whether the non-small-cell lung cancer data, but certainly head and neck cancer.

Let's see, Dr. Pazdur, are we actually voting per tumor?

DR. PAZDUR: No.

CHAIRPERSON ECKHARDT: Okay. Just whether or not there should be any specific restrictions?

DR. PAZDUR: Yes. We would look at these, the FDA would look at these and make a determination on what tumor types we believe from these homogeneous trials would potentially have problems. I'm talking about more the tumor promotion issue here than a general thromboembolic issue here.

DR. LINK: I'm confused. Are you talking about studies to be done, or something to put on the label?

CHAIRPERSON ECKHARDT: No, it would be something specific on the label.

DR. LINK: There is something already on the label?

DR. PAZDUR: No, not to use them.

DR. LINK: You mean, like, not approved for

use in children kind of thing?

DR. PAZDUR: Yes.

CHAIRPERSON ECKHARDT: Exactly.

DR. LINK: Oh, okay.

CHAIRPERSON ECKHARDT: Yes. Other discussion? Yes, Dr. go ahead.

DR. PERRY: The quality of data that you have among these various tumor types is pretty variable. I don't think you have the data in breast cancer. That's a flawed study with what the authors admit is an imbalance in the arms. Wouldn't you rather have something that says "We don't want any more studies of which you're trying to hyperelevate hemoglobin levels" and look across a broad range of tumors?

CHAIRPERSON ECKHARDT: Well, I just want to make a comment. I think one of the issues that comes up when we start restricting is at what level of data are you comfortable doing that? It is a supportive-care regimen. I think we all agree that if you flip the tables and said, "Is there anything in here that is

worthy of approval in the reverse direction, you know, the data is not that solid but we're just looking at safety signals."

The question would be, based on the data that is presented today whether or not in fact there should be one of these diseases until we have more data that should be excluded from receiving this as supportive care? Again, this is treatment that does not prolong life.

DR. PERRY: Absolutely true, but I hate to tell people who take care of breast cancer patients they can't use it based on the BEST trial. I mean, if we had two or three other good trials, I might be convinced.

DR. BRAWLEY: The onus of the law, though, is the opposite, and that is, it is on the company to prove that drug is safe, not for us to prove.

DR. PAZDUR: That it's unsafe.

DR. BRAWLEY: That it's unsafe.

DR. KEEGAN: Yes. It's also a little confusing if you're going to recommend large, simple trials to then look at one of the few large, simple trials we have with survivals and endpoints and say it's

not credible. Maybe you could also clarify that.

DR. PERRY: I'm quoting from the author of the paper, he says:

"Unfortunately, because of drawbacks in the designs of the current study, a possible imbalance between groups of various risk factors and the unanticipated hemoglobin outcomes of the trial, the survival results have been difficult to explain."

You know, if the author of the trial is wishy washy about it, it's hard for me to be very definitive and say, "Gee, I'm going to make a uniform prescription against the use of this for breast cancer patients."

DR. PAZDUR: We understand this; okay. There is no perfect data that exists with all of these tumor types here. That's why we are asking the question do you think that the data that we have, because none of these studies have really addressed the population that is in the indicated population, these are safety signals, "do they rise to enough clinical concern on your part that you would say "Because of the BEST trial I don't think we should use this in breast cancer"? This is what we're asking.

CHAIRPERSON ECKHARDT: Dr. Mortimer.

DR. MORTIMER: I actually think because of the BEST trial we should not use this in breast cancer. I mean, as has already been said, the responsibility of the sponsor to convince us that this is a safe drug, not that a negative result is not negative, by not including metastatic breast cancer, then the trial, the one trial out there that is appropriately designed and powered with an appropriate endpoint would be able to be completed.

I think what we heard from the breast cancer advocacy group today would certainly indicate to us that the breast cancer patients are not enthusiastic about receiving EPO as it stands right now.

CHAIRPERSON ECKHARDT: Dr. Krook.

DR. KROOK: I really think that the group that we should not use these except in the clinical trial are the adjuvant trials. Now, Kathy over here, I mean, she talked a lot about it.

But I think unless it's in a clinical trial in the adjuvant setting and I can go colon or GI or breast and if you want to throw lung in there the same, these

are the people who don't have metastatic disease. If you have metastatic disease, it's a different situation. But these are people who are probably cured by their initial therapy.

CHAIRPERSON ECKHARDT: Dr. Richardson.

DR. RICHARDSON: I'm troubled by two of the curves that we saw today, one this afternoon, which I believe was the Mobus trial and that was the adjuvant group that was separated out. That set of curves looked very much identical to the set of curves from this morning where there was this early separation.

Here you are looking at a group of patients treated in an adjuvant setting where there seemed to be a difference in survival early on in this group, and so there is something happening I think while these patients are on treatment that seems to then disappear when they are off treatment. I find that a little troubling.

CHAIRPERSON ECKHARDT: Dr. Murgo.

DR. MURGO: I share the concerns that have been expressed, but just for clarification, I'm assuming that we are talking about precautions and in no way

talking about contraindications? Can I make that assumption?

MS. KEEGAN: Or, perhaps a statement in the indications "It is not indicated for." It would be different from an contraindication, but it would be somewhat stronger than a precaution.

DR. MURGO: I agree because I think it would be wrong to put it as a contradiction as an implication for patients that even in the adjuvant setting there might be some reason to use it.

CHAIRPERSON ECKHARDT: Ms. Schiff.

MS. SCHIFF: Yes. Two women who spoke today were metastatic and they both have lived so far for, like, eight years. I don't see why we would take them out of the mix people that we don't want to, you know, promote their tumor or we don't want to make them resistant to chemotherapy.

CHAIRPERSON ECKHARDT: Dr. Perry.

DR. PERRY: I just want to make sure my colleagues understand, my breast cancer colleagues who are among the leaders in the field, that if you say no, if you vote the way I understand, you're not going to

make it possible for any dose-dense chemotherapy to be delivered without transfusing patients. Because dose-dense adjuvant therapy for breast cancer has a --

MS. SCHIFF: It's given a lot without tranfused.

DR. PERRY: You give it a lot, but you don't give it entirely. In most of the women who get it in the trial got growth factors.

MS. SCHIFF: Speak for yourself, Dr. Perry.

A PARTICIPANT: Four percent in the sequential arm, not the combination arm.

DR. BRAWLEY: Well, I'll be unpolitic. A hell of a lot of people get growth factors because doctors make 1,200 bucks a shot off of it, not because they need it.

DR. PERRY: Agreed, but those in universities those.

CHAIRPERSON ECKHARDT: Dr. Redman.

DR. REDMAN: Well, two comments. Because you just made that, you and I can't change that, okay, number one. Number two, the BEST trial was trying to push the envelope or push revenue, either way you want

to look at it.

To condemn and say you can't use it in breast cancer to get a hemoglobin between 10 and 12, I think is inappropriate.

The side-effects or the decrease in survival or relapse was seen that I'm trying to push the drug to achieve a hemoglobin greater than any of us would do alone with blood transfusions, and now you're going to take back and say, "Well, between 10 and 12 it shouldn't probably be used, either." It doesn't make sense to me. I may be missing something; I don't know.

DR. MARTINO: I agree with Bruce Redman on this. I bring you back to the basic point that most of the information we know is patients who are treated beyond a point where any of us would tend to bring them in, and certainly way beyond a point where you would transfuse them to.

Maybe some of you think it's fair and appropriate to just sort of take that data and bring it down to patients who have hemoglobins of 9 and 10 and 11, but I'm not sure that I can honestly do that. I am functioning from a perspective of extreme lack of

 

knowledge as I'm going through these questions.

CHAIRPERSON ECKHARDT: Ms. Haylock.

MS. HAYLOCK: Just in relationship to this number two question and number three question, could you just clarify, is there different labeling language that relates to the MDS use versus cancer use in some of the comments that were made this morning by the MDS advocates?

DR. KEEGAN: The erythropoietin products that are marketed in the U.S. are not labeled for myeloid malignancies nor for MDS. We have no data that has been submitted to the Agency in support of that.

DR. PAZDUR: I would strongly echo that these are really different situations, and they really need a supplemental NDA for these indications. The sponsor really should work with us and with these groups to bring in this data to have a supplemental indication on the books.

They are much different from the situation that we are talking about with general anemia of cancer, which we are usually talking about solid tumors that are burnt out, et cetera.

I don't think there is any implication to what they various diseases were in the open public hearing and the indication of the anemia of cancer type of situation. I think those are two opposite, different things.

Unfortunately, I do not want them to get swept away with this. We will discuss with our colleagues in CMS to make sure that that does not occur.

CHAIRPERSON ECKHARDT: I think that would make us all feel better.

Dr. Mortimer.

DR. MORTIMER: If we go on the assumption that hypertreating patients is not fair to judge them in that, then it's up to the company to demonstrate that it's safe to administer this drug under other circumstances.

But I guess the other argument is, why would I treat somebody if I don't have a compelling reason that they are getting benefit from it? There is no clear evidence that quality of life has been impacted, and so I have a hard time excluding breast cancer patients from restriction because I don't see an added value to

treating them.

CHAIRPERSON ECKHARDT: Comments?

Dr. Murgo.

DR. MURGO: I guess my concern is in looking at this is that in order for the amount of information that needs to be put in here for prescribers of patients as well to understand what is meant by the specific tumor types studied. They really need to know a lot of detail.

Because, I mean, even within these tumor types there will be patients where administration of the erythropoietin would be indicated. I'm struggling with how this is going to look. In my opinion and my recommendation, there really has to be given a lot of thought to how this is going to be presented in the package insert.

CHAIRPERSON ECKHARDT: I'm not sure that we can really reconcile all of that now. I think the current issue under discussion is sort of moving towards, and again it could be complicated when it comes to writing the label, but whether or not we actually vote for tumor-specific restrictions in the indication

and the label.

Dr. Pazdur, do we need to actually make any specifics or just yes, no, we believe disease-specific restrictions--?

DR. PAZDUR: We're really not looking for disease-specific restrictions.

CHAIRPERSON ECKHARDT: Right.

DR. PAZDUR: The general concept here is what we're after.

CHAIRPERSON ECKHARDT: Well, the general concept of restricting it--?

DR. PAZDUR: This would require to a tumor type, if the FDA, and we could even bring this back to and Advisory Committee feels that there is sufficient data of a safety signal, albeit, it may be at a different hemoglobin level than is currently.

CHAIRPERSON ECKHARDT: Okay. Any other questions before we--?

Dr. Redman.

DR. REDMAN: It's tumor type, not stage?

DR. PAZDUR: We were looking at the tumor type when writing the question.

DR. MARTINO: Well, we've sort of concentrated on breast cancer here, but I'll remind you lung cancer. If you're looking for signals, lung cancer, okay, head and neck cancers, the hematological.

You know, there are other signals here. To me it's an issue of at what point you want to draw the line of are you concerned. I'm concerned with all of those but not one of those in specific.

CHAIRPERSON ECKHARDT: Then, I think that would mean a yes.

(General laughter.)

CHAIRPERSON ECKHARDT: Other discussion?

(No verbal response.)

CHAIRPERSON ECKHARDT: Okay.

DR. MURGO: One more. Again, what are we saying, I mean, the way that it's phrased right now?

CHAIRPERSON ECKHARDT: I think the idea is if you would want to entertain any disease-specific restriction with the idea that the FDA will scrutinize and have discussions and decide. But the idea is would we put any disease-specific restrictions in there?

DR. MURGO: Without being specific as to what

those might be? No.

CHAIRPERSON ECKHARDT: Today, we do not have to decide on that.

Yes, Dr. Link?

DR. LINK: I don't understand. Of course, if you had compelling data, we assume that you would come to a Committee and do it. Are you asking us do today we have compelling data to do it? That's a different question from if ever we get compelling data.

DR. PAZDUR: I think what we're looking at is the data that you have seen, and we would go over it more clearly and perhaps bring this back to the Advisory Committee.

Obviously, this would have to be a negotiation that we have with the sponsor also. We're looking basically for a general issue here of is this a reasonable way to really make sure that the drug is being used in a safe fashion.

Obviously, if we had data at the recommended hemoglobin and there was a therapy-associated death rate associated with it, we wouldn't having this discussion.

We do have these issues where we have a lot of

imperfect data here and then the subject of protection of patients. That's what we are after here with this question. I think you are drilling down to a real specific level, but we're looking at a more general issue here.

CHAIRPERSON ECKHARDT: Again, I think these are just with what we've seen which, as we all know, is safety signals but not rigorously defined data.

DR. HARRINGTON: Just one comment, then, based on what Dr. Pazdur said. I will vote yes on this, but my yes vote really includes not only strong consideration of changing the labels, but lots of hard work to get the data in that you don't have right now and to come back to ODAC with that data, not with the same data, which will remain inconclusive, but with additional data and with a crisp labeling that we can have when we look at.

CHAIRPERSON ECKHARDT: Can we have permission to sort of reformat that question within that context?

DR. PAZDUR: Okay.

CHAIRPERSON ECKHARDT: Thank you. Oh, this is like the ASCO Board, I think.

(General laughter.)

CHAIRPERSON ECKHARDT: Okay. We're actually voting -- if you vote yes, then it's within the context of obtaining outstanding data with significant review, probably another discussion at ODAC rather than merely making that decision based upon data presented today.

DR. PERRY: That's review of studies with normal hemoglobins rather than super hemoglobins?

DR. KEEGAN: I think it will have to depend upon with we get.

DR. ALBAIN: Will we have another chance to ask the question about adjuvant settings, then, broadly? Because now the way you're rephrased this, then I'm not quite sure here. The question is very different.

CHAIRPERSON ECKHARDT: The original question really revolved, was even sort of stage-independent or it was based upon disease-specific restriction on the label.

I think what we're revolving towards is some insecurity with regards to just the data presented today and the fact that there probably would need to be more scrutiny of the data. Again, it could be looking more

closely at the adjuvant data.

Well, I mean, but again what we have to decide is if the vote is yes, you're saying yes with the idea on the available data, but what we've just said is perhaps that would be after obtaining the data that is outstanding and looking at it and probably coming back to another ODAC meeting before making that definitive decision.

If it's no, it essentially means forget it. We're not going to worry about it. We're going to wait until additional data comes in.

DR. MARTINO: I think what I would love to be able to do is to give the FDA my endorsement. I can't use the word authority because I have no such, but my endorsement that you have the right to say to the pharmaceutical company "You can't use it in breast cancer, you can't use it in this," you know, that you can be that specific. Is that what you want from us?

DR. PAZDUR: In a sense, but I think the issue here is the safety signals are not perfect because they are being used in higher hemoglobins. Does that level in that different population rise to a level that you would

say "I'm not going to use this in breast cancer at all"? Okay?

CHAIRPERSON ECKHARDT: Dr. Link.

DR. PAZDUR: We are asking the question, this is an exploratory question, and we're throwing it out. Obviously, we've had difficulty with it, or we wouldn't be asking you, the gurus.

CHAIRPERSON ECKHARDT: Thank you.

Dr. Link.

DR. LINK: Okay. You've got me confused now. Why don't we vote on do we have enough data today to endorse that you're going to put restrictions on the label based on what you have without anything further? Because that's what the original question was. I don't mind voting on that.

I agree with what you just said. Obviously, if something turns up, I think you would be remiss if you didn't sort of explore it further. That would be a separate question, though.

CHAIRPERSON ECKHARDT: We will go back to the more simple question, which is basically again on the data available and presented today, whether or not we

would recommend that there be disease-specific restrictions.

Yes or no, Dr. Murgo?

DR. MURGO: Murgo, no.

DR. KROOK: Krook, yes.

DR. REDMAN: Redman, no, for its current marketing authorization.

DR. MARTINO: Martino, yes.

DR. ALLEGRA: Allegra, yes.

DR. LINK: Link, no.

MS. HAYLOCK: Haylock, yes.

DR. HARRINGTON: Harrington, no.

DR. DOROSHOW: Doroshow, yes.

DR. MORTIMER: Mortimer, yes.

CHAIRPERSON ECKHARDT: Eckhardt, yes.

DR. RICHARDSON: Richardson, yes.

DR. PERRY: Perry, no.

(General laughter.)

MS. SCHIFF: Schiff, yes.

DR. BRAWLEY: Brawley, yes.

DR. ALBAIN: Albain, yes.

DR. STRONCEK: Stroncek, yes.

 

CHAIRPERSON ECKHARDT: Twelve yes, five no.

Okay. Let's move right along to the next question. Again, here we are starting to drill down on the definition of anemia.

The question is whether or not we should define a hemoglobin level in asymptomatic patients at which ESAs should be initiated. I guess this comes about with regards to some discrepancy between what we use for transfusion and what is often used for ESAS. Now, the other idea here was to proposed the baseline hemoglobin level. I would love to hear some disease on that.

Dr. Perry?

DR. PERRY: First, let me ask a very simple question of our Chairman. What are normal hemoglobin levels in Denver, Colorado?

(General laughter.)

CHAIRPERSON ECKHARDT: That isn't fair.

DR. PERRY: No, I think that's very fair. Hemoglobin levels are very different at altitude and your levels in your lab are very different when you are in the Mile-High City than in Columbia, Missouri, which

is 777 feet at the courthouse steps.

I think it is a little bit difficult to make one hemoglobin level fit everybody at different altitudes. I think the people who are going to suffer is probably the people in Denver because they will have a higher need a lower hemoglobin level.

CHAIRPERSON ECKHARDT: I believe those can be indexed to altitude.

(General laughter.)

CHAIRPERSON ECKHARDT: Dr. Brawley.

DR. BRAWLEY: I will just point out that one key factor that we all have to keep in mind here, and correct me if I'm wrong, it generally takes at least three to four weeks for people to start responding to an erythropoietin. To say we are going to start at seven because we transfuse at seven is probably not reasonable.

CHAIRPERSON ECKHARDT: I would agree.

Dr. Murgo.

DR. MURGO: My suggestion would be to base it according to what the endpoints in the studies were. The endpoint in the study was to see if would reduce

transfusion requirements in which case decisions as to whether to treat a patient with EPO would be based on whether a transfusion is indicated. I'm not sure how to word that in the package insert. Obviously, there will be patients who raise some hematocrit during anemia for those where if the EPO wasn't available you would be contemplating blood transfusion.

CHAIRPERSON ECKHARDT: Other comments?

DR. HARRINGTON: This is where we need more studies? A reduction study as part of a randomized trial would be very helpful here.

CHAIRPERSON ECKHARDT: Dr. Mortimer, did you have a question?

DR. MORTIMER: No.

CHAIRPERSON ECKHARDT: Other comments?

DR. MARTINO: I am most concerned with not so much our setting a lower limit, because I think judgment has to do into setting at lower limit, but rather in what we make the objective of these agents.

The objective has become to get them to a hemoglobin of 12 at least. That's the way most physicians trend to practice is to try to get them to a

minimum of 12; okay.

I'm actually more concerned with that being still the goal by which people practice as opposed to what I see in the new wording, but which I'm not sure people are understanding or using, which is that you give these agents to a point that relates to when you might transfuse a patient. Obviously, I didn't read ahead, but I trust you all get my point anyway.

CHAIRPERSON ECKHARDT: You're commenting on what the higher threshold is?

DR. MORTIMER: Right.

CHAIRPERSON ECKHARDT: Any other comments? Because, I mean, one of the issues could be that we don't necessarily think that it's indicated to define. That's really the new thing is defining the threshold.

DR. KEEGAN: One concern is that we are aware that one interpretation of our labeling is that as soon as your hemoglobin is less than 12, meaning, 11.9, there are community physicians who believe you are now eligible to begin ESAs.

CHAIRPERSON ECKHARDT: You are, that's correct.

DR. KEEGAN: Right. I guess the question is, is that an appropriate practice, particularly since it's being driven by the labeling? In that setting should we reconsider some clarification? Certainly, the clinical study section doesn't suggest 11.9 to find a patient population.

CHAIRPERSON ECKHARDT: Dr. Link.

DR. LINK: I'm hoping that there is some data on this. When they came in for the indication for chemotherapy-induced anemia, what were the starting points that were recommended, and did it accomplish what it was supposed to accomplish?

DR. KEEGAN: I believe eligibility criteria said a hemoglobin of less than 11, so it was 10 or 9, in that range.

DR. LINK: Because I think we have to somehow balance what Otis said about, you know, you can't wait until their hemoglobin is five and then start it. I mean, they managed to get it through before with some study that had some guidelines, so I presume that that's a starting point at least.

CHAIRPERSON ECKHARDT: Ms. Schiff.

MS. SCHIFF: I think the problem has been that a lot of doctors give it to prevent, in terms of prevention, so they are preventing you from getting anemia as opposed to anemia.

CHAIRPERSON ECKHARDT: Yes, okay.

DR. REDMAN: I'm an academic oncologist, and I'm going to step into the community for a minute. Everybody is saying "I think they do this. I think they give the EPO to try to prevent a transfusion.

When our hemoglobin is 14, I think they give EPO, when a hemoglobin is 13 or 12.9. It's wonderful to think that. Is there data that suggests that they are actually doing that?

CHAIRPERSON ECKHARDT: Yes.

DR. REDMAN: Where?

A PARTICIPANT: I'm a community physician and I do plenty of audits for every three cooperative groups.

DR. REDMAN: And that's published.

DR. BAYNES: No.

DR. BRAWLEY: Does the company have that data? I seem to remember 40 percent of EPO is off-label

indication coming from the company? Am I misremembering?

DR. BAYNES: If could get to the slide of utilization.

(PowerPoint presentation is in progress.)

DR. BAYNES: I can tell you that basically we have extensive chart audit review. In fact, the vast majority of ESA use is in fact within label and indeed it is extraordinarily rare for someone to be starting of hemoglobins above 12.

We also have done significant data looking at early versus late intervention, that is to say, starting at a hemoglobin between 10.5 and 12 versus waiting until people get under 10.

Indeed, when we look at those data, there is certainly a transfusion benefit to early intervention. In fact, that has been looked at in a systematic review published by Dr. Gary Lyman including five control studies that have looked at that, and indeed there is benefit in terms of reducing transfusion burden to early initiation. In fact, practice guidelines indicate that it's very reasonable, too.

Slide on.

(PowerPoint presentation is in progress.)

DR. BAYNES: Let me just show you the slide first. This is basically looking at when do physicians transfuse. This is from placebo-control data.

In fact, if we look at the hemoglobin level prior to any transfusion, roughly, 41 percent are below, at least the chart review data. Forty-one percent are hemoglobins less than 8, 52.9 percent are between 8 and 12 for transfusion.

This is the position here, prior to first transfusion with chart type reviews. This is where transfusions are used. When we actually look at the data around ESA use, in fact the use is generally following practice guidelines.

In fact, there are two practice guidelines, ASH/ASCO, which is suggested at 10; and in fact NCC, which suggests 11. In fact, most practicing physicians follow the guidelines used.

CHAIRPERSON ECKHARDT: All right. Thank you.

Let's move on with this vote because I think it's not exactly rocket science. The idea is whether or

 

not we think it's important that in the label that we would be defining that lower threshold. Yes means yes, and then we may want to try to think about what that is. No means that it would be given according to the current guidelines set up by either society.

Let's see, we're starting with Dr. Strocek.

DR. STRONCEK: Stroncek, yes.

DR. ALBAIN: Albain, yes.

DR. BRAWLEY: Brawley, yes.

MS. SCHIFF: Schiff, yes.

DR. PERRY: Perry, yes.

DR. RICHARDSON: Richardson, yes.

CHAIRPERSON ECKHARDT: Eckhardt, yes.

DR. MORTIMER: Mortimer, yes.

DR. DOROSHOW: Doroshow, yes.

DR. HARRINGTON: Harrington, yes.

MS. HAYLOCK: Haylock, yes.

DR. LINK: Link, yes.

DR. ALLEGRA: Allegra, yes.

DR. MARTINO: I'm not sure I understand the question. Am I agreeing that we will set the level?

CHAIRPERSON ECKHARDT: Yes.

DR. MARTINO: Then, my answer is no, Martino.

DR. REDMAN: No.

DR. KROOK: Krook, yes.

DR. MURGO: Murgo, yes.

CHAIRPERSON ECKHARDT: Fifteen to two, yes.

Dr. Pazdur, did you want us to define the level right here and now?

DR. PAZDUR: No, let's move on.

THE PARTICIPANTS: Let's move on.

DR. PAZDUR: I wouldn't want to confuse it with what it should be in the Elks, for example.

CHAIRPERSON ECKHARDT: The Colorado adjusted threshold.

Now, I think this next question is an important one because certainly what we have seen are a lot of studies at the higher level of hemoglobin, and so the question would be currently the label says not to exceed 12 grams per deciliter. Should we be thinking about lowering that higher threshold? If so, probably in another meeting we would define at what level it should be suspended.

I think importantly we should think about

whether or not we have concerns about the current 12-gram limit. I'll take some discussion.

Dr. Link.

DR. LINK: I'll just make one comment. We saw some data about people sort of hovering in the anemic but not symptomatic zone, even though they don't need a transfusion, but I didn't see any data like quality of life or things like that that would help us with saying whether it is better to hand out at 9 or 10 or better to hang out with 11 and 12 in terms of the advantage or disadvantage. If you have some data, it might be nice to see.

A PARTICIPANT: I wonder if you could interrelate data because we have sort of forgotten the geriatric population who might do better with more --

DR. CRAWFORD: Maybe I could just present this one more time. Clearly, what we saw from the randomized trials was when the hemoglobin was restored towards the range of 11 to 12 in the ESA-treated patients whose quality of life was better than the placebo control.

We saw that in the Littlewood data where the hemoglobin was in excess of 11 in the treated and where

quality of life was clearly better in the placebo group who hovered in the high nines throughout the treatment.

(PowerPoint presentation is in progress.)

DR. CRAWFORD: From this data, slide on, again, this is a general relationship against a cross-section analysis, looking at patients throughout their treatment course, looking at quality of life measures, and the hemoglobin at that time.

It shows that there is a higher average quality-of-life score at higher hemoglobin levels than lower levels. That 10 to 12 range corresponds then with the range at which signs and symptoms of anemia would be less and where the risk of transfusion could be lower by restoring hemoglobin to that level.

As we mentioned, all the data, there is a 30 percent risk. If your baseline hemoglobin is 12, you have a 30 percent risk of transfusion in the absence of an ESA. That rate just goes up higher as you go down further. I think that the lower you set the level, the higher the risk for transfusion will be even with the ESA.

Data looking at the sexes, there is not a

clear difference. A hemoglobin of 12 seems to hold up for both men and women.

CHAIRPERSON ECKHARDT: Dr. Albain.

DR. CRAWFORD: I don't think there has been enough age-related data that sorts it out.

DR. ALBAIN: What, practically speaking, is the difference between the score at 10 and the score at 12 in terms of what the patients are telling you met the -- no, the score of what, 47 to 55? What are we talking about in that range?

DR. CRAWFORD: Well, normally, if you look again, going back to the Littlewood data, and I don't know if we want to show that slide by comparison --

DR. ALBAIN: No, just in general.

DR. CRAWFORD: If you are looking for a clerical significance, you're looking for about a 10-point difference. You don't see that here, but that's because all these patients are being treated with ESAs.

DR. ALBAIN: Well, that's my point.

(PowerPoint presentation is in progress.)

DR. CRAWFORD: If you look at the placebo data here -- slide up -- this is what happens. When you

restore hemoglobin to the range of 12, this is the improvement you see in the FACT scores. Those are all in clinically significant ranges by improvement.

In the absence of the use of an ESA, you actually see the decline in quality of life, and so those differences are substantial in terms of what patients can measure. The next slide is --

DR. ALBAIN: Don't. My next question is, are we talking about someone who is very independent and feeling great versus they really weren't and they were sitting on the couch all day? Are we talking about statistically significant changes in a narrow range of the score based on numbers?

DR. CRAWFORD: Again, David Sullivan is sort of an expert on this, but he has defined this as clinical significance as a three-point difference in these scores by the FACT. These all exceed that, particularly compared to the placebo group.

Those are less fatigue, more energy, better quality of life -- all self-reported scores and all issues that I know the FDA is still questioning about some of those markers.

Here is a slide on the linear analog scale that I think was also shown by Paul that also shows the same kind of data. It shows that spread of at least 10 points between the placebo group, who again are hovering around 9, and the group that is up in the 11 to 12 range. That is the range at which we're talking about these differences.

Again, it corresponds with being symptomatic or not symptomatic. To me it's not just an issue of transfusion; it's an issue of quality of life in these patients, whether you want them to be symptomatic through their treatment or whether you can improve that.

CHAIRPERSON ECKHARDT: All right. I think the FDA has a comment.

MS. BURKE: Hi. My name is Lori Burke and I'm in the Study Endpoint and Label Development in the Office of New Drugs. I work with the Office of Oncology Drug Products when we are looking at quality of life data and patient-reported outcome measures.

We have looked at a lot of the quality of life data associated with some of these studies. The measures that are used, we had referred earlier to the

fact that we have problems with the measures of the health-related quality of life data.

The problem is because we don't always know exactly what the measure is capturing and what it's not capturing. When we are talking about fatigue and vitality, those are very difficult concepts to measure.

In fact, there is a lot of consensus in the measurement world that this is a problem and their impact two separate consortia of drug company-supported that are trying to develop measures of fatigue, cancer-related fatigue, fatigue related to chemotherapy or fatigue related to the actual oncology condition and the anemia of cancer.

We have very different things. It is very difficult to measure. We don't know what we're talking about really. Patients, they don't talk in terms of fatigue and vitality; they talk in terms of weakness or tiredness or exhaustion or energy. Or, they might even be talking in terms of discouragement or depression. It's a component of depression, a component of their mood.

All of these things need to be sorted out in

order to be confident that we know what we're measuring and what the results are and that we can make conclusions based on this improvement that we are seeing with these measures.

CHAIRPERSON ECKHARDT: All right. Thank you.

DR. KEEGAN: The other question is we've seen several times that slide that shows hemoglobin and quality of life. I think I heard a comment that sort of confronts what my suspicion was about that slide which was that all of the patients on that curve received an ESA, so in fact that curve does not tell you anything about drug-related effects. It is simply responder analysis. It doesn't mean that the drug in fact caused any of those things to occur. I wanted to be sure that the group listening was understanding that difference.

CHAIRPERSON ECKHARDT: Yes, thanks.

Dr. Link.

DR. LINK: Well, actually what I was asking for and wondering is if there are similar to that and people who really got transfused. In other words, blood bankers must know that if your hemoglobin -- like, I'm a pediatrician so people hanging around at six aren't

asymptomatic.

But they must know about why we've got transfusion guidelines about why it's better to be at a hemoglobin of 11. If we have that data, it wouldn't be confounded by exactly what you're talking about. We would just know where to set the bar.

DR. KEEGAN: You would get that from placebo-controlled trials, which, as I said, we haven't actually seen, so it's very hard for us to comment on any of this data.

Another nuance of setting the upper limit of the threshold is also that we don't know if the risk factor is driven by the hemoglobin itself or if risk with ESAs are partly driven by dosing and different patients require different doses to get to a hemoglobin level.

You might want to consider that when you're talking about maximum hemoglobin achieved, should there also be some consideration of maximum dosing.

CHAIRPERSON ECKHARDT: Dr. Murgo.

DR. MURGO: Yes. I have problems with interpreting those type of data. Because, I mean, sure,

people who are anemic significantly or have significant anemia have fatigue; they don't feel well. The drop in hemoglobin sometimes, and maybe often, goes hand in hand with the other effects of chemotherapy there again.

I don't think you can relate it, the level of hemoglobin directly with the qualify of life. Plus, some patients, I think it's the minority of patients, actually when they see their hemoglobin, it doesn't make them feel all that great.

But I think the bigger problem is interpreting what is due to the hemoglobin and what other effects of the chemotherapy is doing on the patient's status, and also the disease. I think it is problematic even in our blinded study.

CHAIRPERSON ECKHARDT: Essentially, this question is just asking should we lower that upper threshold. I think what we have seen is that it is mainly sort of this quality-of-life data that would support that 12 is better than 10, better than 11.

What we don't know, because we have not seen any dose-response relationship between the other more negative issues like the thromboembolic events and we

also have no idea if there is any such disease promotion, how that relates as you go up the hemoglobin scale.

I think that is sort of the question. Does anybody feel comfortable or feel that we have sufficient data that we should propose a lower ceiling to that hemoglobin? You know, I think all we have going for keeping it at 12 is quality-of-life data. On the other hand, it's sort of the standard level.

DR. REDMAN: If I'm reading this correctly, the current package insert says "Each patient achieve and maintain the lowest hemoglobin level sufficient to avoid the need for transfusion," which leaves it up to the physician, "and not to exceed 12." It's not saying you have to stop at 10.5.

CHAIRPERSON ECKHARDT: Right, and that's the question.

DR. REDMAN: Yes.

CHAIRPERSON ECKHARDT: Any other discussion? People understand what we are voting on?

DR. PERRY: Well, just one comment. I don't think that we know whether there is a relationship

between the dose of the ESA and the adverse events or merely whether it's the presence of the ESA.

DR. PAZDUR: Correct, correct.

DR. PERRY: You could be getting an ESA at a hemoglobin of eight and get a clot as well as you could getting a hemoglobin of fifteen. I think we have to take that part out of the equation.

CHAIRPERSON ECKHARDT: No, that's what I'm saying is we don't have any of that dose response. We clearly even at the higher dose levels were not really shown that.

Okay. This question, then, would be voting for yes or no to lowering the threshold from the package insert of 12 grams per deciliter; correct, Dr. Pazdur?

DR. PAZDUR: (Moving head up and down.)

CHAIRPERSON ECKHARDT: Okay. I think we are pretty clear on that. Any other discussion?

(No verbal response.)

CHAIRPERSON ECKHARDT: Okay. Which side are we starting on.

DR. MURGO: Just a brief question. There is language in there should dosing be titrated to avoid

transfusions currently in the--?

CHAIRPERSON ECKHARDT: Yes.

DR. MURGO: That's currently?

CHAIRPERSON ECKHARDT: Yes.

DR. MURGO: We are just voting on a level; okay. Do you want me to start?

CHAIRPERSON ECKHARDT: Yes.

DR. MURGO: Murgo, yes.

DR. KROOK: Krook, yes, eleven. The second part of the question says specify what each should be, what dosage, so I did eleven.

DR. REDMAN: Redman, it's fine as it is.

CHAIRPERSON ECKHARDT: That's a no?

DR. REDMAN: That's a no.

DR. MARTINO: Martino, no.

DR. ALLEGRA: Allegra, yes.

DR. LINK: Link, no.

MS. HAYLOCK: Haylock, no.

DR. HARRINGTON: Harrington, no.

DR. DOROSHOW: Doroshow, yes.

DR. MORTIMER: Mortimer, no.

CHAIRPERSON ECKHARDT: Eckhardt, no.

 

DR. RICHARDSON: Richardson, no.

DR. PERRY: Perry, no.

MS. SCHIFF: Schiff, yes.

DR. BRAWLEY: Brawley, yes.

DR. ALBAIN: Albain, no.

DR. STRONCEK: Stroncek, no.

CHAIRPERSON ECKHARDT: Oh, we need a check. Okay, so let's move on to the next question, which has to do with the duration of use. As you know, the label specifies that this is for chemotherapy-induced anemia. I think one of the concerns has been that when patients complete -- I think there are two concerns.

One is how long should these be given post-chemotherapy completion with a typical cytotoxic regimen. I think the other concern could potentially be whether or not the use of this needs to be reevaluated when a patient is starting a new regimen which, in fact, may not require an ESA. I would like discussion on this question.

DR. PERRY: Are you treating the hemoglobins or are you treating the chemotherapy regimen? I mean, if the patients hemoglobins fit the criteria, then I

think they justify treatment. If they get to a less myeloexpressive regimen, then their hemoglobin levels will go up and they won't need it, because of what we just voted on before. I think it's moot question.

CHAIRPERSON ECKHARDT: How long would you -- I think one of the parts of this question is in a patient who actually, in fact, has finished their chemotherapy regimen for the time being, how long would you continue the ESA post-chemotherapy?

DR. PERRY: I don't think we need to specify, because I don't everybody is going to return to the same level, but I think most people would continue it until they got up to their 11 or 12 and then stop then.

DR. KROOK: Or, have no response.

DR. PERRY: Yes. To me this is a whole lot less important question than all the other things we have discussed.

DR. MARTINO: Can I argue that at a bit?

DR. KROOK: Have at it.

DR. PERRY: Not that we've ever argued before.

DR. MARTINO: Doctor, absolutely not.

Recognize that one of the trials that was

shown was a trial in patients with cancer who have anemia who are not being treated with chemotherapy where we saw that there is a detriment to their survival, okay.

With that study, which is one of the studies that led to today's meeting, is there a point in a patient where you are planning to not treat any further, yet whose hemoglobin is not rising?

DR. PERRY: It's not rising, but it is stable after the therapy.

DR. MARTINO: Do you mean to treat them at that point? Because they get into this other group of having cancer anemia but not chemo where we have shown that there is a worse survival.

CHAIRPERSON ECKHARDT: Exactly. That's true, the crux of the question there. I would say that a lot of clinics' support staff patients do end up on these agents after having completed their chemotherapy because they still continue to have an abnormal hemoglobin.

DR. PERRY: It also depends on which chemotherapeutic agents you are using. I mean,

fortunately nobody uses nitrosureas anymore. But if we did, you would have to say we have to treat these people for at least six to eight weeks after their completion of their chemotherapy to get them back up to where they ought to be.

DR. MARTINO: I think that's issue.

DR. PERRY: Ron slapped me because he remembers the nitrosurea.

MR. MARTINO: I think that's the issue is do we want to set at least a conceptual framework so that eight months later, because they got chemo eight months previously and they are still anemic and dying, that we still continue because they were on chemo before. That is the point we are trying to get at.

CHAIRPERSON ECKHARDT: I think the number out there was 90 days, right, from some of the groups, ASH and others. Any other questions? Discussion?

(No verbal response.)

CHAIRPERSON ECKHARDT: The vote on the last question, number four, was 6 yes and 11 no.

Let's see, this time we start over here, Dr. Stroncek. Again, what we are voting on is

recommendation of discontinuation regards post-chemotherapy.

DR. STRONCEK: Stroncek, yes.

DR. ALBAIN: Albain, yes.

DR. BRAWLEY: Brawley, yes.

MS. SCHIFF: Schiff, yes.

DR. PERRY: Perry, yes.

DR. RICHARDSON: Richardson, no.

CHAIRPERSON ECKHARDT: Eckhardt, yes.

DR. MORTIMER: Mortimer, yes.

DR. DOROSHOW: Doroshow, yes.

DR. HARRINGTON: Harrington, yes.

MS. HAYLOCK: Haylock, yes.

DR. LINK: Link, yes.

DR. ALLEGRA: Allegra, yes.

DR. MARTINO: Martino, yes.

DR. REDMAN: Redman, yes.

DR. KROOK: Krook, yes.

DR. MURGO: Murgo, yes.

CHAIRPERSON ECKHARDT: Sixteen yes, one no.

DR. MARTINO: We haven't set a time? We simply have conceptually agreed that there should be a

limit?

CHAIRPERSON ECKHARDT: That's correct.

DR. PAZDUR: Evaluation.

CHAIRPERSON ECKHARDT: Number six is somewhat of a touchy-feely question.

DR. PAZDUR: Let's see how much we can disagree on this.

(Simultaneous discussion.)

CHAIRPERSON ECKHARDT: It's cancer anemia versus chemotherapy.

DR. PAZDUR: A big issue here, if I could formulate the big picture here, obviously the indication is for anemia secondary to concomitant chemotherapy. There is a study out there that shows, as Dr. Martino pointed out, an anemia of cancer unrelated to chemotherapy, a detrimental effect on survival.

DR. KEEGAN: And no benefit.

DR. PAZDUR: And no benefit. Do people feel that in the general practice of oncology people are making this analytical distinction. If not, how can we better really drive home this point? There is so much we could with product labeling here, but do people

 

perceive this as a problem?

CHAIRPERSON ECKHARDT: Well, I think it's a huge problem, but we started out with that problem, which is the ad campaign problem.

DR. MURGO: Being in the community, I think it is a big problem. At least watching the community clinics I'm at, it is commonly given even by primary care physicians who people's hemoglobin is dropping, not necessarily having cancer, but it's there.

I think that, again, I don't know whether you can use the same system that's been used, whether you can have the people in the company somehow make that better known or the sponsors, but grandpa with his anemia and not treatment isn't going to get any better.

CHAIRPERSON ECKHARDT: I guess the question is could you do anything like what's on cigarettes where it's kind of that scary thing?

(General laughter.)

CHAIRPERSON ECKHARDT: Dr. Murgo.

DR. MURGO: Well, I think something can be done, but it's probably beyond the scope of the Office of Oncology.

I think that maybe the Office of Oncology can work hand in hand with DDMAC -- is that what it's still called -- to make sure that whatever advertisement or promotion the companies put out doesn't send a message, it might be consistent with what is in the package insert, but it's sending the wrong message. I think that that's an important thing, that should be at least available for patients to actually understand.

CHAIRPERSON ECKHARDT: Ms. Schiff.

MS. SCHIFF: Yes. Unfortunately, I think that we have to combat a campaign that set the wrong tone for the doctors and the patients. How do you do that?

I think we have to reach the advocacy groups. I went on a website and found that the warnings are not on some of the oncology websites. I think we should ask for ads on TV, specifically corrective ads that say that what was done in the past was wrong. I mean, we have to get patients reeducated.

CHAIRPERSON ECKHARDT: Dr. Martino.

DR. MARTINO: Two things, one, is that I'm losing my train of thought here. The primary issue I wanted to just remind people of is that myelodysplastic

syndrome falls into this category, and I do think that we have to recognize them as a group where the question needs to be asked.

Because there you have people who are very transfusion-dependent for prolonged periods of time where decreasing transfusions probably is a real benefit to them, which is a different sort of circumstance than patients who are in the hospice mode, okay, where we are doing things not for the patient but rather for the family and the doctor; okay. I just want to be sure that we don't sort lump those patients into this category.

I think the problem has been that physicians themselves, okay, have also been sold the concept, rightly or wrongly, that in fact quality of life is very much improved as you use these agents. If grandpa is about to die tomorrow, but if I can make his last two hours a little bit better, well, surely I mean to do that.

Now we have at least study in this population that says "But, but, but grandpa might die sooner." I think once we as physicians understand that and then

communicate that to our patients, I think the problem is solvable.

The idea that somehow we're going to get the pharmaceutical company to put up an ad that says "Gee, we're sorry that we misled you" ain't gonna happen; okay.

But I do think you do have the proper avenue, which is physicians knowing that they have to modify the concept with which they have approached these agents.

DR. KROOK: (No microphone, inaudible.)

CHAIRPERSON ECKHARDT: Ms. Haylock.

MS. HAYLOCK: I was thinking there could be just a sort of blanket statement or blanket patient education and professional educational materials that could be distributed to all the grassroots advocacy groups, like, PDQ, State of the Science, and the Office of Cancer Communications, ACS literature, ASCO's "Patients Living With Cancer," all of those websites where patients go, what is it, ACOR, the "Association of Cancer Online Resources."

All these places that cancer patients and cancer survivors go to find literature, I think it would

be helpful if all this information would be put there. You know, what is cancer-related anemia, what are the signs and symptoms, what can you do about it, and differentiate that from what is anemia associated with chemotherapy, or MDS, all those things.

CHAIRPERSON ECKHARDT: Other comments?

DR. MURGO: I mean, one other avenue, and I don't know if this is not the forum to discuss it, but some safety issues do rise to the level where certain communications can be placed on the FDA website, patient information, whether this fits into that or not.

In my personal opinion, I think it does, and that would be a place where patients could actually have access to the information and benefit from certain information.

CHAIRPERSON ECKHARDT: You have a comment?

MS. SCHIFF: I just wanted to ask the FDA, I was under the impression that you do have authority to ask for a corrective ad. Is that correct or not?

DR. PAZDUR: I would really have to check into that. From a legal perspective, I really can't give you advice on that.

CHAIRPERSON ECKHARDT: Other comments?

(No verbal response.)

CHAIRPERSON ECKHARDT: Then, we will move on to our last question, which I think is just in my view would be burning trials at the end of today that you can envision that should be recommended to sort of sort some of these issues with regards to tumor promotion, vascular events, and so on.

DR. KROOK: Yes. The obvious one, which probably, as Mike Perry says will never be done, is a placebo-controlled ESA. The only thing I can see is to piggyback to other clinical trials in metastatic breast somehow.

I think that is the only way you are going to get the answer. You can't have somebody taking off, I mean, at great chance of placebo; so, I think it has to be piggybacked on to other clinical trials.

CHAIRPERSON ECKHARDT: Dr. Brawley.

DR. BRAWLEY: Yeah. A couple of issues. You know, we've seen a lot of sleight of hand here where survival trials are shown that don't meet their endpoint and then we decide that they don't show that they drug

 

is harmful.

What we really need is a well-set-out trial with one good primary endpoint in one or a limited number of diseases. I think that is probably the absolute best thing that we can do for the public health. I'll stop at that point.

CHAIRPERSON ECKHARDT: Okay.

Yes?

DR. REDMAN: I'm all for clinical trials as an executive officer of Southwest Oncology Group. However, most of the trials you're talking about, to answer to this question, are going to be Phase III randomized and you're going to tack on this to a Phase III randomized, which is usually evaluating an investigational therapy against a standard therapy. Now you have two variables.

I don't think it will be done as a standard of care randomized trial versus another standard of care and tagging on this. I don't think it will ever be done, and in fact I think times have changed. Those aren't the priorities of what we need to do in the treatment of cancer.

CHAIRPERSON ECKHARDT: Other comments?

DR. MARTINO: Well, one of the things I would love to see happen is to get rid of all of these trials where they are using doses that we have already decided we don't think are appropriate.

I mean, these folks are spending a hell of a lot of money and time to answer questions that I think we have already sort of said we ain't going to accept.

I realize, again, I have no power, but that would be my thought. I'm just seeing an awful lot of work being done that we are going to throw out.

DR. PAZDUR: Many of these were ongoing, Silvano, and completed.

CHAIRPERSON ECKHARDT: Dr. Harrington.

A PARTICIPANT: (No microphone) All of these trials were stopped in 2003-2004.

DR. BRAWLEY: That's true for J&J. Is that true for Amgen?

CHAIRPERSON ECKHARDT: Dr. Harrington.

DR. HARRINGTON: I think the best possible trial that people are recommending would be the placebo-controlled trial, but I also think it would be very, very hard to do that having seen many no-treatment

control trials fail.

I guess what I would urge is a trial of dose reduction, I mentioned it earlier, or a trial of lower targets for hemoglobin. Let's back our way down to see if, in fact, while standard of care seems to include using these agents, we can begin to reduce the exposure burden and maybe begin to see where there is a dose-response relationship.

CHAIRPERSON ECKHARDT: Other comments?

MS. HAYLOCK: I just can't but wonder what is the relationship of stage of disease in comorbidities. All small-cell is not the same and all breast cancer is not the same. All of these just talk about site-specific as opposed to the stage of disease.

CHAIRPERSON ECKHARDT: All right. Well, if there are no other comments, then I would like to thank everybody. I think we have had a very lively discussion.

DR. PAZDUR: Thank you.

(Whereupon, at 4:13 p.m., the meeting was adjourned.)

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