U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

- - -

THURSDAY, MAY 10, 2007

8:00 A.M. to 4:13 P.M.

- - -

SILVER SPRING HILTON

8727 COLESVILLE ROAD

MARYLAND BALLROOM

SILVER SPRING, MARYLAND

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P-R-O-C-E-E-D-I-N-G-S

(8:30 A.M.)

CALL TO ORDER

CHAIRPERSON ECKHARDT: I would like to call this meeting to order. As you know, this ODAC Committee meeting was convened to discuss the updated risk information on erythropoeisis stimulating agents for the indication of cancer. I would like to note that the discussions today will purely revolve around the oncology indication. I think to start out what we would like to do is to go around the room and introduce the Committee, starting with Dr. Tony Murgo.

INTRODUCTION OF THE COMMITTEE:

DR. MURGO: I'm Tony Murgo. I'm with the National Cancer Institute and I am the NIH representative to the FDA Drug Safety Oversight Board.

DR. KROOK: I am Jim Krook from the Duluth CCOP. I am a former ODAC member of four years, somewhere in the nineties. I'm getting old, so I don't remember what years. Some of the people are back, so I'm back.

DR. REDMAN: Bruce Redman, University of

Michigan, Comprehensive Cancer Center.

DR. MARTINO: Silvana Martino, medical oncology from The Angeles Clinic in Santa Monica, California.

DR. ALLEGRA: I am Carmen Allegra, chief of Hem/Onc and the University of Florida.

DR. LINK: I am Michael Link from Stanford.

MS. HAYLOCK: Pam Haylock, oncology nurse and consumer representative.

DR. HARRINGTON: David Harrington, statistician, Dana-Farber Cancer Institute.

DR. DOROSHOW: Director of the Division of Cancer Treatment and Diagnosis, NCI.

DR. MORTIMER: Joanne Mortimer, medical director, University of California at San Diego.

DR. CLIFFORD: Joanna Clifford, Designated Federal Official to the ODAC.

CHAIRPERSON ECKHARDT: Gail Eckhardt, medical oncologist and head of the division, University of Colorado.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. PERRY: Michael Perry, medical oncology, University of Missouri, Ellis Fischel Cancer Center.

MS. SCHIFF: Helen Schiff, breast cancer survivor, patient rep. I am a member of SHARE, a breast cancer organization in New York City. I am a 17-year survivor.

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

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University of Chicago, Cardinal Bernadin Cancer Center.

DR. ROTHMAN: Mark Rothman, statistician, FDA.

DR. JUNEGA: Vinni Junega, medical officer, FDA.

DR. KEEGAN: Trish Keegan, division director, FDA.

DR. PAZDUR: Richard Pazdur, office director, FDA.

CHAIRPERSON ECKHARDT: All right. Next I would like to follow, since we have a very full day and a lot of committee discussion and a lot of participants out in the audience, I would like to go over a few

housekeeping rules. With regards to the committee, so that we can keep people on time and give each time to speak, if you can please catch Joanna's eye, then she will put you on the list so that we can proceed with discussion in order.

I think everybody knows about the mikes. Just ensure that when you are speaking, you press, and when you are done, please turn the mike off. Then, I think in terms of the audience, if everybody could make sure to turn their cell phones off, that would limit some interruptions.

I think what I would like to do next is just show, go through a quick overview of the agenda which after this Joanna will read the "Conflict of Interest Statement" followed by some remarks by Dr. Pazdur. The presentations this morning will start with Amgen followed by the risks and indications presented by Dr. Stroncek.

We will then follow with the FDA presentation, and this will be followed by a break, with about an hour of the open public hearing, followed by lunch. Really, in the afternoon of this meeting, then, we will spend

time reviewing the questions to the Committee with quite a bit of discussion, with adjournment at 4:00 p.m.

What I would like to do next is turn it over to Joanna Clifford to go over the "Conflict of Interest."

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting based on the submitted agenda and all financial interests reported by the committee participants. It has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

The members and consultants were screened for their personal and imputed financial interests with respect to the products and firms that could be affected by this discussion. Based on the agenda for this issue and the financial interests reported, no conflict of interest waivers were granted a connection with this topic.

We would like to remind members and

consultants, that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to an exclude themselves from such an involvement. Their exclusion will be noted for the record.

In the interest of fairness, FDA encourages all other participants to advise the committee of financial relationships that they may have with any firm whose product they wish to comment upon.

Thank you.

CHAIRPERSON ECKHARDT: Okay. Next, we will follow with opening statements by Dr. Pazdur.

OPENING STATEMENT

(PowerPoint™ presentation in progress.)

DR. PAZDUR: Thank you. Today, we will be discussing the ESAs or erythropoeisis-stimulating agents and their use in the oncology setting. These agents include epoetin alfa, Procrit®, Epogen®, and darbepoetin alfa or Aranesp®. Although there are other indications for which ESAs are approved, particularly in the anemia-related to chronic renal failure, the focus of this

meeting will be on their use in oncology.

There will be at additional meeting in the early fall of the Cardiovascular Renal Advisory Committee to discuss the use of ESAs in patients with chronic renal failure including those on dialysis that ESAs are indicated for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the facts of concomitantly administered chemotherapy. ESAs are not indicated for the treatment of anemia in cancer patients due to other factors. The ESAs are indicated to decrease the number of patients who receive red-cell transfusions.

Please note that neither the indication nor product labeling recommends the use of ESAs for the treatment of fatigue, anemia-related symptoms or improvement in health-related quality of life for cancer patients.

Although clinical trials have been performed, whose primary objective has been to demonstrate improved overall survival, studies to date have failed to demonstrate improved overall survival or improved tumor control with the use of ESAs. The ESAs are supportive-

care drugs, and hence their risk/benefit relationship must be judged in the context of supportive-care products rather than antineoplastic agents with known effects to improve survival, disease progression or, tumor response.

The FDA presentation will provide a discussion of the regulatory history and the description of key clinical trials that have identified new safety findings related to the use of ESAs. Many of these trials have been in off-label indications, for example, patients receiving only concomitant radiation therapy or using higher hemoglobin targets than recommended in product Labeling. Nevertheless, these studies point to important risks that include: increased thrombovascular events, decreased survival, and increased tumor promotion including decreased locoregional control and the possibility of decreased progression-free survival.

The use of ESAs in a risk/benefit analysis must be weighed against, number one, the decreasing risk of red-cell transfusions since their original approval for their oncology application in 1993; and, two, the emerging safety information which will be presented here

during this ODAC meeting.

The FDA will be discussing numerous trials conducted after the approval of ESAs. Many of these trials were enrolling patients when discussed at the May 2004 ODAC meeting were ESA safety and two were promotion were previously discussed. Please refer to the figure that is included with your questions that delineates these numerous trials.

Many of these trials were conducted outside of the United States. We do not have access to the data for some of these trials for review. This situation is different from the usual NDA pivotal studies that are presented here and ODAC where the FDA has access to the trials' primary data, conducts its own analysis, and is able to directly verify any conclusions derived from the primary data.

In March of 2007, the FDA revised product labeling to reflect emergence safety data from trials. This included a black-box morning description of studies with findings of tumor promotion or safety signals and other labeling changes. These will be discussed in detail during the. In light of the evolving

risk/benefit relationship of the ESAs we will be asking the committee questions regarding the continued use of these products. I would like you to keep in mind these questions as you listen to both the sponsor and the FDA presentations.

As previously stated, please note that ESAs are supportive-care medications and hence should have a different risk/benefit relationship than anti-tumor agents. Please also remember the considering these questions that the FDA indication for ESAs is to decrease the need for transfusion for patients receiving concomitant chemotherapy.

There are no data, again, included and product labeling showing that ESAs confer either an amelioration of symptoms of anemia, fatigue, or quality of life in the cancer indications. Completed studies have not demonstrated any survival advantage directly related to the use of ESAs. Our questions for your consideration, and especially consideration during these presentations, include the following.

First, in light of our recent actions should further marketing authorization of ESAs for this

indication be contingent upon further restrictions and product labeling and/or the conduct of additional trials?

Secondly, in light of the decreased survival signals observed in trials that involve homogeneous types of tumors such as breast cancer, head and neck cancer, and non-small-cell lung cancer, should product labeling specifically state that ESAs are not indicated for use in specific tumor types studied in trials that showed adverse safety signals or evidence of tumor promotion? These restrictions would apply until adequate trials are completed and satisfactorily reviewed by the FDA.

Third, should product labeling define a specific hemoglobin level for the initiation of an ESA in cancer patients, and what should that level be? We draw your attention to the current red-cell transfusion practices that generally administer red-cell transfusions if hemoglobin are less than 8 grams and are rarely given to asymptomatic patients with hemoglobins greater than 10.

Four, the current labeling states that the

dose of ESAs should be titrated for each patient to achieve and maintain the lowest hemoglobin levels sufficient to avoid the need for transfusion and should not exceed 12 grams per deciliter. Should a lower level of hemoglobin, for example, 9 or 10, be used to trigger dose modification or suspension of dosing.

Five, the Agency is concerned that ESA use is not reevaluated with changes in chemotherapy regimens, some that may not have the same degree of myelosuppression as the original chemotherapy regimen that initiated the use of these products. Hence, should product labeling recommend discontinuation of the ESA following completion of chemotherapy regimen and reevaluation of the degree of anemia and the need for and ESA with subsequent chemotherapy regimens.

Six, we ask your advice regarding how more clearly to communicate to patients and healthcare providers that ESAs are indicated when the anemia is due to concomitant chemotherapy and should not be used for the general treatment of anemia in cancer patients. This distinction is especially important since a study examining the treatment of anemia of cancer in patients

not receiving concomitant chemotherapy showed a decreased survival in those receiving and ESA.

Finally, we ask your assistance is suggesting additional trials to further assess the effects of ESAs on tumor promotion, survival, and thrombotic events. In the 2004 ODAC meeting, the ODAC provided suggestions for trials and these suggestions will be reviewed. I would like to underscore that our discussion today focuses on the cancer indication for ESAs as I previously stated. A separate discussion, in Advisory Committee, will be held to discuss the unique challenges encountered in the use of ESAs for the treatment of anemia in patients with renal failure.

Thank you.

CHAIRPERSON ECKHARDT: Thank you, Dr. Pazdur.

We will move now on into the presentations. I would like to remind the Committee that questions will be taken after lunch. We will get started with the sponsor presentation, which is Dr. Roger Perlmutter, who is the initial speaker for the Amgen introduction.

SPONSOR PRESENTATION: AMGEN, INC.

INTRODUCTION

DR. PERLMUTTER: Good morning. Dr. Eckhardt and members of the ODAC Panel, I would like to begin by thanking all of you for coming this morning, and expressing my gratitude to you for your deliberations. Speaking as a former professor of medicine and biochemistry and chairman of the Department of Immunology at the University of Washington and having participated in a large number of these kinds of panels in the Nation's Capital, I know how challenging this can be. We at Amgen are grateful for your efforts to help us refine our thinking about erythropoeisis-stimulating agents.

I would like to begin by providing you with a road map of what we are going to talk about this morning. I will begin by introducing the topics. We have as the guest, Dr. Jeffrey Crawford, the George Barth Geller Professor for Research in Cancer, chief of medical oncology at Duke University to give a clinical perspective on ESAs; then Dr. Roy Baynes, who is vice president of clinical development in oncology will speak about the benefit/risk of ESAs from our perspective; and he will be followed by Dr. Alex Zukiwski from Johnson &

Johnson PRD, who is vice president and head of clinical development oncology there, then I will summarize.

I had mentioned that Dr. Crawford is a guest. We have a number of guests that we have brought with us to assist in answering questions that you might have.

In addition to Dr. Crawford, we have Dr. John Glaspy, who is the Sanders Endowed Chair in Cancer Research at the University of California Los Angeles; Dr. Stefan Constantinescu of the Ludwig Institute for Cancer Research and an expert on epoetin receptors and epoetin signaling.

We have Dr. Gary Koch from the Department of Biostatistics, University of North Carolina, and Dr. Clive Taylor who is the chair of the Department of Pathology and of Laboratory Medicine and senior associate dean of the Kech School of Medicine; University of Southern California.

Finally, we have Dr. Ingram Olkin who is from the Department of Statistics at Stanford University. All of these individuals will be available to you to help you in your deliberations.

Now, first let me say how proud I am to be

here this morning representing Amgen. Only a few of my colleagues can make it this morning with me here, but we have scientists, clinicians, and professional representatives across the country who come to work each day with one thing in mind, and that is, using science to improve the lives of patients throughout the United States and in fact worldwide.

At Amgen patient safety is our highest priority. We have consistently performed high-quality studies to evaluate the benefit/risk profile of the erythropoeisis-stimulating agents. Our data have been communicated promptly to regulatory agencies worldwide, and we remain committed to the thorough and thoughtful evaluation of these very important drugs.

I would like to put you in the context of all of the research that's gone on over a number of years on ESAs. It is worthwhile remembering that erythropoietin was originally made practical as a therapeutic agent through the efforts of a single scientist, Fu-Kuen Lin, who cloned the erythropoietin gene back in 1983, and that provided the basis for the subsequent development of a manufacturing scheme and for clinical trials that

ultimately permitted epoetin alfa to be approved in the setting of chronic renal insufficiency in 1989.

Subsequent efforts by J&JPRD permitted the approval of epoetin alpha in the setting of chemotherapy-induced anemia and then some years later darbepoetin alpha, which is a hyperglycosylated version of epoetin and has a longer half-life was studied, approved in the setting of chronic renal failure, and then subsequently approved in the setting of chemotherapy-induced anemia.

Now, during these many, many years, the science underlying erythropoeitic-stimulating agents has also advanced. I want to tell you something about the evolution of this science. Over a period of decades, frankly, preclinical data have been assembled that support the view that improved oxygenation could increase tumor responses.

This is understandable since many cytotxic agents take advantage of the fact that they interrupt processes that can be affected by stress responses in tumors, and those stress responses which could block the effects of chemotherapy and radiotherapy can be

ameliorated in some sense by oxygenation. A body of evidence has emerged that says that with improved oxygenation, which sometimes results from increasing hemoglobin, two responses in preclinical settings actually increase.

Over the years, several clinical studies yielded results that suggested that improvements in patients' survival actually occurred with the SAUs. And so when I joined Amgen back in 2001, the question was, "Gee, was it the case that my improving hemoglobin levels we could actually improve tumor responses and improve survival?"

In this climate, clinical studies evolved beyond the optimal doses that Dr. Pazdur noted to avoid transfusion, which was the initial objective regulatory endpoint, but rather to explore potential therapeutic benefits. Now, it is important to note in this context that those who were studying ESAs obviously would not have pursued such studies if they believed that these epoetins were actually stimulating tumor growth.

It is fair to say that over the last few years additional data have been adduced that make plain that

epoetins do not promote tumor progression, and certainly that the erythropoietin receptor does not have a role in tumor progression. I want to outline those things for you, because I think it's important to keep them in context.

The erythropoietin receptor gene is not an oncogene. It is not amplified in tumors. It is not a site of insertional mutagenesis. It is not found mutated in tumors. It does not behave as an oncogene. Erythropoietin receptor mRNA levels are detectible in many tissues. They are not elevated in tumor cell lines or in tumor versus non-tumor tissues. Tumor cell lines when studied show weak or no detectible erythropoietin binding and no detectible erythropoietin responses in virtually all cases.

In most nonclinical models, there are improved outcomes when erythropoietin is used in tumor settings. I'm referring here in particular to tumor xenograft models. There are more than 20 independent studies that have been done, and tumor progression is not observed in those settings.

Surface expression of the EPO receptor has

been extremely difficult to study and was one of the topics that was discussed at the 2004 ODAC. At this point specific, sensitive anti-erythropoietin receptor antibodies do not exist. The antibodies that have been used in immunohistic chemistry experiments to detect the erythropoietin receptor are polyclonal, and they are also nonspecific; they cross react with others cellular proteins. We will have an opportunity to discuss some of these data, if you wish.

Why are we here? We are here in part to review new clinical data that have emerged since ODAC in 2004. ODAC in 2004 was convened in response to results from two studies, the so-called BEST study published by Leyland-Jones and the ENHANCED study published by DAHANCA, the BEST study looking at breast cancer patients and the ENHANCED study looking at patients with head and neck cancer.

Since that time, 36 randomized-controlled ESA studies in oncology have been completed, for a total body of evidence comprising 55 studies. Those are broken down in terms of the time of appearance at the bottom relative to the original Cochrane meta-analysis

which accrued data from '85 to 2001.

In these studies, three of them, all of which studied doses or populations beyond the approved labels, and we will discuss each of these, have raised additional concerns. It is these concerns that we would like you to focus on, because this is the dialogue that we want to engage in. We want to consider the totality of the evidence and try to understand what is best for patients, that's why we're here.

Now, Amgen has diligently pursued a set of Pharmacovigilance studies. In 2004, at the time of the ODAC review, it was noted that there were five ongoing studies which would yield data that were relevant to the kinds of questions that we are considering here today.

It was important that the studies were ongoing since they were more likely to yield data, then, in a reasonable time frame that we could consider. Indeed, those studies have gone forward. Three thousand five hundred patients have been enrolled in such studies, and we will have an opportunity to tell you about progress in those Pharmacovigilance trials, which became a specific post-marketing commitment in 2006.

I wish to make the following statements. This is our view with respect to the benefit/risk profile of ESAs. It is a containing exploration. The benefits of ESAs in the indication of chemotherapy-induced anemia are a substantial and unambiguous. The totality of data supports the view that ESAs have no demonstrable of the overall survival or tumor progression when used according to the FDA-approved label.

In addition, recent label updates completed in March provide prominent warning of important safety concerns. It is unambiguous there are safety concerns, but these are well known to the oncology community.

Amgen and J&JPRD are both committed to the continued assessment of benefits and risks of ESA therapy. In this context, I wish to say the Amgen and J&J and some of you realize our competitors in the marketplace, but with respect to safety issues, to the extent allowed the securities laws, we have agreed that we work together in order to understand what the safety profile of these molecules is, so this is an integrated presentation.

It is important to stress that J&JPRD has

evaluated their own data and come to their own conclusions, and they will present their conclusions just as we will present ours.

Let me return now to the agenda. I have introduced the topics, and I'm now going to call on Dr. Jeffrey Crawford to provide a clinical perspective on erythropoietic-stimulating agents.

Thank you.

CLINICAL PERSPECTIVES ON ESAs

DR. CRAWFORD: Thank you.

(PowerPoint presentation is in progress.)

DR. CRAWFORD: Dr. Eckhardt, panel members, and guests, it is really a privilege for me to speak to you today. When I was asked to write this editorial for the "JCO" I didn't realize how timely or accurate this title would become.

I have had a longstanding interest in this area, both in my clinical research and in my practice with my patients. Like you I really want to understand the safety issues that have been raised by the recent trials with darbepoetin alfa and epoetin alfa. What I would like to do first is focus on the well-established

clinical benefits for our patients.

I think we have all seen the impact of the boxed warning on our clinical practices already. While safety first has to be our mantra, it is clear we have had some patients who are benefitting from these agents who are currently no longer receiving them.

I think any discussion around risk, any deliberations, really need to take into account the benefits of these agents for our patients and have those benefits also taken in the context of the risk and benefit of alternative strategies.

I think at the end of the what we would like to see is a reaffirmation and preservation of the benefits of these treatments, the safe and effective therapies of ESAs for our patients as well as to preserve the role of the physician in clinical decision-making.

Let's turn to anemia in patients with cancer. We know that 90 percent of chemotherapy patients develop anemia, that anemia is associated with signs and symptoms that do decrease quality of life and overall health. Our strategy prior to ESAs were transfusions as

the main approach to management.

We know that in the absence of ESAs currently 40 to 60 percent of anemic patients require red-cell transfusions, and those transfusions still carry risks with them of volume overload, of infection, and transfusion reactions. We also know that the blood supply is both precious and tenuous, so we are taught as physicians to use blood sparingly and very cautiously.

Why is it that physicians transfuse anemic patients? Well, it is really from this complex of factors. It's the laboratory value; it is the signs and symptoms that patients; it is the impact those symptoms have on specific health-related quality of life indices; and in some way down on the day move some worlds then it is the judgment of the physician relative to the components of that anemia and the patient's unique medical needs, their comorbidities, their treatment course, and the chemotherapy they are undergoing.

Transfusion has been the quantifiable regulatory endpoint for ESA approval, but even in those registration trials physician judgment was preserved in deciding when patients should be transfused.

We see here very interesting data from five Phase 3 randomized trials of chemotherapy-induced anemia using darbepoetin alfa versus placebo. On the left-hand pie chart, we see the hemoglobin at time of transfusion; on the right-hand side, we see the reasons given for transfusion for over 2,000 separate transfusion episodes.

In these trials, it was recommended that patients receive a transfusion if their hemoglobin was less than eight. You see about a third of patients with hemoglobin less than eight were transfused, and that corresponds to that hemoglobin trigger.

What this is says is that two-thirds of patients were actually transfused above that level of hemoglobin and of eight, about ten percent above a hemoglobin of ten, and the majority of patients in this range of eight to ten, based on physician judgment which as they scored it was based on therapeutic and medically indicated reasons presumably related to the signs and symptoms of anemia that the patients had.

The other important thing is to recognize that the strategy of transfusion is different than the

strategy of ESAs in terms of what is achieved. Again, because of the caution around transfusions, we don't transfuse patients until they fall into this individualized patient trigger zone, and we also know that in the face of ongoing chemotherapy, that blood is short-lived and repetitive transfusion will be necessary. We just transfuse them to get them out of the danger zone, but really not up into the asymptomatic zone. By contrast when we use ESAs for the majority of patients, we are able to reverse the anemia and restore patients' hemoglobin into this asymptomatic zone. Note also that when we do this we don't achieve a steady-state hemoglobin. It fluctuates during the course of chemotherapy, and each cycle is only maintained by ongoing therapy in the face of chemotherapy.

We have been able to do this because we have to using the target hemoglobin which gives us a range of treatments that we can achieve, a range of numbers, but if we use a ceiling number, that will actually lower the peak levels and actually tend to depress that curve back into the symptomatic range, an important distinction between target hemoglobin and ceiling hemoglobin levels.

Now, there are additional considerations we need to think about for transfusions. There are well-recognized liabilities. We know that the risk for infection is less than it has been and the risk of bacterial and viral infections are less. What we don't know and what continues to be a source of anxiety for us is, what is the future of the blood supply? What is the risk for future as yet unforeseen bloodborne infectious agents? In addition, there's the risk of volume overload acute and delayed reactions, alloimmunization, iron overload, and a suggestion from the literature that transfusions can actually have an adverse impact on cancer outcomes.

Certainly, if there was a major change in policy, it would place a huge burden on the national blood supply. Lastly, I would say that we haven't really done a trial prospectively of transfusions the way we have done it with ESAs. We haven't maintained patients in a normal hemoglobin or an asymptomatic hemoglobin level to minimize signs and symptoms, and therefore we don't

truly know the overall risk and benefit of that strategy. What we do know is for ESAs that from a very large database that there is at least a 50 percent reduction in red-cell transfusions in a number of controlled trials, shown here with darbepoetin. Shown here is the number of patients needed to treat to avoid one patient being transfused, and that is a number of 4.9, less than 5, a very good number for this type of analysis. We also have this same kind of data from three large systematic reviews, from Cochrane, AHRQ, and the Ross database, all showing similar benefits of a 50 percent or more reduction in red-cell transfusions with ESA therapy.

Think what is most important perhaps is to understand the relationship between risk of transfusion from function of baseline hemoglobin and the benefits of the ESAs. Again, modeled from four Phase 3, placebo-controlled studies in CIA, we see the predictive probability of needing a transfusion as a function of baseline hemoglobin. We see the increased risk for the placebo group increasing as hemoglobin falls.

Above a hemoglobin of 12 the risk is relatively low for transfusion, but even as we fall and 12 and below, the risk is 30 percent for patience and the absence of a ESA. With the use of darbepoetin, there is a clinical benefit across the whole range of hemoglobin from higher levels to levels. But the lower we start, the higher the risk is for our patients of needing a transfusion.

What we can see here is that if we look at the 10 to 11 range for hemoglobin don't use an ESA and don't use an ESA, there is approximately a 40 to 55 percent probability that patients will need a transfusion. That probability can be reduced approximately in half, to less than 20 to 25 percent, if we start patients in that range. But if we wait until the patients are more anemic, that risk is only going to increase.

I think part of this has to be understood in the time-dependence of benefit of the ESAs. In data that we acquired looking at three large community-based trials and focused on the lung cancer subset, we can see despite different ways of giving epoetin alfa, we see a very robust improvement in hemoglobin of about 2 grams

over a couple of months of treatment. That is associated with a reduction in the probability of transfusion from 15 to 25 percent to actually 5 to 10 percent of patients receiving transfusions in later cycles of treatment.

Please note there is absolutely a very little benefit in the first month of treatment, again, speaking to the need of starting with the patient earlier than later to maximize clinical benefit.

I think it is also important to look at the published literature around quality of life impact. Shown here are five different studies that look at a particular health-related quality-of-life impact that relates to the signs and symptoms of anemia, and that is, fatigue.

Here it is measured by the FACT-F by David Cella, and you can see that in all five of these trials the FACT-F clearly favors epoetin alfa and darbepoetin. The point difference exceeds three points, which is the level of clinical significance for this test and correlates with a linear analog scale measurement.

It is important to look at one of the studies prospectively and get a sense for what happens with the

patient. This is the Littlewood trial. You can see with epoetin alfa there are substantial improvements in quality of life in three categories -- the FACT-G, fatigue, and anemia subscales -- as hemoglobin proves in that population.

By comparison, the placebo group showed no improvement in hemoglobin, and therefore actually had a decline in quality of life in the face of ongoing chemotherapy and the disease course.

One other way to look at this, and again returning to this data I was able to look at from the community-based, open-label trial of epoetin alfa, is this linear analog scale looking at overall quality of life and relating that to the hemoglobin at which time the patients reported those values. You can see even lower levels of hemoglobin 7 to 9, there is still very low or very little difference in the quality-of-life measurements.

Really, if we look at the range of 10 to 12, we see more substantial differences in the quality-of-life measures in these higher levels of hemoglobin. There is some continued improvement above a hemoglobin

of 12, but it is a lesser level. Most of the benefit seems to be hovering around this hemoglobin of 12.

What can we say in summary? The benefits of ESAs I think are clear to us in practice: our ability to reverse and prevent anemia and the recurrence of anemia in our patients is important; the signs and symptoms are alleviated; transfusions are reduced. In addition, there is selective quality-of-life improvements related to improving those signs and symptoms and avoiding transfusions.

By comparison, rescue transfusion is really suboptimal. It increases the time for our patients with symptomatic anemia;, exposes them to risks of volume overload, infection, and transfusion reactions; and it places stress on a finite blood supply.

The recent change has gone from a target hemoglobin of 12 to a ceiling hemoglobin has created operational challenging, clinical confusion, and patient access issue around whether a patient can or cannot receive an ESA on the day of their chemotherapy.

Given the potential impact of this meeting on individual patient management, I welcome a rigorous

evaluation of the scientific evidence today, and I look forward to our discussion.

Thank you.

With that I will introduce Dr. Baynes.

BENEFIT/RISK

(PowerPoint presentation in progress.)

DR. BAYNES: Good morning, Dr. Eckhardt and members of ODAC. In my talk today on the risk/benefit of ESAs, I would like to use the following general road map to go through the discussion.

Before starting this, however, I will draw your attention to the fact that a number of the data slides that I will be showing will differ subtly from the materials which were provided in the briefing book, and the reason for that is additional data have come to hand and we have updated datasets. I would encourage you not to try to look for exactly parity between these slides because, as I've said, they have changed slightly.

The road map I will follow is initially to look at combined patient-level analyses in CIA. In this particular analysis, I will include data from the

recently completed 145 Study, and this will lead me then into a discussion of the 145 Study, a study we believe is most important.

Thereafter, I will move to a combined study-level analysis of ESAs in the CIA indication. I will then provide some updates on the area of tumor progression, anemia of cancer, and high-hemoglobin targets in radiation therapy before ultimately moving on to an approach to risk management.

First, to talk about the combined patient-level analyses. On the right-hand side, we see the placebo-controlled, randomized studies conducted with darbepoetin that have been used to provide this dataset.

I will draw your attention to the fact that this is exactly what we do in a regulatory filing. We provide an integrated summary of safety. This is consistent with ICH principles, and so this in fact exactly that dataset that would be looked at. I draw your attention also to two studies here, the 161 Study, which was prominently featured in the FDA briefing book, and we would be happy to engage in a further discussion of those during the

question-and-answer session. I draw your attention also the new 145 data. We will spend some time on that after the individual patient-level analysis. This combined dataset encompasses 912 placebo-treated patients and 1,200 darbepoetin-treated patients. I should draw your attention to the fact that for the majority of these trials, the entry hemoglobin level was less than or equal to 11 grams per deciliter.

Other than for the 145 Study, which actually was a high-hemoglobin study and actually had entry criteria of less than or equal to 13, those withholding for the majority of these trials were at hemoglobins greater than 14, except for the 232 Study where the withhold was at greater than 13.

The combined analysis then was conducted of individual subject-level data, and the analyses were stratified by study protocol.

First, I will turn to the overall survival curve. This curve gives very significant reassurance. There you see that for the placebo and treated arms, the curves are superimposable. The hazard ratio for

survival is neutral at .97 in favor of darbepoetin with a confidence interval from .85 to 1.10.

Yet, we see the progression-free survival determined by the investigator, and, again, a reassuring curve of superimposable curves; hazard ratio, again neutral at .93 in favor of darbepoetin; with a confidence interval from .84 to 1.04.

Here we see the picture of the forest plot of the risk of adverse events. I draw your attention first to the survival and progression endpoints. You see that across these 912 placebo patients and 1,200 treated patients there is in fact neutrality. Indeed, the confidence intervals all span unity.

One area where there is a difference is in this area of thromboembolic and cardiovascular events. After the 2004 ODAC, a systematic approach consistent with the recommendations from that ODAC to the collection and analysis of adverse events was employed, particularly adverse events of interest in this particular category.

This is an overarching term, and it includes such things as myocardial infarction, cerebral vascular

accident, cardiac arrhythmias, and congestive cardiac failure. These are not shown on the graphic because they were all neutral.

The one area where indeed there is a difference is in the area of so-called embolism and thrombosis. The vast majority of these are deep-vein thrombosis. In fact, the hazard ratio for DVT is 1.57.

This is a number you will see, roughly, the same across many different datasets that I'm sure we will discuss today. This rate has been stable since these drugs were approved and has always been encapsulated in the label.

Now, as Mr. Perlmutter indicated, our colleagues at J&JPRD conducted the same patient level type analysis across their randomized placebo-controlled trials. These were independent trials conducted by independent investigators and analyzed independently of Amgen.

Most reassuringly here with the overall survival plot, we see an almost identical picture. In fact, the survival curves are superimposable. The hazard ratio is neutral at 1.02 with confidence

intervals from .93 to 1.13.

In terms of investigator-determined, progression-free survival, you see again a reassuring overlapping plot with a hazard ratio of .97 and confidence intervals from .85 to 1.11.

I should mention that those data included the BEST study, one of the studies you have heard already alluded to today and which was the subject of the 2004 ODAC.

Indeed, when in fact response criteria were applied to the study and in fact progression-free survival assessed, you will see that there is no difference in progression-free survival.

This was included in the 2005 "JCO" publication. The hazard ratio for progression-free survival was neutral at 1.00 with a confidence interval from .85 to 1.18.

Here you see the adverse-event hazard ratios on a forest plot, and it looks almost identical to the Amgen data. You see that in terms of the survival and progression endpoints, neutrality.

You see that there is this increased hazard

ratio, in this case 1.42 for TVEs, and again predominantly deep-vein thromboses. Importantly, when the sensitivity analysis is done looking just at correction of anemia, the same sort of pattern is observed.

Next, I would like to turn to the 145 Study. This study was the first of the so-called Amgen Pharmacovigilance studies, which was recognized by the 2004 ODAC and which became a post-marketing commitment in 2006.

Amgen has worked diligently to complete the study in a very rapid time. In fact, this is an important study for a number of reasons. It was initially designed to address the potential superiority of outcome of hyperoxygenation, so it is a high-hemoglobin study, but it turns out to actually be a very important safety study because a number of safety principles are addressed.

It is a study in a homogeneous population. It is a study at higher hemoglobins than in the label. If you were looking for a safety signal, it is very reasonable to stress that curve with a high-hemoglobin

approach.

Indeed, the highest doses of darbepoetin that have ever been used in a placebo-controlled trial were in fact employed. The dosing was 300 micrograms QE for four weeks; thereafter 300 Q3W, and patients who dropped below 11 were then redosed. The entry criteria in here was hemoglobin less than or equal to 13.

Patients were randomized to receive either six cycles of platin-based chemotherapy plus darbepoetin or six cycles of platin-based chemotherapy plus placebo that were then followed afterwards till death. This was an event-driven trial, so it was addressing specifically the survival issue. In fact, once the 496th death, which was on 22 February, data were rapidly collected, analyzed, and fully communicated to the FDA.

I should mention that the single-level patient data that I showed you has been submitted completely to the FDA. They have the pooled dataset, and indeed this complete primary dataset for the study has also been submitted, as well as a study report.

I should mention that in this trial rigorous scanning was applied and the response criteria you will

see culled out today and the progression free survival are in fact investigator researched, and a central review of the radiology is progressing at this time.

Now, turning to the overall survival curve, we see a most reassuring pattern here. We in fact see the curves are superimposed. There is no space between these curves. The hazard ratio for survival is .93, neutral, in favor of darbepoetin with a confidence interval from .78 to 1.11. In terms of the investigator-assessed, progression-free survival, we see again a reassuring, overlapping pattern with a hazard ratio of 1.02 with confidence intervals from .86 to 1.21.

The approach was also successful in reducing transfusion burden. Here we see indeed that on the placebo arm there was a, roughly, 60 percent increase in transfusion burden, a coprimary endpoint of the study was hemoglobin. In fact, hemoglobin was well maintained in that treatment arm and was statistically significantly different from the placebo arm.

To conclude, the 145 Study, darbepoetin alfa maintained hemoglobin significantly and reduced red-

blood cell transfusion burden. Superiority was not achieved, but no difference in overall survival was observed at the hazard ratio of .93 with confidence intervals from .78 to 1.11.

An increased risk of death of greater than or equal to 11 percent can be excluded with 95 percent confidence intervals. There was no difference in progression-free survival is observed.

Increased risk of thromboembolic events was again observed, again predominantly deep-vein thromboses, and it was of a magnitude comparable to what I've shown you previously and consistent with what one might expect with ESAs in the indication.

Next, I would like to turn to combined study-level analysis in CIA. This is in fact a combined analysis of all of the placebo-controlled randomized clinical trials that have been conducted.

I draw your attention to the fact here that in fact a number of individual tumor types are represented. You will see here, for example, a study in breast cancer. You will see another study that focuses primarily on breast cancer.

Indeed, when we look across all of these placebo-controlled studies, we find that the hazard ratio for survival is neutral at 1.06 by the fixed-effects model and 1.04 by the random-effects model with confidence intervals clearly spanning unity.

Now, what we did going forward with the combined study-level analysis was to use the Cochrane report of 2006 as a useful baseline. This has been well recognized globally as an important analysis, and indeed the FDA has recognized this. It is incorporated in the current ESA labels.

The 2006 analysis looked at all studies conducted through April 2005 that met criteria. Indeed in the CIA indication 29 studies covering 6,659 patients showed a neutral hazard ratio of survival of 1.04 with confidence intervals from .97 to 1.10.

Since that time, 12 additional CIA studies have either completed or have been updated. That is in accordance with the criteria that we used by the Cochrane by selection.

Here we see the individual studies. In fact they are important because in most cases address

homogeneous populations. The sample sizes are significant, and they do address tumor types where issues have been raised.

Here we see a breast cancer study in metastatic disease, here we see another breast cancer study, and here we see yet another breast cancer study, which clearly are important in informing the conversation around the best results.

I will draw your attention to the fact that these are all odds ratios, and indeed the odds ratios are all essentially neutral with confidence intervals spanning unity.

I will draw your attention also to the 161 Study. This study, as I indicated, was prominently discussed in the FDA briefing book, and we would be happy to discuss it further during the conversation.

In addition, I draw your attention to the fact that we are showing odds ratios here and the confidence interval of 95 percent.

Now, looking at the combined study-level analysis, 39 studies are included including 9,652 patients. Indeed, by both the fixed and random-effects

model, the hazard ratio for survival is 1.03, a neutral finding with confidence intervals from .93 to 1.15. These are most reassuring data.

I would now like to update you on the question of tumor progression. We have scouted the literature and looked at all the published data that have meaningfully addressed the progression endpoint. In fact, eight controlled studies in the CIA setting have evaluated response to chemotherapy and tumor progression. This included, 3,388 patients.

A combined study-level analysis was not attempted because of the heterogeneity of the response in progression endpoints reported out. However, the meta-analysis -- pardon me, the combined analysis, I should mention, was covered in detail in the briefing book. Indeed, we would be happy to discuss this further during the discussion period.

None of these studies reported significantly worse outcome with ESAs including the final published reports of the BEST study. My colleagues from J&JPRD will be happy to discuss the BEST study further during the discussion period today.

To summarize, the very considerable hierarchy and weight of evidence in the CIA indication, ESAs are effective in reducing transfusions and avoiding symptoms and signs of anemia. Dr. Crawford has spoken most eloquently to this.

In terms of overall survival, ESAs have a neutral finding in the CIA indication even at hemoglobin targets above the currently label ceiling. ESAs do not promote tumor growth or progression in CIA.

You have heard from Dr. Perlmutter that the preclinical do not indicate in any way support for EPO receptor mechanistic involvement in any putative process. ESAs are associated with a well-quantified and well-described increased risk of ETEs, and these are predominantly deep-vein thromboses.

Moving now to the anemia of cancer, this is a heterogenous group of conditions. At its broadest it is defined as the anemia which is present when patients who have a diagnosis of cancer are not receiving chemo or radiation and are not planning to receive chemo or radiation.

Most clinicians will recognize that indeed

anemia is a problem in these patients, and for this reason both sponsors have addressed studies to this question.

In fact, here you see a summary of early controlled studies in the CIA indication -- pardon me, AoC indication using this very broad definition. It is important to recognize that these initial studies showed a favorable benefit/risk profile.

Now, two studies have suggested safety concerns, one is the Wright study or the EPO-CAN 20 study. This is actually not a new study. This was discussed at the ODAC in 2004. It is a small complex study. In fact, J&JPRD representers will be happy to discuss this during the discussion period. The new data is the Amgen 103 study which was conducted in anemia of cancer patients.

Now, I should mention that this was a very specific subset of anemia of cancer patients. When we actually entered into regulatory discussions around a registrational pathway, we were steered very specifically in the direction of studying patients who were not in complete remission, who had active cancer,

who were not receiving chemo/radiation and were not planned to receive chemo/radiation. I think we could all recognize as clinicians that that may well describe a particularly ill population.

The study involved 193 sites in 21 countries. Indeed two of the high-accruing Eastern European countries had transfusion practices which were different from expected, and this unfortunately prejudiced the transfusion endpoint.

Now, the study design is complex. It has been covered in the briefing book. Essentially, to highlight, this study was done primarily to address transfusion. Consequently, stratification was primarily with the transfusion endpoint in mind.

Stratification involved five stratification factors and ended up with 48 different strata. There were a panoply of tumors studied. In fact, 25 different cancers were studied. You can see this is a very heterogenous group of patients.

The study designed randomized patients to either darbepoetin or placebo. They got 16 weeks of treatment. They then were either followed for two years

or were allowed to crossover or continue on with the investigational product as randomized and to continue for another 16 weeks.

Now, I've alluded to the stratification and the multiple stratification factors and the multiple strata, and it's our belief that this led to significant imbalances.

In fact, I draw your attention to some important imbalances that are readily obvious, a huge difference in sex and a significant difference in prior chemotherapy and duration since prior chemotherapy.

The survival curve I'm showing has been updated since that in the briefing book. The reason for that is the rollover study has now completed and the additional long-term followup have been added. We see that, in fact, the overall survival is disadvantageous to darbepoetin with a hazard ratio of 1.22 with confidence intervals from 1.03 to 1.45.

Now, I should mention that there was no prespecified analysis planned for safety. Indeed, if you adjust this analysis for stratification factors at randomization, enrollment status and covariates, and I

have indicated that there were significant imbalances, the hazard ratio reduces to 1.15 and it is no longer significant.

We have, however, elected to use what we believe to be the clinically most conservative interpretation of these overall survival analyses.

As I mention, this spans some 25 different tumor types. I draw your attention here to the fact that for the majority of the solid tumors, in fact, the survival data were in fact neutral. I highlight here specifically: breast cancer, ovarian cancer, and cervical cancer.

The two areas where, in fact, this appeared to divert from neutrality was in the setting of non-Hodgkin's lymphoma and multiple myeloma. This came as a surprise because we actually have an existing body of data which suggest favorable outcomes in these settings, but again remember that these were a very heterogenous group of patients.

Clearly, the 103 study has a very significant limitations. It is a distinct population from CIA. Just by the very definition, patients could not be

getting chemotherapy and were not planned to get chemotherapy.

It is also a very, very specific subset of AoC. It is essentially patients who had exhausted therapeutic options in large measure and who had active and ongoing cancer. This is attested to by the overall high mortality rate.

I have spoken to the multiple stratification factors, the multiple tumor types, and the important baseline imbalances. Indeed we agree with the FDA in their briefing book that the design of the study was not adequate to assess tumor proliferation.

Moving now to the high hemoglobin target therapy studies in radiation therapy. The new data here, and I think FDA in its briefing book indicates this is the only data to suggest a tumor progression issue.

This is DAHANCA-10. This was a study that was conducted very similarly to the Henke trial. I should mention that in this particular trial patients were randomized to get radiotherapy for locally advanced head and neck cancer with or without darbepoetin.

The aim was to keep hemoglobin at a very high level, you see, 14 to 15-1/2. Importantly, both arms received a radiosensitizer known as nimorazol. This is commonly used in Denmark where the study was conducted.

The primary endpoint was locoregional control. FDA in its briefing book documented that, in fact, there is some limitation here because this endpoint was determined only clinically. There was no systematic radiologic evaluation.

Now, what we know about the study is that the principal investigator and the cooperative group, the DAHANCA group, posted on its webpage notification that enrollment of the study had been stopped for futility.

They had looked at the study and determined that it was unlikely that darbepoetin would be superior in terms of outcome. They noted that preliminary interim data favored the control in terms of clinically determined locoregional progression.

Now, it's important to recognize that data acquisition is ongoing; final analysis has not been completed; and neither the principal investigator nor, for that matter, anybody else has seen the final data.

Importantly, the principal investigator has become alarmed by the overinterpretation of these data and has, in fact, specifically and unsolicitedly written to Amgen indicating that the cautions against overinterpretation.

This has been forwarded to the FDA, this unsolicited communication, and we would be happy to discuss this during the discussion period.

Finally, I would like to turn to an approach to risk management. Now, in terms of CIA, in terms of the assessment of risk, and in terms of overall survival, no adverse effect has been observed with ESAs in the CIA setting.

In terms of tumor progression, no adverse effect has been observed with ESAs and the preclinical data do not support a mechanistic role for EPO receptor.

In terms of the question of cardiovascular and thromboembolic events, it needs to be recognized initially that the background risk in cancer patients is very high. From a number of systematic databases, the risk has indeed increases some four-to tenfold in the cancer patient as a baseline. This was exacerbated by

multiple therapeutic modalities.

I think it is true to say that despite this well-recognized increase the management and the outcomes of the hypercoagulable state in the cancer patient is poorly defined and poorly understood in terms of how best to manage it.

There is with ESA treatment in the CIA setting a well-established increased VTE risk. This has been stable since registration. It has been well-captured in the label. Clinicians are familiar with this. Indeed, the primary driver for this is deep-vein thrombosis.

It is important to recognize from the data I showed you that, despite the fact that there is a raised rate of VTEs, this does not translate into an adverse survival signal.

Survival in all of these pooled data, pardon me, combined datasets of both study-level and patient-level data show neutrality in terms of survival.

In terms of AoC, we recognize that adverse mortality was seen in the 103 study. This is a single, large, complex trial and we don't believe these data are readily extrapolatable to the CIA setting. We have also

alluded to the Wright study, which is a small, complex study.

In terms of radiation therapy, an adverse effect has been recognized at high hemoglobins when used in an attempt to drive the hyperoxygenation hypothesis.

The Henke study is really the only data that indicates this at this time. This particular dataset was fully discussed at the '04 ODAC and remains a controversial dataset.

The DAHANCA trial I have indicated to you is weighted in terms of final analysis, and the principal investigator has cautioned vigorously against overinterpretation.

Now, as you heard, there has been a recent change to the U.S. label and additional warnings have been elevated to box status. In terms of the CIA setting, we believe that we have a very conservative label already adopted.

The current label prominently communicates the risk of VTE and tumor progression despite the fact that there are virtually no data to support the tumor progression notion.

We have changed from a target hemoglobin of 12 to a ceiling of 12. You have heard from Dr. Crawford the implications of those for clinical practice.

In terms of the anemia of cancer, the boxed warning indicates that it should not be used in patients where in fact they have anemia associated with active malignancy and have exhausted other anti-tumor options.

In terms of radiation therapy, ESA should not be used to achieve a hemoglobin above a ceiling with a goal of improving response to therapy.

Finally, I would like to update you on the progress in the Pharmacovigilance Program. This program, as you heard, was recognized by the ODAC in 2004 as an ongoing program that would provide data. It became a former postmarketing commitment with the FDA in 2006, and we have made diligent and steady progress in this postmarketing commitment.

The 145 data, as I indicated to you, has completed. The primary data and study report have been provided to the FDA. The study completed on 22 February, and in fact this was at the FDA on the 23 April.

The GELA study, an important study addressing ESAs in the non-Hodgkin's lymphoma setting, continues to accrue. An interim data set was presented at ASH of 2006, and indeed that abstract has been provided to the FDA. Reassuringly, the findings are neutral. In fact, at the interim analysis the finding was neutral for survival and progression-free survival and directionally in favor of the ESA.

The PREPARE study in neoadjuvant breast cancer has completed enrollment. Patient followup continues. Amgen is working diligently with the sponsors of the study as well as the principal investigator to expedite data acquisition and analysis.

The ARA 03/PLUS study in adjuvant breast cancer continues to accrue and we anticipate that interim data will be shown at ASCO upcoming.

The DAHANCA-10 trial I have indicated has been stopped for futility. At this time the Pharmacovigilance Program is tracking in fact to the committed plan.

I would now like to introduce Dr. Alex Zukiwski, vice president and head of clinical

development oncology at J&JPRD to update the J&JPRD Program.

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT PROGRAM UPDATE

(PowerPoint presentation is in progress.)

DR. ZUKIWSKI: Good morning. I am Alex Zukiwski from the Oncology/Hematology Clinical Development Group at J&JPRD. As a sponsor of Eporex, the closely related ESA, J&JPRD has been invited by our colleagues at Amgen to present at this ODAC.

Due to the limited time provided for our formal presentation, we will focus on key information from ongoing trials and the ongoing efforts of J&JPRD. However, we will be happy to provide you any additional details required during the ODAC discussions.

In the sponsor's briefing book in Dr. Bayne's presentation, recent updates and meta-analysis of our data continue to support the safe use of ESAs as labeled and show no discernible effect on tumor growth and overall survival. As indicated, the TVE risk for ESAs is well known and is reflected in the product labels.

In our presentation, I will summarize J&JPRD's

efforts and commitments to increase the understanding of the safe use of epoetin alfa in patients with cancer.

We will discuss Phase IV commitment trial 93-004, a followup on the studies, provide additional information that was presented in the 2004 ODAC, and an update on the status of the Phase IV commitment trial study 3010.

Let me first summarize a study done as part of the Phase IV commitment trial, Study 93-004. It was done to evaluate the possible stimulatory effects of epoetin alfa treatment on the growth of solid tumors.

This study was conducted in patients with newly diagnosed small-cell lung cancer with limited or extensive disease. The treatment was etoposide and cisplatin.

It was designed as a noninferiority trial to exclude a 15 percent reduction in objective response rate. The study did meet its primary endpoint, demonstrating noninferiority.

The objective response rate for Procrit was 6 percent above the placebo arm, and the lower bounds of the confidence interval excluded an inferiority of more

than 6 percent.

Because there was a shifting standard of care away from the etoposide and cisplatin, mainly for the limited small-cell lung cancer, the study did not recruit fully and the power to demonstrate overall survival differences was limited. There was, however, no difference in overall survival noted in this trial.

Though some of the studies outlines in this slide were closed to accrual at the time of the 2004 ESA ODAC, these studies have continued to follow patients for survival and other outcomes.

J&JPRD has been diligent in obtaining the followup data. In some cases, we have altered the protocols, informed consents, and study plans to obtain additional followup beyond what had originally been planned.

Time does not permit me to update each of these studies. To summarize, with the exception of the recently published CAN-20 cooperative group data, where epoetin alfa was studied in an off-label setting in the non-small-cell lung cancer patient population, we have observed no new adverse effects of epoetin alfa on

survival, progression-free survival, or other adverse tumor outcomes.

We would be glad to discuss the details of the study designs, the results, and our diligence regarding the regulatory submissions during the discussion session.

In 2004, the BEST study, which evaluated an investigative dosing schedule of epoetin alfa in patients with breast cancer, raised safety concerns. In light of this, we designed Study 3010 with input from the 2004 ESA ODAC Panel, the FDA, and an International Advisory Board.

In an attempt to definitively assess and confirm the safety of epoetin alfa when used according to label guidance in women with breast cancer. The 3010 Study schema is here.

Patients with metastatic breast cancer would be randomized to protocol-specified chemotherapy and that is taxane, anthracycline-based. Patients who are eligible to receive trastuzumab may also be enrolled in this trial. J&JPRD is providing all of the chemotherapy for this international trial. Patients will receive

epoetin alfa plus supportive care or just the standard supportive care.

The primary endpoint of his trial is progression-free survival, which will be independently determined. Secondary endpoints are outlined here, and we are prospectively collecting data on thrombotic vascular events.

This protocol is ongoing, but, as anticipated, is facing substantial accrual challenges. A detailed update of the status and the mitigation activities conducted for this 3010 Trial was provided to the FDA in March of this year.

This slide summarizes the concerns of the International Advisory Board that was convened in July 2004. These are relevant to the ODAC discussions today as the challenges relative to 3010 were recognized and discussed with the FDA in 2004 and have been realized in 2007.

Briefly, these concerns are as follows. Limitations on where the study can be conducted, we were not able to conduct this trial in the United States or in Western Europe.

Limited interest in patients and investigators in participating, this is reflected by the intense competition for patients or subjects with metastatic breast cancer as there are numerous novel therapeutic studies ongoing.

Then, there were practical operational issues which would limit enrollment such as the protocol-specified chemotherapy.

I would now like to outline some of the issues regarding the patient recruitment into Study 3010. Sites where the use of ESAs are not standard of care are participating in the study. The accrual data is shown on the next slide.

As you can see here, 286 sites were contacted as of April 30, 2007. Out of the 286 sites, 117 are actively participating in 14 countries outside of the United States and Western Europe, 964 patients were prescreened, and 270 patients were consented. Of those 270 patients consented, only 127 were found to be eligible and were randomized into this trial.

As of close of business yesterday, these numbers have increased. 1,060 patients have been

prescreened; 278 consented; and 134 randomized.

This slide outlines some of the additional and ongoing steps we hope will address the accrual challenges in this study. Additional sites have been identified to replace the nonperforming and to add new sites, taking the total number of sites from 117 to around 140.

We have proposed some protocol amendments to modify the inclusion criterion. However, some of the amendments may potentially influence the concept of homogeneous patient populations and homogeneous treatment, thus we will have to have a discussion with the FDA before these are implemented.

Operational aspects to reduce the burden on the sites have been implemented, and we are continuing to have ongoing site meetings and staff training. To date, we have undertaken six investigator meetings, and my senior clinical staff have performed 50 individual site visits around the globe in an attempt to increase the accrual to this study.

We recognize and are addressing the accrual challenges in Study 3010 and believe these interventions

should enhance the study accrual. I would be happy to elaborate on these during the discussion session.

In summary, a large and expanding body of data supports the safety and efficacy of ESAs in the treatment of chemotherapy-induced anemia when used according to label guidance.

We recognize and appreciate the importance of improving our understanding of this class of drugs, particularly in light of the emerging data, and we remain committed to doing so.

I would now like to turn the presentation back over to Dr. Perlmutter.

SUMMARY

DR. PERLMUTTER: Thank you.

Well, you have heard an overview of material that is described in a great deal more detail in our briefing book. We have, in addition, a lot of backup information that can assist you in your deliberations. I would like to take just a few minutes to summarize our findings.

First of all, you have heard that based on the totality of data the benefits of ESA therapy in the CIA

setting, chemotherapy-induced anemia, for which registration was obtained, are substantial and unambiguous.

Lower hemoglobin levels are associated with an increased burden of symptomatic anemia, as Dr. Crawford described, and a burden of transfusions, that was the regulatory endpoint.

Transfusions are associated with well-recognized risks and the potential risks from emerging infections. The ESA risks in chemotherapy-induced anemia are well-characterized at the recommended dose and are supported by the totality of data.

Now, data are available from studies that span a very wide range of hemoglobin targets. As I've indicated, the reason for that is because there was a widespread interest in the idea that hyperoxic treatment, improved oxygenation, would actually improve tumor responses.

What we can say is that across this wide range of hemoglobin targets there is no adverse effect of ESAs on overall survival or tumor progression. It makes sense in that context that if there is no adverse effect

at the higher hemoglobin targets, we can comfortably extrapolate down to the lower hemoglobin targets that are currently recommended in the label.

Amgen and J&JPRD do not advocate targeting hemoglobins above 12. We are not attempting to advocate to this Committee that we should change that target.

The recent label updates provide prominent warning of risks associated with ESA use. Along those lines I would like to mention that as soon as we receive the data from the 103 Study and from the 145 Study we have made those datasets available to the FDA.

We also on our own initiative have provided "Dear Healthcare Provider" letters with regard to those data. We have posted summary data for the 103 and 145 Studies on "clinicaltrials.gov."

In addition, in agreement with the FDA, we sent our professional representatives specifically to inform physicians about the new label changes that were implemented in March, and that is the only activity that they have been engaged in with respect to the use of darbepoetin in the cancer setting.

We have worked very, very hard to try to

inform physicians about these risks as they became known to us.

Now, as we have presented and as was contained in the briefing book, considerable new data from ongoing Pharmacovigilance studies will be available within the next 12 months.

After discussions, J&JPRD and Amgen are committed to the further exploration of these benefits and risks. One way to do this is to take our patient-level data and make them available for independent evaluation.

We would like to try and get other sponsors who have ESAs to participate in such an effort, which would assist us in looking in more detail across very, very large number of patients to ask additional questions about the benefit/risk profile of these molecules.

I think there are some open questions that could be addressed in future studies, and likely these have occurred to you as you have gone through our presentations and looked at the briefing book.

I think one question clearly is the use of

ESAs in the anemia of cancer setting and in different populations of patients with anemia that is secondary to malignancy but not to chemotherapy.

Clearly, head and neck cancer is an area where additional studies of anemia treatment could be performed, particularly since the standard of care in such settings has moved away from sole radiotherapy.

Lastly, risk management strategies for ESA-related VTEs, as Dr. Baynes has indicated, VTEs are an acknowledged risk of ESA therapy. It is very plain that there is an increased risk.

Although there is no augmented risk that is specific to cancer patients, I think this is something that we could productively discuss and think about as we look through these large datasets.

With that in mind, I would like to thank you again for taking time to go through this material, for listening to our presentations, and we look forward to the future discussions.

Thank you very much.

CHAIRPERSON ECKHARDT: Thank you for the presentations. What we are going to do is move back one

step in the agenda, and Dr. David Stroncek will now update us on transfusion medicine.

RISKS AND INDICATIONS FOR RBCs TRANSFUSIONS

DR. STRONCEK: Hi. I'm Dave STRONCEK. I'm the from the Department of Transfusion Medicine at the Clinical Center at the NIH. I was asked to give a brief presentation on risks and indication of blood transfusions for the context of this meeting, so I will just take about 10 minutes to do this.

First, just a brief summary. You've heard some of this already, but some of the concerns about blood transfusion, for many years the biggest concern has been viral infections, the chief ones being hepatitis B, hepatitis C, and HIV; less often there is still a risk of transfusing with HTLV I and II. Recently, there has been the emergence of West Nile virus associated with transfusions. CMV is a treatable disease or a transient disease, but again it can be transmitted with blood.

The incidence of these diseases has varied quite a bit over the years. The reason for that is twofold, one is the incidence in the population and also

the testing and screening.

As these diseases have been understood better, we screen blood donors better based on their behavior risks and demographics, various demographic risks, and also the testing has gotten much better over the years, especially with nucleic acid testing.

Currently, these are the best estimate I could find on the current risk of these viruses with blood. There are two good studies, recent studies, one from 2002 in the United States, Red Cross data, and then more recently Canadian blood systems data.

The risk of transmitting hepatitis B has remained fairly high at 1 in 2000 units, but the risk of transfusing hepatitis C has fallen greatly from about 1 in 2 million units transfused. HIV the risk is anywhere from 1 in 2 million to 1 in 7 million or 8 million. HTLV I or HTLV is about 1 in 3 million to 1 in 4 million.

The reason why the risk is higher for HBV is that the nucleic acid testing really doesn't provide much benefit because there is not a period of low viremia you can pick up the disease.

There are a number of other risks associated with blood transfusion, other pathogens. There is a very small risk of having bacterial contamination of the blood, transmission of other diseases such as malaria, babesia, and more recently a concern about chagas.

Now, as mentioned before, there are probably some risks we don't know about and other risks that may emerge in the future.

Other risks of blood transfusion of course, for many years one of the leading causes of death was transfusing the wrong unit, the wrong ABO type and having a hemolysis, a hemolysis-related death. That risk has decreased and this is now not the leading cause of deaths with transfusion.

You can get delayed transfusion reactions where antibodies are produced to non-ABO antigens and cause delayed homlysis. Of course, there has been a lot mentioned on leukocyte-mediated problems, transfusing patients with red cells can not only result in red cell alloimmunization but alloimmunization to HLA antigens, which can make platelet transfusions more difficult. When antibodies to leukocytes are present in the

transfusion recipient, the recipient can experience febrile transfusion reactions.

Currently, the leading cause of death in transfusion recipients is transfusion-related acute lung injury. That occurs for a variety of reasons, but one of the leading causes is the transfusion of antibodies to leukocytes inadvertently with that unit of blood. It results in acute lung injury and sometimes death.

Other problems with red-cell transfusions, as we have heard, are fluid overload and anaphylaxis can occur. You can get various types of rashes and other allergic reactions. Graft-versus-host disease can be a problem if a person is immunosuppressed and the blood isn't irradiated. Then, there are a number of studies that show that blood does modulate the immune system, and some studies show that transfusion creates an increased risk of infection and tumor relapse in patients.

Here kind of summarizes the leading causes of fatalities due to blood transfusions reported to the FDA. This summarizes from 2002 to 2006. Thirty-nine percent of those deaths were due to transfusion-related

acute lung injury; the second leading cause was a mix of other causes including non-ABO hemolytic transfusion reactions; third was bacterial contamination; fourth was ABO hemolytic reactions, and then unknown is the final category.

Now I just want to change directions a little bit and give you a little rationale for transfusion triggers and which ones are used.

Again, the major function of red cells is to deliver oxygen from lungs to tissues. Oxygen transport of course is dependent on the hematocrit, how much oxygen combining ability capacity is in the blood per unit volume and also on the cardiac output and then how much oxygen is extracted as the blood flows through the tissues.

As hematocrit falls, blood viscosity decreases markedly and also the ability of blood to carry oxygen. But that is made up for by increased cardiac output by the heart, which increases the stroke volume, and the pulse increases.

Overall, the delivery of oxygen for quite a while even at low hematocrits is maintained to tissues.

At some point the ability of the blood to carry oxygen falls as hemoglobin falls.

But at that point, then, the extraction of oxygen from the blood increases, and really the oxygen consumption to the tissues remains constant till quite low hemoglobins.

At some point the critical hemoglobin is reached, and at that point the ability of blood to carry oxygen can't be met. Or, the ability to carry oxygen can't meet the body's needs, at that point anaerobic metabolism takes over, and a lactic acidosis results in cardiac arrest.

Again, really it's quite low hemoglobins where this occurs, it's approximately 4 grams of hemoglobin or even less. People can, if anemia comes on over a gradual period of time, levels can go quite low.

Now, that said, the triggers for transfusions have been quite different. In the 1940s, it was recommended that surgery patients have a hemoglobin of 8 to 10.

This was based on really poor-risk patients, poor-anesthesia-risk patients, but it did lead to a

recommendation of a hemoglobin of 10 for surgery patients.

This trigger, this transfusion for a hemoglobin of 10 and hematocrit of 30, really was around for quite a few years. It wasn't until the 1980s where better invasive monitoring techniques came about and a better understanding of oxygen delivery and consumption was obtained. At that point it was believed that lower hemoglobins could be tolerated.

I will show you some results of studies on what types of hemoglobins people have found are tolerable, but first just a reminder what normal hemoglobins are.

In females, the mean hemoglobin is 14 and 2 standard deviations below the mean is 12. In males, the mean hemoglobin is 15 and 2 standard deviations below the mean is 13-1/2.

Currently, there have been a couple nice studies out of Canada on transfusion triggers. What you have to remember about these, though, is they are intensive-care unit patients. What these studies did is randomized patients to either conservative or liberal

transfusion regimens.

The conservative regimens used a hemoglobin level of seven to trigger a transfusion and maintained hemoglobins between seven and nine. The liberal transfused patients for a trigger of a hemoglobin of 10 and maintained their hemoglobin levels from 10 to 12.

When they analyzed those results, what they found out when they looked at 30 days mortality, there was no difference in 30-day mortality between the restrictive and liberal group.

When they looked at the patients that were less ill, patients that were less than 55 years old and had less ill by APACHE II scores, again, there was no difference between the liberal and restrictive group.

In the cardiac disease group, even patients with cardiac disease, there was no difference between the liberal and transfusion group.

There have been some other studies that have looked at this issue, too. Again, the same group looked at intensive-care unit patients, pediatric intensive-care unit patients. That study was recently published. They did show that there is no difference, again, if

they use a transfusion trigger of 7 or 9.5.

Patients with moderate to severe head injuries were also analyzed, and, again, no difference in long-term 30-day mortality between a trigger of 7 and 10.

There have been some studies of patients with cardiovascular disease that suggest that maybe a higher transfusion level of 10 might be worthwhile, and, again, that study was completed by the Canadian group.

Overall, in patients that have good cardiac function, at least the transfusion medicine community feels that a transfusion level of seven, a trigger of seven to eight is adequate based on these studies.

There have also been questions on, well, what is the optimal hemoglobin, and that is a very difficult question to answer. There is one study. It's old, it's from 1967.

This is based on a laboratory study in mathematical modeling that measured blood flow and oxygen-carrying capacity in blood flowing through glass tubes.

They wanted to know what hematocrit caused the maximum oxygen delivery. The issues involved with this

is the oxygen delivery is dependent on both the hematocrit and the blood flow rate.

As the hematocrit decreases, so does the viscosity, and blood flow increases. Based on a lot of mathematical modeling, they came up with an optimal hematocrit of 35. Again, this is a laboratory.

In a clinical situation, some patients do need higher hematocrits in hemoglobin. Overall, the transfusion triggers are just guidelines. We like to think about it as the risk, a transfusion is justified if the risk of increasing hemoglobin is justified by the clinical benefits.

In conclusion, red blood cells are much safer than they were 20 years ago, but transfusion practices have become more restrictive. The transfusion threshold at most institutions is a hemoglobin of seven to eight for most patients. However, higher thresholds are needed for specific patients, particularly cardiac patients.

Thank you for your attention. I just want to remind people that these are my personal opinions and not those of the National Institutes of Health or the FDA or the Department of Health and Human Services.

Thank you.

CHAIRPERSON ECKHARDT: Thank you for that presentation.

Now we will move on to the FDA presentation. Dr. Juneja will present on behalf of the FDA.

FDA PRESENTATION

(PowerPoint presentation is in progress.)

DR. JUNEJA: Welcome everyone, especially members of the Advisory Committee. Thank you for attending our talk today on the continuing reassessment of erythropoeisis-stimulating agents in patients with cancer.

I am Vinni Juneja, and I am a medical officer at the FDA. For brevity sake, throughout the presentation I will be referring to erythropoeisis-stimulating agents as ESAs.

Well, obviously this is not a one-person effort, so I would like to thank the rest of my wonderful team for making the late nights at work more enjoyable. Let's start with an outline of the presentation.

For our presentation, we will outline the

relevant issues for today's discussion and the regulatory history of ESAs. We will then look at an overview versus of the benefits versus risks of ESAs.

Next, we will look at safety signals from trials using ESAs of cancer patients that led up to a previous Oncology Drug Advisory Committee, "ODAC," in May 2004. These trials showed decreased survival, increased tumor promotion, and increased thrombovascular events.

We will then review ODAC's recommendations from May 2004 regarding future trial design components that would help address these issues.

Keeping 2004 ODAC recommendations in mind, we will review a number of trials that were accruing patients as of ODAC 2004, a large breast cancer trial that was previously mentioned by Johnson & Johnson, that was initiated after ODAC 2004, and review data of recent trials that have shown safety signals. Finally, we will discuss considerations surrounding meta-analyses.

Let's start with an introduction. Let's talk about why we are here today. Assessment of the risks versus benefits of ESAs has been going and was the

subject of a previous ODAC in May 2004. These are the risks of ESAs in cancer patients that we would like to emphasize for this discussion.

The first is decreased survival, the second is increased tumor promotion, and this can be manifested by a decreased locoregional control or a theoretical concern of decreased progression-free survival.

Decreased survival and increased tumor promotion have occurred in trials that target a higher hemoglobin than the current recommendation of a maximum hemoglobin of 12, and in trials in patients who are not receiving chemotherapy.

The third risk is a risk of increased thrombovascular events, which we will be referring to as "TVEs" throughout this talk. TVEs encompass: myocardial infarction, angina, cerebrovascular accident, cardiac arrest, pulmonary embolism, and deep-venous thrombosis.

This slide provides an overview of ESAs that are available within the U.S. and outside the U.S. The first ESA to be approved in the U.S. is PROCRIT, or epoetin alfa, and was approved in 1993.

Darbepoetin, or Aranesp, was approved in 2002

in the U.S. The ESAs, Eprex® and NeoRecormon® are approved for use outside of the U.S. and are relevant because numerous studies have been conducted using these agents.

I would like to note that with reference to the previous slide, FDA considers all ESAs as members of the same product class and risk of ESAs apply to all products.

Now we will discuss the regulatory history of the ESAs. The first ESA to be approved in the U.S. was epoetin alfa. Epoetin alfa products licensed in the U.S. were manufactured by Amgen, and by contractual agreement epoetin is marketed for dialysis patients and Procrit is marketed for all other indications. Labeling for these two products is identical. Throughout the rest of this talk the initials "J&J" will refer to "Johnson & Johnson."

Here we have outlined the approval history of epoetin alfa in the U.S., starting with the approval in non-cancer patients. In 1988, approved for anemia of chronic renal failure; in 1991, for AZT-related anemia in AIDS patients; and in 1995, for the reduction of

perioperative transfusion requirements.

For the cancer approvals: in 1993, three times a week dosing was approved for anemia associated with chemotherapy. In 2004, weekly dosing was approved for this indication. In terms of pertinent revisions to the label, in May 2004, after ODAC 2004, the effects of ESAs on response rate, time to progression, and overall survival in solid tumors was added to the label.

Let's start with the approval of epoetin in 1993 for the cancer indication. This agent was approved based on a reduction in the proportion of patients receiving red-blood cell transfusions who were on chemotherapy.

In 1993, the infectious risks of blood transfusion was higher than they are in the current time. Later, we will examine the risks of blood transfusion due to these concerns about the safety of the blood supply in 1993, the risk-to-benefit ratio of epoetin-supported approval.

The approval was based on pooled data from six randomized, double-blind, placebo-controlled trials in a total of 131 patients with different malignancies.

At the time of approval there was a theoretical potential for tumor promotion based on erythropoietin-receptor expression in tumors and vasculature that was unresolved at that time.

Therefore, our post-marketing commitment study to address the impact of Procrit on tumor response and survival was performed, and we will be talking about that study later on.

Now moving on to Aranesp, this agent was first approved in 2001 for the anemia of chronic renal failure, and then in the cancer indication there were subsequent approvals in cancer patients.

In July 2002, there was approval for anemia associated with cancer and chemotherapy with weekly dosing, then in March 2006, every three-week dosing for anemia associated with cancer chemotherapy.

In 2002, Aranesp was approved for cancer patients, similar to epoetin, based on a reduction in the proportion of patients transfused who were receiving chemotherapy. The approval was based on Study 980297, a randomized, double-blind, placebo-controlled trial in patients with lung cancer, both the non-small cell, and

small-cell lung cancer.

The post-approval followup has not shown a difference in PFS or OS, but the study was not sized to detect small but clinically meaningful differences in progression-free or overall survival.

If this is what the current label states for both PROCRIT and Aranesp. The dose of ESAs should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 grams per deciliter. Of note, the prior labeling allowed for a hemoglobin as high as 13 before the dose was held.

The current label also states ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effects of concomitantly administered chemotherapy.

ESAs are indicated to decrease the need for transfusion in patients who will be receiving concomitant chemotherapy for a minimum of two months, and ESAs are not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or GI bleeding, which

should be managed appropriately.

Now we will discuss the benefits versus the risks of ESAs. The clinical benefits of ESAs were demonstrated in anemic patients receiving chemotherapy who were able to avoid red-blood-cell transfusions and their concomitant risks.

For patients needing red-blood cell transfusions, the use of ESAs reduced the proportion of patients receiving red-blood cell transfusions and their concomitant risks. These are the actual benefits of ESAs with respect to reducing the proportion of patients on chemotherapy who are transfused.

Now, looking at the top table, the 1993 approval of Procrit demonstrated that 22 percent of patients were transfused in the Procrit arm while 43 percent of patients were transfused in the placebo arm.

Referring to the bottom table, the 2002 approval of Aranesp demonstrated that 21 percent of patients were transfused to the Aranesp arm while 51 percent of patients were transfused in the placebo arm.

The patients in the Procrit approval received both platinum and non-platinum-based chemotherapy.

Patients in the Aranesp approval received platinum-based chemotherapy.

ESAs do not eliminate the need for transfusion but an approximately 50 percent reduction in the percentage of anemic patients receiving red-blood-cell transfusion who are at risk for red-blood-cell transfusion. Not every cancer patient on chemotherapy requires ESAs. Only those at substantial risk for red-blood-cell transfusion.

Now I would like to illustrate the contrast between the current practices of the use of ESAs versus red-blood-cell transfusion. ESAs are initiated when cancer patients on chemotherapy are deemed anemic. The financial reimbursements for ESAs begin when the hemoglobin is less than 12. In contrast, the general recommendation for red-blood-cell transfusion is at a hemoglobin of seven to eight or as clinically necessary.

This leads to the question, because the benefit of ESAs is avoidance of transfusion, should ESAs be initiated at or titrated to achieve a lower hemoglobin than currently practiced? Which patients really need a transfusion?

We will be talking about this on the next slide. Now, on this slide, we will discuss the issues related to blood transfusion.

Transfusions are rarely given for a hemoglobin greater than 10. The human body can compensate for chronic anemia by the following. There can be an increase in two to three diphosphoglycerate, which causes a shift in the oxygen dissociation curve, which causes an increased release of oxygen to body tissues.

Another compensatory mechanism is increased peripheral vasodilation. Lastly is increased cardiac output, which usually does not occur until the hemoglobin is less than seven. Correspondingly, symptoms due to chronic anemia may not appear until hemoglobin is less than seven to eight.

For patients who need blood transfusion, this slide illustrates the decreasing transfusion-related infectious risk of hepatitis B, hepatitis C, and HIV since the original approval of Procrit in 1993. You can see a decreasing risk of infection from these three agents from 1993 to 2005 in this slide.

Now, this slide illustrates the risk at the

current time of red-blood-cell transfusion per unit of red-blood-cell transfused. The horizontal bars represent the range of risk available from the current literature.

Starting with the risk of HIV, estimated to be between less than 1 in 1 million to 1 in 7.8 million; for hepatitis C, 1 in 1 million to 1 in 3.6 million; for hepatitis B, 1 in 150,000 to 1 in 1.4 million.

The risk of bacterial infection is currently between 1 in 10,000 to 1 in 100,000. What I would like you to note is the significantly decreased risk of fatal bacteremia as compared to bacterial infection. The risk of fatal bacteremia is estimated 1 in 13.9 million.

The risk of mistransfusion or clerical error is currently estimated at between 1 in 5,000 to 1 in 14,000. The risk of TRLI, "transfusion-related lung injury," is unclear and has a very wide estimate ranging between 1 in 432 to 1 in 557,000.

The risk of transfusion-associated graft-versus-host disease, which is lowered by irradiation of blood, is estimated to be between 1 in 10,000 to 1 in 40,000.

Now, these are the effects of ESAs that have not been established with substantial evidence. Improved quality of life, fatigue, and other symptoms associated with anemia in cancer patients have not been established in properly conducted randomized, double-blind placebo-controlled trials. Improved survival or improved tumor control in cancer patients has not been established with the use of ESAs.

The majority of trials that we will be mentioning today have been designed to detect evidence of improved survival or tumor outcome. None of these trials have shown improved survival or tumor outcome.

Again, these are the risks of ESAs in cancer patients. First, the increased risk of thrombovascular events. This will cause increased morbidity and a potential increased mortality. This risk needs to be weighed against the benefit in reducing the proportion of patients transfused. Second, the risk of decreased survival; and, third, the risk of increased tumor promotion.

Five studies show evidence of increased tumor promotion or decreased survival. These studies had an

excessively high target hemoglobin ranging between 12 to 15.5.

The studies that are listed here, there is one study in breast cancer, two studies in head and neck cancer, one study in lymphoid malignancies, and one study in non-small-cell lung cancer.

In addition, one study shows evidence of decreased survival when the target hemoglobin was consistent with prior labeling, less than 13. This study was conducted in a variety of tumor types.

Now I will examine safety signals from different trials that led to ODAC 2004. Before we do that, I would like to provide you with an overview of the different trials that we will be talking about today and a brief discussion regarding trial design and data submission.

This slide is, hopefully, not too overwhelming. It provides a roadmap for where we have been prior to ODAC 2004 and important trials then presented at ODAC 2004 and events that have occurred subsequent to ODAC 2004.

We will be referring back to the slide at

numerous points throughout this discussion, and we will also be discussing several of these trials in more detail. A copy of this slide has been provided with your ODAC questions.

I am now going to empty out this map and build it back up. Again, as I stated at the time of original approval of epoetin in 1993, there was as theorectical concern for tumor promotion. The pooled studies that resulted in the original approval for epoetin in 1993 were not designed to assess the tumor promotion.

After the original approval in 1993, the post-marketing commitment study N93-004 in small-cell lung cancer was agreed upon between Johnson & Johnson & FDA to assess the tumor promotion potential of epoetin.

The BEST and ENHANCE studies were conducted prior to ODAC 2004 and both showed decreased survival which led FDA to convent ODAC 2004.

Now, the studies that have appeared in yellow in the right-hand side of the slide, were studies that were discussed at ODAC 2004. Now, these studies were already ongoing at the time of ODAC 2004 and according to Amgen and Johnson & Johnson were designed to answer