and a group from France is presenting their data, a retrospective comparison of 284 patients from France treated with EPO with or without G-CSF to 163 well-documented supportive-care patients from the

International Prognostic Scoring System Database.

Multigrade analysis is reported to show that the EPO-treated patients are less likely to develop AML than the supportive-care group with a hazard ratio of 0.2, 95 percent confidence bound 0.1 to 0.3; and a better overall survival hazard ratio of 0.26, 95 percent confidence bounds, .18 to .38.

Now, MDS patients can be carefully selected for their appropriateness for ESA therapy because it is now well-documented that MDS patients whose endogenous EPO concentration, serum concentrations, exceed 500 units per milliliter are unlikely to respond to ESAs and the patients who have the best chance of responding are those with the lower transfusion burden.

As I mentioned before, a certain subset of patients require the addition of G-CSF. This includes patients with refractory anemia with ringed sideroblasts. Patients should be monitored thoughtfully with monthly reticulocyte counts. As Dr. Silver noted, if patients haven't responded within two or maximally three months, the dose of ESAs should either be increased or the care plan should be changed. In this

population of patients, high doses of ESAs are required from 1,000 to 2,000 units per kilo per week of EPO, 300 micrograms per week of darbepoetin.

I would like to conclude my comments by noting that chronic transfusions represent a very major burden to the quality and, potentially, quantity of life for our MDS patients.

ESAs provide important palliation of anemia In a significant subset of MDS patients and render many of them transfusion-independent. They may, in fact, improve survival in a subset of MDS patients, and they are extremely well-tolerated in this patient population.

We believe that it is extremely important to maintain access to ESAs for these appropriately selected MDS patients. I thank you for your attention and the time to speak. I'm happy to answer any questions.

MS. CLIFFORD: Thank you. Our next speaker is Maryann Napoli.

MS. NAPOLI: Good morning. I am Maryann Napoli from the Center for Medical Consumers in New York. We have never taken any pharmaceutical

industry money in our 32-year history and no drug company has ever wanted to give us any.

(General laughter.)

MS. NAPOLI: I write often about cancer and drugs because our mission as an organization is to help people to look for and to understand the evidence that supports all of their doctors' treatment recommendations.

The story of these anemia drugs and how they were oversold to the public and how financial incentives encouraged oncologists overprescribe them is truly outrageous.

Like me many Americans probably first became aware of them while watching the evening TV news. Those ubiquitous Procrit ads all have the same scenario, the cancer patient undergoing chemotherapy cannot continue the work he or she loves because of disabling fatigue. Procrit quickly turns things around, and the cancer patient is back on track enjoying work again.

Who among us on chemotherapy would not ask their doctors for this drug? Even if you didn't have cancer at the time of this ad campaign, very likely that

message would stay with you, that there is a drug that quickly cures chemotherapy-induced fatigue.

Imagine my surprise When I read two months ago of an FDA briefing about the new warnings to be added to the labels of the anemia drugs.

Dr. Pazdur announced that there has never been any evidence to support the claim that these drugs alleviate fatigue in people undergoing chemotherapy.

Why then did the FDA allow those Procrit ads? No Procrit ad that I ever saw ever had a cancer patient go up to the camera and say, "This drug helped me reduce my risk of having one transfusion."

I'm glad that the FDA sent warning letter to members of professional organizations, but what about the cancer patients? There are numerous cancer patient groups across the country. Surely, they, too, should have been notified.

I'm glad that the FDA held that press briefing. But what about the TV-watching public? That is, after all, the majority. As a result of that press briefing, some articles appeared in the print media, but the newly identified risks of anemia drugs and the

circumstances in which they are likely to occur are simply too complicated for TV medical reporters.

They would have to explain off-label use and how the greatest harm appears to be associated with off-label use and that raising hemoglobin isn't equivalent to reducing fatigue and how anemia can be caused either by chemotherapy or the cancer itself. Weigh these complicated issues against that simple uncomplicated Procrit TV message.

Johnson & Johnson was allowed to train current and future cancer patients to ask for these drugs that we now know as an evidence-free indication. Given what we now know about the increase in deaths, the deep-vein blood clots and the heart damage associated with anemia drugs, the FDA should require J&J to run a corrective ad campaign with the same on-TV, prime-time TV with the same demographics as the evening news and at the same frequency.

The huge expense and the range of prices of these anemia drugs are troubling, especially since the FDA has used the three as equivalent. From what we have known for years about financial incentives -- that is,

the deep discounts offered to oncologists by the drug companies for the most expensive drugs -- it is likely that these discounts fueled the inappropriate use of anemia drugs.

We know from the 2006 study that these deep discounts achieved just what the drug companies wanted. They increased the use of the most expensive drugs, because the most costly drugs come with the largest discounts and therefore the most generous profit margins for the oncologists in outpatient practice.

Oncologists are in effect running their own pharmacies. Consumers would naturally be suspicious of the herbalist recommending and selling his own herbal medicine or the vitamin doctor selling vitamins in her office.

As "The New York Times" so aptly just demonstrated yesterday, it's time for the public to understand that things are far worse at the oncologist's office.

Fifteen years after these anemia drugs went on the market we learned that they can hasten death and cause severe injury. Why did it take so long to know

this?

The situation points to the necessity of major changes. The FDA should be given the power to require better safety studies in the preapproval process, and the Agency must have the power to exact a large penalty on any drug company that fails to comply with recommendations such as those from the ODAC Committee in 2004.

I thank you for this opportunity to speak.

MS. CLIFFORD: Thank you.

Our next speaker is Carolina Hinestrosa.

MS. HINESTROSA: Good morning. I'm Carolina Hinestrosa. I am with the National Breast Cancer Coalition. The National Breast Cancer Coalition receives funding from different sources that include limited funding from pharmaceutical companies including Amgen and Ortho Biotech.

I am a two-time breast cancer survivor and the executive vice president of the National Breast Cancer Coalition. I am pleased to have the opportunity to testify before ODAC about the need for rigorous evaluation of supportive therapies in breast cancer,

first, to make sure patients are not harmed; and, second, to ensure that they don't receive costly treatments they don't need.

The National Breast Cancer Coalition has been fighting for improvements in breast cancer research, access, and care since its inception in 1991.

NBCC is a coalition of hundreds of organizations and tens of thousands of individuals nationwide who represent a diversity of breast cancer. Our mission is to end breast cancer, to educate and empower those affected by these decisions, to influence research, quality of care, and public policy agendas.

The NBCC embraces the philosophy of evidence-based healthcare. We believe that as a community -- scientists, clinicians, regulators, manufacturers, patients, and society -- need to learn what really works for women with and at risk for breast cancer to make sure that knowledge is incorporated into clinical practice.

We must also figure out what it costs us, healthwise and financially, to make fully informed determinations of what is acceptable and appropriate

care.

There is an underlying trust patients and consumers have in scientists, doctors and the FDA regulators, to look after their best interests as you evaluate the benefits and harms of the drugs, tests, and all interventions that become available to fight cancer.

Consumers trust the system to offer interventions that are based on a high-quality evidence, and appropriately designed randomized trials are the gold standard to obtain evidence of benefits and harms for all interventions, therapeutic or supportive. The National Breast Cancer Coalition believes strongly that for the system to be truly responsive to consumers' needs, we, the consumers, need to be involved at all levels for important decisions about our lives that are made. We are pleased to see true consumer representation at this ODAC meeting.

The news last March of the FDA and manufacturers or ESAs had agreed to add box label warnings on harms to patients due to off-label use of ESAs was in part reassuring but mostly sobering.

FDA action was clearly needed to inform consumers and educate decisions about the very serious dangers of off-label use of these agents. It was also a case in point of a distorted system where care is allowed to be based on poor or not evidence, and the interest of secondary stakeholders take precedence over those of the primary stakeholder, the patient.

Over the decades, we have witnessed a philosophy of cancer care where more must be better. We have used before we have evidence, and harming women in the process, high-dose chemotherapy with autologous bone marrow transplantation.

We have tried toxic treatment over toxic treatment in order to obtain marginally better and often short-lived outcomes and have used and overused supportive therapies to help us sustain that approach. A cancer patient trusts that all that care is needed to save her life.

I don't know how many of you have been diagnosed with cancer. I can tell you that it is hell. Every day women go through the hell of diagnosis and the hell of treatment with the hope that in the end she will

be or she will live and will be okay.

She is the primary stakeholder. All others must focus on the best way to help this woman live and minimize harms to her. It is not about selling more drugs or getting them approved faster or about supporting startup companies or the growth of existing companies. It is about saving people's lives, truly.

ESAs were first approved in cancer to meet a medical need, to lower the risk of blood transfusions due to anemia caused by chemotherapy. At that time the FDA raised concerns about the potential for these agents to promote tumor growth. There is also limited information about harmful effects of these agents.

The medical community went ahead and incorporated them into clinical use on- and off-label. Only approaches to breast cancer treatment such as those and advanced chemotherapy are supported by the use of G-CSF therapy to repopulate white-blood cells and ESAs to stimulate the production of red blood cells.

This for marginal improvement in outcomes without a fair assessment of the true benefits and harms of supportive treatment and at a great cost to patients

and the healthcare system. Now know that off-label use of ESAs can speed disease progression and death and have other effects.

It is well-known that there are perverse financial incentives in our system to motivate a decision to prescribe these and other costly drugs, imaging and other procedures regardless of whether they are indicated or despite their questionable value to patients.

I realize it is not up to FDA to fix this part of the problem, but it must do its part to demand quality data from high-quality studies to inform patients and practitioners and to assure the public that it is looking after its best interest.

The questions FDA asked of ODAC today are important. We believe it is appropriate to reassess today whether the net clinical benefits of ESAs outweigh the risk for cancer patients.

As a patient, I found it surprising that for 10 years after their approval, after supportive therapy in cancer, the risk for ESAs at the approved dose and schedule have not been characterized for cancer

patients.

It is disheartening that physicians' behavior, called "decision expectations" in the briefing report, are an obstacle to obtaining this critical information.

It isn't acceptable that primary data from the study has not been submitted to the FDA and, in some cases, not even to the manufacturers.

I am also concerned about the persistent flaws in study design described in the briefing document, which severely limits our ability to draw meaningful conclusions about the effect of ESAs on patients survival and tumor effects at the approved dose.

The May 2004 ODAC meeting made very specific requests for these studies. How come we have no answers? Or, worse, how come industry researches and fails to incorporate them in well-defined clinical trials?

I am left with the sense that we really don't know what we're doing. We know much more about the effects of ESAs at unapproved doses than we know about their effects at the approved doses.

As a Committee, you must assess and rely on

the quality of the evidence before you in order to make recommendations to the FDA. Your role is critically important to patients who trust these decisions are made keeping their best interests at heart.

MS. CLIFFORD: Thank you.

Our next speaker is Lila Romeo.

MS. ROMEO: Hello. I'm Lila Romeo, and I have no financial ties to any company represented here today. I appreciate the opportunity to speak to the distinguished panel.

What I bring to the table is experience. I have breast cancer. I was first diagnosed in 1995 in Stage 1 with a recurrence in 2000. As with many recurrences, the returning cancer was extremely aggressive, and I was treated with an equally aggressive protocol.

Adreamycin and Taxol together formed my first cocktail followed by CMF. When the CMF allowed the cells to spread to the chest wall, I was put on navilbene and herceptin combinations. I am pleased to report that that particular treatment has managed until recently to keep the cancer at bay.

Since my chest wall bears the evidence of the cancer cells, monitoring has been quite simple. A few months ago, we noticed that the navilbene and herceptin combination was no longer managing the rash on the chest wall, and I am now on a Zolotoyabko protocol. I am delighted to tell you that this new regimen has picked up where the old left off, an I am doing very well.

The reason I feel compelled to share this personal history with you is to emphasize how without today's drugs I would not be here speaking to you. I very much believe, as does my family, that without the advances that have been made in breast cancer treatment I and many like me would no longer be alive. I am a huge fan of modern technology and very grateful that these drugs were developed and approved and that my insurance company agreed to cover their use.

Over the course of these seven years of treatment with only one short chemo vacation, I have had many doses of Procrit and Aranesp. The recent discussions of the risks of using immuno-drugs has caused me considerable worry.

I know from my work on the SHARE Breast Cancer

Hotline that I am not alone. The issue has raised fears in all of us who have used and continue to use these medications.

In my case, I was advised that it would be necessary to use these drugs when my hemoglobin count dropped below 10 grams per deciliter or when I was experiencing extreme fatigue. I was assured that it was safe.

I now know that that assurance was questionable. Was it really safe? In an effort to avoid transfusions, was I put at greater risk? Did the Procrit and the Aranesp cause tumor progression?

Did they bind themselves to the receptors on my tumor cells? How do we know that 10 was the magic number? Should I have been treated at eight so that my counts would go up to 10, perhaps 12? Of course, like most laypeople, I assumed that all of this had been established in clinical trials.

I assumed that survival had been studied in those same trials, that tumor progression had been unequivocally dismissed before such a drug was sanctioned.

As I have researched this issue, I have learned that there were many unanswered questions. While that is perhaps inevitable, I remain troubled at the lack of transparency and of respect for my own ability to make a sensible personal judgment about the benefits and risks of treatment.

I see three particular areas where the system fails to safeguard and to respect patients. First, drug approval should not be the end process. Drug companies, insurance companies, and the government should assure that evidence is continually gathered on the drugs' efficacy and safety.

The fullest evidence possible should be reported of patient experience as the drug use expands in the market. This strikes me as particularly important in the modern biotech era. We are seeing miracle drugs, but we are in many respects only guessing about how they work in human beings, human beings like me.

In the case of the EPO drugs, I believe that they stimulate oxygenation. But in stimulating the blood cells, have we also stimulated and encouraged the

cancer cells? Have the growth factors that would assume to help avoid blood transfusions and the effects of anemia led to tumor progression instead?

Does the increased risk of blood clots outweigh the alleged benefits of having greater levels of energy? How is it possible that what was meant to help me might actually have made things worse? I submit that scientists don't really know.

Second, the criteria for prescribing and the dosage prescribed both deserve much more attention. I know that these issues are addressed in clinical trials, but we all know that the results at the time of approval are often preliminary.

Experience often shows that other dosage levels, frequently lower levels, would be safer and just as effective. Yet, because followup is inadequate, doctors are often left to wing it.

While I have always believed that my own doctors prescribe in good faith, I now understand better the financial incentives, both for the doctor and the drug company, to prescribe at higher doses and off-label.

In such a situation, dosage ambiguity becomes a major risk to patients. Dosage issues merit considerable followup. With the EPO drugs, doctors were treating at various blood level counts, readings, and various doses all based less on evidence than on their best guesses.

Of course, these issues are not restricted to EPOs. Many of us who are cancer patients believe that approved and recommended dosages of many drugs, for example, Xeloda®, are probably above what is necessary or tolerable.

Those of us under treatment know that our bodies are being bombarded with chemicals. We would prefer to minimize the damage we know they are causing in their quest to help us. We may be metastatic, but that isn't simply an invitation to test us and treat us as if the risks were negligible.

Third, evidence must be transparent. Why do the drug companies fail to publish negative results? Why do our doctors often discount them? In the case of EPOs, many of us were distressed that Amgen delayed the release of the results of the now well-known Danish

study. Did they believe the results were irrelevant or scientifically flawed, that we were not bright enough to understand them and then balance risk and returns, or was the delay due to a fear of seeing stock prices fall?

I do not begrudge the drug companies their financial success, but success should be derived from a drug's true performance, not from the hype created by a clever marketing team.

Many of us obviously were saddened to see the ads for Procrit praising its ability to enhance the quality of life of patients. Was the ad's not so subtle promise science-based or simply fantasy?

As far as I know, there has been no demonstrable change in energy levels in people on EPO drugs, yet we've seen all the advertisements of parents and grandparents without the energy to play with their children and grandchildren suddenly taking on a new-found sense of vitality after a dose of Procrit. We've seen them toss balls, dance, fish, and swing their little ones in the air. False hope is both insulting and cruel.

Of course, I want these drugs to be available.

Indeed, I hope that they are available to all whose life depend on them regardless of ability to pay, but even critically ill patients deserve honesty along with hope.

I plead with you to help ensure that we are informed with true and valid expectations, that we can see the evidence, that we with our doctors can make decisions that are decisions that are right for us based on fact and not delusion.

I understand that revenues for EPO drugs reached $10 billion last year, but wouldn't it be nice just occasionally to hear drug companies talk of helping 10 billion people with safe, effective, and evidence-based medicine instead?

Thank you.

MS. CLIFFORD: Thank you.

Our next speaker is John Theriault.

MR. THERIAULT: Good morning. My name is John Theriault (pronouncing "ter-ree-oh"), and I am a member of the board for the Aplastic anemia and MDS International Foundation.

We are a separate foundation from the MDS

Foundation that presented the you a few minutes ago, but our comments will likely mirror and build on those that you heard from the MDS Foundation as our patient population obviously mirrors theirs.

I am here today because of my father who was diagnosed with a bone-marrow failure disease five years ago this month. I am here today on his behalf and the thousands of patients like him with bone-marrow failure diseases that our foundation serves. They, like my father, have benefitted from the careful administration of ESAs and wish to continue doing so.

I would separate the comments that I am about to make from the extremely articulate comments that the cancer patients have made to date as our situation is somewhat different and somewhat of an aside from what you heard from those, again, very articulate comments.

We appreciate the opportunity to come before you, Dr. Eckhardt, and this Committee to present our views on ESAs. I want to assure the Committee up front that as a volunteer representative on the board of directors and representing the Foundation today I have no financial interests in ESA manufacturers other than

what may or may not be contained in mutual funds.

Moreover, no company has sponsored our participation in this thoughtful hearing today. Since 1994, our organization has received only minor support from an ESA manufacturer. We have a very strong code of ethics, and that has been to support some educational projects, and it is total, less than $35,000 over a 13-year period. It is not material to our thought process.

The AAMDS Foundation is a nonprofit organization. It is governed by a volunteer board of directors of folks like myself who have had someone in their life, or may be a patient themselves, affected by bone-marrow failure diseases. The Foundation is also honored to have a very esteemed medical advisory board. It is comprised of prominent experts in the field across the country including Johns Hopkins. It is chaired by Dr. Richard Stone of the Dana-Farber Cancer Institute, who happens to be part of the care team taking care of my father. We are here today because we are interested in the continued use of ESAs for bone-marrow failure patients. Because ESAs promote red blood cell growth,

many of our members have benefitted from these growth factors, which are prescribed off-label for patients with diseases like MDS, Aplastic anemia, and PNH.

Medicare covers this off-label use because of practices supported by research cited in approved compendia, namely, the USPDI. This finding is not surprising considering that EPAs are approved to address anemia in certain patient populations, and obviously the most common signs and symptoms of patients with MDS is in fact anemia.

The Foundation appreciates the steps that FDA are taking today through this process to ensure drug safety for all patients. Given that recent studies have shown significant and life-threatening events in certain patients who have taken these growth factors, concern is certainly warranted and appropriate.

However, from our perspective, these studies do not appear to have included patients with bone-marrow failure diseases such as MDS but only patients who have had end-stage solid cancers and/or renal diseases.

Moreover, in these studies the patients'

hemoglobin levels were typically kept above 12 grams per deciliter. Bone-marrow failure patients really reach such a hemoglobin level even with the addition of growth factor drugs.

Findings from these studies, therefore, cannot be said to apply to patients with MDS, again, unlike the very articulate comments from cancer patients spoken earlier today.

The adverse events discovered in these studies, namely, an increased risk of thrombotic events and stimulation of tumor growth are not likely to be relevant to patients with bone-marrow failure diseases.

MDS, for example, does not involve tumors or vascular diseases, and therefore there is not an increased risk for blood clots or strokes for one with just MDS.

Both of these potential problems, meaning blood clots and strokes, are likely to involve erythropoietic effects of the EPO on the endothelial cells or on tumors where there are EPO receptors, although repressed, at a low level.

Moreover, most patients with bone-marrow

failure diseases have extremely low platelet counts, a condition which tends to decrease the chance of clotting.

There have been some studies of ESAs in bone-marrow failure patients. These studies do not find a negative impact of ESAs. Studies assessing the long-term use of EPOs with or without granulocyte colony-stimulating factors in MDS patients compared to either randomized controls or historical controls have shown no negative impact on survival or on the evolution of AML with such treatments.

In addition, the Jefferson study completed in 2006 indicates improved survival in low-risk patients with low-transfusion needs who have been treated with these agents.

An even more recent article provides additional evidence for improved survival in low-risk MDS patients. We are unaware of any data that would contraindicate the use of ESAs in responsive bone-marrow failure individuals.

The risk/benefit of ESAs in MDS patients strongly favors their positive effect for minimizing

blood transfusions in this already highly compromised patient population.

A greater number of blood transfusions, as has already been pointed out, can result in higher iron overload burden, which correlates with diminished survival rates in MDS patients.

Equally important, ESAs eliminate the issue of obtaining irradiated platelets for transfusions. This is a unique issue to our patient population, but I ask the Committee to consider in its deliberations not receiving irradiated platelets can be problematic for MDS patients, especially those who undergo chronic transfusions.

Doctors in many local or rural hospitals often have difficulty in obtaining irradiated platelets for bone-marrow failure patients. In my father's case, for example, the local hospital had to send out for such platelets, and they had to be shipped from Boston or Providence. It would sometimes take a day or more for him to have to wait for such a transfusion.

The American Society of Clinical Oncology and the National Comprehensive Cancer Center Network have

published clinical guidelines that support the use of ESAs for the treatment of myelodysplasia in select patients.

Further, the consensus from experts in hematology based on their clinical experience is that MDS patients do not generally share the same risk of patients who are part of the ESA studies being discussed today and in "The New York Times" article.

Physicians, of course, still must monitor hemoglobin levels in bone marrow-failure patients receiving ESAs, especially those with renal or, in the case of my father, heart disease to make certain that their levels do not rise above 12 grams per deciliter. In my father's case, these are monitored on a biweekly basis by local hematologists and then followed up in Boston on a monthly basis.

More studies on ESAs and bone-marrow failure patients would help everyone to better understand the drug and its impact on this unique patient group. In the meantime, while the warning from the FDA should be assessed by doctors for each individual patient with forms of bone-marrow failures, patients with these

diseases should be able to continue to access and receive ESAs when clinically indicated.

We thank you for review of these comments and for your consideration of our patient population with bone-marrow failure diseases. If the Foundation or any members of our medical team can be available for you as you continue your deliberations, please do not hesitate to call upon us.

Thank you.

MS. CLIFFORD: Thank you.

Our next speaker is Loretta.

MS. LORETTA M: Good morning. I also speak from experience. I am a three-time breast cancer survivor. I was originally diagnosed in 1995 with Stage II breast cancer, infiltrating breast cancer with two lymph nodes positive, and then with metastatic disease in 2000.

In the past 12 years, I have never been without some form of treatment, whether it be traditional chemotherapy, radiation therapy, hormonal therapy, and I'm fresh off of a treatment yesterday.

I am a member of the Metastic Breast Cancer

Network in New York and the South Jersey Breast Cancer Coalition founder and president.

Again, we have all seen the commercial where the elderly gentleman is unable to play with his grandchild because of his fatigue caused by his cancer treatment. That implies that within a few days later the gentleman is not only playing with the child but able to run behind the bike with this new-found burst of energy supplied by the drugs he received.

This commercial paints a nice picture, but is it the whole picture? Has the patient been told that perhaps their disease could come back sooner, or that they could possibly develop serious medical conditions during their treatment because of these drugs?

The anemia drugs have been highly publicized on television, and sales of these drugs have skyrocketed to $11 billion because the commercial implies that these drugs can make chemotherapy easy and promising. It is not easy and sometimes it's not always promising.

According to the American Cancer Society's statistics for 2007, there an estimated 1,444,922 new cases of cancer this year. Cancer is big business. The

National Institutes of Health reported that in 2006 the overall cost of cancer was $206.3 billion. The drugs are being marketed to the consumers directly and to physicians that these drugs are the be-all and end-all for everyone going through chemotherapy. But, are they safe?

The FDA has issued a black-box warning for these drugs telling physicians there is an increased risk for death, heart attacks, blood clots or they can encourage tumor growth.

What do we know? We know that these drugs were approved to reduce the amount of blood transfusions. We know that these drugs raise the levels of hemoglobin.

We know that clinical trials have been stopped because of higher mortality and higher fatal blood clot event rates. We have all seen those examples this morning, especially the BEST study was particularly of interest to myself.

What don't we know? We don't know if fewer patients are receiving transfusions. Nobody has given those things to us. Why do these drugs cause health

problems? What happens to the tumor in the cancer patient using these drugs?

From a doctor's point of view, I think he wants to provide the best care for his patients. The patient wants to feel the best they can, and they want a drug that is perfectly safe.

As a patient with metastatic disease and as an advocate, I think we need more information about the drug but not at the expense of the metastatic breast cancer patient.

Thank you so much. In addition, we have no financial ties to pharmaceutical drugs.

MS. CLIFFORD: Thank you.

Our last speaker this morning is going to be Roy Beverage with U.S. Oncology.

DR. BEVERAGE: Thank you. My name is Roy Beverage. I am here on my own volition. No manufacturer is paying me to be here. I would also disclose that I live four miles from here so maybe, Steve, I can beat you there.

I am a community oncologist. I am one of the medical directors at U.S. Oncology. I work extensively

in patient advocacy. I have worked in committees with ASCO and ASBMT and the National Marrow Donor Program and have done significant research in terms of the pharmaco-economics of growth factors of red-cell factors and of transfusions.

Today, I really want to talk more about my being here as a community oncologist. Community oncologists do recognize and are concerned with the safety signal that these current studies have and support a reexamination of the evidence supporting the use of these drugs.

I think we are all well aware of the societal costs of ESAs and strongly support and endorse the application of NCCN pathways and U.S. oncology guidelines in terms of the use of these products.

One thing that I do want to make sure that the Committee understands is that we as community oncologists distinguish AOC, anemia of cancer, in chemotherapy-induced anemia as being two very fundamentally different things.

In my practice, 95 percent of patients who receive an ESA are patients who are in the chemotherapy-

induced anemia arena. Most of the data that was discussed today in terms of safety issues related primarily to patients in terms of anemia of cancer.

I also want to emphasize that I personally believe that cancer patients when faced with decisions in terms of using ESAs are well-versed in the concept of risk versus benefit.

I think we as oncologists talk with our patients about the risk versus benefit in terms of chemotherapy drugs, in terms of what to expect, and I think generally oncologists do the exact same thing with supportive drugs.

I also want to make a comment in terms of the discussion this morning in terms of the data presented in terms of the hematocrit cutoff, the hemoglobin cutoff of seven to eight. Remember, that the studies that were quoted in there primarily in patients who were in the intensive-care unit and on the floor.

As a medical oncologist, I am treating patients who are your neighbors, your friends, your coworkers who are working, have kids, and are being treated in my office. This is a very fundamentally

different group of patients than being in the intensive-care unit in terms of a trial between an ESA and red cells.

There is no question by medical oncologists that ESAs reduce the transfusion requirement. I think everyone agrees with that. I want to strongly emphasize that those of us who care for patients strongly believe that the quality of life is significantly improved in patients who are on these when the drug is used appropriately for the package insert.

Resorting to transfusion in this cancer population is very problematic in today's world. There are the obvious safety issues that have been discussed earlier today. There is a taxing of the limited supply of blood that we have, but there is also a very significant taxing of the delivery system.

I was actually at Fairfax Hospital this morning before I came here. It opens at 6:00 a.m. in the morning. It closes 13 hours later. It is open seven days a week. The next time that we can schedule a blood transfusion, if one wanted to do it today, would be 13 days from now. The system is very saturated.

I think 20 years ago we didn't have the supportive drugs, but then again we had remarkably ineffective chemotherapy. I think in today's world we have really very good chemotherapy for a lot of things, but I think the associated toxicity is similarly greater. The need for supportive-care drugs is larger now than it was at that point. I think medical oncologists and hematologists would ask the Committee to remember what it was like 20 years ago and not turn the clock back.

Thank you.

CHAIRPERSON ECKHARDT: Thank you.

Now we will proceed to a lunch break and reconvene at 1:00.

(At the house of 12:04 p.m. the luncheon recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:00 P.M.)

CHAIRPERSON ECKHARDT: All right. We are going to go ahead and get started. Just to sum up the morning session, as you know, we had both the sponsor presentation which reviewed the ongoing and previous

trials to date within the context of some of the safety updates that were convened to consider, followed by an analysis by the FDA on their assessments regarding these updates and some of the clinical trial designs.

I think in the next hour, if it takes that long, then what we would like to do is to propose questions coming from the Committee to get clarifications on the data that we heard from the sponsors as well as from the FDA.

I will go ahead and take any questions.

Dr. Mortimer.

DR. MORTIMER: I'm going to bring up a question that was raised by a number of the advocates to either group I guess. Throughout the briefing documents actually from the sponsor there are comments about the patients who do the best are those that actually have incremental improvements in their hemoglobins.

One question is, can you determine a subset of individuals who are actually benefitting from ESAs? The converse would be can you identify a subset of patients for whom the thromboembolic complications are predicted?

DR. PERLMUTTER: Thank you, Dr. Mortimer, for

the question. It is a general observation in our experience in studies using ESAs that the outcome for responders is better than it is for nonresponders, but I want to caution that those kinds of analyses are terribly confounded because those who respond likely respond for a reason.

The right kind of study is a much more challenging one to do in which one would actually look at the people who should have responded but, in fact, received placebo. I think that is a much more challenging kind of experiment to do.

At this point what we would say is when we look at the analysis, in terms of those who achieve a hemoglobin response, they do seem to do better when they are given ESAs.

We don't have any easy way to identify patients who are nonresponders and who would do worse in that setting without doing a much more challenging I think kind of study, for example, some sort of randomized withdrawal

kind of study.

CHAIRPERSON ECKHARDT: Dr. Albain.

DR. MORTIMER: Sorry. And the venous thromboemboli complications?

DR. PERLMUTTER: Yes. We've also wanted to be able to prospectively identify patients who might be at higher risk for venous thromboemboli, but we don't have a mechanism for doing that, either. As you know, venous thromboemboli are more common in cancer patients and it varies quite a bit from tumor type to tumor type as well.

If we could have the slide on, please?

(PowerPoint presentation in progress.)

DR. PERLMUTTER: This is an analysis that shows from a Cox proportional-hazards model independent predictors of time to thromboembolic events based on, again, these single-patient data that Dr. Baynes reviewed with you, 912 placebo and 1,200 in the darbepoetin alfa arm.

You can see that not surprisingly those things that one characteristically associates with a higher likelihood of having thromboembolic events, in

particular a prior history of thrombosis are scored as well as hypertension history and cardiovascular history. Those are the things I think that we can pay attention to as representing a high risk in these patient populations.

CHAIRPERSON ECKHARDT: Dr. Albain.

DR. ALBAIN: Thank you.

I was wondering if in your backup data bank here, if you could expand on the slide that was shown summarizing the quality of life endpoints? In particular, could you show any of your data regarding fatigue, regarding some of those other Phase II trial endpoints that really did lead to the embracement, so to speak of these agents for that particular symptom, and if that's possible?

Thank you.

DR. PERLMUTTER: Yeah. Let me call upon my colleagues from J&JPRD, because they are the ones who have primarily done those studies, and they will give you some additional detail on that.

DR. ZUKIWSKI: Okay. I think we all saw the quality of life data that Dr. Crawford presented. I

would like to elaborate on that and also talk a little bit about some of the evidence in more detail INT-10 because I think that study in many ways meets some of the criteria that was talked about by the FDA for generating robust patient report outcomes data.

Slide up.

(PowerPoint presentation in progress.)

DR. ZUKIWSKI: Beyond the evidence that Dr. Crawford presented, there is a body of evidence demonstrating improved patient report outcomes from controlled clinical studies. That has been reviewed in meta-analyses, and I will discuss some of those in a minute.

Again, I do want to focus on the INT-10 study because it is a placebo-controlled, double-blind pivotal trial in which several patient report outcomes were demonstrated to be significantly improved in the epoetin alfa treated patients, specifically: fatigue, cancer-related fatigue, ability to perform daily activities, and energy level.

It is also important to emphasize that this study does provide the basis for patient report outcomes

labeling in both Europe and the "Canadian Product Monograph."

While the instruments used to measure patient report outcomes in both INT-10 and in several controlled clinical trials have been well-accepted within the oncology community, specifically the FACT-N and the visual analog scale, the CLASS, for example, we do recognize that there are some limitations based upon the methodological standards that exist today as well as the FDA draft guidance for patient report outcomes instruments that perhaps make these instruments not sufficient for labeling, but don't take away from a body of evidence demonstrating improved patient outcomes for EPO-treated patients.

If I can have the next slide. Next slide. Slide up.

(PowerPoint presentation in progress.)

DR. ZUKIWSKI: Again, this is INT-10 and again I do want to emphasize it is a double-blind, placebo-controlled study. It was the pivotal study to European labeling and did result in inclusion in the label of the statement "Significant reduction of anemia-related