slide here with respect to the question of dosing by week on study. These patients again did start at 10 mg. Median time to response was between 4 and 5 weeks.

Most of the responses that we observed were in the context of dosing at this 10 mg level. Again, there was a period of interruption typically in the first several weeks of therapy, which again correlated with the time where we were suppressing or eliminating the malignant clone and before we saw these improvements in the bone marrow with the resolution of the cytogenetic abnormalities and the restoration of a more normal bone marrow morphology.

[Slide.]

So, to kind of summarize that, if we look at our actual dose the patients were receiving in conjunction with the time when their transfusion independence response started, that dose was 10 mg. It is quite possible that some patients or many patients would respond as well if we started at 5.

This is what we did, and it worked in

terms of getting a very high transfusion independence response rate, and again, we feel that with the appropriate monitoring and adjusting the dose to the individual patient tolerance, that we have a very effective treatment regimen.

We will continue to work to refine the dosing and to understand if there is anything we can do differently in the future that would further accentuate the risk-benefit of the drug, but we think that today, we have a very good regimen in terms of both effectiveness and safety.

DR. HUSSAIN: I just want to get back with you. You obviously don't necessarily believe what you said, because you are choosing to go to a 5 mg dose in your prospective Phase III trial, correct? Did I not see that there was a 5 mg dose? You obviously, I mean you--

DR. DeLAP: We believe in the safety and effectiveness of the 10 mg starting dose. We believe in the validity of testing other doses to see how they will perform, and certainly in the future, if the discovery is that the 5 mg dose is

perfectly sufficient to get a good benefit, then, that is where we would go.

I would remind you, though, that we are already dosing these patients at 10 mg, whereas, patients with other malignant conditions generally, they are tolerating doses of 25 or 30 mg.

We have reduced the dose because we needed to, because the deletion 5q patients are more sensitive, but it is the malignant or the dysplastic clone what is sensitive here, and the question is how far down do you want to go on the starting dose, because what you are seeing, true, it's a toxicity, but it is also reflecting the pharmacologic activity of the drug against the dysplastic clone.

DR. HUSSAIN: And why you chose not to do a Phase III trial when you were asked to do that?

DR. DeLAP: We are proceeding in an orderly sequence here. We started with a Phase II pilot study that indicated to us that this drug had special promise in this subpopulation of MDS patients, and then we had the two, as Dr. Burton

showed in his introductory slides, we then went to the two basically identical expanded Phase II trials, but we separated out the deletion 5q from the non-deletion 5q, so that we could really see if what we had found in the initial pilot study would hold up with a much larger Phase II experience, and it has.

We are going to go to Phase III. We are going to be doing a placebo-controlled trial. I have to say that in discussing that trial with the investigators, there is actually reluctance to put patients on placebo for very long based on the benefit that has been seen here.

So, what we were able to work out was a plan where everybody receives the best standard supportive care, of course, with transfusions and other supportive care that they need for this condition.

The patients who receive placebo, receive that for 4 months. If they are not responding, and we think that essentially, none of them are likely to respond from what we know, then, they will have

the opportunity to go on to lenalidomide and continue on that as long as that seems to be benefiting them.

We will be looking at taking advantage of that design, as Dr. Pazdur alluded to, to look at some more of the time-to-event endpoints and safety comparisons, and so forth, and getting better estimates of some of those parameters.

But, again, we do feel that what we have so far is really a pretty striking result in terms of the effectiveness and the safety we believe is quite manageable as long as patients are well monitored with the routine complete blood counts weekly in the first 8 weeks of therapy.

DR. MARTINO: Does the FDA have a comment?

DR. KAMINSKAS: I want to make a few comments regarding Dr. Cheson's question. The sponsor's investigators attributed 4 of the deaths as being possibly drug related. On my review of the narratives, I added another 9 to the sponsor's, because some of them were disingenuous. Something called multi-organ failure when somebody comes in

with profound neutropenia and pneumonia, of course, before we all die, we end up in multi-organ failure, so this is not a catch-all diagnosis.

I want to make two more comments. One is that I was impressed how long lasting thrombocytopenia and neutropenias are. I am talking sometimes they reverse within a week or within a month, and sometimes they last for months and years. This was quite impressive.

Secondly, how quickly and unpredictably they begin. Someone is started on 10 mg a day, and after 6 days, the white count has gone from 5,400 to 600, or from a platelet count of 193,000 to 26,000 in 28 days.

However, somebody may be on the drug for months and suddenly have again a very sudden decrease in counts. This is not something that I would think of as being typical of myelodysplastic syndrome.

So, I would say that management of patients with this drug is not going to be easy, and one has to be careful with it.

Thank you.

DR. MARTINO: Does the company wish to re-comment to those comments?

DR. DeLAP: I would like Dr. List to come up and just speak again to treatment tolerance. I would just comment that more than half of the patients in the 003 study were basically still on study after a year, so clearly, there are patients that are tolerating this drug well for long periods of time.

DR. LIST: I think one thing that might be helpful for the committee to keep this in perspective, is this is a cytotoxic agent for deletion 5q. This is not growth factor, so we are not talking about another erythropoietin here. So, we are actually killing the clone.

You don't see that same effect that you described in people in the 002 study. They do get myelosuppression, but the frequency of more severe myelosuppression is much, much lower, it's more than half.

What you have described are some of the

extremes of that. It can happen very early and very quickly, but long term, years' worth of severe thrombocytopenia, I don't know of any cases, unless there is something I missed, yes, they can have moderate thrombocytopenia.

I think a good way to point this out is that case I described to you. That patient started with a supernormal count, a platelet count of around 400,000, which reflected his disease, and then goes down to levels and stays there over time of around 90- to 100,000. Yes, it's thrombocytopenia, but those are very manageable and acceptable.

The other issue about recovery is to remember if you were giving a cytotoxic agent to a patient with MDS, as has been done with chemotherapy, it does take a lot of recover. I don't think we are getting rid of MDS here, I don't think anybody believes that. You are probably left with the MDS stem cell clone that is going to have to recover, and sometimes it can take some time.

DR. MARTINO: Dr. Eckhardt.

DR. ECKHARDT: Yes, I had a couple of questions. One, it looks like you had enough patients dosed at 5 mg versus 10 mg. Have you done an assessment of toxicities between those two dose levels?

Then, the second question was, because you clearly would have been able to assess in quite a few patients, the 5 mg dose level in terms of most severe toxicity, and then the second question, which is slightly related, would be whether or not neutropenia and thrombocytopenia severity was looked at between responders and non-responders.

DR. DeLAP: In terms of the comparative toxicity of 10 and 5, the problem with looking at that kind of analysis would be the patients who are on 5 got there because they had some kind of toxicity on 10, so you are looking at a select population.

Really, to know that, you really should have a randomized comparison between, say, 5 and 10, and be able to directly compare the toxicity profiles.

In terms of, well, I will ask Dr. Knight, do you have some further comment on the relative toxicity observed with 5 and 10?

DR. KNIGHT: We didn't treat anyone at induction with 5 mg, so the 5 mg was given afterwards, presumably when they had a healthier marrow, and most patients tolerated that as a so-called maintenance dose, and with a few patients, I don't know, up to a quarter of those patients requiring at some time a decrease to the 5 mg every other day.

DR. ECKHARDT: For instance, you know, this happens all the time in Phase I trials, you can essentially look at your 5 mg dose level and over time, the number of courses that were treated at 5 mg, and per course, what were the toxicities seen regardless--I am not talking about their induction, I am talking about your core data at 5 mg versus your core data at 10 mg.

DR. KNIGHT: During the maintenance therapy, it was tolerated quite well, not by this slide, but during the core slide that you saw, the

ANCs, and the platelet counts were relatively well maintained during transfusion independence for the responders, and, as well, the curve for the non-responders hung around 1,000 even for the non-responders and a platelet count just a little bit below 100,000.

[Slide.]

This slide shows a list of the most common adverse events between the responders and non-responders. It is relatively similar between the two groups.

DR. ECKHARDT: Do you have the grade there? Do you have any grade of neutropenia?

DR. KNIGHT: That's any grade, that's correct.

DR. MARTINO: Can I just make a comment here? I am not sure that there is really a maintenance dose. What I am hearing is that patient were at the 5 mg, and that isn't maintenance, but, in fact, because there were toxicities that required a lowering. That is not maintenance in the true meaning of the word. So,

it is toxicity that caused the reduction.

DR. KNIGHT: Right. Could I have Core Safety 5.

[Slide.]

The only point I am making is that while on the 10 mg dose, the median time to response is right here, 4 to 5 weeks, so over 80 percent of the people had their last transfusion while they were still on the 10 mg dose.

So, they entered their period of transfusion independence while on the 10 mg dose. Then, there was a period of dose interruption, and then they were put on the 5 mg dose.

DR. ECKHARDT: I will stop after this one, but I guess what I am trying to get a sense of is that you clearly have patients that were, quote, "induced" at 10, and then dose reduced to 5 mg, and we have been discussing a lot of issues about, you know, AEs regarding neutropenia and thrombocytopenia, and I am just trying to get a sense whether there were more issues with the patients that were then at 5, or are we talking

about patients who--you know.

DR. KNIGHT: There were less issues. I mean approximately 80 percent of these cytopenias occur in the first 8 weeks, in that first period.

DR. DeLAP: If I can answer slightly differently, people got to 5 from 10, because they had some need, again based on the fact that we were treating to Grade 4 neutropenia, they got there, and they needed to have dose reduction.

Then, we would have reduced them again if we got there again, but for most of them, we didn't. So, that is another way of looking at the same question.

One other thing I would like to add that we did not formally do in this study, but is an interesting question for further research, is that there were a few patients in the study who after a period of dose interruption, were put back by the investigator on the same dose rather than reducing a dose.

Actually, in those patients, it seemed like the second time around, they tolerated the

treatment much better, which goes along with having a more healthy bone marrow at the time the drug was restarted.

DR. MARTINO: Dr. Perry.

DR. PERRY: I have a question for Dr. Cheson, of all people, and then a question for the company.

In the International Working Group response criteria for MDS, one of the statements that we saw from the FDA was improvements must last at least two months in the absence of ongoing cytotoxic therapy.

When your committee put this together, was it the assumption, then, that the only therapy would be intravenous therapy that would be interrupted for a period of time, or did your group have the foresight to concede or conclude that maybe there would be a chronic maintenance drug like this that could be given long term, so there wouldn't be an uninterrupted period?

DR. CHESON: Well, when one makes up these guidelines, and then implements them, there is

always problems that supervene, but, in fact, we are in the process of redoing them now, but the issue was when you look at patients with low risk disease--we separated our patients with high risk disease from those with low risk disease.

Patients with high risk disease, in general, get more cytotoxic approaches. Patients with low risk disease until now, since this drug is being considered a cytotoxic agent, mostly got growth factor support or antibiotic support.

So, it was in that context that a patient would have gotten erythropoietin with or without a myeloid stimulating factor or an androgen, or whatever else was out there in the streets that month, and then maintain the transfusion without someone coming in with some other chemotherapy drug to maintain some sort of response.

So, it was just so there wouldn't be another drug thrown into the mix to complicate it, but the initial drug in those days, way back then, was just, in general, a supportive care sort of agent.

Now, we have toxic drugs that are being used for that population of patients, so that is going to have to be considered as we revise the guidelines.

DR. PERRY: So, this criteria alone no longer holds.

DR. CHESON: It holds, but it doesn't.

DR. PERRY: Thank you for that clarity.

DR. CHESON: In the context of not having another intervention during this period of time, it holds, and I think that is how you have to look at it. It wasn't like in the middle of this, they got erythropoietin, or the middle of this, they got a little azacitidine under the table.

It was because of this drug and this drug's effect lasted more than two months, that would be acceptable.

DR. PERRY: Thank you.

Then, my question for the company is if I understood correctly, when you were talking about the Phase III study, there is going to a placebo-controlled arm, is that correct?

DR. DeLAP: Yes, for a period of 16 weeks.

DR. PERRY: Do you think you are going to be able to accrue anybody to that study, since you have already published in the New England Journal of Medicine the effectiveness of this drug?

I mean I think from a scientific point of view, I agree with you completely. From a practical point of view, I think you would have to be a fool to be randomized to a placebo arm for four months before you got the active ingredient.

DR. DeLAP: Well, the simple answer is that this study is open, and it is accruing. Dr. Knight, do you have the numbers?

DR. KNIGHT: Yes, the study is open, and it is accruing. We have over 20 patients at this time. We do allow for a crossover if after four months--it a double-blind trial, so those patients who have not achieved transfusion independence by 16 weeks, they are unblinded. If they are on the placebo group, they can cross over to the Revlimid treatment group, and even we have a crossover, as well, for the 5 mg.

If the 5 mg arm, if they have not achieved transfusion independence and they are tolerating the therapy well, they can cross over to 10 mg. So, that is how we have been able to accrue.

DR. PERRY: Twenty patients and how many centers and what period of time?

DR. KNIGHT: Right now, actually, that is from the 3 centers, 2 in France and 1 in Sweden, and that has been over the past two months.

DR. MARTINO: Dr. O'Brien.

DR. O'BRIEN: This is an aside, but you can definitely get patients to enroll in a randomized trial no matter how crazy the other arm is, if they think they have a chance of getting the investigational agent witness imatinib versus interferon.

I think that Bruce spoke to the fact that there is some heterogeneity amongst these patients. I must say that my perception--and I will get to my question in a second--is that 5q minus notwithstanding, this is not a particularly good group of patients.

What I heard is that 20 percent had RAEB, the median number of transfusions required was 6 in 8 weeks, 73 percent of them had had prior EPO, 39 percent had had chemotherapy, and that is one of my questions, and a third of them had clonal abnormalities in addition to 5q minus, and unlike the standard 5q, in fact, baseline cytopenia was allowed at diagnosis.

So, I have a couple of questions to try and maybe delineate the patient population a little bit better.

The first is can you tell us what percentage of the patients went on study already cytopenic, so with a neutrophil count less than 1,000, or platelet count less than 100,000?

DR. DeLAP: Dr. Knight, can you present for us the proportion of patients on the study with lower degrees of platelet count and white count?

DR. KNIGHT: In the deletion 5q population, they generally have relatively normal ANCs and platelet counts, so there were only about 25 percent of the patients had a platelet count

less than 100,000, and only 10 percent of the patients entered the study with an ANC less than 1,000.

DR. O'BRIEN: Although obviously, if somebody goes on with a platelet count was 60, it is not going to be very difficult for their platelets to go below 50 no matter whether they give them any therapy or not.

My second question is you remarked that 39 percent of these patients had prior chemotherapy. Can you tell us about that?

DR. DeLAP: Yes. Dr. Knight.

DR. KNIGHT: Yes, there were a few patients that had 5-azacitidine, and actually, a number of patients were treated with low-dose cytosine arabinoside, and a number of patients received thalidomide, as well.

DR. O'BRIEN: I think that is very relevant. Obviously, these are people who their physician was willing to give them chemotherapy prior to this.

The other question is, can you provide any

data on the likelihood of response based on the number of transfusions they were requiring going in? So, for example, your median was 6, but it ranged from 0 to 18. If you break that into quartiles, so that, in other words, in the patients who were requiring the most transfusions, do they have the same efficacy as the ones who had less transfusions in terms of response?

DR. DeLAP: Yes. The tendency was for patients who achieved a response to have a slightly lesser baseline transfusion requirement than the patients that did not achieve a response.

The median baseline transfusion requirement for the patients who were responders was about 4.5 units per the 8-week period, whereas, the overall for the study was 5 or slightly over. So, it is true that the baseline transfusion requirement was slightly less for those patients who ended up in the responder category, but not really very different.

DR. O'BRIEN: I am guessing it wasn't allowed in the trial, but is there any data, so,

for example, with the imatinib, it is not uncommon that you have to dose reduce very early, and then as you get improving response and disappearance of the Philadelphia chromosome, you can actually often go back up on the dose.

Did you have any provision or is there any data on people who went down at some point, potentially, going back up later, or that wasn't allowed in the trial?

DR. DeLAP: That was not allowed in the trial. There were, as I mentioned briefly, previously, a couple of patients who restarted the same dose, and seemed to tolerate it better the second time around. So, I think that would be a very reasonable question to look at going forward.

DR. O'BRIEN: I was struck by the difference in the dose reduction between Alan's trial and the multi-center trial, which obviously could be related potentially to single-center versus multi-center, but was there a difference in terms of requirement for dose reduction between the 001 and the 003 trials?

DR. DeLAP: Dr. List.

DR. LIST: There was no difference, but remember the initial one did not restrict to 5q. You know, there is a big difference in the frequency of dose reduction for 5q versus non-5q, so we had 12 5q out of the 45 in all.

DR. MARTINO: I will allow one more question, and then we will take a break, and then we will have the public hearing. You may resume your questions thereafter.

Dr. Carroll.

DR. CARROLL: I have a comment and then two questions for Dr. List.

The MDS community is very pleased to learn that Revlimid is certainly less toxic than thalidomide, and actually more potent than the other drug.

The number of responders seeing elimination of transfusion or the reduction is also, of transfusion levels, is also very, very impressive. The questions I have are these.

How much dosing interruption due to the

drug no longer working and then reintroducing the drug, either the 10 mg or the 5 mg dose, actually produced results again for these patients?

DR. LIST: Dr. Carroll, I don't know they had the precise numbers, but I can tell you that of patients that received a transfusion later on, so considered a failure at that point, then, was allowed to resume it again, they did establish transfusion independence. I don't know if we know those precise numbers.

DR. CARROLL: The next question. How many patients whose platelet and neutrophil counts dropped from their entry level, actually got the counts back again to what they were at entry?

DR. LIST: Remember that people with lesion 5q, at least those that have the isolated lesion 5q, tend to have an elevated, a normal to elevated platelet count, so many of them would come in with 400,000, 300,000, so these would come down to levels that actually were less than the normal range generally.

[Slide.]

This slide gives you an idea for the entire population. After they would come down, they would come back to a level around 100,000 or a little bit higher than that. Over time, they seemed to increase in the people that maintained responses for long term, they seemed to continue to creep up and up and up.

DR. CARROLL: Thank you, Alan.

DR. MARTINO: At this point, ladies and gentlemen, we will take a 15-minute break. I would like you back here and ready to go at 20 after.

[Break.]

Open Public Hearing

DR. MARTINO: The next portion of this meeting is the Open Public Hearing. Those of you who have asked to address this committee, please use the microphone at the end of the tables, and as you prepare for that, I need to read you a statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To

ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

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

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: Our first speaker is Kaete Angel.

MS. ANGEL: Good morning. I am one of your MDS patients and I was diagnosed in 2001 in May with myelodysplastic syndrome with a 5q minus. I was told by our oncologist that there was nothing they could do for me, there are a lot of things in the works, but I should go home and come back in 6 months.

Well, I never heard of myelodysplastic syndrome, I didn't even know what it was, so being a realtor, I know how to use my computer for my work, but I really have never been on the Internet before. So, now I went on to see what was myelodysplastic syndrome.

Well, after I got into the Internet, I was crushed. I was crushed because it told me I have 3 to 6 months to live. So, in 6 months, I probably won't be here anymore. I called my daughter and she said, "Oh, mom, don't take it all so serious, you will make it."

So, anyway, my next thing was I called Sloan Memorial Hospital because I always got their newsletter, and I asked for a second opinion, and

they were marvelous to me, because I really wanted to go on my trip to Australia, and I had my tickets, and I asked the doctor what he thought what I should be doing with my last visit, and he says, "You go."

So, I did go. He says, "Just don't get sick, wash your hands, and do all this." So, I did, and I had a wonderful time, and I came back and I went back to Sloan.

Well, Sloan checked me out for 4 hours, my daughter and I spent with the doctor. They went back and forth, and so they sat and confirmed that my diagnosis was myelodysplastic syndrome with a 5q minus. My Dr. Clemick [ph], she says we can keep you comfortable, there is a lot coming out, we can keep you comfortable, and we start with Procrit and Neupogen, and see if that will help you.

I did that for a year, and also after about 4 months, after I have been to Sloan, I started to feel completely fatigued. So, she said, we will try this, and there is something coming out, and once you have the convention in France,

she called me. She says, "We got it, we will give you this new medication."

I was so blessed that I got sick at the right time in my life. If it would not have been for Revlimid, I most likely would not be around anymore, but my goal has always been I want to be 100, which Dr. Clemick, she just smiled.

I feel like Revlimid and my doctor and staff might achieve making me live my 100 years. Four years ago, when I was first diagnosed with myelodysplastic syndrome, I had never heard of it. I had no idea how it would impact my life.

I was an active realtor and I traveled extensively to Europe to visit my family on a regular basis. My ultimate goal, like I said, is to be 100, because I always exercise, I ate right, I do not drink, I do not smoke, I thought I live a healthy life.

My world was transformed to one of fear, constant fatigue, and shortness of breath, with heartbeats hammering in my ears. It you were to ask me to compare my life before and after

Revlimid, well, I would have to tell you that before this miracle drug, my life was ruled by how long I could last between using a transfusion. Walking to the mailbox was an effort. Making my bed was an effort. Some mornings I just couldn't even get out of bed. It was a monumental effort.

It has been almost 2 years if I last needed a transfusion. I am one of the blessed ones. My life has almost become normal. I can do almost all the things I used to do before my illness was diagnosed, like travel and exercise. I can do my walking again where before I had to sit down in between every quarter mile.

Now, I wake up in the morning, I feel good to be alive, and ready to tackle each new day. I now feel I will have a chance to become 100.

Thank you so very much.

MS. CLIFFORD: Thank you.

Our next speaker is Robert Weinberg.

MR. WEINBERG: My name is Robert Weinberg. I live in Wynnwood, Pennsylvania. In accordance with your request at the beginning, no expenses

were paid for me to be here today, however, I do own stock in Celgene with the concept that I might win two ways.

DR. MARTINO: Forgive me. Can you raise your microphone? I would like to be able to hear you well. Thank you.

MR. WEINBERG: Okay. What I said is I do own stock, some stock in Celgene, which I purchased back in April or May.

I am an MDS patient and have been an MDS patient since 1998. I am on the board of the MDS Foundation. My purpose here is not to be an advocate for the drug. I hope this process works the way it is supposed to work, and the best result is obtained. But I wanted to put a human face on all of the statistics that you are seeing.

I am a trust and estate lawyer with 20 years experience, work at a large law firm, and live on the billable hour, so I have a fairly high-pressure existence.

I was diagnosed in 1998 at the age of 48 with MDS RARS, refractory anemia with ringed

sideroblasts. I have normal chromosomes. I am not 5q minus, and I have no identified bone marrow transplant donor. That at the moment is not considered an option for me or not one that I am considering seriously.

I have had over 300, probably closer to 350 units of red blood cells in the last 7 1/2 years. My transfusion requirement in the beginning was 6 weeks between transfusions, went quickly to 4, and by the end of the first year, after diagnosis, was at the 2-week level.

I am currently receiving transfusions somewhere 7 and 9 days, 2 units each time. I am currently on the trial for Revlimid. I am in the category of having been interrupted because of myelosuppression. I am waiting for my platelets to resume. My white count is responsive to G-CSF, so I am not as concerned about that.

I simply want to let you know what MDS is like for a person, especially one who is the prime of their working life with a family and what it can do.

I am exposed to constant fatigue and headaches, which become worse right before I need the transfusion, so it's an interruption in my career just to be able to do and perform the duties that I am supposed to do to stay with an active career.

I am at the hospital weekly for CBCs, sometimes twice a week, which takes time not to have the test run, but simply because of how long it takes to be at the doctor's office and to wait for all the things that go on.

The transfusions take 7 hours, almost consistently 7 hours from the time I walk into the hospital until the time I walk out of the hospital. The blood goes in an hour and a half. Because of my age I am able to take it faster, but by the time that you get IV inserted, that the blood is brought, all the various things are done at a hospital, it takes time. There are other patients. So, it is clearly a loss of a day, and now a loss of a day a week in my career that I am getting the transfusions.

I was free of blood transfusion reactions until last week, and which I had a reaction that was called a TRALI, which I think stood for something along the lines of transfusion-related lung injury, which involved the breaking of blood vessels in my lungs, filling my lungs with fluid.

During the transfusion, my blood pressure dropped to 70/34, and I was taken up to the ICU where I spent a day and a half, and here I am a week later. Obviously, that was another interruption in the life of an MDS patient trying to maintain their career.

I chelate daily 8 hours sub-Q with a pump with desfuroxamine. I had maintained for the last 8 years a very low--not very low--but slightly above normal ferritin level, however, now that my transfusions are more frequent that once every 2 weeks, my ferritin level has increased from 350 to 950 over the last 60 days.

I want to impress on you that MDS is not a chronic disease. It is not a disease that you say, well, I lived my life with MDS, and it is not

disease of the old. It's a disease of even children.

If something is invariably fatal, it is not chronic, whether it happens to be 15 years, 5 years, or 5 months. In addition, the iron overload, it is very difficult to live a life knowing that you have got this sort of hammer that is about to fall because of the iron overload problem, and that the transfusions simply stop working, and I am after 8 years or 7 1/2 years, I am at the point where the transfusions are stopping their efficacy.

So, I am here to educate you in that sense of what it is to be an MDS patient, nothing more. Thank you.

DR. MARTINO: Thank you.

I believe we have one more speaker.

MS. CLIFFORD: Anne Quinn Young.

MS. YOUNG: Thank you so much to the committee for allowing me to speak at the last minute. I promise to be brief.

My name is Anne Quinn Young. I am program

director of the Multiple Myeloma Research Foundation based in New Canaan, Connecticut. The MMRF is a national 501(c)(3) nonprofit organization, recognized as the world's leading private funder of myeloma research.

Per the committee's request to disclose financial relationships, the MMRF does receive unrestricted educational grants from Celgene and a number of other companies including Millennium, Novartis, Johnson & Johnson, Amgen, and others. The organization was not asked to attend by Celgene today, and we did not receive any financial support to attend this meeting.

Again, I wanted to thank you for allowing me to speak on behalf of the nearly 200,000 patients, family members, and friends that are associated with our organization. Although this meeting is focused on discussed the proposed indication of Revlimid for a type of MDS, as an organization, we felt it was very important for the committee to understand the importance of Revlimid for the myeloma community, as well.

As you know, myeloma affects approximately 50,000 individuals in the U.S., and has an abysmal 5-year survival rate of just 32 percent with few treatment options. Patients who are diagnosed with the disease today face similar odds of dying within 5 years as compared to those who were diagnosed 30 years earlier when the 5-year survival rate was 24 percent.

It is also a disease that disproportionately affects African-Americans. The incidence and mortality rates are twice as high in this population as in others.

In 2003, the myeloma community was encouraged by the availability of Velcade, the first treatment to be approved by the FDA for patients in over a decade. However, with the median time of progression of 8 months, which is a tremendous advantage over prior therapies, it is important that patients have other solid treatment options.

Currently, when myeloma patients disease progresses following treatment with Velcade and/or

thalidomide, which is considered another standard treatment for the disease, the options are generally limited to early stage clinical trials or high-dose chemotherapy followed by stem cell transplant. Unfortunately, for many patients, neither of these options is appropriate.

Revlimid, in combination with dexamethasone, holds the greatest potential of any treatment in development for this disease. It is a disease characterized by few strong treatment options and many unproven drugs in Phase I and II trials.

Revlimid is supported by impressive Phase III clinical trial data showing a 61 percent response rate as of the last time the data was presented, and a median time to progression of 15 months in a multi-national population of more than 700 patients with relapsed disease.

The combination also holds significant promise for earlier stages of disease. A recently published Phase II trial suggests that the combination has a 91 percent response rate in this

population.

Also, trials suggest the drug does not have many of the toxicities associated with currently available therapies including thalidomide. However, while it is potentially used across all stages of disease, and its tolerable profile are exciting, what is truly most important is the hope that its potential availability provides the thousands of relapsed and refractory myeloma patients who have failed every other available therapy and may not even qualify for a clinical trial.

We receive phone calls and e-mails daily from patients, caregivers, and even healthcare professionals who want to know the status of the drug. We are anxiously awaiting the start of the expanded access program, because in the meantime, patients are unfortunately dying as they have run out of options to treat this devastating and uniformly fatal disease.

So, I thank you again for giving me the opportunity to speak for a few minutes on the

myeloma community's behalf, and I half the committee will consider the potential benefit that the availability of Revlimid would have for thousands of myeloma patients, as well.

DR. MARTINO: Thank you.

At this point, I will resume questions from the committee to either the sponsor or the FDA, and, Dr. Fleming you are up next, please.

Questions from the Committee (Continued)

DR. FLEMING: Could I have Slides CE-18? I want to go through a few slides. I am struggling with the challenge of sorting out, in this heterogeneous clinical condition, the level of effects here that truly are signal from what could be attributed to noise or to bias.

So, the areas of efficacy where some of the most apparently impressive results are shown, it is Slide CE-18, where you are looking at change in hemoglobin from baseline, and then transfusion independent response and duration of response.

[Slide.]

So, starting from this slide, my

understanding from what the FDA has indicated is that these data reflect the change when one looks at the minimum hemoglobin value in the period preceding the first dose versus the maximum during the response period of during the post-dosing.

Is that correct?

DR. DeLAP: For this particular analysis, that is correct.

DR. FLEMING: So, in essence, because there is always variability, even if I had a placebo, and I took the minimum of a series of measurements at baseline and the maximum of a series of measurements on intervention, then, even a placebo is going to show a drift toward the positive.

Whether it's this much or not obviously remains to be determined, but some of this difference clearly is attributable to the bias for how this measure was selected.

DR. DeLAP: Yes.

DR. FLEMING: Let me keep going, Dr. DeLap, because I have several issues, and I know my

chair will have some limitations here.

[Slide.]

So, if we then go to Slide CE-15, where we are looking at the data on response rates of 64 percent, again, I am struggling with trying to get a sense of how much of this is treatment effect, what would a proper control have shown on this measure, how many people would have responded, and again, this is a measure where we are looking at does the patient achieve an 8-week period of no transfusions over an average period of 33 weeks for a cohort at baseline that had an average of 2 transfusions per 8 weeks.

Well, there are a few issues here. First of all, there is open-label bias. We know that these people are all on active therapy, and the transfusion is a decision that the investigator, in fact, can have some influence about.

We also have a well-known regression to the mean bias, because when you select a patient cohort based on an existing condition at baseline, then, you tend to be overestimating what that

actual rate of events would be.

Even if you weren't, the probability that a patient, even on an inactive therapy would over a 33-week period, experience some intervals without having a transfusion, is non-negligible, and if there is regression to the mean bias here, which there almost certainly is, then, clearly, there will be a substantial fraction of patients in the control arm that would also have had a response.

Now do we know? Is it 64 percent? We don't know what that rate would be.

Let me go to one more slide, and that is Slide CE-19.

[Slide.]

CE-19 is looking at the duration of response. Is this a Kaplan-Meier?

DR. DeLAP: Yes.

DR. FLEMING: Okay. Secondly, the FDA, in their briefing document, indicated that response duration was measured from the last of the consecutive 56 days.

Is the FDA correct in that

characterization? Was this for any patient based on the last of their 56-plus day intervals?

DR. DeLAP: This particular graphic is from the first of the 56 days, so I think what you are driving at, you can get an 8-week kind of difference in the result depending whether you measure from the first day, when the patient is not getting a transfusion, or if you wait until 8 weeks after that first day to start to measure.

DR. FLEMING: Well, there are two issues here. One is you don't have a time zero cohort here, so these Kaplan-Meiers are not valid, they are not interpretable. The only way to interpret a Kaplan-Meier is to have a well-defined time zero population that you would follow over time.

Systematically, people are eliminated here if they don't, in fact, have an 8-week period. Furthermore, if we are looking at from the first or from the last, there is still the bias of not looking at the totality of the data.

So, to lead up to a single question, each of these types of analyses are reflecting

potentially some signal, and certainly they are characterized with noise, and there are definitely, for some of these analyses, substantial bias in the absence of having a proper control.

I don't think you have provided us, for any of these three measures, what we would expect for an inactive therapy. How do we assess how much of this effect if attributable to intervention?

DR. DeLAP: I will bring Dr. List up in just a moment. I would like to just work with your first comment first, about how the methodology is applied for measuring the hemoglobin change.

We have looked at different methodologies for doing that. So, if we can go to--

DR. FLEMING: But I would like to keep the response fairly short, because I have some additional questions, so I would like to focus on these three analyses that are critical analyses, and how, in these three analyses, we are able to understand how much is signal versus how much is bias and noise.

DR. DeLAP: Okay. I will just turn it to

Dr. List then.

DR. LIST: I am not a statistician, but I am certainly a clinician. I feel like I can give you some good insight into any potential bias here.

I think everyone would agree if people were going 8 weeks without a transfusion, that could be bias. This is certainly much more meaningful than that.

To get to the issue of the Kaplan-Meier, the protocol actually was defined this way. From the time of transfusion, the first day of transfusion dependence, we are looking at duration transfusion free, not duration of response, based upon transfusion independence.

So, the FDA did a different analysis. This is the protocol-defined analysis.

DR. FLEMING: But you don't have a time zero cohort.

DR. LIST: That's a different issue, but this is what we planned in the protocol.

DR. FLEMING: Well, but if you don't have a valid analysis, the fact that it was planned in

the protocol doesn't inherently then make it valid.

DR. LIST: So, let me just show you, getting to your issue is there bias.

DR. FLEMING: But can you stick to these three analyses, because there is other issues I would like to get into.

DR. LIST: This gets to the issue of bias.

DR. GRILLO-LOPEZ: Madam Chairman, a point of order. I object to how Dr. Fleming is carrying out--this is a cross investigation. You are the chairperson, you are the one who should decide how long the responses last, and they should not be interrupted while they are responding, because he did not allow them to interrupt him when he was making his statement.

DR. FLEMING: I am simply looking for--

DR. MARTINO: I understand the questions, and I understand your objection. I will allow this line of questioning and response until it suits me otherwise. Thank you.

DR. FLEMING: Knowing time is limited, simple questions are related to the bias of these

three analyses.

DR. LIST: I will be quick. So, issue of bias. There are 3 randomized trials that have been completed. As far as I know, there is only one published placebo-controlled trial, and that is the third one here on this slide.

If you look on the right-hand side, this is the application of the International Working Group, 8 weeks without transfusion, and you can see on the bottom two, there are no responders, but on the top one, there is a 4 percent response rate.

Now, Celgene has done a randomized, placebo-controlled trial with thalidomide, and on the arm with placebo, it was 10 percent if you just apply 8 weeks, but if you applied the 1-gram rise minimal for 8 weeks with that, there are none.

So, I think we can feel--I feel very comfortable that we wouldn't see an improvement in hemoglobin for a minimum of 8 weeks.

Was there a difference in transfusion frequency?

[Slide.]

We have analyzed the transfusion threshold, pre-treatment and post. This is a box plot showing that. The median essentially overlaps, so they look identical. So, these are not by patient by patient, but they look the same if you look by patient, by patient, as well. So, that looks very good.

I think the other time to take home here is that there is a rapid rise in hemoglobin. That was the CE-17, if you have a copy of those slides.

[Slide.]

Within a matter of cycles 2 to 4, the hemoglobin shoots up--here we go--very quickly. So, these are not just holding out for avoiding transfusions. These are going up to levels of 12 to 14.

Now, the other issue here is if we were concerned about responses that are actually not adequate, because they are 8 weeks, look at the duration of benefit of response with the rise in hemoglobin and duration transfusion-free.

There are 84 patients that are out beyond

6 months. There are 57 beyond a year already. We have actually updated the data, and I don't know if can show that--can I show that, as of the end of August?

[Slide.]

So, if we have that, from the end of August, we still have not reached the duration transfusion-free, not duration of response. So, it is still very respectable. So, these patients are not just holding out between transfusions, they are going over a year and with a rise in hemoglobin.

DR. FLEMING: Dr. List, while you are up here, you showed us Slide--I think it was CC-4, and you were comparing the results on survival with the survival results I think from a Mayo experience.

DR. LIST: Yes.

DR. FLEMING: Were those Mayo patients all also restricted to IPSS low- and intermediate-1?

DR. LIST: This was published in 1985, before the IPSS, so I can't say that we know that.

DR. FLEMING: So, given that we were restrictive in our trial to those patients, in

those IPSS subgroups that are strongly prognostic for outcome, your conclusion here is that we may be altering the natural history of disease in this unfavorable disease subset by, if I understand, the visual impression that the MDS survival is better than the Mayo survival.

Isn't that incredibly treacherous to say that when we don't know for a fact that the Mayo patients were also in this prognostically highly favorable group? In particular, given that the data that we have are indicating we should expect 5- to 7-year median survivals in that subgroup, and the Mayo group seem to be less than that.

How do you validly make this comparison?

DR. LIST: I think it's a good question. First, I would like to clear one thing up. These are not 5q minus syndrome. In fact, only 27 percent of the patients had 5q minus syndrome. So, we have three-quarters of the patients that are not in that good prognostic category.

This comparison, I agree, you know, it is a valid comparison, but I can tell you that data

just published last month, in Leukemia Research, looking at 5q minus, all cytogenetics, in fact, but looking at 5q minus versus 5q plus other in the lower risk, and it looks identical to this, the survivals are poor.

Dr. Gioganitis [ph], in Dussberg, has also published similar data about a year ago. It does have an averse effect, and I wasn't concluding that it does. I think it may, and that is what I said. I think that is something I would like to see in the future studies.

DR. FLEMING: And I guess just coming back to one last question. Dr. Hussain had asked Dr. DeLap a very important question, which was why wasn't a randomized trial done, and, Dr. DeLap, I think the answer, and my interpretation, that you gave more or less described what you found as opposed to answering her question, which was if, in fact, your intention was to do a registrational trial, and if, in fact, you believe you are seeing differences where according to your efficacy measures, if you have a 62 percent response rate,

if, in fact, a lot of that is attributable to therapy, even if half is attributable to therapy, it would only take 100 patients in a randomized trial to be able to reliably sort our whether or not there really are differences or not differences, and we would have a much better sense as to whether all these safety issues are attributable to therapy or the disease process.

Why wasn't a randomized trial conducted for registrational purposes, or is the answer that one is being conducted for registrational purposes, we just have to wait year and reconvene when the results come in?

DR. DeLAP: This is a traditional drug development approach, of course, to identify a population that seems to be well treated for purposes of further study in a Phase III trial. The happy problem that we have is the results are basically just so good in this expanded Phase II experience that although we are on track to do a Phase III trial, we had difficulty even coming up with a design that people were happy with, which

because it did involve putting people on a placebo for 4 months basically.

So, we are proceeding with the traditional drug development. We have just seen such strong results at this point in time, that the issues that we are not evaluating in the Phase III trial are really no longer whether or not the drug works really, or even whether or not it has a favorable risk-benefit.

The issues that we are evaluating there are more what are the effects on some of the other endpoints that relate to what you are actually doing for the progression of the disease, you know, what can we do to better, more precisely characterize the side effect profiles.

But we are convinced based on what we have seen in the Phase II expanded experience that this is a--

DR. FLEMING: Well, this is your discussion of your interpretation of where you are now. The question was when the FDA advised doing a randomized trial--

DR. MARTINO: Excuse me, gentlemen. At this point, I do want to stop this question. You have asked it. We understand you are not getting the answer that you want. The fact is this is what they have done. It is this that we have to judge today. A Phase III trial is ongoing, and whatever their reasonings were aren't going to change the judgment that you need to think about today.

So, I am going to stop that question at this point.

Do you have any other questions?

DR. FLEMING: No.

DR. MARTINO: Dr. Grillo-Lopez, you are next.

DR. DeLAP: If I could--

DR. MARTINO: I think, in all fairness, I don't think you need to answer the question any further. You are doing what you are doing, I appreciate that.

DR. DeLAP: We have taken advice from the FDA right along in this program, and we, in fact, designed the program in conjunction with FDA. So,

it is really a matter of looking at the results at this time.

DR. MARTINO: We are done with that issue. Thank you.

Dr. Grillo-Lopez.

DR. GRILLO-LOPEZ: Thank you, Madam Chairman.

I just wanted to address two issues that have come up during the meeting today that I think need clarification, and one is that in my 40 years experience as a drug developer, and therefore interacting with the FDA during that time, what I have found is that the FDA will usually ask for randomized trials.

What would be unusual would be for them to ask for a single-arm trial. So, it is not unusual at all that they have asked this particular sponsor to do a randomized trial because that is their standard, they ask for that. However, they do not require or impose that. It's a suggestion.

The second point is that actually, the FDA regulations do not exclude the possibility of a

single-arm trial for approval, and, in fact, there is precedent for approvals based on single-arm studies, and in my own personal experience, and this is recent experience during the last eight years, I have had two drugs that I developed approved based on single-arm trials. So, I just wanted to clarify those two points.

DR. MARTINO: Rick, do you want to answer that, please?

DR. PAZDUR: Yes. I want to bring people back to the kind of regulations, and there is a mantra, adequate and well-controlled trials, adequate and well-controlled trials, adequate and well-controlled trials. I am mentioning that three times, because I think that is at the heart of the question here.

When we accept a single-arm trial, these are carefully defined situations, and usually, we are looking at a response rate. A response rate has a particular importance, because when a tumor shrinks, that is all due to the drug, okay.

If I say that drug X has a 10 percent

response rate in lung cancer, that response rate is due to the drug. It is not due to the natural history of the disease. Therefore, we can quibble as much as we want that 10 percent is not clinical benefit or not likely to predict clinical benefit, but that response rate is 10 percent, and that is due to the drug.

The control usually in that situation of single-arm trials is one where we would consider that there is no other available therapies, and that is why we frequently look at very refractory disease populations.

Another alternative, however, would be to, if one was going to do a single-arm trial, would be to get such outstanding results, that this could not be considered to be due to the natural history of the disease.

Here again, that is one of the questions that we are going to be asking the committee, but for us to approve a drug, and this is not Dr. Pazdur's interpretation or Dr. Temple's interpretation, it is right there in the rules and

regulations, it is adequate and well-controlled trials.

We have to answer that question here or internally, and therefore, that is, as Tom was pointing out, kind of a central element, and that is why we are focusing some of the questions on that.

But adequate and well-controlled needs to be answered in some kind of context of decision-making.

DR. GRILLO-LOPEZ: Continuing the very positive trend that we started yesterday, Dr. Pazdur and I are in full agreement. It is adequate and well-controlled. I would only add that it doesn't say randomized, and that well-controlled might be internally controlled, historically controlled, it doesn't mean randomized.

DR. PAZDUR: You are right, but we have to have confidence that that is a controlled trial, and therefore, there has to be a well-defined population, a well-defined natural history, and if one has other alternative therapies or the natural

history may impact on the endpoint, then, one has to have a magnitude of benefit that one would have to say this clearly is not subject to the interpretation of an impact on the natural history of the disease, and be able to make the interpretation here of what would be the natural history's impact on that, et cetera.

DR. MARTINO: Thank you.

Dr. Levine.

DR. LEVINE: Again, I have several questions. To be honest, I am not very terribly bothered about the response rate. My concern relates to the toxicity, and I just can't get there.

Revlimid, I know is being used in other trials and diseases that don't involve hematopoietic progenitor disease, so to speak, and one of those is myeloma.

Can you please tell us what are the toxicities as far as neutropenia and thrombopenia in patients who have myeloma treated with this, and what is the dose, and all that?

DR. DeLAP: With respect to the neutropenia and thrombopenia in the myeloma trials, the overall results are in the same magnitude of events, but you have to consider that those studies are being done at a higher dose. It's 25 to 30 mg dose level.

I would like to ask Dr. List to come up again and see if we can perhaps better address the concerns that you have.

DR. LEVINE: Along with that would be the late development of thrombocytopenia or neutropenia, as was discussed by the FDA. If, in fact, similar to Gleevec, and so forth, if, in fact, the beginning neutropenia is just related to knocking down the abnormal stem cell, then, how would you explain the late thrombocytopenia and neutropenia?

DR. LIST: I realize that toxicity is the main issue for making a decision really on this. I think that any of us here accept that this is a very active drug.

[Slide.]

One thing I think that helps, yes, there may have been that 80 percent of patients had dose adjustments, but the vast majority occurred in the first 8 weeks, so this is a very predictable neutropenia and thrombocytopenia that can occur, and we can see that about 20 to 25 percent of people long term stayed on the 10 mg dose, and there are other doses in between, so at the 10 mg, for people who tolerate it, it stayed okay. For other people, they may have needed a dose adjustment. We don't know if they could have gone back to 10. There were a few isolated patients that did, and they actually did okay. So, the whole idea that when we have a better marrow to deal with, the tolerance is better is possible.

[Slide.]

But I think our best assurance that we can give you, this is the data that we had showed you earlier, looking at the median ANC and the platelet count by week on study. These are the responding patients.

You can see they go from their normal to

supernormal platelet counts down to levels that drop to around 90- to 100,000, and then start working their way back up and staying at a range of around 100- to 120,000, in that range.

We are not seeing a dip again later on of concern about more toxicity occurring later. The same is true in the red or the orange there you can see from the neutrophils. They come up, they tend to stay there, and for most of these individual patients, when you look at them, they tend to come up a little bit more with time.

DR. LEVINE: And so the patients that were discussed, the "late droppers," quote, unquote, discussed by the FDA, in your view, those would be non-responders, and not on that curve, is that what you are saying, or who are those patients who did--

DR. LIST: Some of those are actually later responders. Although the median time to response was in that 4- to 5-week period, there are some later responders, and other people, it took them that long to get to their first Grade 3 toxicity.

Let me show one more slide that might be helpful, as well, to help put a little bit of clarification on this.

[Slide.]

If you look at the reasons for discontinuation, because we are concerned that myelosuppression is the reason here for discontinuation, you can see that there are only 8 patients that discontinued because of thrombocytopenia or 5 or 4 percent, and for neutropenia, it is only 4 patients.

So, this was predictable and because it occurred early and people were informed to look for that, stop it appropriately, and then resume the drug later after you have a better marrow function.

DR. LEVINE: May I ask another? Your Slide CS-8 says that there is, on the continuous 10 mg dose, there is zero percent Grade 4 febrile neutropenia, and yet we hear, on the FDA documents, that there were 3 or 4 patients who died of neutropenic sepsis or pneumonia, neutropenic pneumonia.

How do you discuss that, how do you think that discrepancy came about, and how do you see those cases as having died?

DR. DeLAP: Dr. Knight of our Oncology Program will discuss that.

DR. KNIGHT: Well, that is what was reported. I understand that these people who had sepsis and then died subsequently, perhaps these people developed--it may be that they developed the sepsis and the febrile neutropenia, you would expect to go along with that after they came off the trial, and we didn't collect it in our data, but that is what we had.

DR. LEVINE: I have one more just changing topics a bit, related to the toxicity, the potential fetal toxicity. I am getting all kinds of mixed messages, and I don't know what the truth is, I guess.

No. 1, you study a rat model as your primary model, when I don't know it, but you I assume knew that that was not the model that was previously shown to be the model in thalidomide, so

I am wondering why you did that, and then my second question is you are saying that this is not a teratogenic drug, and yet you are also saying at the same time that only specialty pharmacies will be able to dispense it, and so forth. So, again it's a mixed message. What is the data here, is this something that is of concern to you, so why is it going to a specialty pharmacy? So, that whole area needs to be discussed.

DR. DeLAP: It is our belief that from the studies we have performed, that we have seen no evidence of thalidomide-like teratogenicity with this drug.

Now, what has been discussed is the adequacy of the studies to make that final conclusion, and the difficulty is that we have again some additional data that has not yet been reviewed by the FDA, so I think it is difficult to come to closure on that specific point.

But from the company's viewpoint, including all the data that we have seen, including the data that has not yet been written up and

finally submitted to the FDA, we have not seen any evidence that there is a teratogenic potential here with respect to limb malformations.

The rat is a model that is used, and it does have effects. If you are looking for the classic limb malformation kind of effect, the rabbit is the best model, but the rat is also a valid model for looking for effects. It is just that the best model that we have for these kinds of effects are the rabbit, and, of course, we have done both.

Dr. Christian, would you like to speak further about the different models?

DR. CHRISTIAN: I am Mildred Christian. I am a teratologist by training, and I have performed the animal studies for approximately 35 years, and have evaluated the studies. I am a consultant for Trazel-Gene [ph] in teratology specifically.

The question as to whether a rat responds or not is something that has to be addressed, because in my opinion, the rat is a responsive species. Why? Because there are four things an

embryo can do in terms of insult.

It can die, it can be smaller, it can be functionally deficient, or it can be malformed. For thalidomide, since the original human case was seen, it has been shown that the rat responds with three of those four endpoints.

Additionally, the reason it is tested in the rat is that we find that thalidomide is a very special compound. It is a compound that affects the embryo at doses that are therapeutic to the mother, and lenalidomide does not have that property.

All the animal studies that we have done have shown that at doses that were safe for the mother, there were no effects on the conceptuses, and just to be sure, conceptuses means from embryo all the way up to birth.

On that basis, I feel that the rat is an appropriate model for evaluation of the compound, and that there are two species that have been evaluated for developmental toxicity. Let's address the second study.

The second study was done in Europe. It

is true that there were animals that were not eating on this study. That is a very common finding in rabbits. What one has to do in interpreting that type of data is eliminate those animals from the interpretation, and I did that.

There were also animals that died on the study, and there were animals that aborted, and in my interpretation of the data, there was maternal toxicity present.

At the lowest dose at which there was maternal toxicity, and at which abortions were not seen, there were no adverse effects at all on the conceptuses in that study. However, because of the sensitivity about this compound, that study was repeated. It is almost completed. The end-life portion has been completed. The evaluation of the conceptuses have been made, and although the data has not yet been submitted to FDA, it doesn't change the interpretation of the data.

DR. MARTINO: Does the FDA wish to respond to that in any way?

DR. PAZDUR: Yes, let me just kind of put

this in perspective. We would like additional data on this whole topic, and our plans for any steplike program would be reviewed upon receipt of additional data and review of that data.

So, even though because of the sensitivity of the class of this drug, we are recommending a steplike program. That will be revisited when we get additional data in, so we are looking at that basically as a conservative approach to manage an area where we, at this time, feel uncomfortable, but would be more than happy to revisit when we get additional data in.

So, I think from a safety perspective, given the history of this class of drugs, this would be in order.

I have an additional question, though, that I would like Dr. DeLap to comment on, and that is the expanded access programs both in MDS and also in multiple myeloma.

What is the status of the expanded access program in MDS, and would approval of this drug stop the planned expanded access program for

multiple myeloma? Would you be looking at off-label usage for that, or would you plan on using the expanded access program?

DR. DeLAP: I will ask Dr. Knight to comment on that. We are, as you commented, we are having expanded access programs set up, both in MDS and in myeloma, and myeloma is a bit further along.

DR. KNIGHT: The expanded access program for myeloma will actually start enrolling patients in the next few weeks, and that will continue whether or not approval occurs for MDS.

DR. PAZDUR: What is the status of the MDS expanded access program?

DR. KNIGHT: That is probably about two to four weeks behind.

DR. LEVINE: I am sorry to take up so much time here. Another couple.

One is this is going in for full approval meaning that you don't have to do this Phase III randomized. What will the company do--and I guess I will ask the FDA, as well--what will the company do if the Phase III shows that the benefit-risk

ratio is not appropriate? What do we do then?

DR. DeLAP: We are anticipating that--we have already shown a lot about the benefit-risk with the dosing regimen that we are pursuing approval for today--that, we feel we have shown a very strong benefit and an acceptable treatment toxicity profile again with the appropriate monitoring of patient and dose modifications where appropriate.

We are working in our Phase III program to see if there is anything we can do to make things better in terms of some slight modifications of the dosing regimen. Obviously, if those don't look as good as the regimen that we have today, then, we will not go forward with those. If they look better, we would definitely go forward with them, or if they simply look like plausible alternatives, we would have discussions with FDA and see if we might have multiple alternative dosing regimens, so this is really just typical drug development in my view.

We are looking at taking a drug that we

think has a very strong risk-benefit profile and seeing if we can make it any better.

DR. PAZDUR: You must be convinced in making a decision on this drug that this is an adequate and well-controlled trial, that the effect on the endpoint, which is clinical benefit, is clinically meaningful and statistically persuasive.

DR. LEVINE: And then I have one more, and that is, it says someplace in the company's stuff that this an orphan drug, that this has orphan drug status, and so my question to the FDA, does that do anything, does that influence our vote, or does that have anything to do with anything?

DR. PAZDUR: Not in making a decision of approving this drug or not, no, it does not.

DR. MARTINO: Dr. Rodriguez.

DR. RODRIGUEZ: I am sorry to belabor this point, it is again back to the toxicity. Dr. List said that it is predictable within the first 8 weeks, but, in fact, if we look at the graphic that he showed, if I am interpreting the graphic correctly, in fact, throughout time, there is a

continuous dropping of dose because there was a subsequent stepdown from 5 mg to 5 every other day, and as I interpret that graph, that continues to happen in a good 20, 30 percent of patients or more will have had that change by the 24 weeks that you showed in your graph.

So, in fact, there is continued and ongoing dropping of the dose, so it suggests that there is cumulative toxicity from this drug.

Am I interpreting this correctly?

DR. DeLAP: Dr. List.

DR. LIST: Let me clarify for you. There is an immediate early precipitous drop that occurs early on, but I will put the slide back on.

[Slide.]

But overall, around 20 to 25 percent may go on to need additional dose adjustment later, but it is not precipitous. This is something that doesn't occur very fast. So, there may be a dose adjustment in about 20 to 25 percent. That means 75 percent don't require another dose adjustment then.

DR. RODRIGUEZ: I have another question, if I may.

This has already been brought up by Dr. Pazdur and Dr. Levine in her questions, and this is in reference to the indication of this drug for multiple myeloma.

This is not to downplay the importance that this drug may have in myelodysplastic syndrome, but, in fact, there is a larger, much larger population of patients out there that may benefit from this drug, and it is those with lymphoid disorders. It already has ongoing studies that have demonstrated efficacy, as I interpret the studies, in myeloma.

Where does the company stand in reference to bringing that drug for application in that disease, and does our approving it today for this particular indication--I think it has been indirectly addressed with regards to the expanded access program, but, in fact, when the drug is now commercially available, there is no stopping its use outside of the, quote "approved" indication.

Can you address these concerns, please?

DR. DeLAP: We are aggressively pursuing the filing for multiple myeloma. That is a top priority for us, you know, right after this meeting, and actually, alongside the preparations for this meeting.

We do have the expanded access program for myeloma. As you hear, it's the expectation that program continues until we reach closure on that as an indication. We will be working to educate physicians and we will be working around the approved indications.

We will not be obviously encouraging people to use the drug off label until we have gone through the process and received validation, as it were, that we have the adequate and well-controlled trials for myeloma.

DR. MARTINO: Dr. Reaman, last question.

DR. REAMAN: Given the toxicity profile of this agent, and all of the dose modifications that were required during the trial, the fact that the protocol specified dosing wasn't consistently

followed, and that some patients whose doses were decreased were apparently increased later, do you have specific plans on what the package insert will include as far as dosing recommendations and dose modifications? And if so, could you define them or describe them?

DR. DeLAP: We will be recommending dosing in the package insert that reflects what we have studied. I would say there were a couple of patients that were not treated in accordance with the protocol, as I mentioned earlier, who actually were restarted after an interruption, on the same dose rather than at a reduced dose, but overall, the compliance with the directions was very high, and, in fact, those couple of patients who were restarted at the same dose rather than at a reduced dose seemed to tolerate that dose better the second time around, again, perhaps because their bone marrow had responded to the earlier treatment.

So, we will proceed with the program that we know to be safe and effective basically. We know that this is a way to use the drug that

provides the benefit that you have seen, and the number of patients that discontinued, you saw before, discontinued for thrombocytopenia is like 8 patients over the entire program. This is not a lot of discontinuation for AEs.

DR. REAMAN: I am not sure that I understand the answer. So, what you will recommend is basically the protocol-specified guidelines, you won't recommend that patients resume at the earlier dose?

DR. DeLAP: What we know is what we studied, and I think that is the most prudent thing is to recommend what we have studied, and not to go beyond that until we have established that it is appropriate to do so with clinical study data.

DR. MARTINO: The last question is to be for me, just a simple, basic understanding here.

I need to understand more clearly while patients were on study, what triggered, what would allow them to get a transfusion, because there is a fair amount of judgment that goes into when I transfuse a patient. What triggered that, what was

allowed to trigger that?

DR. DeLAP: Dr. List.

DR. LIST: There were transfusion guidelines written into the protocol, but there were really two different types. We all know if you have a patient who is 80 and with coronary disease, their threshold may be 10 as opposed to 8, but the protocol wrote for at 8 or lower to get a transfusion, and the alternate in the protocol was continue to transfuse at their pretreatment baseline, at that threshold of hemoglobin and symptoms. So, it was always defined by the physician.

When we looked at the box plots that I showed you earlier, the median trigger for transfusion was identical pre- and post.

DR. MARTINO: During that period, it sounds like they were allowed to get some supportive things. They were allowed to get growth factors for their white cell count. Were they allowed to get any Procrit or agents to enhance the red cell line other than your agent?

DR. LIST: No. Erythropoietin was excluded from the trial. Myeloid growth factors were allowed at the discretion of the investigator, although not many patients received them. I think it was about 25 or so--23 total that received that.

They could receive transfusions, they could receive desperol, the iron chelation, as well, antibiotics, anything except for erythropoietin.

Committee Discussion

Questions to the Committee

DR. MARTINO: As this point, you will have to hold your questions, and I would like to now focus you on the actual discussion of this application, and I would like to do it from the point of view of truly answering the questions.

If someone can put the questions up on the viewbox there, so the rest of you can see them, and I will read them for you. All of these will require a vote.

Question No. 1. Randomized controlled trials allow for direct comparisons of treatment

effect and safety between arms. A single-arm study has been submitted using a 8-week run-in period to serve as baseline for each patient's transfusion requirement.

A comparison is subsequently made to a follow-up 8-week period of agent to compare transfusion requirements in the same patient.

Does this study design allow adequate characterization of the agent's treatment effect in the population described in this proposed indication?

Who wants to start this? If not, I shall choose.

Dr. Cheson.

DR. CHESON: Well, in the hematologic community, who have been following this drug, are intrigued by its activity, and I think that these data demonstrate that there is a signal here and a fairly strong signal.

I would much rather talk about the next question when we get to it, because I do think that having taken care of and still involved in taking

care of MDS patients, there is some background noise. They do require transfusions sometimes, and not others, but the durability of some of these responses I think is more than you would see with signal, more than you would see with just background noise.

So, I am reasonable comfortable that there is treatment effect with this agent.

DR. MARTINO: Anyone else? Dr. Levine.

DR. LEVINE: I will agree, and what impresses me, as well, is the duration, so this is going on a year or more, and I don't in any sense disbelieve those results.

DR. MARTINO: Yes, you, the attractive woman in blue, whose name escapes me at the moment.

DR. O'BRIEN: O'Brien.

DR. MARTINO: Dr. O'Brien.

DR. O'BRIEN: But that's okay, you can call me that if you want.

I think the endpoint of the study was the transfusion requirement, and I would be willing to be much stronger in stating the clear efficacy of

this drug. Not only was the transfusion requirement diminished, which can be quasi admittedly, but you saw that the median hemoglobin rose 5 grams, that the response was incredibly durable. There are 52 patients still out more than one year with no transfusions, and the other point that I think really has not been focused on is that in many of these patients, the malignant clone is disappearing, so this is not a cosmetic effect. There is actually a suggestion we are getting rid of the disease, and I would be so bold as to say could there even be a cure fraction with long enough therapy. We don't know that now, but there is no question, if they only had a nice rise in the hemoglobin that was durable, and they still all had 5q minus, I still would probably be in favor of the drug. But don't forget that the clone is actually disappearing, you are getting rid of the disease in the bone marrow. You are not just relinquishing the transfusion requirement.

So, I think that the efficacy is unquestionable.

DR. MARTINO: Dr. Eckhardt.

DR. ECKHARDT: That was actually going to be my point, as well. I think that whenever you see the transfusion endpoint here, that you need to have supportive data. In my mind, partly that was--I mean a big part of it was the cytogenetic response, and I think, secondarily, was the fact that you actually had a kinetic response with regards to the hemoglobin and the transfusion requirement that appeared to be very quick and, to me, looked more related to a drug effect.

So, I think that those supporting data really back up the primary endpoint.

DR. MARTINO: Dr. O'Brien, do you have a comment you wanted to make? Okay.

Maha.

DR. HUSSAIN: I was hoping that the comment about attractiveness was about me.

DR. MARTINO: All the women on this committee are attractive.

[Laughter.]

DR. HUSSAIN: But I would like to think

with brains also.

I guess the question, as I read it, isn't do we think there is a signal, because I think we all agree there is a signal. It is the last line, which says does the study design allow adequate characterization of Revlimid's treatment effect in the population described in the proposed indication.

I don't think--I guess what I would like to hear from my hematology colleague, do they believe that it is actually adequate characterization. If I have not misunderstood, the population was a bit more heterogeneous than what was intended, than what we were led to believe that this population should be like.

With this being not, as Rick was pointing out, a response as such, and understanding that there is some noise in the background, which does not take away from the fact that there is efficacy, I would come with the conclusion that the question does the study allow adequate characterization, to me, it is not, and I would like to hear those who

say yes, to convince us that this is actually a yes. Beyond yes, there is activity we all agree, but it is the adequate characterization.

DR. MARTINO: Would anyone care to take that challenge? Yes, Dr. Bukowski.

DR. BUKOWSKI: I am not going to take up that challenge, but I think I will just echo my colleagues' statements that the fact that this drug produces the hemoglobin rise that we see, in addition to the cytogenetic responses, to me, that is very convincing data in this particular population of patients, although it is heterogeneous, I do admit. Nevertheless, there is without a doubt a treatment effect being demonstrated in this group of individuals.

DR. MARTINO: Yes.

DR. CARROLL: The point I want to make is that there are no other clinical trials that I am aware of, nor the one drug that has been approved by the FDA, that had the dramatic effect of reducing the transfusion dependency on the number of patients as this clinical trial has. I think

that is important to remember.

DR. MARTINO: Dr. Fleming.

DR. FLEMING: I think from previous discussion, it is apparent that I am something between two roses, hopefully, not a thorn.

DR. MARTINO: I will not comment on that.

DR. FLEMING: For me, this is a difficult question, and I think for reasons similar to what Dr. Hussain was pointing out. The question is does this provide an adequate characterization.

My understanding is, in essence, we have a single trial, the 003 trial is the single source of evidence here. We actually have another substantive trial that we reviewed, and that's the 002 trial, although that is in patients without the 5q abnormality, and actually, it shows a far lower response rate, pointing out that there really is considerable issues here with heterogeneity.

There is clear evidence for a signal at some level. That is my sense here. It is also, though, very apparent due to the nature of sampling and issues and bias that I was referring to in my

earlier questions, that we certainly cannot attribute the entirety of this response to treatment effect.

There certainly is noise and there is bias in the way this is being assessed. So, if the question here is--and it comes back again to this issue of adequate and well-controlled trials--if the question is as simple as do these studies provide or does this trial provide substantial evidence for some level of benefit, which is what I heard Dr. Bukowski saying yes to, I would concur with his answer of yes, but everything is benefit to risk, and the issue is, if this safety profile is pristine, then, that answer is probably adequate. If the safety profile, though, is not necessarily pristine, and difficult to understand, then, to my way of thinking, adequate and well-controlled trials means not just can we show that there is a signal for something, do we have reliable evidence to allow us to assess benefit to risk in a conclusive fashion, so that if there is, in fact, substantial risk, can we reliably indicate

what is the level of benefit, and I am struck by the almost complete absence of an indication of what an appropriate comparator arm would do on these key measures that we are asked to look at for efficacy, measures, such as change in hemoglobin levels, numbers of patients that have transfusion independence, and duration.

I am persuaded there is something happening here. I do not have a good sense of how much of it is attributable to therapy, and in the context of uncertainty about safety, I would agree with Dr. Hussain, it doesn't allow me to say, then, this is an adequate characterization.

DR. MARTINO: I would like to put the question to a vote. Again, the key words here are does this study design allow adequate characterization of the agent's treatment effect in the population proposed.

I would like to start on my left, please. Please state your name and your vote.

DR. CARROLL: Dr. Robert Carroll. My vote is yes.

DR. O'BRIEN: O'Brien. Yes.

DR. FLEMING: Fleming. No.

DR. HUSSAIN: Hussain. No.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: Cheson. No.

DR. ECKHARDT: Eckhardt. Yes.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez. I don't have a vote, but I would vote yes, because I think there is a clear signal here that this is clinically active and of benefit to the patient.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. No.

DR. MORTIMER: Mortimer. Yes.

DR. LEVINE: Levine. Yes.

MS. HAYLOCK: Haylock. Yes.

DR. REAMAN: Reaman. Yes.

DR. MARTINO: The vote is I believe 11 to 4 with the yes's having it.

The next question is in this single-arm trial, 80 percent of patients enrolled in Study 003

had dose reductions and/or delays, and 80 percent of the patients experienced either Grade 3 or 4 adverse events. Data do not exist on the efficacy and safety of lower doses of this agent.

Approval of a drug is contingent upon being able to write adequate product labeling requiring a recommended dose and characterization of a safety profile for that dose.

Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of its safety profile?

So, the issue again has to do with this specific dose and the toxicities inherent in it.

Who would like to start that discussion? Dr. Eckhardt.

DR. ECKHARDT: Well, I think that this is probably the stickiest part of this application, and I am struggling with this, because I can see the rationale with regards to assuming that the malignant clone is reacting to this drug with a cytotoxic response. However, I think that is a bit of a stretch. We don't know that, because we

haven't really adequately assessed the 5 mg dose.

So, I am assuming that if one assumes that this is a cytotoxic agent, certainly, in the solid tumor arena, we have had many drugs that go to market based upon the body of data that supports a starting dose with the idea that patients have to be followed very carefully for dose reductions.

Examples would be CPT-11, another example would be things like capecitabine, that actually with frequency required dose reductions and careful monitoring.

So, I think that there is certainly a precedent, but I guess my concern is that this is really going in with the idea that we have two questions. One is do you really need to achieve sort of this dose intensity against the clone in order to get the best response, and that is a little bit fuzzy.

Secondly, we just flat-out don't have the data with regards to induction at 5 mg and what the benefit would be.

DR. MARTINO: Dr. Cheson.

DR. CHESON: As I said before, I am convinced there is activity here, there is definitely a signal, but I am very worried. What we heard is that the participants in this clinical trial who are used to, at least someone doing clinical research, can't tell if cytopenias are related to the drug or the disease with any sort of reliability.

The majority of deaths on this trial were not attributed by the investigators to the drug, but on a secondary independent review were identified as drug--or at least suggested to be drug related deaths.

So, the physicians out in the community have difficulty, not only identifying toxicities, but also whether the drug is potentially lethal in a certain indication. Here, we have a dose for which 80 percent of the people cannot tolerate it. We don't know whether 5 mg won't give you the exact same effect, and we are told that we will put this on the street and look at counts check weekly by the practicing community oncologists and leave it

up to them to modify the dose accordingly, when they couldn't modify it appropriately during the conduct of a clinical trial, where some were re-establishing therapy at one dose, others at another dose.

So, whereas, I would love to see this drug on the market because it will benefit some patients, I am convinced. I think the dose is an unsafe dose. I think the schedule is difficult for most practicing oncologists in a busy practice to manage, particularly those who are not experienced in dealing with cytotoxic therapy of hematologic malignancies, notably myelodysplasia.

So, I would love to see it out there, but I am very uncomfortable at the number of patients that are going to suffer untoward adverse events and possibly death because of the complicated management of this agent in a community setting.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I also have concerns that I really don't know, I wouldn't know how to use this drug right now in several ways. Number one, maybe

you use 10 mg for the first 8 weeks and then automatically go onto a maintenance of 5. You know, maybe that is a way to think about it, but I don't know that, and we don't have data around that.

As far as the myelosuppression, I clearly understand the concept of hematopoietic progenitor disease, and so forth, but you said that even at a higher dose, but still you said that the drug is associated with the same degree of myelosuppression in myeloma, albeit at a dose of 25 to 50, which is not a CFUGEM disease, so I am going to interpret that there is some evidence perhaps of myelosuppression due the drug.

I don't want to come back to this, but I am worried about the kidney. I don't think we know how to dose this with renal insufficiency, and I think we need to know that.

Lastly, I am not really worried that much on the teratogenicity, but I will say one thing, and that is I am not worried in this patient population. They are older people, and so forth,

but it is going out into the community, which means that all kinds of folks could theoretically be using it.

So, it would just make me feel more comfortable if we really knew the final answer in that regard, too, although I am much less worried about that than the myelosuppression and renal issues.

DR. MARTINO: Dr. Mortimer.

DR. MORTIMER: The other question that I am kind of uncertain about is the role of growth factors and the impact on cytotoxicity with that initial dose, and I don't think it was really addressed.

So, if we give growth factors concurrent with the Revlimid, are they going to get more myelosuppression or less myelosuppression, and my guess is that that is what is going to happen in the community.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I want to echo my colleagues' concern about toxicity. I am not

convinced that we know the dose, I am not convinced that we know the schedule, and I am not convinced that we know to start and when to stop throughout the treatment.

The fact that there are so many questions, really reflect on Question No. 1, that the trial is not adequately designed to answer definitive questions, and the fact that everybody has questions like we are raising right on the schedule and such, would point out, even though the vote was yes on Question No. 1, and we can't go back to it, it is really not an adequately designed trial.

It was not designed for registration, and it just so happened that the results were so good, and, well, let's go register, and I think that is a problem for me.

DR. MARTINO: At this point, I would like to take a vote on this question. Again, the question is: Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of safety profile?

Again, I would like to start on my left.

Please state your name first.

DR. CARROLL: Dr. Robert Carroll. Yes.

DR. O'BRIEN: O'Brien. No.

DR. FLEMING: Fleming. No, and let me just kind of--because I didn't get a chance to earlier--that I am concerned about both aspects of this question, do we have data for recommended and adequate to establish a recommended dose, and an adequate description of the safety profile.

As my colleagues have pointed out, we have a very high level of adverse events and SAEs occurring in the trial. Now, it is entirely possible, if not likely, that there is a fair amount of this that is disease related, and not treatment related, but the absence of a control leaves us in a very uncertain situation about that.

We certainly have very significant issues with neutropenia and thrombocytopenia. I am impressed that this is a setting that has, from a survival perspective, quite a good prognosis compared to the more advanced IPSS scales, and as a result, I would think that means there is a lower

threshold for treatment-related deaths.

I don't know how many truly are treatment related deaths. We know that 7 percent have deaths within 30 days, and according to the investigators' assessment, 2 percent have treatment-related deaths. This is a key issue to understand when it comes down to benefit to risk, and in the absence of a control arm here, this is really working against the product and against the sponsor to determine whether or not these issues are, in fact, real or attributable to the disease process.

Finally, as has been pointed out, with 80 percent of patients having dose reductions, it clearly leaves us in a position here where there is a great deal of uncertainty about what the right dose is, so for both aspects of this question, I would say no.

DR. HUSSAIN: Hussain. No.

DR. DOROSHOW: Doroshow. No.

DR. BUKOWSKI: Bukowski. No.

DR. CHESON: Cheson. No.

DR. ECKHARDT: Eckhardt. No.

DR. GRILLO-LOPEZ: If I had a vote, I would vote yes.

DR. PERRY: Perry. Yes. I remember how to reduce the dose of chlorambucil.

DR. RODRIGUEZ: Rodriguez. In reference to this particular question, the answer is no.

DR. MARTINO: Martino. No.

DR. MORTIMER: Mortimer. No.

DR. LEVINE: Levine. No.

MS. HAYLOCK: Haylock. No.

DR. REAMAN: Reaman. No.

DR. MARTINO: The vote is 13 no and two yes's.

The final question, No. 3 actually, No. 3 really is the question here to be answered as far as I am concerned.

Please characterize the magnitude of Revlimid's benefit and risk in the indication being sought. After this characterization, does this risk-to-benefit analysis warrant approval?

So, I will hear a little discussion, but, in fact, this is the approval question, and