Now, do I worry about the drugs being safe for my patients? Of course, I worry. I worry about it every day, every day. You may not believe it, but it is really true.

The hypothesis that the erythropoietin receptor is important is just that, it's a hypothesis. Now, I have an offer for you. We will help you answer the question, we have got 1,200 docs, we have a national EMR, it has got clinical information.

We are used to doing clinical studies and collecting tumor specimens. We will help you answer the question if you want us to, because at the end of the day, we want the best thing for our patients.

DR. MORTIMER: Thank you.

Carolina Hinestrosa from the National Breast Cancer Coalition.

MS. HINESTROSA: Thank you. The National Breast Cancer Coalition receives limited financial worth from pharmaceutical companies including Amgen and J&J. It is a policy that is approved by our board of directors and is on our website.

I am a breast cancer survivor and Executive Vice President of the National Breast Cancer Coalition. I had

the opportunity to testify before ODAC in March of 2007. This presentation will again reinforce our call for the rigorous evaluation of supportive therapies in breast cancer, first, to make sure patients are not harmed and, second, to ensure they don't receive costly treatments they don't need.

The National Breast Cancer Coalition has been fighting for improvements in breast cancer research and care since its inception in 1991. We are a coalition of hundreds of organizations and tens of thousands of individual members. Our mission is to end breast cancer.

We embrace the philosophy of evidence-based health care. We believe evidence-based care is patients and care, and that, as a community, we must learn what really works for cancer patients and make sure that knowledge is incorporated into clinical practice.

We must also figure out what price we pay healthwise and financially to make a determination of what is acceptable and appropriate care. We are troubled that the rampant philosophy of cancer care where most must be better is harming patients.

Not long ago the oncology community promoted

before we had evidence of harming women in the process high-dose chemotherapy with autologous bone marrow transplantation. Today we continue to pile up toxic treatment over toxic treatment in order to obtain marginally better and often short-lived outcomes and we use and overuse supportive therapies to help sustain that approach.

Let us not forget that the patient is the primary stakeholder. All others must focus on the best way to help these individuals live a quality life and minimize harm to her. It is not about selling more drugs or getting them approved faster, or about supporting start-up companies or the growth or viability of existing ones. It is about saving people's lives.

Since last year's ODAC, the alarm over the use of ESAs in cancer has increased. Age studies now show either decreased survival or increased tumor progression in patients with breast and other cancers.

The label for these drugs now reflects the data. But is this enough? We still lack critical knowledge about their safety.

On the questions that were asked of the Committee, this is what we believe. The use of ESAs must be restricted

to specific types where the safety has been adequately assessed. It should be contraindicated in clinical settings where potentially deadly effects have been demonstrated in breast and head and neck cancers and it should be also restricted where there are no data about safety.

We strongly object to and find offensive and unethical the suggestion that ESAs are safe should be restricted to patients with metastatic disease. We place less value in patients' lives as to find it somewhat acceptable that in using ESAs we might speed up their death.

We also object to the recommendation that communicating safety information on ESAs to patients the informed consent will be an appropriate safeguard this time.

We strongly support the patient engagement in healthcare decisions But, today, informed consent is more about consent than information. This aspect of the FDA decision may throw the ball in the patient's court and will leave others--.

DR. MORTIMER: Thank you.

Christin Engelhardt from the Aplastic Anemia and Myelodysplastic Association International Foundation.

MS. ENGELHARDT: Thank you. The Aplastic Anemia

and MDS Foundation is a nonprofit that represents thousands of patients with rare bone marrow failure disease, aplastic anemia, paroxysmal nocturnal hemoglobinuria and myelodysplastic syndromes, or MDS.

Governed by a lay volunteer board of directors, not tied to any manufacturers, the Foundation also has a volunteer expert advisory board chaired by Richard Stone at Harvard University.

I note here that I personally have no financial interest in any pharmaceutical company other than what may be 403b retirement mutual fund.

No company has ever sponsored the Foundation's presence at agency meetings and, since 1994, the Foundation, with an annual budget of more than a million dollars has received support from Amgen for some educational projects, but less than $35,000 over eleven years. The last contribution was for an NIH symposium in 2005. We have never received funding from J&M or Ortho.

Given the limited time I can only highlight the points made in our written comments and ask the panel to refer to them carefully. We do appreciate why the FDA is holding this hearing. But we urge ODAC to remember that MDS

is a different disease from the cancers discussed today.

None of the studies cited as a concern by the FDA last spring or since appear to have included patients with bone marrow failure but only patients who had end-stage sold cancers and/or renal disease.

Moreover, in most of the studies cited by the FDA, the patients' hemoglobin levels typically are kept above 12 while MDS patients rarely reach a hemoglobin levels that high even with growth factors.

Findings are these studies cannot be said to apply to MDS. Further, the adverse events discovered are not likely to be relevant to patients with MDS. This diagnosis does not involve solid tumors or vascular disease that can increase one's risk for blood clots and strokes.

Moreover, patients with MDS have low platelet counts typically, which tends to decrease the chance of clotting.

There are no known risks with the use of ESAs in MDS. Even CMS, in its proposed decision memo last summer, could cite only one case report, published in 2001, of an MDS patient who progressed to acute monoblastic leukemia, a progression not definitely caused by an ESA and which was

reversed and not a cause of death.

If this progression were seen more often clinically, there would be more case report and possibly even studies. Instead, there is a significant body of evidence to support using ESAs for MDS and we were pleased that CMS, in its final NCD, maintained its coverage policy.

We recognize that ESAs are not appropriate for all patients with bone marrow failure and not all patients respond. But ESAs can reduce or eliminate the need for blood transfusions in patients with bone marrow failure. For some patients, ESAs are primary therapy.

There are no alternatives to ESAs other than blood transfusions, which are not appropriate for this population because of their need for irradiated platelets and their risk of iron overload, which is especially important because of the revised Exjade label.

More studies on MDS would help to better understand the drug and its impact. The Foundation believes that ESAs are appropriate in patients who respond or who are undergoing a reasonable trial of 12 weeks. But the Foundation did write to the three companies asking them to do FDA approval for appropriate bone marrow failure

syndromes.

We have also convened with the Leukemia and Lymphoma Society, a working group of experts, to look at this issue and to design a clinical trial that will answer the questions and we have also asked the FDA and CMS for its input into the design of the clinical trial.

DR. MORTIMER: Thank you.

Diane Dorman from the National Organization of Rare Disorders.

MS. DORMAN: Thank you. NORD has received funding from both companies to fund our research programs, our patient assistance programs, and our educational program for people with rare diseases. I have no personal interest myself.

The National Organization for Rare Disorders is a nonprofit voluntary organization representing an estimated 25 million Americans with between 6- and 7,000 known rare diseases. There are several hundred different forms of cancer and only five or six of them affect more than 200,000 people in the United States today at one particular time.

Thus, we address the ESA problem on behalf of the many Americans who are afflicted with rare forms of cancer.

Evidence indicating the ESAs prescribed for cancer patients may cause safety problems has been emerging for some time.

In the past, FDA has requested labeling changes on these products which some patient advocates feel are insufficient to adequately protect cancer patients from the risk of tumor progression that may occur as a result of taking an ESA.

In spite of the labeled changes that includes a black box warning in 2007, concerns about the safety of ESAs for cancer patients have continued to mount instead of diminish.

NORD believes the current indication for cancer chemotherapy patients should be removed from the ESA label until convincing evidence that an ESA provides a clinical benefit for a patient with hemoglobin above 10 has been submitted to, reviewed by, and approved by the FDA.

The ESA safety concerns that worry so many of us in the patient advocacy community are compounded by the perverse economic incentives that the companies make available to physicians who prescribe ESAs.

Because of this perverse practice, NORD believes that the companies should remove these incentives now and

until they have proven that ESAs do not cause cancer patients to be at a risk of dying while taking ESAs.

When patients are not able to protect themselves, it is up to the FDA to protect them and to make the scientific decisions that will protect them from this unwarranted risk.

The latest evidence indicating that ESAs can make tumors grow is very serious and patients have the right to know. It is incumbent on the FDA to ensure that patients and physicians are informed about these safety problems whenever they use ESAs, and for the FDA to remove this indication from the label until more is known about the safety for cancer patients.

Thank you.

DR. MORTIMER: Thank you.

Dan Cohen from Government Relations and Public Policy.

MR. COHEN: Thank you. US Oncology is one of the largest purchasers of chemotherapeutics from both sponsors. I have no direct conflict of interest.

Thank you for allowing me this time this morning to discuss the use of ESAs with you today. I am here to

present the perspective of the largest community oncology provider network in the United States. US Oncology consists of nearly 1,250 oncologists in 39 states, providing treatment at nearly 450 sites of service.

Last year we treated over 550,000 patients. We have developed a unique chemotherapy drug distribution center that guarantees direct drug delivery from manufacturer to patient to prevent entry of counterfeit drugs into our network and at any point in time, our physicians are enrolling patients in between 60 and 80 clinical trials.

Because of the breadth of our service we provide, our network has invested over $30 million in a comprehensive oncology-specific electronic medical record system that is used by over 600 oncologists today, will expand to over 800 oncologists in our network this year.

We are a patientcentric network. To ensure that our patients are treated with the finest evidence-based protocols, our physicians have developed clinical pathways based on the best published medical evidence.

This process incorporates a real-time peer review of any treatments that are not in line with the pathways.

Our physicians strongly believe that pathways result in the best, most cost effective care for our patients.

This patientcentric model, combined with our clinical pathways and the EMR, allows us to offer to help to design and participate in respective observational trials. In this instance, those trials would examine issues such as comparing clinical outcomes when ESAs are administered according to the requirements of the recent National Coverage Determination and when they are administered in accordance with the clinical guidelines as published by ASH, ASCO and NCCN.

We believe there is a potential for a CMS demonstration project on ESA use to assist the FDA's effort in obtaining more complete data on adverse events associated with ESAs. We can rapidly obtain information on ESA use and adverse events in such a large community practice.

Such studies could include endpoints that include the complete staging and cancer characteristics, transfusion frequency, regression-free survival, overall survival, the frequency of TVE.

In addition, the study could show whether or not there is evidence showing adverse events in patients with or

without ESA receptors on tumors, hemoglobins less than 12 and are using ESAs and if there are clinical correlates to the biological markers.

To collect meaningful data, another option would be to implement existing FDA authority and establish an ESA registry to control use within labeled indications. Our research network has significant experience in obtaining tissue for biological correlate trials and therefore our goals include trying to understand the role of ESA receptors and tumor and whether or not they play any role in disease progression.

DR. MORTIMER: Thank you.

Carlea Bauman from the Colorectal Cancer Coalition.

MS. BAUMAN: Thank you. Carlea Bauman, Colorectal Cancer Coalition.

CCC is a nonprofit, nonpartisan advocacy organization committed to winning the right against colon and rectal cancer through research empowerment and access.

In 2006 and 2007, CCC received funding from Amgen in the form of a charitable donation. Johnson & Johnson held a meeting in February 2008 in Washington, D.C. and paid

the travel expenses of a CCC board member. Neither of these companies nor any of our other corporate supporters have influenced our comments on this issue.

Today, I speak on behalf of the tens of thousands of people who receive treatment for colorectal cancer each year. They believe these treatments will save or prolong their lives and wouldn't dream of taking something that might hurt their chances of survival. They are used to looking at complex risk-benefit situations in their treatment plans. This situation, however, includes several frustrating and concerning issues.

For example, these drugs which provide supportive care to patients in treatment for cancer help patients avoid transfusion. They also increase the risk of death due to blood clots and could actually cause a patient's cancer to grow faster.

There is a systemic inability to find and analyze all of the relevant data - who has it, who owns it and who can see it.

There is a perceived lack of progress. ESAs have been on the market for many years, billions of dollars have been spent by insurers. Millions of patients have been

treated and yet we still have many of the same unanswered questions we had at the 2004 ODAC.

There is a mistrust of the manufacturers, the oncology professional associations and the patient advocacy organizations because of potential financial conflicts of interest.

CCC believes that we are at a point where the questions outweigh the answers. Therefore, we feel it is appropriate to restrict use of these drugs to situations where data is gathered in an effort to get more answers.

We believe that it will be very difficult to complete enrollment in the proposed Phase 3 trial while these drugs are widely used by oncologists. Our letter details our concerns with this proposal and with the RiskMAP strategy proposed by the sponsors.

Thus, we suggest implementation of a registry program. FDA implemented a patient registry and informed consent process for drugs such as nataluzimab and thalidomide through the special restricted distribution program. This program has enabled patients to have access to these potentially helpful, but potentially harmful, drugs in a controlled way which can also help inform future use of

the drugs.

CMS worked with several organizations to implement the National Oncologic PET Registry, which has collected information about PET scans since May 2006. Registries have strengths and limitations. We are interested to hear FDA's and ODAC's thoughts on the feasibility of a registry for ESAs.

Thank you for your consideration of our comments. If you do not have our written comments in your packets, I have extra copies with me.

Thank you.

DR. MORTIMER: Thank you.

Karen Pasqualetto.

MS. PASQUALETTO: Hi. I have sat here and listened from a patient's perspective to all of the information and data and I would like to lend a context to what you are considering.

I was diagnosed Stage IV colon cancer 21 months ago. It was one week after my daughter was born, my only child who is now 20 months old, and for me I have experienced both the use of ESAs, as well as blood transfusions.

I would strongly urge you to consider the patient's perspective and a quality of life issue when you are looking at the risks and benefits of using ESAs.

For me, to be able to have an ESA allowed me to continue my treatment, it allowed me to spend more time at home with my child, it allowed me to avoid any prolonged hospitalization or 6 to 8 hours of being infused, and it really lended to increasing my ability to enjoy the life that I had available to me.

When I was diagnosed, I was given 6 months to live. It has now been, as you know, 20 months and, for people who are suffering from cancer, it is very real that they have to balance the time that they have to spend with their family or pursuing their career or pursuing their interests, whatever they might be with their care.

In sitting here, it is very difficult for me to grasp some of the issues that relate to marketing, incentives for the drug manufacturers and trying to penalize that sort of behavior with giving patients less options. I would say that from a patient perspective, educate me on the risks, allow me to make the decision that fits in with my life and my needs in light of my diagnosis and give me that

option.

I have to also say on some other notes regarding comprehension of patient education, for example, it is kind of a tough road because you have to look at it from a practical perspective.

In all that is going on in a patient's life in dealing with life-threatening illness or perhaps, you know, a diagnosis of mortality, taking home a CD-ROM and reviewing that for information is probably not a practical way for me to look at information. So I would urge, if you are going to look at educating the patient, you look at everything in the context of an actual patient's experience rather than hypothetically or theoretically.

So I wanted to just lend you a context and I urge you to consider the patient's perspective and what these ESA's give to us. A blood transfusion for me would have delayed treatment and really would have affected my quality of life, and the ESAs worked very well for me and my stage of diagnosis.

Thank you.

DR. MORTIMER: Thank you.

Peter Ellis from the University of Pittsburgh

School of Medicine.

DR. ELLIS: I have no financial ties to the pharmaceutical industry.

UPMC Cancer Centers is the largest provider of cancer care in western Pennsylvania, seeing over 30,000 patients a year. We are not-for-profit.

We certainly understand and support the past recommendations of this committee regarding ESAs and we thank you. We have made every effort to ensure compliance by developing guidelines and doing internal audits regarding the use of ESAs in our practice, and our compliance is further evidence by a significant drop in ESA usage.

Oncology has been the driving force in the development and evidence of evidence-based care. National study groups thrive based on the volunteers' work of medical oncologists. UPMC Cancer Centers has developed an extensive program of clinical pathways to ensure that all care delivery is evidence-based and appropriate.

Most therapeutics that oncologists employ have benefits and risks that must be weighed to determine the benefit for the patient. The goal of every oncologist is to interpret the data from available clinical trials and use it

to provide maximum benefit for the patients.

A perfect example of that is the adjustment of the risk-benefit ratio of toxic chemotherapy drugs in the treatment of testicular cancer, which has resulted in the saving of numerous lives over the last 20 years.

Clearly, supportive care drugs are and should be held to a different standard of risk-benefit. But we still need to define that risk and the benefit of each drug in order to facilitate appropriate treatment decisions.

We at UPMC Cancer Centers believe that the use of ESAs that drives the hemoglobin above 12 clearly can increase the risk of VTE and mortality. We clearly believe that the use of ESAs does reduce the risk of blood transfusions and possibly improves the quality of life.

We believe that studies that are powered to evaluate the effective appropriate ESA use in CIA on patient' outcomes have not shown an increased mortality or disease progression.

We do not believe that ESAs, as used in the NCD, has been shown to increase patient safety while maintaining or improving effectiveness. We do not believe that the risks associated with appropriate ESA use override the

benefits in limiting the need for blood transfusions, and we do not believe that a link has been proven to exist between the presence of receptors on certain tumor cell lines and adverse clinical outcome for our cancer patients.

Based on the data available to us at the time of this presentation, we do not see the risks of the use of ESAs as significant in order to change the labeling. We understand that there is a risk to blood transfusion. We understand that that needs to be better defined.

We are absolutely and fully committed to gathering further data as our colleagues at US Oncology are for looking at ways to mitigate potential risks in the interests of finding the optimum risk-benefit ratio for our patients.

We absolutely embrace safe and informed patient decisions as we have with all chemotherapy over the past years.

We ask the Committee to consider these issues as they analyze the data to allow latitude for physician determination of risk-benefit ratio in consultation with the patient, not to impose overly restrictive rules where the data is lacking, and to acknowledge that oncologists are constantly assessing the risk-benefit ratio in all aspects

of cancer care including supportive care drugs.

Thank you for your time.

DR. MORTIMER: Thank you.

Samuel Silva, University of Michigan.

DR. SILVA: Thank you. My name is Samuel Silva.

I am a hematologist/oncologist and Professor of Internal Medicine at the University of Michigan. I am here today on behalf of the American Society of Clinical Oncology, ASCO, and the American Society of Hematology, ASH.

I have no financial association with any pharmaceutical company. I am a paid consultant to Bear Stearns and the Gerson Lehrman Group. My transportation at this meeting was provided by ASH.

We appreciate the opportunity to provide our views to ODAC regarding the safety and appropriate use of ESAs. ASCO and ASH published an update of our ESA guidelines on the use of ESAs in cancer patients in October 2007 with a further update in January, reflecting and integrating November 2007 FDA label information.

The update was based on extensive systematic reviews and meta-analyses of the published scientific evidence. The guideline further revised the update to

explicitly advise clinicians to consider the FDA's warning that data were not sufficient to exclude the possibility of shortened survival and tumor progression in cancer patients when ESAs are dosed to reach a hemoglobin level between 10 and 12.

Even before the FDA's action in November 2007, the ASCO/ASH expert panel had revised the guidelines to address recent data on the safety of ESAs. The 2007 guideline included a new section on thromboembolic risks of ESAs and underscored the point that the transfusion-sparing benefits of ESAs are obtained at the potentially increased risk of thromboembolic complications.

To summarize, the guideline update recommends dose reduction when hemoglobin rise exceeds 11, cautions that the risk of thromboembolism should be considered when determining dose reduction schedules, recommends against the use of ESAs in patients not receiving concurrent chemotherapy and provides a detailed review of studies, both published and unpublished, that reported a detrimental effect of ESAs on survival or tumor response.

The ASCO/ASH guideline update focuses on chemotherapy-related patients receiving ESAs at doses

titrated to achieve and maintain a hemoglobin level of less than 12. Because the more recent clinical trials were conducted in non-indicated patient populations or raised hemoglobin levels to a target above 12, it is not clear whether or how the results of these newer trials apply to the ASCO/ASH guideline recommendations.

Pending the publication of more definitive and peer-reviewed data on safety signals in the target population of the guideline, ASCO and ASH do not see sufficient evidence of harm to support recommending complete cessation of the use of ESAs across all patients with malignancies.

Furthermore, as we have indicated to the FDA in previous comments, we believe that there is compelling evidence to support safe use of ESAs in anemic patients with low risk myelodysplasia.

A recent cohort study by Park et al. published this January in Blood, showed a significantly better overall survival in the ESA-treated cohort, suggesting that ESA treatment may have a favorable survival impact in low risk MDS.

We realize that low-risk MDS is not a labeled

indication, but access to ESA should continue to be available to these patients.

While ASCO and ASH do not believe that there is evidence to deny all patients with cancer access to ESAs, our organizations do believe it is critical to better inform patients about the risks and benefits of this therapy.

ASCO and ASH have begun to develop additional guidance in communication tools for clinicians to improve the communication with patients about the potential risks and benefits of both ESAs and red cell transfusions and the option of no supportive anemia therapy.

ASCO and ASH strongly believe additional studies are necessary to address lingering safety questions. The 2007 ASCO-ASH guideline update provided a preliminary list of research priorities and our organizations are very willing to work with the FDA and industry to discuss appropriate clinical trials to answer some of the outstanding questions discussed at this meeting today.

Thank you and I would be happy to answer any questions that you have.

DR. MORTIMER: Thank you.

David Henry.

DR. HENRY: Thank you. I am a practicing hematologist/oncologist at Pennsylvania Hospital. I have never been a stockholder in any of the companies providing ESAs. My travel here today is provided by me.

Although I have been involved with the clinical trials, as a matter of fact, I was involved with the writing and the execution of the original Procrit trial that led to the licensing for the CIA indication in 1993 as discussed this morning.

I think the data have shown us that we have seen before and heard at the meeting this morning that used on label, there is essentially no survival safety signal when used appropriately on label, however it was only later on as we targeted higher doses and especially kept those doses going to non-responding patients that we started to see the problems.

It gives me great reassurance as a member of ASH/ASCO and comments of Dr. Silva who heads up one of our committees, that ASH/ASCO, NCCN, and the EORTC in Europe have all looked at this volume of information, much of what we have seen this morning, and believed that we should consider using the ESAs when the hemoglobins in CIA hit 10

or less, and consider using them as they fall toward 10 or less, because, as was alluded to this morning, I think all hemoglobins--Dr. Pazdur brought this up--are not created equal.

So a patient is finishing his or her chemotherapy regimen and is hitting 11 is done, needs no ESA or consideration of transfusion. But, if you are a 13, next cycle 11, well, next cycle you are going to be going down, and that potentially poses two risks for you, the worst of both worlds where you get now blood transfusion and ESA risk.

ESA risk in that falling, non-responding patient of DVT and survival, in fact, also alluded to this morning by the FDA presentation was the Amgen 103 study in AOC where the target hemoglobin was higher. But the average hemoglobin achieved was 10.6--well, not stated in that presentation was that the responders who went higher were not those showing the survival safety signal. It was those who kept going down, kept getting ESA, kept getting transfusion and with a greater risk of death.

I believe that ESA is appropriate to use in CIA indication, that the physicians should first rule out other

causes of anemia that are treatable, start appropriate dosing and stop if the drug is not working.

I therefore encourage the committee to decide today based on the evidence and, as has been mentioned before, I believe ESA use is safe when used responsibly by conditions in discussion with their patients on label.

Thank you very much.

DR. MORTIMER: Thank you.

Julia Bohlius.

DR. BOHLIUS: Ladies and gentlemen, my name is Julia Bohlius. I will present the progress report of the individual data meta-analysis on randomized, controlled trials on ESA in cancer patients.

My disclosures are on the slide.

As we have seen today, results from individual studies are inconsistent. In addition, results from literature-based meta-analyses are inconclusive because of ecological biases and different lengths of follow-up reported in ESA trials.

In contrast, meta-analyses based on individual patient data offer several advantages, because the detailed information of each individual patient and each time point

under observation is available, IPD will enable us to adjust for prognostic factors that may have confounded the original treatment comparison to investigate subgroups in which treatment may be either more or less effective or even harmful and to assess survival at prespecified time points.

Thus, some of the limitations of literature-based meta-analyses can be overcome with an individual patient data meta-analysis.

We set up a collaborative group to conduct such an analysis. To guarantee scientific rigor and transparency, we developed a detailed protocol and statistical analysis plan. Our primary endpoints are overall survival during study in patients receiving chemotherapy, as well as all cancer patients.

We set up an independent steering committee with international experts for oncology, medical statistics, and a consumer representative. All companies and independent investigators who submitted data are members of the advisory board of this project.

The advisory board has the right to review the protocol and the results of the analysis and to make suggestions, however, the advisory board is not authorized

to make any decisions regarding the analysis or publications. The project is funded by the German Federal Ministry for Research and Education. Funding from pharmaceutical companies has not and will not be accepted.

To date, we have collected individual patient data from more than 50 randomized controlled trials. We expect validated and sound results including insights into patient groups that might be harmed by ESAs within a short time.

The study will provide an independent and comprehensive analysis of the available data which will inform evidence-based decisionmaking.

DR. MORTIMER: Thank you.

Sharon Lenox.

MS. LENOX: My name is Sharon Lenox. I am the widow of a cancer patient. I am not a scientist or a doctor, I am a mail carrier. This is a summary of my interpretation of what went on.

My husband of 37 years, Jim, died 62 days ago. We have five children and 14 grandchildren. He bled to death from his mouth and nose as I attempted CPR, four hours after a 40,000 unit injection of Procrit. The doctor simply put lung cancer as the cause of death on his death certificate.

In 1998, he was diagnosed with non-small cell lung cancer. He had surgery and radiation and he did very well. April 2005, he had bilateral pneumonia and sepsis. He beat the odds again. In March of 2007, he was diagnosed with metastatic non-small cell lung cancer. He trusted his medical oncologist and began chemo with Taxotere and carboplatin on April 10th.

He was given Neulasta after every treatment and Aranesp every three weeks during chemo and even after. A PET scan in August 2007 showed significant improvement and tumor shrinkage. We now question why Aranesp was continued. He had two pints of blood in August, blood transfusion, Aranesp was continued even after that.

December 5th, tumors showed up in his brain. Radiation oncologists said if he took well to radiation, he could live six months or longer. He did take it very well. His last treatment was on January 7th, 2008, five days after his 54th birthday.

January 9th, he was hospitalized for dehydration as he had been in the past. His hemoglobin at that time was 13.5. January 11th, two days later, after rehydration, he felt wonderful. January 10th, he had an EKG and CT scan,

all as well. At 4:00 p.m., as we were being released from the hospital, on the 11th, the nurse came in with an injection. My daughter and I asked her what it was. She said, well, his hemoglobin is 9.8, so he is being given some Procrit.

He said, well, his hemoglobin was 13.5 two days ago, how could it possibly be 9.8. She said that was a false reading because of being dehydrated. So, we believed her, trusted the doctors. We asked why Procrit was given when he has always had Aranesp before. And she said we can't afford that expensive stuff over here at the hospital even though the cancer is part of the hospital, it's right next-door.

I later demanded medical records. I found that it was the highest possible dose, 40,000 units. For the past 60 days, my daughter and I have researched and printed thousands of pages on ESAs. We found the black box warning which we were never shown. It should be required to sign a consent form for these drugs so patients have the choice not just the doctor.

We have to sign the HIPAA law. We sign for Rx's at the pharmacy. McDonald's even tells you their coffee is

hot. I sat during his treatment and watched the drug companies bringing food in almost on a daily basis.

If he had not been given these drugs, would he still be alive? We don't know. Would his tumors have progressed? We don't know that either. But I think it should have been his choice, not the doctor's.

Thank you.

DR. MORTIMER: Thank you.

The Open Public Hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

Questions to the ODAC and ODAC Discussion

DR. MORTIMER: The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

I would like to take the prerogative of the Chair to just sort of make some comments and ask an unplanned question.

Yesterday, this committee met to review the efficacy and toxicity of romiplostim, a thrombopoietin agent proposed for the treatment of ITP and, while the FDA was not

questioning that it was an effective drug and refractory ITP, it came before this committee because of concerns that because of small numbers and short follow-up, the long-term toxicities were really not well clarified.

So I think the elephant in the room here is if we were presented with the data that we were presented with today initially for using the ESAs for the management of chemotherapy-induced anemia, would the committee opt to approve this drug based on what we have heard today.

I would just like people just to raise your hand if you would approve the drugs.

[No hands raised.]

DR. MURGO: Just a point of clarification, there are two approval mechanisms, one under Subpart H is the accelerated approval mechanism, and the other is a full approval. So perhaps you might ask people to--modify your question--

DR. PAZDUR: They still both require substantial evidence of effectiveness.

DR. MORTIMER: I think that is the question. Is there substantial evidence of benefit to the supportive care agent that would outweigh the potential risks that we see as

signals and, on the basis of that, would you approve the drug?

DR. REDMAN: I have a question, because we were not presented all the data, we were not presented the original studies that got it registered. We were presented questions about safety. So I think we can't make a decision based on the evidence presented today. I don't think that is a logical question to ask unless you want to go back and look at the data from 1990, what got it approved for its indication.

DR. MORTIMER: Okay. We will move on then to the questions at hand.

The first question, which is a voting question, which is a yes or no question:

1. Considering all the available data on the benefits and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indication listed above?

Discussion? Dr. Link.

DR. LINK: Do we get some caveats to the question? I mean in the light of, are there going to be appropriate

controls in place, is it going to be, you know specifically for not so much the black box but indicated for the hemoglobin level? We need a little bit more than just the five lines here.

DR. PAZDUR: I think we have a series of questions here based on, you know, we are asking a risk-benefit relationship as it stands now. And we are asking questions regarding if yes, then to recommend some further labeling instructions and then basically also consider an informed consent and a restricted distribution program.

But I think it is important perhaps, Joanne, to read the first part of that, the preamble to the question because it really kind of sets the stage.

DR. MORTIMER: Okay. Sorry.

To obtain marketing approval for a new drug or biologic product, an applicant must demonstrate that the product is safe and effective, when administered in accordance with product labeling.

Specifically, there must be substantial evidence of clinical benefit (efficacy) demonstrated in adequate and well-controlled clinical trials and FDA must find that the risks of the product do not outweigh the benefits.

The key issues we would like you to discuss are whether available data continue to demonstrate that there is a favorable benefit to risk relationship for ESA use for treatment of chemotherapy-induced anemia in patients with cancer and if so, whether the current product labeling is sufficient to ensure safe and effective use.

Dr. Kramer.

DR. KRAMER: I have listened carefully to the public comment session and it is really striking that there is a lot of confusion with regard to the proper basis of our decision and deliberation.

One of the things that just serendipitously, I happened to re-read in the past week, I think would be important for all of us to listen to and it is just three quick bullets.

The federal Food, Drug and Cosmetic Act, which is the law--not regulations drafted by FDA, but the law drafted by Congress in, let me mention, 1938, actually addresses what we are dealing with today.

It states under the demonstration of safety that an application could be refused--it is written in the negative--if investigations did not include all tests

reasonably applicable to show whether the drug is safe when used under proposed labeling.

(b) That the results of tests either show that it is unsafe or do not show that it is safe, and (c) the information submitted or any other information available are insufficient to determine whether it's safe.

I realize these are very broad and very subjective, but these safety requirements, as I understand it, are identical to what is in place today. And the one thing you take away from this is the question that has been posed, and that is, how long do patients have to continue to be exposed to a drug that we are not sure is safe.

It seems to me that we are conducting investigations while patients, frequently uninformed, are receiving this drug. And we are terribly conflicted because it is so much more convenient and it is so common that people even not receiving chemotherapy who have cancer would prefer to get an injection in their doctor's office or by a home health nurse than to come in for a transfusion, totally understandable. But if we are accelerating their mortality, have we been responsible.

I think that we really need to base our decision

on the law, and it is not something that was written by the individuals working for FDA. It is what our Congress passed and it has stood up the test of time since 1938.

DR. MORTIMER: Thank you, Dr. Kramer.

Dr. Wilson.

DR. WILSON: I would like to get back to the other side of the question, which is benefit, although that has not been the focus. What we have heard is that the benefit has been based on a reduction in the need for transfusions. But that is assuming that there is a down side of getting blood and, other than the convenience, that has not been shown and some of the down sides, such as risk of getting viruses and GVH, have been ameliorated through screening and use of radiation of blood products.

The other point that these studies have not looked at is actually the number of the transfusions that have been reduced by this. The patients that have the highest bone marrow toxicity from therapy are the ones who are going to have the greatest transfusions where you would like to reduce that the most, and they are probably also the patients who probably benefit from the use of these drugs the least.

I have seen no data that actually looks at the reductions in number of transfusions, just the reductions in numbers of patients that have required them. So I do think in considering risk-benefit, we have to look back on the benefit piece. And, to me, currently, other than convenience, there is not hard data on this.

DR. MORTIMER: Other comments? Dr. Perry.

DR. PERRY: I guess I would take a slightly different view from my learned colleagues. Transfusion is difficult, it is time consuming, but it is also hazardous. The risk of infections may be reduced, but the risk of transfusion-related lung injury, which we didn't recognize years ago, is increasing. And, if we have to multi-transfuse people, it becomes more and more difficult every time to cross-match their blood.

If they have to be multi-transfused, then, they wind up with iron overload. So it is not a very simple question to say, well, we will stop using ESAs and then just substitute transfusions. The number of people in the United States who are eligible to donate or who are donating is smaller than ever before--excuse me, let me rephrase that--is smaller year by year. Fewer and fewer people choose to

donate while the population continues to rise.

If we stop using ESAs, it is likely that we will encounter a shortage of red blood cells at some point in the future. I have a unique perspective on this I think. As far as I know--and I don't need to know anybody else's history--I am the only person on this panel who had both a transfusion and the benefit of an ESA and, if you give me the choice, believe me, I would rather have the ESA.

DR. MORTIMER: Thank you.

Ms. Schiff.

MS. SCHIFF: I just wanted to say that I think it is really unknown at this point what the risks are of a transfusion versus an ESA versus skipping your chemo or not doing anything and I don't see how we can make a decision.

I mean everyone is just hypothesizing. We don't know. And the original trial was done on 150 people in six trials and it was not enough to look at safety, enough people. The only thing it did was that it reduced the number of transfusions, but we don't know really if that is good or bad.

DR. MORTIMER: Dr. Stroncek.

DR. STRONCEK: I guess I am the transfusion

medicine, full-time transfusion medicine, person on the committee, but a couple comments. One is that the transfusion triggers since the original, this drug was approved for us in oncology, have really decreased and now, for stable patients, most guidelines suggest that a transfusion trigger would be about 8 grams of hemoglobin, and even some studies are even suggesting it should be lowered down to 7.

The second comment is I think we need to--as far as availability of blood, yes, it is always short. But that has been that way for years, and people, when there is a need to donate blood, people come forward. So I am confident that there will continue to be blood available.

DR. MORTIMER: Dr. Day.

DR. DAY: On the benefits side, there has not been demonstrated quality of life benefits is what we are told based on the research. Some patients and patient advocates today say that there is.

Can someone just quickly summarize the studies on that? I mean there are many instruments on quality of life and we were not provided that in our current background material.

DR. MORTIMER: I think Dr. Juneja just sort of summarized the results. I don't know if you want to make a comment about it, or Rick, or Pat, Dr. Keegan?

DR. KEEGAN: There have been randomized studies that have employed quality of life questionnaires typically used in cancer, and is the most common and, in FDA's review of such data, we have come to the conclusion that you can't really make a judgment that there is an improvement in quality of life primarily because of a lot of missing information and lack of information and how exactly to handle that.

So we really can't say based on that kind of data, that there is evidence of a quality of life benefit.

DR. DAY: So it's the quality of the data, not the fact that half were helped and half were not helped, and it averaged out.

DR. KEEGAN: Right.

DR. MORTIMER: I think the one thing we know is there is a decreased transfusion that has been demonstrated.

DR. TENDLER: Can we comment on the quality of life for improving patient outcomes?

DR. MORTIMER: Go ahead.

DR. TENDLER: If I can have PR5.

Just to reiterate Dr. Keegan's point, one of the issues has been on content validity of the tool that is used. Many of these trials, a tool that was developed by Dr. Cella, known as the Fact End tool, a fatigue sub-scale was used, and the concept of content validity is described on the slide here.

[Slide.]

Is the concept, in this case, we are measuring fatigue relevant and important to the particular patient population on the study, are the items that are used to measure that on the tool actually capturing the patient's relevance, fatigue, in this case receiving chemotherapy.

The other aspect is that the tool is supposed to be developed with patient input, that would make it a validated tool as per the FDA guidelines.

PR6, please.

[Slide.]

So, really, here are the questions on the tool. And when FDA is questioning the validity of the fact end fatigue subscale, they are really asking the question whether these questions that you see described here are

relevant and are they comprehensive to measuring fatigue in a patient receiving chemotherapy.

In terms of the data, just last slide, PR1, please.

[Slide.]

So the Cochrane group, which you heard from Dr. Bohlius, had actually just done an updated meta-analysis looking at interventions that could improve cancer-related fatigue. This is the summary of the studies that they looked at that were placebo-controlled trials using either of the ESA products.

You see any of the bars going to the left of the line favor ESAs, and they have done the meta-analysis. And their conclusion, as you heard before, was that these products do statistically significantly improve cancer-related fatigue and that the difference is clinically meaningful.

DR. MORTIMER: My understanding of the data is that only one of these trials was actually a double-blind study so all of these were open label trials.

DR. TENDLER: No, that is not correct. The nine studies that I am showing on the slide are the nine that

were designated as placebo-controlled trials using an instrument that the Cochrane Group felt accurately measured fatigue.

DR. MORTIMER: But are they open label studies? They are open-label trials.

DR. TENDLER: No, that is not correct, they are placebo-controlled, blinded trials.

DR. KEEGAN: Follow-up, we do at FDA have some concerns about the validity of the assay measurement but that is not the totality of our concern. As I mentioned before, our major concern is missing information. And the general way of handling a lot of this missing information is to impute the last value carried forward.

But we know in these cancer trials that when a patient drops out of study, they are unlikely to be dropping out for good reasons. It is almost always that they are having disease progression or toxicity, so to take their last value carried forward is a major methodologic issue for us.

Between the missing data and the appropriate way to handle that has always been problematic. So, when we looked at this data, we really cannot reach a conclusion

that there is a benefit regardless of whether you think the questionnaire is valid or not.

DR. MORTIMER: Thank you. Dr. Harrington.

DR. HARRINGTON: I always find the labeling proposals restrictive when we get to our first vote because as I understand this one, we either vote yes on this and then we look at all the restrictions, or we vote no and the rest of the questions along with the drug are off the table.

As I look at the data with all of the uncertainty around both safety and efficacy here, it looks a lot like second-line therapy to me. It looks a lot like the sort of settings where we approve drugs knowing that if there is a very good reason for a patient not to get a preferred treatment, which in this case might be transfusion, then, a clearer understanding of risks and benefits might proceed.

So, is it possible that this label could be revised to say that erythropoietins could be used in patients for whom transfusion was not appropriate, or that the second-line therapy for transfusion?

DR. PAZDUR: We could consider that when we get to the labeling issue.

DR. MORTIMER: Other questions? Do people

understand the question? The question is essentially are we going to keep these drugs on the market. And, if the answer is yes, then, we will go--

DR. PAZDUR: Not on the market, the indication.

DR. MORTIMER: I am sorry, the indication of chemotherapy-induced anemia. Thank you.

If the answer is yes, then, we will go through, as Dr. Harrington said, the restrictions on that. Dr. Perry.

DR. PERRY: I need to remind everyone that we are an advisory committee to the FDA and, if we vote in the negative, we are not responsible for the drug being taken off the market or modified. That's the FDA's decision. We are merely giving an opinion, we are an advisory committee. We do not have power to enact anything.

DR. PAZDUR: Couldn't have said it better.

DR. PERRY: Thank you.

DR. MORTIMER: Are there other comments? Are we ready to vote?

The question is: Considering all the available data on the benefits and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for

the indication listed above?

Yes means that you want it to stay on the market for chemotherapy-induced anemia. No means that--

MS. SCHIFF: What about for one drug?

DR. MORTIMER: Then, we can go through the specifics. We are going to go through the specific indications. Is everybody clear?

We are raising our hands. All the yeses, raise your hand. Could you state your name into the record and we will start with your vote. Dr. Harrington, I think you are first.

DR. HARRINGTON: David Harrington. Yes.

DR. PERRY: Michael Perry. Yes.

DR. RICHARDSON: Ron Richardson. Yes.

DR. LINK: Michael Link. Yes.

DR. MORTIMER: Joanne Mortimer. Yes.

MS. MASON: Virginia Mason. Yes.

DR. REDMAN: Bruce Redman. Yes.

DR. WILSON: Wyndham Wilson. Yes.

DR. LESAR: Timothy Lesar. Yes.

DR. MURGO: Tony Murgo. Yes. Can I make a comment? The reason I am voting yes is that--I get back to

the so-called accelerated approval, Subpart H--and I think back in '93, I can't recall if those regs are in place yet or not, but I think the level of evidence as far as--let me put it this way.

I think one can consider the use, the decrease in the transfusion requirements might be a surrogate for clinical benefit and I think that, under those circumstances--and I think the limited number of data, the amount of data that there is, would probably--in my opinion, would have been sufficient for that type of approval.

So that is why I am voting yes here.

MS. SCHIFF: Yes.

DR. STRONCEK: Dave Stroncek. Yes.

DR. DAY: Ruth Day. Yes.

DR. MORTIMER: Could I have the noes? Raise you hand, give your name and vote. Dr. Kramer?

DR. KRAMER: Dr. Kramer. No.

DR. MORTIMER: So, 13 yes and 1 no.

The next question is: If you recommend that the current indication should be retained, that is, for chemotherapy-induced anemia, should the FDA require that the produce labeling be modified? We are going to talk about

the four potential approaches to mitigating risks through revised labeling. We are going to address each of these individual questions separately.

The first question addresses the data in small cell lung cancer.

To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving EDAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic disease settings), lymphoid malignancies and cervical cancers. Tumor types, other than those listed above, have not been adequately studied.

So, the question posed to the committee: Should the current indication be modified to restrict use only to patients with small cell lung cancer?

Discussion? Dr. Wilson.

DR. WILSON: I think we have talked about how we have to hold drugs such as this to a higher standard. And I think it has been very well put that the absence or proof is not that there is no proof that it is adverse.

I think that this particular setting is one

setting in which there appears to be more clear evidence that the drug may not have the same adverse consequences, whereas, in the other settings, I think that there is emerging evidence and, in some people's minds, pretty good evidence that there could be risk.

So I just put forward the notion that if we require a higher standard, we want to approve it only in diseases where we have shown that there is little or no risk, whereas, the others I think one needs to still do additional studies.

DR. MORTIMER: Other comments?

[No response.]

DR. MORTIMER: Shall we take a vote on this?

The question at hand is: Should the current indication be modified to restrict use only to patients with small cell lung cancer? This is a yes or no.

All yeses raise your hand.

[Show of hands.]

Can we go around the room and say your name and your vote. We will start with you, Dr. Stroncek.

DR. STRONCEK: Dave Stroncek. Yes.

DR. KRAMER: Judith Kramer. Yes.

MS. SCHIFF: Helen Schiff. Yes.

DR. MURGO: Tony Murgo. No.

DR. MORTIMER: We are just doing the yeses.

DR. LESAR: Timothy Lesar. Yes.

DR. MORTIMER: Joanne Mortimer. Yes.

DR. WILSON: Wyndham Wilson. Yes.

DR. MORTIMER: Now, could we have the noes raise their hands. We will start with Dr. Harrington.

DR. HARRINGTON: David Harrington. No.

DR. PERRY: Michael Perry. No.

DR. RICHARDSON: Ron Richardson. No.

DR. LINK: Michael Link. No.

MS. MASON: Virginia Mason. No.

DR. REDMAN: Bruce Redman. No.

DR. MURGO: Tony Murgo. No.

DR. MORTIMER: Are there any abstentions?

DR. DAY: No.

DR. MORTIMER: There are 6 yes, 8 no.

The next question we are being asked to vote on is: The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk-benefit assessment is

different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers.

Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments?

MS. SCHIFF: Clarification. So, do you vote if you are for limiting it in the adjuvant setting, but you vote yes, but you are not for making a distinction between the two?

DR. MORTIMER: Yes is no, it is not indicated for patients receiving--you vote yes if you don't want it indicated for curable disease, you are right, Helen.

Dr. Perry.

DR. PERRY: The reason these women are receiving neoadjuvant therapy is that they have large bulky tumors that have already spread to the axilla. These are women at high risk and, while they may be treated for cure, and everyone hopes that is going to be the case, in the cases it is not going to be cured, it is simply going to be palliative and prolong the point at which they recur.

I don't see a point for distinguishing them from

the others. And I think that if I recall this study correctly, it shows a trend rather than a statistically proven decrement in survival in a small number of patients.

I am not ready to make a judgment for the totality of patients. Also, in this group, who are often relatively young patients, the need for transfusions or ESA is going to be relatively less. I think we are making a bigger deal than we need to in this situation.

DR. PAZDUR: I want to make it clear we are not just talking about breast cancer here. This could be about testicular cancer, large cell lymphomas, other curative studies.

DR. MORTIMER: I think in the briefing document, there was a clarification between locally advanced and neoadjuvant therapy. So anybody getting neoadjuvant therapy and the entry criterion for the PREPARE study I believe was a 2-centimeter primary tumor, greater than a 2-centimeter primary tumor. So I would argue that those are potentially curable women.

DR. PERRY: Some of them, yes.

MS. SCHIFF: It says neoadjuvant and adjuvant.

DR. PAZDUR: Here again, this is not just about

breast cancer. This is a philosophical question regarding curative approaches to a disease.

DR. PERRY: I think if the question had been written without the first sentence, it perhaps would have been a little clearer. If you specify PREPARE trial and then want to broaden it thereafter, you need to write the question to be less confusing.

DR. MORTIMER: Can we modify the question that patients who are receiving potentially curative therapies?

DR. PERRY: That is fine with me.

DR. MORTIMER: Dr. Curt.

DR. CURT: One thing I am a little uncomfortable with. And following off on Dr. Perry's remark is the different strength of trends for supportive care as opposed to treatment drugs. I am wondering if Pat could clarify that for us.

DR. KEEGAN: Given that we don't have a lot of data in curative settings, I mean we have the trial that you heard of, PREPARE, and the rest I think were all in metastatic--

DR. MORTIMER: The O'Shaugnessy trial, there was a cognitive function trial. It was an adjuvant trial.

DR. KEEGAN: We have not reviewed that. We have some preliminary evidence on I believe the Mobus study, which also was trending in the wrong direction. I mean we really don't have a lot of data. So all I can say is that the trend is on the wrong side of 1. But it is not that we have enough to really make a definitive statement about all situations where there might be curative therapy.

DR. MORTIMER: Dr. Jenkins.

DR. JENKINS: I just think it is important to clarify so that everyone is clear on this is a cascading series of questions. We asked you the most restrictive question first, which was should these remain available for use in cancer chemotherapy. If you didn't answer that question saying that you didn't think they shouldn't be available, then, you go on to the next question.

As Rick said, this is a philosophical question, if you are treating for curative intent, should these be used in that setting, yes or no. We are going through a series of increasingly less restrictive labeling options so we started out with should they be indicated at all, yes or no.

Then, we moved on, should it be limited to a disease where it seems that the data may be adequate to

suggest a lack of increased risk. Now, we are moving on to the curative intent versus where it is non-curative intent and then there is a cascade after this of less restrictive labeling changes.

DR. BOWERS: May I be recognized on just a point of clarification? If I could have that slide on.

[Slide.]

In regard to that Mobus trial, again just to make sure that the record reflects correctly the results of this trial, the aqua line is the epoetin alfa treated group, the gray line is the placebo or, excuse me, standard of care treated group, no epoetin alfa.

There is a slide early separation favoring the epoetin alfa group. The hazard ratio for the entire curve is 1.01, the confidence interval spans 1.

DR. JENKINS: We take the comment constructively that maybe we confused the question by referring to the breast cancer in the preamble to the question. This is really about the hypothetical of curative intent treatment and do you recommend that they be used in those settings or not. We take your constructive criticism that we could have written the question more clearly.

DR. KEEGAN: Could I actually just clarify also. If I said there is not a lot of data, and we didn't intend to suggest that only data from the adjuvant breast cancer data be considered but that all the available information and the data from the metastatic setting might be generalizable to the potentially curable setting.

DR. MORTIMER: Ms. Schiff.

MS. SCHIFF: I wouldn't be asking this again but other people around me are still confused. I am against making--I don't think--women with metastatic disease, or people with metastatic disease, they can live a long time. We know that. So I don't think that they should receive ESAs any differently than people in the adjuvant setting really.

You know, if someone has a five-year life span, you don't want to cut it to two and a half. In fact, they might be even be at more risk for tumor progression because they have more of a tumor burden.

So, which way do I vote? That is all I want to know.

DR. MORTIMER: I think the question is--we haven't gotten to metastatic disease yet, and we will get there--the

question really on the table is, if you have a signal in advanced disease, and recognizing this is a supportive care agent that may or may not convincingly have effects on fatigue but definitely does decrease need for transfusions, do we exclude patients with curable cancers so that they don't receive these agents? Dr. Wilson.

DR. WILSON: Maybe I could reframe this.

I think that by going into the potentially curative group, we are significantly increasing risk to patients if, in fact, there is an adverse effect on this. So I think this group has a higher risk if, in fact, an adverse effect happens, because you may convert somebody from a curative patient into a non-curative patient and this is a lifetime difference for them.

So, I just want to emphasize that I think that this is grading risk.

DR. MORTIMER: Dr. Murgo.

DR. MURGO: Just a clarification. I don't think this question would have any impact of whether a patient is excluded or included. This is just an indication, this is not a contraindication. It's a recommendation. I would assume it's a recommendation that would be put into the

package insert but not as a contraindication.

DR. PAZDUR: It is not a contraindication.

DR. LINK: But would it affect reimbursement?

DR. PAZDUR: We don't get into that.

[Laughter.]

DR. PAZDUR: This should be based on a risk-benefit analysis, not on a financial consideration.

DR. MORTIMER: I am going to come at this from a breast cancer treating standpoint. We know that women who have early stage breast cancer will accept a 1 percent risk of benefit in order to take chemotherapy.

All of the chemotherapy that we use in the adjuvant setting is derived from efficacy in advanced disease. So if there is a signal in advanced disease, and I think there are good signals in the neoadjuvant and in the BEST trial, that there is concern about disease progression in women who receive ESAs, that I think they should not be used in the adjuvant setting.

Any other comments? Are we ready to vote on this?

Just we have this clear, the question at hand is that ESAs should not be indicated in patients who have potentially curable treatments. So, by voting yes, you are

not giving them to curable patients.

MS. SCHIFF: But are you making a distinction then?

DR. MORTIMER: No, no, no, nobody is doubting the value of a woman with metastatic breast cancer in her life.

Is everybody clear on what the question is?

Should the current indication be modified to include a statement that ESAs not be used in patients with potentially curable treatments?

Could I have the yeses raise your hand and then we will go around the room?

[Show of hands.]

We will start with Dr. Harrington.

DR. HARRINGTON: Harrington. Yes.

DR. RICHARDSON: Richardson. Yes.

DR. LINK: Link. Yes.

DR. MORTIMER: Mortimer. Yes.

DR. MASON: Mason. Yes.

DR. WILSON: Wilson. Yes.

DR. LESAR: Lesar. Yes.

DR. MURGO: Murgo. Yes.

MS. SCHIFF: Schiff. Yes.

DR. KRAMER: Kramer. Yes.

DR. STRONCEK: Stroncek. Yes.

DR. MORTIMER: And the noes?

DR. REDMAN: Redman. No.

DR. PERRY: NO in capital letters.

DR. DAY: Ruth Day. Abstain.

DR. MORTIMER: There are 11 yes, 2 no, and 1 abstention.

The next area addresses I think Ms. Schiff's concern. The vote here is: Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies – breast cancer and head and neck cancer.

Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast and/or head and neck cancers?

Comments? Discussion? Dr. Redman.

DR. REDMAN: It's my old comment. I have sat here all morning and afternoon and I am still waiting for the study that shows increased tumor progression. I haven't seen it and that statement in there I think is misleading.

DR. MORTIMER: Dr. Juneja.

DR. JUNEJA: The tumor promotion issue I think most relevant is for head and neck cancer. Let me bring up one of the slides. Basically, you have the DAHANCA and the ENHANCE study, again, head and neck cancer, patient on radiotherapy. Both of the studies showed--well, let me backtrack.

The ENHANCE study showed decreased loco-regional progression-free survival and patient on ESAs, while the DAHANCA study showed decreased loco-regional control, the patient on ESAs. This is really what we were referring to in terms of tumor promotion.

As I previously stated in the PREPARE study, for neoadjuvant breast cancer patients, that is where we saw a trend to decreased relapse-free survival for patients receiving ESAs.

DR. REDMAN: I understand that you had a national meeting here the other day that stated that there is no evidence to suggest that EPO or EPO receptors have any confirmed evidence that there is any evidence of tumor progression.

I just take--the definition of tumor progression,

what you are showing is a lack or decreased efficacy of the combined treatment, being the chemotherapy or the radiation therapy and EPO versus lack of EPO. To imply, because I have heard it from the audience, they are using the term "tumor progression," that is a very dangerous thing to cite, that EPO or ESAs cause tumor progression.

The data is not there to suggest tumor progression. It may suggest that combining EPO with radiation therapy may decrease the efficacy of the radiation therapy. I think you can state that from the ENHANCE trial, but you can't state that the EPO or the ESA is causing tumor progression. The data isn't there to support that.

DR. JUNEJA: I don't mean to imply that tumor progression is being caused by an ESA. I am just saying we are not sure. But these are the data.

DR. MORTIMER: So we will use the term worse tumor outcome. Is that okay?

DR. REDMAN: Yes.

DR. MORTIMER: Okay. Dr. Murgo.

DR. MURGO: I was going to comment on the word tumor promotion. This doesn't say progression. I agree with everything that was said but, just for the record, I

think tumor promotion means something entirely different and I don't think it is appropriate to use that word here.

DR. MORTIMER: Are there other comments here?

DR. PERRY: Can we read the question we are going to be voting on now?

DR. MORTIMER: Dr. Curt wants to say something.

DR. CURT: I am also a little uncomfortable using the head and neck data which was in the setting of radiation therapy, and the indication that we are talking of is in the setting of chemotherapy-induced anemia.

DR. MORTIMER: Dr. Link.

DR. LINK: So is the answer to this question a follow-on to the answer to the last question? Since we have already eliminated in the adjuvant setting for breast and head and neck, this would be then for essentially saying that it is not indicated for patients with metastatic head and neck cancer or metastatic breast cancer.

DR. MORTIMER: Yes.

DR. LINK: So this would be eliminating that one subgroup.

DR. MORTIMER: Yes.

Dr. Wilson.

DR. WILSON: I just wanted to say that I think the threshold for concern from these various trials is lower when it comes down to toxicity and, while understanding that radiation and chemotherapy are different, I think that if there is, in fact, a signal, that you may be reducing the effectiveness of therapy. I think one is incumbent to prove the other side, which is that it is safe with chemotherapy, that that should be the default safety position in setting like this.

DR. MORTIMER: Other questions? Comments?

Are we prepared to vote on this?

DR. PERRY: If we vote yes, that says we don't want this drug to be used in people with metastatic breast cancer?

DR. MORTIMER: Correct.

DR. PERRY: Or head and neck cancer?

DR. MORTIMER: That is correct.

DR. PERRY: I don't do head and neck cancer, I am concerned with breast cancer patients. So, all my little old ladies tottering out are going to have to be transfused rather than get growth factor, is that correct?

DR. MORTIMER: That is correct.

DR. PERRY: Not a good idea.

DR. MORTIMER: The question at hand that we are going to vote yes or no on: Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast or head and neck cancers?

Could the yeses raise their hand and then we will go around the room from Dr. Day this time.

[Show of hands.]

DR. DAY: Ruth Day. Yes. Excuse me. Can the word "metastatic" be put in there? Can we put it in there to make it perfectly clear?

DR. MORTIMER: Yes.

DR. DAY: Just before the word "breast." Thank you. Ruth Day. Yes.

DR. STRONCEK: Dave Stroncek. Yes.

DR. KRAMER: Judith Kramer. Yes.

MS. SCHIFF: Helen Schiff. Yes.

DR. LESAR: Timothy Lesar. Yes.

DR. WILSON: Wyndham Wilson. Yes.

MS. MASON: Virginia Mason. Yes.

DR. MORTIMER: Joanne Mortimer. Yes.

DR. HARRINGTON: Dave Harrington. Yes.

DR. MORTIMER: If I could have the noes raise their hand, announce their name.

Dr. Perry?

DR. PERRY: No. Perry. No.

DR. RICHARDSON: Richardson. No.

DR. LINK: Link. No.

DR. REDMAN: Redman. No.

DR. MURGO: Murgo. No.

DR. MORTIMER: Any abstentions?

[No response.]

DR. MORTIMER: There are 9 yeses and 5 noes.

The next topic is the level of hemoglobin. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of red call transfusions, however, not all patients with anemia require a red cell transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be initiated.

Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.

Rick, can you give us guidance here?

DR. PAZDUR: When we wrote this question--so on

the table which was provided by the company was a hemoglobin less than or equal to 10, I believe. Conservative initiation for transfusion avoidance. Initiation of ESAs at a hemoglobin less than or equal to 10.

Do people want to discuss that and would they recommend something lower or higher?

DR. MORTIMER: Dr. Richardson.

DR. RICHARDSON: I think it comes down to the question of in an asymptomatic patient, what is the indication for doing a transfusion. If you are trying to avoid transfusion, then, the question is okay, where is your threshold for transfusion. That would be your potential threshold for starting an ESA.

But I think I would agree with Dr. Stroncek, from his comments this morning, that in otherwise asymptomatic patients without comorbidities, that the hemoglobin level of 8, which is the one that seems to be widely applied these days is a very relevant one.

DR. MORTIMER: Dr. Link.

DR. LINK: I just have one comment. Maybe it's a question. If you use a threshold of 8, or whatever number it is, you are going to give a transfusion when you hit that

thing, you know, you have got to pull the trigger right then. So in order for an ESA to work, since I don't have that much experience with it, how much in advance do you have to star the erythropoietin in order to avoid getting a transfusion, how much lead time do you need?

DR. MORTIMER: Does the sponsor want to make a comment?

DR. BOWERS: Because of the delayed pharmacodynamic effect, you would need to start between 2 and 4 weeks before you will see a meaningful increase in hemoglobin.

DR. LINK: So I assume correctly that if you wait until you get to the trigger point, you have lost the opportunity then to give an ESA, to prevent the transfusion, if you will--

DR. BOWERS: That would be correct.

DR. LINK: So you have got to figure out how many grams people are dropping per week and then sort of multiply by 4.

DR. MORTIMER: Dr. Wilson.

DR. WILSON: I think the end points have been in these trials, if I understand them, as to whether or not you

were able to avoid any transfusion. But certainly if you were to start the EPO at a lower level, you may buy yourself a single transfusion if you are in this window.

But, over the course of multiple cycles, you, in fact, may be able to reduce the absolute number. And that is what I had mentioned before, that these studies haven't looked at the actual reduction in the number of transfusions, just whether or not a single patient had one or didn't.

I would say that there is emerging evidence that the more EPO you give, the more risk there is to the patient. And it has already been noted that 7 to 8 is really our threshold these days whereas it used to be higher back in the 1990s.

I would say that you could certainly go as low as 8 to 9 and, even if you did buy yourself a single transfusion, if the drug worked, presumably you would be reducing subsequent ones.

DR. REDMAN: I would tell you I think less than or equal to 10, it gives the physician the ability to manage the patient who is watching on the second cycle the hemoglobin was--the initial is 14, second cycle it's 12,

third cycle it's 10, 9.9, and then goes, well, we will have to wait for a couple more cycles until you do drop down to 8, when you know where that patient is going.

I mean chemotherapy-induced anemia is not you have got one cycle of therapy and you went from 14 down to 7 grams of hemoglobin, that is not chemotherapy-induced anemia, that is called hemorrhage.

I think you have to allow the leniency of the physician managing the patient to have some leeway in the decisions and set guidelines. I think if you set 8 and then CMS comes up and say you can't use EPO agent until somebody has a hemoglobin of 8, you are taking away that window when a physician can intercede in the benefit of that patient.

DR. MORTIMER: Dr. Murgo.

DR. MURGO: Actually, that was my concern is that I think in regards to this question, I think this has to be really--it depends on the individual patient, and here is where physician judgment has to come in.

I think having this cushion I think would be very important. I mean we see many patients who run around with hemoglobins of 8 without any problem and where you would feel comfortable just to continue to do that.

But I think there might be some patients where even with hemoglobin of 10, where you might have some concern below 10, like 9, I think it has to be really physician's judgment on this.

DR. MORTIMER: I agree. Ms. Schiff.

MS. SCHIFF: I think one of the problems is that you also have to look at the risks of treating people who might never go that low. They might not need a transfusion and they might not need any ESA. The more you raise it, the more you are subjecting people to risks.

A lot of people stabilize at 10 or 11 or 9 and they don't really need anything. So, you know, in a way that is why you need the evidence is to figure out which is better, whether to treat everyone at 10 or 11 so that they don't ever need a transfusion, or to treat the fewer people who need the transfusion.

So that depends on how much risk there really is with ESAs, which we don't know.

DR. MORTIMER: Dr. Richardson.

DR. RICHARDSON: I think the question is a difficult one mainly because you are talking about this hypothetical patient that doesn't exist. There are very few

maritime runners that end up getting chemotherapy these days.

So most of the patients that I see, in fact, are older folks who not only have one comorbid condition in addition to their cancer, they have got 10 comorbid conditions. So your threshold for transfusing that patient, in fact, is going to be a lot different than if you have got somebody who is asymptomatic without these comorbidities.

DR. PAZDUR: We were totally aware of that. That is why we put that caveat in, to try to take those other clinical parameters out. But we appreciate your comment on that.

DR. MORTIMER: Dr. Redman.

DR. REDMAN: That was exactly my point. The physician treating the patient is the best one within certain guidelines to make a decision. I have patients with 9 grams of hemoglobin and, if I transfused them to 15, they still wouldn't be doing anything different than what they are doing now.

We can make that decision as a treating physician. You just can't blanketly say 8 grams we can start but, if you are between 8 and 10, you know, you can't get this

agent.

DR. MORTIMER: Dr. Wilson.

DR. WILSON: I think we have to go back and look at the data. The discussion sounds as though most patients who are to get this drug at a hemoglobin of 10 are going to, in fact, benefit from it. In fact, we know from the data that only 1 in 3 benefits from it.

So, right off the bat we know a hemoglobin of 10 is not a very accurate number. I routinely treat patients with chemotherapy and, toward the end of their multiple cycles, they can in fact cycle down around 8. But then within the week off they can come back up again. In fact, that is probably more the pattern we see than somebody who continues to sail down.

I think the reason for even considering a lower hemoglobin number is because, number one, we are not capturing very well those patients who really benefit and, number two, because there is a worrisome association between the amount of EPO given and toxicity.

DR. MORTIMER: Dr. Perry.

DR. PERRY: I would hate to think that a committee of 14 people, some of whom are actively treating patients,

some who are not, could take a hypothetical patient and therefore promulgate a regulation that affects millions of people. I think this is not good science. I think this is good talk in the bar, but I don't think it is the way you set levels.

If you look at the levels that have been done, where patients get the most improvement in their ability to carry out their activities and their quality of life, it is usually between 10 and 11. So I would prefer a level of 10 if we have to decide an arbitrary number and I so move.

DR. MORTIMER: Okay. So I think out on the table is that assuming the patient is asymptomatic and has no comorbid conditions--I am going to make this a yes or no--that the hemoglobin level at which initiations--

DR. PAZDUR: I don't think we wanted this a voting question. We just wanted people's comments on it.

DR. MORTIMER: Comments, okay.

Ms. Mason.

MS. MASON: Just a point of clarification. The word there is asymptomatic. And I would hope we are not treating anybody who is asymptomatic if they don't really need it.

DR. MORTIMER: Shall we keep going with the last question or should we take a break? Keep going, okay.

No. 3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them. So this is a vote question.

An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments.

The question is: Should the FDA require the implementation of an informed consent patient agreement for the treatment of chemotherapy-induced anemia?

DR. PAZDUR: Could I just add a clarification here to both of these questions? Here again, there are a lot of

logistic situations here and issues of how this would be handled. What we are really looking for is just the principle rather than how specifically it is going to get to the patient, who signs it, da-da-da-da.

We are just really interested in a principal issue in both of these questions, the last two questions, whether given the nature of the risk here, should there be a very adequate discussion with the patient that is documented, that would be documented to a degree that both the physician and the patient signs an informed consent. The specifics of how it would be handled we would try to work out and is really an issue that really is outside the purview of the committee.

DR. MORTIMER: Dr. Link.

DR. LINK: So just a question. Do you envision sort of like the Gann Act in California, that you have to give the patient an information booklet, get a consent, that kind of thing, so that they are really fully informed. So it actually would make giving this versus a transfusion kind of you would be totally informed about the risks of both?

DR. MORTIMER: Ms. Schiff.

MS. SCHIFF: Yes. I was on the Medication Guide

Committee and there were two things that I think are wrong. One is that you give the patient or the informed consent at the time that they have to decide whether they want the shot or not. It is very hard for someone to make a decision then and they don't have any time to do any of their own research or consult with other people, number one.

Number two, actually, the guide does not go into the risks and benefits of transfusions. It just assumes at this point at least, what I know of it, that treating anemia is in and of itself a good thing and nothing about being asymptomatic versus symptomatic.

DR. MORTIMER: Dr. Perry.

DR. PERRY: When we treat people with chemotherapy for whatever condition, there are a lot of side effects engendered, there are a lot of risks. We kill people with febrile and neutropenia episodes all the time, hopefully always inadvertently.

If we have to put through a separate process for every drug we give the patient, next, we are going to be going through a long list of declarations, to say if I give you Decadron as an anti-emetic to keep you from getting nauseated and vomiting and preventing electrolyte loss, I am

going to ruin your diabetic control, which possibly will lead you to nephropathy, retinopathy, blindness, et cetera.

We are approaching the point I think of silliness in trying to overmandate things. I think the physician has incumbent upon himself or herself the responsibility to talk over with the patient the side effects of everything they give and let the patient get involved in the decisionmaking.

Mandating another signature for the patient and the physician is increasing work time and not improving the product.

DR. MORTIMER: But you would agree that adequate patient education, I mean we heard at our public hearing, a woman whose husband received erythropoietin, she had no idea why he was still getting it and is now disgruntled about it.

DR. PERRY: Absolutely. That doesn't seem to me to be the standard of care in anybody's practice and I would think that that was the exception rather than the rule.

That is certainly not the way--what I know of your practice and mine is the way we do it. But I don't think it is going to help your patients any having them take the time out to sign a form particularly if it's another 18-page form that they are going to read before they make a decision.

They are going to sign it and say, whatever you want, Doc, I will sign it, and get on from there. So they are either not going to be informed or they are not going to get the drug.

DR. MORTIMER: Ms. Schiff.

MS. SCHIFF: From talking to women, I have learned that it is mainly the nurse who makes the decisions and is just a numbers question.

DR. MORTIMER: Dr. Wilson.

DR. WILSON: If I heard Dr. Pazdur correctly, this vote is not necessarily on whether or not there will be a signed informed consent but, if I hear him correctly, it is about some kind of criteria that the patient be informed of the risks.

I think we have already heard that there are risks and, Dr. Perry, you have also stated that you always inform your patients of risks. So I would be concerned that to vote no on this would be to say that this does not raise to the level of explaining risks to the patients for this drug, the same types of risks that we explain for all of the various therapies we give to our patients and from a cytotoxic point of view.

DR. PERRY: Line 3 said signatures would be required.

DR. WILSON: Right, but I thought Dr. Pazdur had amended that and said this was not supposed to be specifically written informed consent.

DR. PAZDUR: This is about a written.

DR. WILSON: This is a written informed consent, okay.

DR. MORTIMER: Other comments?

Okay. Are we ready to take a vote on this? So this is a question about should the FDA require the implementation of an informed consent/patient agreement for the treatment of chemotherapy-induced anemia.

All the yeses, if you could raise your hands.

[Show of hands.]

We will start with Dr. Kramer.

DR. KRAMER: Dr. Kramer. Yes.

MS. SCHIFF: Helen Schiff. Yes.

DR. LESAR: Tim Lesar. Yes.

DR. WILSON: Wyndham Wilson. Yes.

MS. MASON: Virginia Mason. Yes.

DR. MORTIMER: Joanne Mortimer. Yes.

DR. LINK: Michael Line. Yes.

DR. DAY: Ruth Day. Yes.

DR. MORTIMER: Could I have the noes, please, raise your hand. We will start with Dr. Perry.

DR. PERRY: No.

DR. MORTIMER: Dr. Perry. No.

DR. RICHARDSON: Ron Richardson. No.

DR. REDMAN: Redman. No.

DR. MURGO: Murgo. No.

DR. STRONCEK: Stroncek. No.

DR. MORTIMER: Anyone abstaining?

DR. HARRINGTON: Harrington. Abstain.

DR. MORTIMER: 8 yes, 5 no, 1 abstention.

The last question that we are posed. There are examples of restricted distribution programs including STEPS for thalidomide, RevAssist for lenalidomide, iPLEDGE for isotretinoin. Restricted distribution systems link product access to planned safe and effective use.

These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use.

Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations, such as hemoglobin, chemotherapy type and malignant diagnosis.

Should the FDA mandate a restricted distribution system for oncology patients receiving ESAs?

I know Dr. Perry has a comment.

DR. PERRY: I think this is silly, period.

DR. MORTIMER: Dr. Link.

DR. LINK: We heard sort of a first steps of this from the sponsors. But they also pointed out some of the difficulties in this as compared to some of these others, both in terms of the known risks. We heard about this yesterday, as well, actually, in the same context.

I just want to get some idea from you folks, you know, you don't want us to talk about how it is going to be rolled out, but do you really think it is doable?

DR. PAZDUR: Well, it poses some difficulties. Here again, we want this discussion, it is not that we are saying we are doing it. That is why we are asking the question here.

Obviously, there are two indications or several

indications for this which poses a problem. Usually, a restricted distribution revolves around a drug and not an indication; hence, it involves a difficulty which may or may not be surmountable.

The question, here again the philosophy, the issue on the table is do you think that a type of restricted distribution would help ensure the safety of this drug and the safe use, and that the patient has adequate information again about the potential uses here.

The specifics of how this is implemented, whether it be what is being suggested by the company, we didn't have the company's proposal when we wrote this question, or even a more restrictive program, we could deal with that after the meeting.

Here again, we are more interested in would some type of restriction be of benefit to patients to ensure safe use of the drug.

DR. MORTIMER: Dr. Murgo.

DR. MURGO: Just for clarification, Rick, the company did propose some risk minimization plan, which included things along this line.

Are we voting for something--

DR. PAZDUR: Here again, I want to make this real clear. We are not voting on any specific plan here, just in general, looking at risk minimization programs, do you feel that given the uncertainty in the safety of this drug, would this be of assistance to patients in assuring safe use.

Here again, a more philosophical question rather than getting down into the specifics of the program, it can't be ironed out here in the next 10 to 15 minutes here. So would this, in general, help you. Don't read that much into this question.

DR. THOMAS: Adrian Thomas on behalf of the sponsors. The philosophy is important because what you talked about was an individual patient level, restricted access program. I think that is very important.

The sponsors put forward a controlled distribution to sites for providers. We will be asking the numerous numbers of patients outside the oncology indication to prove at the retail pharmacy level and therefore their prescribers in nephrology to prove that they are not an oncology patient.

Given the nature of the way the Committee has recommended the indication be changed, that is a significant

burden being applied to a different indication.

DR. MORTIMER: Dr. Wilson.

DR. WILSON: I think that if the FDA narrows in whatever judgment they have changes the indication somewhat for this and that there is an informed consent process, I think one could argue that to restrict access in the manner that they have done for Revlimid would probably be overly onerous for a drug like this.

There are many drugs that we give where there are many toxicities that could be accrued if, in fact, they were given wrong, and that is one reason why we all go to medical school, because we learn how to give these drugs correctly.

The impact of Revlimid, et cetera, are all on birth defects. We understand that those are just extremely high risk. So I would argue that having a mandated restriction ala Revlimid would not be indicated with a drug like this.

DR. MORTIMER: Dr. Richardson.

DR. RICHARDSON: I think I would like to bring back something Dr. Perry mentioned this morning and that is this question of physician incentives to use these drugs. I think if the sponsors are sincere about safe and effective

use, they ought to address this issue of reducing physician incentives so there isn't that temptation to use this drug because you have got that rebate rolling back to you at the end of the year.

I think these decisions need to be made strictly on the basis of evidence at hand rather than some sort of financial interest.

DR. MORTIMER: Dr. Lesar.

DR. LESAR: I am trying to run a drug distribution system at our hospital. I know this is probably problematic. I guess the word "restriction" is I guess perhaps maybe the wrong word. I would be more in favor of a controlled or monitorable system would be much more palatable and probably more doable.

DR. MORTIMER: Dr. Perry.

DR. PERRY: I will vote in favor of this, at the same time we put a restriction on digoxin, which probably kills more people in the United States every year than these drugs.

DR. MORTIMER: Other comments? Dr. Pazdur, tell me what the question is here that we need to vote on or not?

DR. PAZDUR: As written, should the FDA mandate a

restricted distribution program for oncology patients receiving ESAs? Yes or no.

DR. MORTIMER: If we could have people raise their hands for yeses.

DR. RICHARDSON: Philosophical only.

DR. MORTIMER: Yes. Ms. Schiff, do you want to say your name and your vote?

MS. SCHIFF: Helen Schiff. Yes.

DR. MORTIMER: Any other yeses?

[No response.]

DR. MORTIMER: The noes? Let's start with Dr. Harrington.

DR. HARRINGTON: Harrington. No.

DR. PERRY: Perry. No.

DR. RICHARDSON: Richardson. No.

DR. MORTIMER: Mortimer. No.

DR. REDMAN: Redman. No.

DR. WILSON: Wilson. No.

DR. LESAR: Lesar. No.

DR. MURGO: Murgo. No.

DR. MORTIMER: Abstention?

Dr. Day, I am sorry, I missed your side of the

table.

DR. DAY: Ruth Day. No.

DR. STRONCEK: Stroncek. No.

DR. KRAMER: Kramer. Abstention.

DR. LINK: Link. Abstention.

DR. MORTIMER: I think we have accomplished all we planned to accomplish.

The vote is 1 yes, 10 noes, and 2 abstentions.

I can only hope for our patients' sake that physicians feel as strongly about anti-emetics and pain management as they do about anemia control.

We are now going to adjourn. Thank you.

[Meeting adjourned at 3:00 p.m.]