Trends-in-Medicine

September 2005
by D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Oncologic Drugs Advisory Committee Recommends Approval of Revlimid for MDS

Bethesda, MD
September 14, 2005

The FDA's Oncologic Drugs Advisory Committee voted 10-5 to approve Celgene's drug Revlimid (lenalidomide), an oral drug to treat anemia in patients with MDS (myelodysplastic syndrome), a potentially fatal blood disorder. MDS comprises a group of disorders in which blood cells don't fully develop. Patients often require blood transfusions as frequently as every eight weeks.

Celgene is asking for FDA approval to market Revlimid for patients with transfusion-dependent anemia due to low or intermediate-1 risk (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Revlimid is a new version of thalidomide (Celgene's Thalomid), which is approved for the treatment of leprosy but is often prescribed off-label for treating multiple myeloma. Users are carefully screened to avoid pregnant women getting the drug due to the risk of serious birth defects. FDA staff members said that the agency is reviewing the drug's potential harm to developing fetuses.

An FDA staffer said that the FDA had recommended looking at randomized studies of the drug but that the company had instead used a single-arm study. He said, "As we pointed out, randomized trials give us more information…and allow us to better characterize the toxicity of drugs. Nevertheless, the sponsor decided to use a single-arm trial…I point out that we must have a population of patients that is adequately defined, has a large transfusion requirement that is well characterized, and the effect of the drug should be able to be distinguished from the natural history of the disease." He added that the FDA must recommend a dose of the drug and allow adequate characterization of the toxicities of the drug to allow a risk:benefit relationship. He noted this is more commonly done in randomized trials and that single-arm trials sometimes have difficulty examining the issues.

The Company Perspective

A Celgene vice president said that Revlimid has:

- Rapid absorption.
- Extensive distribution into tissues.
- Low protein binding.
- No inhibition or induction of major cytochrome P450 isozymes.

- Partial metabolism related to hydrolysis (observed in vivo).
- Rapid excretion via the urine, mainly as unchanged drug.

Celgene's Senior Vice President for Regulatory Affairs told the panel that Phase II results were robust in a well-characterized population of:

- Low/intermediate-1risk del 5q patients.
- Conventional cytogenetic testing.
- The largest prospective clinical study of del 5q MDS.

Revlimid was described as showing significant clinical benefit:

- Durable resolution of refractory anemia (67%).
- Significant rise in hemoglobin.
- Cytogenetic response and remissions.
- Marrow normalization and improvements.
- Well-characterized, manageable adverse events.

Celgene's Chief Scientific Officer said that Revlimid and thalidomide are pharmacologically different drugs based on chemistry/metabolism, cellular biology, molecular biology, clinical profile, and non-clinical reproductive/development toxicology. In reproductive and developmental toxicity studies in rabbits, no malformations were found, and an analysis and report is underway.

A Celgene consultant, who is a hematomorphologist and chair of the MDS Foundation, described MDS classification and prognosis: Patients with low/int-1 risk MDS present with anemia and fatigue, which limit their ability to function in a normal way. Treatment includes recombinant erythroid growth factors, 5-azacytidine (Pharmion's Vidaza), and transfusions. He said that Vidaza is the only FDA-approved drug for MDS, but it is useful only in a limited population. He said that transfusions are an "imperfect solution" because of transient hematocrit (Hct) improvement. Hct is not restored to normal, and there are morbidities associated with transfusions, including iron overload, infectious diseases, and transfusional reactions. He said, "Transfusions also put a demand on the blood supply and have an impact on patients' lives. Quality of life is also significantly affected…Obviously, there is a real cost of providing transfusions, which at our center is in excess of $500 per unit."

Another Celgene speaker presented the efficacy results from two Phase II studies. In the pivotal 148-patient study, the primary efficacy endpoint was red blood cell (RBC) transfusion independence (TI). TI was defined as no RBC transfusions for two months or longer (56 days). Duration of TI response was from the day after the last RBC transfusion to the day before the next RBC transfusion.

Secondary endpoints were:

- Duration of response.
- Change in hemoglobin (Hgb) level.
- Minor erythroid response.
- Cytogenetic and pathologic bone marrow response.
- Neutrophil/platelet responses.
- Safety. A Celgene speaker presenting safety data said that the drug has a favorable safety profile, with the most common adverse effects neutropenia/thrombocytopenia, which he described as "manageable" with dose interruption/reduction. He said that non-hematologic adverse events were mild and infrequent.

Transfusion Independence Response in Del 5q (Study MDS-003)

Measurement	NDA submission 9-14-04	Updated data 3-31-05
ITT, n=148	65%	67%
Median time to response (range)	4.1 weeks (1-19 weeks)	4.6 weeks (1-49 weeks)
Modified ITT, n=94	57 (61%)	64%
Median time to response (range)	4.7 weeks (1-19 weeks)	5.1 weeks (1-49 weeks)

Grade 3/4 Hematologic Adverse Events ≥2% in Del 5q (Study MDS-003)

Adverse event	Grade 3		Grade 4	
	10 continuous n=103	10 cyclic n=45	10 continuous n=103	10 cyclic n=45
Neutropenia	17.5%	15.6%	50.5%	17.8%
Thrombocytopenia	44.7%	35.6%	6.8%	17.8%
Febrile neutropenia	3.9%	6.7%	0	2.2%
Anemia	1.9%	6.7%	4.9%	2.2%
Hemorrhagic events	1.9%	6.7%	0	2.2%

Serious Adverse Events >2% in Del 5q (Study MDS-003)

Adverse event	Serious adverse events n=148	Suspected drug-related adverse events n=148
Pneumonia	9%	4%
Neutropenia	7%	6%
Pyrexia	4%	3%
Febrile neutropenia	4%	3%
Thrombocytopenia	4%	3%
Dehydration	4%	0
Acute leukemia	4%	0
Anemia	4%	1%
Congestive heart failure	3%	<1%
Sepsis	3%	<1%
Diarrhea	3%	0
Vomiting	3%	<1%

The speaker said that 11 patients (7%) died in the 003 study. Three (2%) were suspected as drug related: neutropenia/ pneumonia, neutropenia/Kiebsiella sepsis, and pancytopenia/ sepsis. He said the deaths were early trial and that no deaths have occurred since a modification of entry requirements.

In pooled data of the three trials, there were 26 deaths (6%) out of a total 408 patients. Five of the deaths (1%) were suspected as drug related. Median age at time of death was 80 (62, 93%).

A Celgene speaker told the committee that the drug shows significant clinical benefit and that toxicity problems are manageable with dose adjustment.

Celgene said that the company is proposing a risk management program for lenalidomide, called RevAssist. The program will focus on patient and physician education and pregnancy testing for females of child-bearing age. Specialty pharmacy distribution is also part of the plan.

THE FDA PERSPECTIVE

FDA reviewers agreed Revlimid shows efficacy in reducing transfusion dependence, but they had several concerns with the drug, including:

- **Value of primary endpoint.** The primary endpoint was independence from transfusion, but the staff questioned that endpoint, asking whether demonstrating eight weeks free of blood transfusions was a good clinical benefit measure.
- **Toxicity.** FDA reviewers expressed concern that the drug dosage may be too toxic. About 80% of patients had to have their 10 mg dose reduced or withheld.
- **Use of single-arm trial.** Reviewers asked the panel whether a single-arm trial in a heterogeneous disease (MDA) is sufficient. The FDA had asked for a randomized clinical trial.
- **Teratogenicity.** FDA staffers criticized Celgene's female embryo development studies, one using rats and one using rabbits. A reviewer said that the rabbit study was insufficient, "This study was inadequate. Drug-related effects on maternal or developmental endpoints in the high dose group did not meet standard study criteria." She added that the rat study was not an appropriate model for full assessment of the embryo-fetal effects of the drug, concluding, "The structural similarities of lenalidomide and thalidomide suggests risk, and there is insufficient information to fully determine, the effects on embryo-fetal development for lenalidomide." The reviewer said that if the drug is approved, Pregnancy Category D is recommended, similar to most other oncologic agents, and further studies are needed.

Most deaths were due to infections, AML, bleeding, and cardiac events. An FDA safety reviewer talked about dose modifications due to adverse events, "Virtually all patients had adverse events; 80% had one or more Grade 3 or 4 adverse events...Rashes were impressive, sometimes covering 80% of the body, resulting in discontinuation of the drug…The key question is whether neutropenia, or thrombocytopenia are due to the disease, MDS, or the drug?...The benefits of RBC transfusion independence versus the risks of neutropenia and thrombocytopenia need to be assessed."

RBC Transfusion Independence Response

Population	Transfusion independent
ITT (n=148)	66.9%
FDA evaluable (n=96)	66.7%

FDA Safety Review of Revlimid

Adverse event	Revlimid
≥1 Grade 3/4 adverse event	80%
Serious adverse events	38%
Blood-related adverse events	11%
Infections	8%
Deaths (mostly due to infections, AMI, Bleeding, and cardiac events)	28 on-study 14 in patients with continuing toxicity
10 mg/day dose reduction or interruptions in dosing	80%

Another FDA speaker said that the major safety concern regarding risk management is teratogenicity, and the major goal is prevention of fetal exposure to Revlimid. She charged that the embryo-fetal development was not adequately addressed.

The panel had some questions, including one about dosing. A Celgene vice president moderating questions said that the company monitored dosing. The company used continuous dosing until a Grade 4 adverse event occurred. It also cycled dosing with 21 days of drug followed by a 7-day break.

PANEL DISCUSSION

Renal Failure

The Chair asked about effects of the drug in the urine and renal failure. A company spokesman said they have not done a study about this yet.

Deaths

Panel member (oncologist): "There was a question about the last patient who died of an intercerebral bleed…It is hard not to attribute this to an effect of the drug. To say that a death is unknown…you give the benefit to the patient, not the drug."

Panel member (oncologist): "If I'm not mistaken, I saw a 40% adverse event, with 80% interrupting treatment. Why do you think you have the right dose?"

Celgene official: "These patients with MDS and with 5q deletion have a cell clone that is giving a rise to…a lot of platelets, and as we give a drug that causes the clone to be suppressed or eliminated, there can be a period of time before more normal cells can go back to the marrow, and the patient can become neutropenic or thrombocytopenic…We will work to refine the dosing, but we feel we have a good regimen in terms of both effectiveness and safety, with continued monitoring…We believe in the validity of the 10 mg dose, and we believe in testing other doses. If we find the 5 mg dose is sufficient to get good benefit, that might be the way to go. We're already dosing 10 mg – and others are tolerating 25 mg. We reduced the dose because we had to, but it's the malignant or dysblastic clone…More than half the patients in the study are still on the study after a year, so there are patients who are tolerating this drug well for a long period of time…This is a cytotoxic agent for the disease; we are actually killing the clone. Some of the extremes, it can happen very quickly. But long term thrombocytopenia – severe – I don't see that. Moderate, yes."

FDA: "Some of (the sponsor's definitions of deaths) were disingenuous – calling something multi-organ failure when someone comes in with profound neutropenia and pneumonia. This is not a catch-all diagnosis. Two more comments: I was impressed how long-lasting the neutropenias and cytopenias are. Sometimes they're reversed within a week or month, and sometimes they last for months and years. This was quite impressive. Secondly, how quickly and predictably they begin. Someone has started on 10 mg a day, and after six 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 count. This is not something that I would think of as being typical of a myelodysplastic syndrome. So, I'd think that management of patients with this drug is not going to be easy, and one has to be careful with it."

Plans for a Phase III trial

Celgene official: "We're proceeding in an orderly sequence here. We started with a Phase II pilot study, but it indicated that this drug had promise in this subset of 5q patients. We then went to the two Phase II trials, but separated out the deletion 5q from the non-deletion 5q to see if it holds up, and it has. We are going to Phase III. We are going to do a placebo-controlled trial. There is reluctance to put patients on placebo for very long based on the benefit seen here. Everybody will receive the best standard supportive care, but patients who receive placebo receive that for four months. If they're not responding, and we don't think they will, then they'll have the opportunity to go on lenalidomide and see if that benefits them. We'll be taking advantage of that design… getting better estimates of some of those parameters. We do feel what we have so far is a striking result in terms of the effectiveness, and safety is quite manageable as long as patients are well monitored with weekly blood counts in the first few weeks of therapy."

Toxicities

Panel member (oncologist): "Have you done an assessment of toxicities between the 5 mg and 10 mg dose levels?"

Celgene: "In terms of the comparative toxicity of 10 and 5, looking at that analysis would be that patients on 5 mg got there because they had some toxicity on 10, so you're looking at a select population. To do that, you need a randomized comparison, and no one was treated with 5 mg at induction… People got to 5 from 10 because they needed to have dose reduction. We would have reduced them again…but for most of them we didn't. That's another way of looking at the same question. There were also a few patients in the study who, after a reduction, were put back on the same dose. It seemed like the second time around they tolerated the treatment a lot better."

Chronic maintenance dose possibility

Panel member #1 (oncologist) to another panel member: "In the international congress, did your group have the foresight to see that there might be a chronic maintenance dose that would be given long term?"

Panel member #2 (hematologist/oncologist): "In fact, we're in the process of doing that now. The issue was when you look at patients with low-risk disease. We separated out low risk from the high risk. Patients with high-risk disease, in general, get more cytotoxic approaches. People with low risk, until now, mostly got growth factor or antibiotics support. So, in that context, patients got and then maintained the transfusion without someone coming in with some other chemotherapy drug…but the initial drug way back then was, in general, a supportive care sort of agent. Now we have toxic drugs being used for that population."

Panel member #1: "So this criteria alone no longer holds?"

Panel member #2: "In the context of not having another intervention during this period of time, it holds, and I think that's how you have to look at it. Because if the drug lasted for more than two months, that would be acceptable."

Panel member #1: "Will you get anyone to be in a Phase III study? I think you'd have to be a fool to randomize for four months before you get the drug."

Celgene official: "We have more than 20 patients at this time. We allow for crossover. Those patients who haven't responded – by 16 weeks are unblinded."

Panel member (patient representative): "I'm impressed in the efficacy. How much of dosing interruption is due to the drug no longer working and then reintroducing the drug, either 10 mg or 5 mg actually producing results for these patients?"

Celgene official: "I don't know if we know those precise numbers."

Panel member (patient representative): "How many patients dropped platelet levels from entry level and then got levels back up to entry?"

Celgene official: "Remember, many will come in with elevated levels. These would come down to levels less than the normal range, around 100,000 or maybe a little bit higher than that. They seem to continue to creep up and up."

PUBLIC COMMENT

Three members of the public who spoke during the public comment session included:

- An MDS patient on Revlimid: "It has been almost two years since I last needed a transfusion…My life has almost become normal. I can do almost all the things I used to do before I was diagnosed, like travel and exercise."
- An MDS patient not on Revlimid but whose transfusions are starting to stop working.
- The head of an myeloma support organization, who said, "Revlimid holds the greatest potential for this disease…We receive phone calls daily from (people) who want to know the status of the drug."

THE PANEL DISCUSSION

Efficacy

Panel member (biostatistician): "In areas of efficacy, my understanding is that the Hgb improvement slides…Because there's always variability. Even if I had a placebo and took a minimum series of measurements at baseline and maximum at end, I'm struggling again to know how much is treatment effect. What is the effect of control? How many people would have responded? First, there's open label bias; that's an issue. We also have a well-known progression to the mean bias because, when you select a patient cohort, you're estimating what the rates will be. If there's progression to the mean bias here, which there almost certainly is, then clearly there would be patients in the control arm who would have some response. Then there's duration of response (slide is shown). The FDA, in its briefing document, said that measurement was made from the last of the 56+ day intervals."

Panel member (biostatistician): "These Kaplan Meiers aren't interpretable; the only way to interpret it is if you have a baseline…How much of an effect is due to intervention?"

Celgene: "Everyone would agree; as people are going eight weeks without a transfusion, that would be bias. Regarding the Kaplan Meier, it was designed like that. The FDA did a different analysis; this is the protocol-defined analysis. This is what we planned in the protocol…There's rapid rise in Hgb. Within a matter of cycles 2 to 4, the Hgb shoots up. These are going up to levels 12 - 14. Look at the duration of benefit. There are 84 patients out beyond six months, and there are 57 out beyond a year. From the end of August, we still have not reached the end of transfusion-free. These patients are going over a year and with a rise in Hgb."

Panel member (biostatistician): "Your conclusion here is that we might be altering the natural history of the disease in this subset by the visual impression that the MDS survival is better than the Mayo Clinic survival. Isn't that an incredible (jump?) How do you validly make this comparison?"

Celgene: "These are not 5q minus syndrome – 25% were in that subset…I can tell you that data was published last week looking at 5q minus and plus, and it looks better than this."

Why no randomized trial?

Panel member (biostatistician): "First, why wasn't a randomized trial done?...If your intention was to do a registration trial, and if you have a 62% response rate, if a lot of that is attributable to therapy – even if half – it should only take 100 patients in a randomized trial to sort out if there are differences or if there are not differences. Why wasn't a randomized trial conducted for registration purposes, or is there one being conducted, and we have to wait a year for the results to come in?"

Celgene: "The happy problem that we have is that the results are so good in the expanded Phase II experience. Although we're on track to do a Phase III trial, we have difficulty coming up with a design that people are happy with because it does involve putting people on a placebo for four months. We've just seen such strong results that the issues…are no longer whether the drug works or whether it has a favorable risk/benefit. The issues are what are the effects on the various endpoints? What can we do to more precisely characterize side effect profiles?"

Panel chair: "I do want to stop this now. It is this that we have to judge today. Whatever their (Celgene's) reasoning, they aren't going to change the judgment that you make today."

A Celgene speaker said the company had worked on every step with the FDA, which caused FDA staffers to turn off their microphones and laugh among themselves.

Is a single-arm trial sufficient?

Panel member (non-voting industry representative): "The FDA usually asks for randomized trials. What is unusual is a single-arm trial. That is their standard. However, they don't require or impose that. Second, FDA regulations don't exclude the possibility of a single-arm trial for approval, and there is precedent for approvals based on single-arm studies. I have had two drugs that I've developed approved based on single-arm trials."

FDA: "There is a mantra (at the FDA): adequate and well-controlled trials, adequate and well-controlled trials, and adequate and well-controlled trials. I think that's at the heart of the questions here. When we accept a single-arm trial, these are carefully defined situations, and we are usually looking for a response rate. We can quibble over clinical benefit. The control usually, in the situation of single-arm trials, is one where we would consider that there are no other therapies. An alternative would be to get such outstanding results that this would not be due to the natural history of the drug. But, in the rules and regulations, it's adequate and well-controlled trials. We have to answer that question. That's a central element, and that's why we're asking that…And if not (randomized and well-controlled), then one must have a magnitude of benefit so one can say this can't impact on the natural history of the disease."

Response rate, toxicity, and fetal embryo studies

Panel member (biostatistician): "I'm not terribly bothered about the response rate. My concern is on the toxicity, and I just can't get there. Revlimid is being used in other trials, and one of those is myeloma. Can you tell us the toxicities in neutropenia, etc., in these trials?"

Celgene: "The overall results are in the same magnitude of events, but they are being done in a 25-30 mg dose level."

Panel member (biostatistician): "And another concern is the late development of neutropenia and cytopenia."

Celgene: "I know that toxicity is the main issue in making the decision. Yes, maybe 80% of patients had dose adjustments, but the vast majority occurred in the first two weeks, and 20%-25% of people stayed on the 20 mg dose. For other people, they may have needed a dose adjustment. But, looking at the median ANC/platelet counts by week for T1 responders, you see a drop in the first 10 weeks, and then they go up and stay there."

Panel member (biostatistician): "So the late droppers discussed by the FDA would be the non-responders?"

Celgene: "Some of them were late responders. In other people, it took them that long to get to their first Grade 3 toxicity…If you look at the reasons for discontinuation, you can see that there are only eight patients discontinued because of thrombocytopenia, and for neutropenia it was only four patients. They were told to look for it, stop, and wait for better marrow function."

Panel member (biostatistician): "Three or four patients died of neutropenic sepsis or neutropenic pneumonia. How do you see those cases?"

Celgene: "That's what was recorded. I understand people had sepsis and then died subsequently. It may be that they developed the sepsis, and you'd expect the neutropenia after they went off the trial."

Panel member (biostatistician): "Related to the potential fetal toxicity, I'm getting all sorts of mixed messages. One, you knew that the rat model was not the model. I'm wondering why you did that. Secondly, you're saying this is not a teratogenic drug, yet you're saying only special pharmacies will be able to dispense it. Why?"

Celgene: "It is our belief that we have seen no evidence of thalidomide-like teratogenicity with this drug. What's been discussed is the adequacy of the studies to make that final conclusion, and we have some additional data that has not been reviewed by the FDA, so it's difficult to come to closure. But from the company's viewpoint, we have not seen any evidence that there is a potential here for limb malformations. The rat model is one that is used, and it has effects. If you're looking for the limb malformation, the best model is the rabbit, and we've done both."

Celgene (consultant): "In my opinion, the rat is a responsive species. Why? Because there are four things an embryo can do: die, be malformed, be functionally insufficient, be small. For thalidomide, it was shown the rat responds with three of the four endpoints. We find that thalidomide is a special compound that effects the embryo at doses that are therapeutic to the mother. At doses that were safe for the mother, there were no effects on the conceptuses. On that basis, I feel that the rat is an appropriate model for evaluation of the compound, and there are two species that have been developed for toxicity. The second study was done in Europe, and it's true the animals were not eating in the study. That's common for rabbits. You eliminate them from interpretation. That's what I did. At the lowest dose at which there was maternal toxicity, there were no effects at all on the conceptuses in that study. However, because of the sensitivity about this compound, that study was completed, and it's almost ready for submission. It doesn't change the interpretation of the data."

FDA official: "We would like additional data on this topic, and plans would be reviewed upon receipt on additional data. We are recommending a S.T.E.P.-like program that will be revisited when we get the information. That is a conservative approach in an area where, at this time, we feel uncomfortable but will be willing to review it. I do have a question about the expanded access programs both in MDS and multiple myeloma. What is the status? And would approval of the drug stop the planned expanded access program for multiple myeloma?"

Celgene: "We are having expanded access programs set up both in MDS and in myeloma. Myeloma is a bit farther along…We will start enrolling patients in the next few weeks, and that will continue whether or not approval occurs for MDS. Status for MDS is about two to four weeks behind."

Risk:benefit ratio

The panel's biostatistician said, "This is going in for full approval, meaning that you don't have to do the Phase III randomized trial. What will the company do if the Phase III shows that the risk:benefit ratio is not appropriate? What do

we do then?" A company official responded, "We have shown a lot about the risk:benefit with the dosing regimen that we're going for today. We find an acceptable toxicity treatment profile with monitoring of patients and adjustments when appropriate."

Dose and toxicity

A panel member asked, "Throughout time, is there a continuous drop down of dose? 20%-30% will have that change…so there is a continued dropping of the dose. Is there a cumulative toxicity with the drug?" A Celgene official responded, "There is an early, immediate, precipitous drop, but overall, around 20%-30% may need dose adjustment later on, meaning that 25% don't require another dose adjustment."

Lymphoid disorders

A panel member questioned, "There is a much larger population out there that may benefit from this drug, and it's (the population with) lymphoid disorders. Where does the company stand in reference to bringing the drug for that application and that disease?" A Celgene official answered, "We are aggressively pursuing the filing for multiple myeloma. That is a top priority for us."

Dosing recommendations

A pediatric oncologist on the panel asked, "Do you have specific plans as to what the package insert will have as to dosing recommendations and modifications?" A company official said, "We will be recommending dosing that reflects what we studied. There were a couple of patients not on the protocol, but, overall, the compliance with the directions was very high and in fact those couple of patients seemed to tolerate that dose much better the second time around. So, we will proceed with the program we know to be safe and effective."

Causes for transfusions

Panel chair: "I need to know, for the patients on study, what triggered them getting a transfusion?"

Celgene: "There were transfusion guidelines written into the protocol. The protocol wrote for 8 or lower to get a transfusion. The other was to continue to transfuse at the previous transfusion."

Panel chair: "During that period, were they able to get any agents to enhance RBC other than yours?"

Celgene: "Myeloid factors were allowed, but there were only 23 who received that. Anything except erythropoetin."

FDA Questions to the Committee and the Vote

Question 1: *Randomized controlled trials allow for direct comparisons of treatment effects and safety between treatment arms. A single-arm study has been submitted using an 8-week run-in period to serve as a baseline for each patient's transfusion requirements. A comparison is subsequently made to a follow-up 8-week period on Revlimid to compare transfusion requirements. Does this study design allow adequate characterization of Revlimid's treatment effect in the population described in the proposed indication?*
YES by a vote of 11 to 4

Panel comments included:

- "These data demonstrate that there is a signal there and it's a strong signal. Having taken 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 is more than you'd see with just background noise. So. I am reasonably comfortable that there is treatment effect with this agent."
- "What impresses me is the duration. This is going on a year or more, and I don't disbelieve those results...I'm persuaded there's something happening here but am uncertain about safety."
- "Not only was the transfusion requirement diminished, but the response was incredibly durable, and…in many of these patients, the malignancy disappeared. There's actually a suggestion that we're getting rid of the disease…If they only had a nice rise in the Hgb, I'd still be in favor of the drug, but the clone is actually disappearing – you're getting rid of the disease in the bone marrow."
- "A big part of it was the cytogenetic response, and second was a kinetic response with regard to the Hgb and transfusion requirement which, to me, was very quick and looked like a drug effect. So, the supporting data back up the primary endpoint."
- "There is, without a doubt, a treatment effect being demonstrated in this population."
- *Patient representative:* "There is no other trial going on now that has the same effect…as this trial has."

Question 2: *In this single-arm trial, 80% of patients enrolled in MDS-003 had dose reductions and/or delays, and 80% of patients experienced either Grade 3 or Grade 4 adverse events. Data do not exist on the efficacy and safety of lower Revlimid doses. Approval of a drug is contingent upon being able to write adequate product labeling, requiring a recommended dose, and characterization of a safety profile. Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of a safety profile?* **NO by a vote of 13 to 2**

Panel comments included:

- "I'm struggling because I can see the rationale… However, I think it's a bit of a stretch. This is a cytotoxic agent, and we have many drugs that go to market that support a starting dose followed by the idea that there would be dose reductions with careful monitoring. So, there is a precedent, but this goes in with the idea that do you really need to start in with this intensity to (fight) the clone. We also don't have the data on the introduction at 5 mg."
- "I'm convinced there is a signal, but I am very worried. What we heard is that the participants in this clinical trial can't tell if cytopenias are related to the drug. The majority of deaths were not attributed to the drug, but on a secondary independent review they were. So, the physicians have difficulty…Here we have a dose where 80% of people can't tolerate it, we don't know if 5 mg has the same effect, and we're going to put it on the street and let physicians on the street monitor it. Whereas I'd love to see this drug on the market because it would benefit some patients, I think the dose is an ***unsafe*** dose, and I think the schedule is difficult for most busy oncologists to manage, particularly those not experienced with cytotoxicity. I am very uncomfortable with the numbers of patients who may suffer and possibly die because of the management of this drug in a community setting."
- "I also have concerns because I wouldn't know how to use this drug in a number of ways. I'm worried about the kidney. I'm not worried in this patient population, but it's going out into the community, which means that all kinds of folks could be taking it. I'm also worried about myelosuppression issues."
- "I want to echo my colleagues concerning toxicity."

Question 3: *Please characterize the magnitude of Revlimid's benefit and risk in the indication being sought. After this characterization, does this risk:benefit analysis warrant approval?* **YES by a vote of 10 to 5**

Panel comments included:

- "Adjusting drugs…is not rocket science. I voted no on No. 2, but I was so struck by the efficacy that it's much more important to get the drug out there."
- "To me, the risk to benefit ratio answer would be a no. A 7% death rate is a high rate with experienced doctors."
- "When the drug gets out into the community, patients have had prior treatment, and we have to learn to modify it. The data are incredibly compelling. I think that we would do a disservice to patients if we didn't approve this."
- "The company has made a compelling case for the efficacy of this drug. I'm not surprised at the myelosuppression. I think I can handle it."
- "The drug is efficacious. There is no doubt the data are compelling. It's hard to say no to this drug at the present time."
- *Patient representative:* "I have personally had over 700 units of blood. There are more and more cases of MDS every day, including infants. Anything that reduces the number of transfusions is life-saving. There is also quality of life – to be able to go six months to a year without having to spend seven or eight hours in a hospital each week…To date, there is no cure for MDS except maybe for a successful bone marrow transplant. Making patients transfusion-independent is the next best thing, and for MDS patients, there is only one drug on the market approved by the FDA, and it is not as effective in reducing the number of transfusions for the number of patients that this study seems to show."
- *Panel chair:* "This is not a drug that is being promoted for everybody, so we have to think about this in a somewhat limited context."

Question 4: *At this time, lenalidomide, a thalidomide analogue, does not have adequate non-clinical studies to assess reproductive/developmental safety. Should a risk/management program with a goal of no fetal exposures to Revlimid be instituted until the reproductive/developmental safety assessments are addressed?* **No vote felt necessary**

The Panel chair asked, "Do we have to vote on this? It seems the company is doing something on this." An FDA official responded, "I don't think we need a vote." ♦