FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

(ODAC)

Virtual Meeting

Thursday, March 14, 2024

9:30 a.m. to 3:30 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. MADAN: Good morning, and welcome, everyone. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her e-mail is currently displayed.

My name is Ravi Madan, and I will be chairing this meeting. I will now call the March 14, 2014 Oncologic Drugs Advisory Committee meeting to order. Commander LaToya Bonner is the designated federal official for this meeting and will begin introductions.

Introduction of Committee

CDR BONNER: Thank you, sir. My name is LaToya Bonner. I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We will start with the standing members, starting with Dr. Advani.

DR. ADVANI: Ranjana Advani, Stanford University.

CDR BONNER: Thank you, ma'am.

Dr. Choueiri?

DR. CHOUEIRI: Good morning, everyone. Toni Choueiri, Dana-Farber Cancer Institute, Boston.

CDR BONNER: Thank you, sir.

Next we have Dr. Conaway.

DR. CONAWAY: Mark Conaway, University of Virginia School of Medicine.

CDR BONNER: Yes.

Next we have Dr. Gradishar.

(No response.)

CDR BONNER: Dr. Gradishar?

(No response.)

CDR BONNER: We will move to Dr. Kunz?

DR. KUNZ: Hi. Good morning. My name is Dr. Pamela Kunz. I'm a GI medical oncologist at Yale Cancer Center.

CDR BONNER: Next, we'll have Dr. Lieu.

DR. LIEU: Good morning, everybody. My name is Chris Lieu. I'm a GI medical oncologist at the

University of Colorado.

CDR BONNER: Next, we will have our chair, Dr. Madan.

DR. MADAN: Hi. I'm Ravi Madan, a medical oncologist at the National Cancer Institute in Bethesda, Maryland.

CDR BONNER: Next, we will have our consumer representative, Mr. Mitchell.

MR. MITCHELL: Good morning. I'm David Mitchell, and I'm the consumer representative to the ODAC. I'm President of Patients for Affordable Drugs and I'm a multiple myeloma patient.

CDR BONNER: Thank you, sir.

Next, we will have Dr. Nieva.

DR. NIEVA: Good morning. I'm Jorge Nieva. I'm a thoracic medical oncologist at the University of Southern California, Norris Comprehensive Cancer Center.

CDR BONNER: Thank you, sir.

Next, we will have Dr. Rosko.

DR. ROSKO: Hi. Good morning. Ashley Rosko, Division of Hematology at The Ohio State

University.

CDR BONNER: Thank you.

Next is Dr. Spratt.

DR. SPRATT: Hi, everybody. My name is Dr. Dan Spratt. I'm the Chair of Radiation Oncology at University Hospitals Seidman Cancer Center in Case Western Reserve University, Cleveland.

CDR BONNER: Thank you, sir.

Next, we have Dr. Vasan.

DR. VASAN: Hi. Good morning. Neil Vasan. I'm a breast oncologist and a lab-based physician scientist at Columbia University Cancer Center.

CDR BONNER: Next, we will have our industry representative, Dr. Frenkl.

DR. FRENKL: Good morning. Dr. Tara Frenkl. I am the industry representative and the Head of Oncology Development at Bayer Pharmaceuticals.

CDR BONNER: Thank you.

We will start with our temporary voting member, starting with Dr. Garcia.

DR. GARCIA: Good morning. I am Jacqueline

Garcia. I'm an oncologist at Dana-Farber Cancer Institute in Boston, Massachusetts. I'm an MDS and AML clinical investigator.

CDR BONNER: Thank you. Next is Dr. Hunter.

DR. HUNTER: Good morning. I'm Anthony Hunter. I'm a leukemia faculty member here at Winship Cancer Institute at Emory University.

CDR BONNER: Thank you, sir.

And next, we will have our patient representative, Ms. Powell.

MS. POWELL: Good morning. I'm Joan Powell. I'm from Laguna Niguel, California. I am an MDS patient, as well as an advocate.

CDR BONNER: Thank you, ma'am.

We'll move on to our FDA participants, starting with Dr. Pazdur.

DR. PAZDUR: Dr. Richard Pazdur, Director, Oncology Center of Excellence, FDA.

CDR BONNER: Thank you.

Next, we'll have Dr. Theoret.

DR. THEORET: Yes. Hi. Good morning. Mark Theoret, Deputy Center Director of Oncology Center

of Excellence and Acting Supervisory Associate Director of the Office of Oncologic Diseases in CDER.

CDR BONNER: Thank you.

Next, we'll have Dr. de Claro.

DR. DE CLARO: Angelo de Claro, Division Director, FDA.

CDR BONNER: Thank you.

Next is Dr. Norsworthy.

DR. NORSWORTHY: Hi. Kelly Norsworthy, Deputy Division Director, FDA.

CDR BONNER: Dr. Ehrlich?

DR. EHRLICH: Good morning. I'm Lori Ehrlich, Clinical Team Lead, FDA.

CDR BONNER: And last, we will have Dr. Kim.

DR. KIM: Nina Kim, Clinical Reviewer, FDA.

CDR BONNER: Thank you.

I'll turn the floor back over to our chair, Dr. Madan.

DR. MADAN: Thank you, Commander Bonner.

For the topics such as those being discussed at this meeting, there are often a variety of

opinions, some of which are strongly held. Our goal at this meeting will be a fair and open forum for discussion of these issues, and one where individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Commander Bonner will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, sir.

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208,

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of

new drug application, NDA, 217779 for imetelstat for injection, submitted by Geron Corporation. The proposed indication for this product is for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk with myelodysplastic syndromes but failed to respond, or have lost response to, or are ineligible for erythropoiesis-stimulating agents. This is a particular matters meeting during which specific matters related to Geron's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting numbers, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Anthony Hunter. Dr. Hunter's waiver involves his employer's research contracts for two studies funded by competing firms, Novartis and Syntrix Biosystems. Under each contract, Dr. Hunter's employer will receive between $0 to $50,000 per year. Additionally, Dr. Hunter will receive between $0 to $5,000 per year in salary support from Syntrix

Biosystems for his role in the study.

The waiver allows this individual to participate fully in today's deliberations. FDA's reason for issuing the waiver are described in the waiver document, which is posted on the FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and by searching on March 14, 2024 ODAC. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this

meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

Back to you, Dr. Madan.

DR. MADAN: Thank you, Commander Bonner.

We will now proceed with the FDA introductory remarks from Dr. Lori Ehrlich.

Dr. Ehrlich?

FDA Introductory Remarks - Lori Ehrlich

DR. EHRLICH: Good morning. I'm Lori Ehrlich, a pediatric hematologist/oncologist and a

clinical team lead in the FDA's Division of Hematologic Malignancies I. I will provide a brief introduction to the imetelstat application and the issues under discussion.

Imetelstat is a lipidated oligonucleotide, depicted on the right, and it is a telomerase inhibitor that targets the overexpression of telomerase activity in malignant cells. Notably, the negatively charged oligonucleotide class of therapeutics are known to cause thrombocytopenia, which is important for the discussion to follow.

As a brief regulatory history, the initial investigational new drug application was submitted in 2005, and the protocol for the proposed indication, which is the basis for the discussion today, was known as 63935937 MDS3001, or IMerge, and will be referred to in the FDA presentations as MDS3001 and was initiated in 2015. Subsequently, the new drug application was submitted in June of 2023. The applicant is seeking traditional approval for the treatment of transfusion-dependent anemia in patients with lower-risk myelodysplastic

syndromes who are ineligible for ESA or after ESA failure. The treatment regimen is shown on the right. Imetelstat is administered via IV infusion over 2 hours every 4 weeks.

Before discussing the issues with MDS3001, I'd like to briefly review the evidentiary criteria for FDA approval. Under the Federal Food, Drug, and Cosmetic Act, for a new drug to be approved in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product labeling.

The demonstration of effectiveness requires substantial evidence that the drug will have the effect that it purports or is represented to have. For a single randomized trial to support an application, results must be sufficiently robust and compelling. Because all drugs have adverse effects, the demonstration of safety requires showing that the benefits of the drug outweigh its risks.

I'm reviewing these criteria because the

applicant seeks an indication for imetelstat for patients with lower-risk MDS, with transfusion dependence after ESA failure, which is a population with a relatively longer survival compared to patients with higher risk MDS, and these patients are otherwise treated with supportive care alone. We're seeking the committee's input on whether the data from the single randomized trial, MDS3001, supports a clinically meaningful and persuasive treatment effect in this lower-risk setting and that the benefits demonstrated outweigh the serious risks observed.

I would like to briefly introduce the patient population studied in MDS3001. MDS is a heterogeneous disorder arising from clonal expansion of a hematopoietic progenitor. This leads to bone marrow dysplasia, ineffective hematopoiesis, and a risk of transformation to AML. Patients with MDS are broadly classified into lower-risk and higher-risk disease categories based on several factors that impact survival, though the exact definitions of lower risk and higher risk are

not well defined.

On the left, I'm showing an older classification system known as the International Prognostic Scoring System, or IPSS, because this is the classification system that was used for enrollment in MDS3001, which included patients who are a low or intermediate-1 risk. In this system, the median survival was 5.7 years for low risk and 3.5 years for intermediate-1 risk, with some patients surviving up to 1 to 2 decades.

Higher red blood cell transfusion density has been correlated with decreased overall survival, and the figure on the right highlights one report of survival in patients with a higher transfusion burden. The blue box and arrows indicate approximately the population enrolled in MDS3001, with at least 4 units per 8 weeks at baseline, which corresponds to a median OS of 2 to 4 years. While the baseline transfusion density may be prognostic, there have not been prospective trials to indicate that an improvement in transfusion burden with any therapy will lead to

an improvement in overall survival.

As the applicant is seeking an indication for the treatment of transfusion-dependent anemia due to lower-risk MDS after ESA failure, I'd like to take a moment to briefly review the treatment landscape. ESAs, or erythropoiesis-stimulating agents, have been the long-standing U.S. standard despite not being approved for this indication. Luspatercept is an erythroid maturation agent, which was initially approved for a subset of patients with lower-risk MDS after ESA failure and recently approved for the treatment of anemia and lower-risk MDS without ESA failure.

Lenalidomide is an immunomodulator approved for a subset of MDS, and finally, hypomethylating agents may be used but are generally reserved in the lower-risk setting to patients who are refractory to other therapy and not maintained on supportive care. Importantly, patients who had received prior HMA or lenalidomide were excluded from the phase 3 portion of MDS3001.

I would like to briefly review the basis of

approval for agents that are approved for use in MDS. That we colloquially use the term "lower-risk" and "higher-risk" MDS, these disease categories are not well defined and the risk classification system has evolved over time; however, for illustration purposes, I've used that terminology in this slide.

For agents that are disease modifying and have been approved broadly for the treatment of lower or higher risk MDS, the basis of approval has been disease response as measured by complete or partial remission, and the only agent that has shown a survival benefit is azacitidine. These endpoints are sometimes supported by the rates of red blood cell and platelet transfusion independence; however, agents that are indicated for the treatment of anemia due to lower-risk MDS have been approved on the basis of red blood cell transfusion independence.

With that background, I will now review the submission for imetelstat for the treatment of transfusion-dependent anemia due to lower-risk MDS

after ESA failure. Here, I will review the design of MDS3001. The trial consisted of two parts, a single-arm, open-label study of a single-dose level of imetelstat, followed by a randomized-controlled trial compared to placebo.

Patients were adults with IPSS low or intermediate-1 risk MDS who were relapsed or refractory to ESA or were ineligible for an ESA, and patients were required to have a transfusion-dependent anemia defined as at least 4 units of red blood cells per 8 weeks.

Importantly, patients were also required to have an absolute neutrophil count of 1500 at baseline, independent of growth factor support, and platelets were required to be greater than 75,000 at baseline, independent of platelet transfusion. Patients were treated with imetelstat 7.1 millimeters per kilogram IV every 4 weeks, given as a 2-hour infusion or matching placebo. The primary endpoint was 8-week red blood cell transfusion independence with other secondary endpoints listed here.

I will next summarize the major topics for discussion. There are a number of important considerations regarding the results of MDS3001 that warrant a public discussion. The first topic I will highlight today is the magnitude and duration of RBC transfusion independence without demonstration of an improvement in survival responses or patient-reported outcomes compared to placebo.

This slide summarizes the applicant's primary analysis of red blood cell transfusion independence. The rate of RBC transfusion independence in the imetelstat arm was roughly 40 percent compared to 15 percent in the placebo arm, with a 25 percent difference from placebo. The clinical meaningfulness of an 8-week transfusion independence period in the context of lower-risk MDS is uncertain, and the applicant evaluated alternative definitions, including 24-week RBC-TI, and the point estimate of the response rate decreases with longer target durations of transfusion independence, with a more

modest improvement at later time points.

Additionally, the applicant reported that the median duration of response was 52 weeks for imetelstat versus 13 weeks for placebo, shown on the lower row of this table; however, this was only when looking at the longest red blood cell transfusion independence interval for the subgroup of patients who achieved an 8-week RBC-TI response, not the entire study population. When looking at the entire study population, the median duration of the longest RBC-TI interval was only 5 weeks for imetelstat compared to 4 weeks for placebo, which is only a 1-week difference in duration of transfusion independence for the entire population.

I will next summarize other measures of clinical benefit in MDS3001. Hematologic improvement erythroid, or HI-E, per the IWG 2006 criteria was a prespecified secondary endpoint and did not show a significant difference from placebo; and it is also notable that the HI-E response in the placebo arm was more than 50 percent, which questions the utility of this outcome. Based on

both the independent review committee and the investigators at the time of the primary analysis, there were no complete or partial remissions in either arm; and while MDS3001 was not adequately powered to detect an improvement in overall survival, there were numerically more deaths in the imetelstat arm, with no difference in overall survival per arm.

The applicant may present some updated additional analyses of response; however, the magnitude of difference seen in transfusion independence or responses did not translate to a survival benefit. There is some uncertainty in the OS results given the low event rate and the expected long duration of survival, but a trial need not be powered for overall survival to provide important information, and the FDA relies on the overall survival analysis, even if descriptive, to inform the benefit-risk determination, as overall survival is an important metric of both safety and efficacy.

Finally, the patient-reported outcomes

showed no clear difference between treatment arms. The patient-reported outcomes were not controlled for type 1 error and so are considered exploratory, but this summarizes the deterioration in fatigue, which was the prespecified PRO of interest and showed no difference between arms.

The next topic I will highlight today is the safety of imetelstat, focusing on the myelosuppression observed. Tolerability and dosing concerns will be covered in detail in the main FDA presentation. The incidence of cytopenias, particularly neutropenia and thrombocytopenia, were notably higher in the imetelstat arm compared to the placebo arm. The figure in this slide shows the incidence of grade 3 or higher decreases in hematopoietic parameters based on data provided in the laboratory data set. Patients who received imetelstat had much higher rates of neutropenia, leukopenia, and thrombocytopenia compared to patients receiving placebo.

Subjects treated with imetelstat also required more interventions for cytopenias such as

myeloid growth factors and platelet transfusions compared to patients receiving placebo. Thirty-five percent of patients required myeloid growth factor at least once during treatment in the imetelstat arm compared to 2 patients in the placebo arm. Most of these patients required multiple administration of myeloid growth factor. Eighteen percent of patients in the imetelstat arm required at least one platelet transfusion during treatment, with patients requiring platelet transfusions in up to 10 separate episodes, and as a consequence would require unscheduled physician visits for management.

Prolonged neutropenia increases the risk of infection, with a higher risk of longer or more severe infections. Despite the increased use of growth factor support for patients who experienced neutropenia in the imetelstat arm, a higher rate of infection was observed in patients who received imetelstat. Although the rate of grade 3 to 4 infections was similar between the two arms, it should be noted that grade 4 infections were more

common on the imetelstat arm.

Similarly, thrombocytopenia increases the risk of hemorrhage with a higher risk for longer or more severe bleeds. Patients receiving imetelstat experienced more hemorrhagic events overall and marginally more grade 3 to 4 events. It is also notable that all events in the placebo arm were grade 1, with the exception of a single patient who experienced grade 3 to 4 GI bleeding, whereas patients on the imetelstat arm experienced more grade 2 events, as well as 2 patients with grade 3 to 4 GI hemorrhage and one with grade 3 hematuria. Thus, hemorrhage was more common and more severe on the imetelstat arm.

And lastly, I will review the overall benefit-risk for imetelstat. To summarize, the outcomes of MDS3001 raise a number of important topics for discussion. These include the improvement in the primary outcome measure of 8-week RBC transfusion independence supported by an improvement in 24-week RBC transfusion independence, but in the context of requiring

monthly infusion visits, no demonstration of disease response or survival benefit and no clear benefit in patient-reported outcomes. This is balanced with the safety profile, where most patients had grade 3 or higher neutropenia or thrombocytopenia, with many requiring myeloid growth factor or platelet support, and despite the supportive care, an increased risk and occurrence of infections and bleeding. Finally, there's residual uncertainty regarding the tolerability and optimal dose of imetelstat, which will be discussed in more detail in the main FDA presentation.

The applicant seeks an indication for the treatment of anemia due to lower-risk MDS after ESA failure on the basis of the single randomized trial; however, these findings create uncertainty about the benefit-risk of imetelstat in this population who would otherwise receive supportive care only. Ultimately, it is incumbent upon the applicant to provide robust evidence to the FDA to support that the drug is safe and effective in the intended population.

I will now present the discussion topic for the committee. Please discuss the efficacy of imetelstat for patients with lower-risk MDS, based on the results of the MDS3001 trial considering the safety profile. Following the discussion topic, we will ask that the committee vote on the following question.

Do the benefits of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-1 risk MDS who have not responded to or have lost response to, or are ineligible for erythropoiesis-stimulating agents?

This concludes my presentation. Thank you for your attention.

DR. MADAN: Thank you, Dr. Ehrlich.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based on the outcome of the meeting.

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

So with that caveat, we will now proceed with Geron Corporation's presentation. Thank you.

Applicant Presentation - Sharon McBain

MS. McBAIN: Thank you.

Good morning, Dr. Chair, members of the ODAC, and the FDA. I'm Sharon McBain, Senior Vice President and Global Head of Regulatory Affairs at

Geron. We'd like to thank the agency for the opportunity to present the data in support of imetelstat and the patients who participated in the trials and made this program possible. Let me begin with some background information.

Transfusion-dependent anemia due to lower-risk MDS has a debilitating impact on patient outcomes, as well as their lifestyle. Currently, only two products, luspatercept and lenalidomide, are approved in the indication of transfusion-dependent anemia in the lower-risk MDS post-ESA setting. Both are restricted to specific small subpopulations and neither provide the extended and continuous duration of transfusion independence seen with imetelstat.

In our clinical development program, MDS3001 phase 2 and 3 studies delivered consistent and robust evidence of efficacy. The primary and key secondary endpoints were met and, importantly, the safety profile has been well characterized, and the risks can be managed by healthcare professionals. Overall, imetelstat offers a much needed additional

treatment option with clinical advantages over existing therapies, as well as a positive benefit-risk profile.

Let me explain the mechanism of action. MDS are a group of disorders characterized by ineffective hematopoesis arising from malignant hematopoietic stem and progenitor cells that have higher telomerase activity compared to healthy cells. Imetelstat is a non-antisense oligonucleotide that specifically binds with high affinity to the RNA template of human telomerase and acts as a direct competitive inhibitor of enzymatic activity of telomerase. In lower-risk MDS, inhibition of telomerase by imetelstat results in apoptosis of the malignant cells and recovery of erythropoiesis, leading to increased hemoglobin and subsequently red blood cell transfusion independence. Importantly, the mechanism of action of telomerase inhibition differentiates imetelstat from other approved and investigational treatments in MDS.

Turning to the regulatory history,

imetelstat has been granted both orphan drug and fast-track designation in MDS. We had a number of type C interactions with the agency and importantly held two meetings to agree on key aspects of the study design, including the endpoints and dosing regimen for the phase 3 pivotal study, which was intended for registrational purposes and was initiated in May 2019. Our full NDA was submitted in June 2023, and Geron is seeking full approval via traditional 505(b)(1) regulatory pathway.

The proposed indication for imetelstat is the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk MDS who have failed to respond or who have lost response to, or are ineligible for erythropoiesis-stimulating agents. The proposed dosing regimen as used in the phase 2 and 3 studies is 7.1 mgs per kg, expressed as the active moiety and administered as a 2-hour intravenous infusion once every 4 weeks.

Now, turning to today's discussion, in addition to FDA's question on whether the benefits

of treatment with imetelstat outweigh the risks, here are some additional key points for consideration at today's meeting. We agree with FDA's recent publication that describes a high unmet need in the target population.

The FDA briefing book states that Study MDS3001 met the primary and key secondary TI endpoints; however, FDA also states that HI-E, CR, PR, overall survival, and PRO are not supportive of a disease-modifying treatment effect with imetelstat. Furthermore, the FDA states to support a marketing application, transfusion independence data should be supported by evidence of direct clinical benefit to the patient, and the examples given are survival benefit, CR/PR benefit, or improvement in quality of life.

Geron's position is that imetelstat meets the regulatory standards for approval given we are seeking an indication in transfusion-dependent anemia. Regulatory precedent exists where TI endpoints in the absence of disease-modifying effects have been used for the basis of approval

for products treating transfusion-dependent anemia in MDS.

So now turning to the central question for today, the data we'll share today demonstrate that imetelstat offers a positive benefit-risk profile for patients with transfusion-dependent anemia due to lower-risk MDS. In the pivotal placebo-controlled phase 3 study, imetelstat treatment resulted in statistically significant and clinically meaningful improvements in transfusion independence rates. In particular, transfusion independence seen with imetelstat is long and continuous across subgroups of MDS.

In addition, imetelstat provided meaningful increases in hemoglobin and reduced transfusion burden, and overall, the safety profile of imetelstat is well characterized, and grade 3/4 neutropenia and thrombocytopenia were short-lived and without clinical consequences beyond what was observed in the placebo group. Importantly, the clinicians who treat MDS expect these toxicities and are experienced in managing neutropenia and

thrombocytopenia. Lastly, although the data are immature, there are no signs of a survival detriment.

Here is an overview of the agenda for today's presentation. All outside experts have been compensated for their time and travel to today's meeting. We also have additional experts with us today. Thank you. I'll now turn the lectern over to Dr. Savona.

Applicant Presentation - Michael Savona

DR. SAVONA: Good morning. I'm Michael Savona. I'm the Director of Hematological Malignancies Research and Professor of Internal Medicine and Cancer Biology at Vanderbilt University. Over the past two decades, I've worked on developing new therapies for patients with MDS. My laboratory focuses on the etiology and treatment of MDS, and in the clinic, I've led many clinical trials for these patients, and I'm pleased to be here today to discuss an unmet medical need that I see in my patients with lower-risk MDS.

The community of specialists that

investigate MDS around the world is fairly intimate. Because MDS represents a spectrum of diseases, we spent decades cooperatively working to harmonize practice patterns, hematopathology interpretations, classification of subtypes, and prognostication to perform clinical trials to test new agents. Now, when clinicians evaluate patients for MDS around the world, we universally risk stratify patients with the International Prognosis Scoring System, or the IPSS, to assess risk and determine the proper treatment.

Prognosis can range considerably. Those deemed to have very low-risk disease may have several years of survival and those with very high risk disease have estimated means survival of less than one year. Across the United States, there are approximately 45,000 new cases of MDS per year, with a median age of diagnosis around 70 years.

The majority of these patients are diagnosed lower risk, but lower risk is relative. Patients with lower-risk MDS require increasingly intensive lifelong management of their cancer and still have

considerably diminished overall survival. The disease is progressive, and about 30 percent of patients with lower-risk disease can transform to leukemia over time, and for those who do not transfer to leukemia, the ravages of MDS lead to premature mortality and significant morbidity in most patients. The poor oxygen carrying capacity seen in anemia amplifies other comorbidities such as cardiovascular disease seen in older patients, and progressive bone marrow failure may lead to bleeding and infections.

Patients with MDS also have a diminished quality of life and they use more healthcare resources compared to their age-matched peers. I'd like to take a moment to talk about the natural history of lower-risk MDS.

In low- and Int-1, or intermediate-1 risk patients, commonly termed "lower risk," the median survival is only about five years. Over time, this progressive disease, most commonly with anemia, worsens, and the patients become transfusion dependent. The standard of care therapy for

moderate to severe anemia in MDS is erythropoietin-stimulating agents, or ESAs; however, ESA treatment ultimately fails these patients, and when it does, median survival and transfusion-dependent, lower-risk MDS is only about three years. In this scenario, most death and morbidity are a function of anemia and transfusion dependence. This is the patient population we're talking about today, lower-risk transfusion-dependent patients after ESAs have failed, and they need more treatment options.

So now let's take a closer look at MDS-related anemia. Anemia is the most common presentation of MDS. When we look specifically at patients with lower-risk MDS, approximately 85 percent are anemic at diagnosis and most are symptomatic. MDS patients who develop chronic transfusion-dependent anemia suffer from shortness of breath and subsequent vascular events, inflammatory symptoms, and severe fatigue.

The decision to start RBC transfusions is based on several clinical factors rather than one

predefined hemoglobin threshold. While clinicians stay consistent by following international guidance, we also consider patient-specific clinical factors, and in most cases transfuse patients with a hemoglobin in the range from 7 to 8 grams per deciliter.

Transfusions can provide short-term relief, but transfusions also come with long-term clinical consequences. Frequent RBC transfusions could lead to alloimmunization and difficulty in identifying a matched donor to support the continuous transfusion need. Cumulative transfusions increase the risk of transfusion reactions and cardiovascular complications due to volume overload or immune reaction and increased risk of infection. Over time, patients can develop end-organ dysfunction due to iron overload.

Finally, and not insignificantly, patients experience significant social and psychological burden managing the healthcare, which leads to diminished health-related quality of life. I hear directly from my patients frequently about the time

it takes to visit the clinic, have labs drawn, and get their transfusions. This is a valuable time that is spent away from work and family. I have patients who live 6 hours away in Eastern Kentucky. These patients may have to drive 1 to 2 hours to get access for a transfusion at a local hospital but they may have to wait 8 hours for the blood to arrive. They have the choice to do this or drive to Nashville, 6 hours each way.

This involves considerable expense and time. These factors can all affect quality of life. Patients make difficult quality-of-life decisions based on access to the transfusions. I've run multiple MDS trials, and while these consequences are very difficult to capture during a study, my colleagues and I know that these factors have a clear negative impact on our patients. For all these reasons, transfusion independence has emerged as the key therapeutic goal for patients and physicians.

Despite some new therapeutic options, the universal first line of treatment is with ESAs. In

clinical practice, when a patient's hemoglobin falls below a threshold, ESAs are given. For patients who do respond, that response usually lasts for 12 to 18 months. If a patient's endogenous serum EPO level is high or they become transfusion dependent, the chance of the response to ESAs is less than 10 percent. At this point, the next steps would depend on the scenario. Right now, there are very limited options.

The approvals of lenalidomide in 2005 and then luspatercept 15 years later established the precedent for the clinical benefit and validity of TI as a primary endpoint in phase 3 studies for patients with transfusion-dependent lower-risk MDS. Both of these treatments are restricted for the use of specific subgroups of patients and neither of these studies demonstrated a survival benefit or a benefit in the most important anemia-related PRO of fatigue. Hypomethylated agents, or HMAs, are approved for the treatment of MDS broadly and may reduce anemia in higher risk patients; however, lower-risk MDS patients who have primary anemias

after ESA failure typically respond poorly to HMAs, and these are not typically used.

Today, you're being asked to discuss the benefit-risk of imetelstat, and this chart is helpful to convey that after failure of ESAs, there is no good therapy for most patients. There are only two approved therapies for lower-risk MDS to treat anemia after ESA failure and both are limited to small subpopulations. Without question, lenalidomide responses are most robust in those with the 5q minus abnormality. For the remaining 90 percent of patients who do not have the isolated 5q or del 5q, it's helpful to consider whether patients have ring sideroblasts in their marrow, and we call that RS positive or RS negative, signifying the presence or absence of ring sideroblasts.

After ESAs, luspatercept is approved for non-deletion 5q, RS-positive patients, and while RS-positive patients with a low transfusion burden have a very meaningful response with luspatercept, those RS-positive patients with high transfusion

burden should expect less than a 10 percent TI rate. That leaves a significant unmet need here outlined in pink. Unfortunately, regardless of genetic subtype, for patients who are heavily transfusion dependent, the current approved therapy does not lead to acceptable rates of transfusion independence; therefore, the majority of patients with lower-risk MDS are not well served by the approved treatments. This is why I'm very encouraged by the data Dr. Feller will share next on how imetelstat has been studied in all these contexts and has activity in all of them.

In short, patients with lower-risk MDS and their physicians have a high unmet need for anemia treatment options. Lower risk transfusion-dependent MDS is serious. It's life threatening and anemia and fatigue are the key clinical features. Once patients become relapsed or refractory to ESAs, only two FDA-approved therapies remain for transfusion-dependent anemia, and these options do not currently meet the unmet medical need for about 75 percent of lower-risk MDS

patients. There is a clear unmet need for a new treatment option that achieves durable transfusion independence in patients with transfusion-dependent anemia.

Thank you. I'll now turn the presentation back to the sponsor to review the clinical results.

Applicant Presentation - Faye Feller

DR. FELLER: Thank you. I'm Faith Feller, Chief Medical Officer at Geron. Today, I'll be presenting the clinical trial results for imetelstat, starting with the efficacy data.

Study MDS3001 was a global, two-part, phase 2/3 study. Phase 2 was an open-label, single-arm study. All patients received imetelstat 7.1 milligram per kilogram every 4 weeks IV. This dose resulted in clinical activity and an acceptable safety profile. Phase 3 was a double-blind, placebo-controlled study. Patients were randomized 2 to 1 to receive imetelstat or placebo and stratified by transfusion burden and IPSS risk category. Treatment was continuous every 4 weeks until a patient experienced disease

progression, unacceptable toxicity, or withdrew consent. Today's presentation will focus on the results from the phase 3 part of the study.

Turning to the inclusion criteria, in addition to a diagnosis of low or intermediate-1 risk MDS per IPSS, patients were required to be relapsed or refractory to ESA treatment or ineligible for ESA treatment due to endogenous serum EPO levels greater than 500 milliunits per mL. Importantly, patients were also required to be transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period. Of note, this is a higher transfusion burden requirement compared to other registrational studies for other approved products. Patients also needed to meet criteria for non-del 5q and had no prior treatment with lenalidomide or HMA.

The primary endpoint was RBC transfusion independence of at least 8 weeks during any consecutive 8 weeks. The primary endpoint was agreed upon with the FDA prior to initiation of this phase 3 study. The key secondary endpoint in

MDS3001, included in the statistical testing procedure, was transfusion independence of at least 24 weeks during any consecutive 24 weeks. Additional secondary endpoints included duration of TI in responders and hemoglobin increases.

The study planned to enroll approximately 170 patients to detect a difference of 22.5 percent between imetelstat and placebo and with a power of approximately 88 percent. We applied a sequential testing procedure for the primary and the key secondary endpoints at a type 1 error rate of 0.05. Importantly, no imputations for missing data were made for the primary and secondary endpoints, meaning TI responders could not have any missing transfusion data.

Turning to demographics, the median age was 72 and 73 years. There was a larger percentage of males and most were white, and although the majority of patients enrolled were from the European Union, overall, the demographics are representative of the U.S. MDS population. Key disease characteristics were balanced between

groups and representative of lower-risk MDS patients with anemia.

Forty-eight percent and 45 percent of patients had a prior transfusion burden of more than 6 units over 8 weeks. Sixty-two percent of patients were RS positive and the majority were characterized as low IPSS. Ninety-two percent and 87 percent of patients had already received and were relapsed or refractory to prior ESAs, and approximately one-third of patients had serum erythropoietin levels greater than 500 milliunits per mL screening, indicative of a very low likelihood to respond to any ESA-based treatment. And finally, over half had an ECOG score of 1 and 2.

Now, I will move to the efficacy results. The primary endpoint was met with a highly statistically significant and clinically meaningful improvement in the transfusion independent rate for patients treated with imetelstat. In the imetelstat group, 40 percent of patients achieved at least 8 weeks of continuous TI compared to

15 percent in the placebo group. Furthermore, the TI lasted a median of 52 weeks.

Here is the swimmer's plot of the primary endpoint responders. The blue lines are intervals of transfusion independence, the pink circles indicate RBC transfusion periods, and ongoing treatment is indicated with a black triangle. To the left of the vertical dotted line represents the RBC transfusion frequency before study entry. Imetelstat demonstrated continuous and sustained transfusion independence. Eighty-three percent of imetelstat responders experienced a single period of TI uninterrupted by RBC transfusions.

Importantly, as you can see on the right hand of the slide, patients treated with imetelstat achieved transfusion independence for a median of 52 weeks compared with 13 weeks for those receiving placebo. This translates to saving a median of 38 RBC units per responder with imetelstat versus 11 units with placebo during the periods of TI. In contrast with the FDA representation of TI duration, this analysis shows patients achieving at

least an 8-week response, and this is consistent with clinical trial practice for assessing duration of response.

The key secondary endpoint of at least 24-week TI further demonstrates the durability of TI with imetelstat. Overall, 28 percent of imetelstat-treated patients, compared to 3 percent on placebo, obtained a statistically significant improvement in TI, and for those 28 percent achieving TI, the median duration was 80 weeks.

There are a few key points to note here. Firstly, the magnitude of benefit or the difference between imetelstat and placebo for this endpoint of at least 24-week TI was 25 percent, which is the same as the magnitude of benefit for the primary endpoint. Also, the 8- and 24-week TI rates in this phase 3 study were in line with those of the phase 2. All these points of consistency validate the imetelstat treatment effect. Importantly, as the FDA indicate in their briefing document, the consensus among MDS physicians has been to move toward longer TI durations of at least 16 weeks as

clinically meaningful; therefore, this highly statistically significant result for the endpoint of TI duration of at least 24 weeks more than fulfills this criteria.

Furthermore, as an ad hoc endpoint, the percent of patients who remained without RBC transfusions for at least one year was assessed. Eighteen percent of imetelstat-treated patients compared to 2 percent on placebo did not receive transfusions for one year or more, and for those 18 percent achieving TI with imetelstat, the median duration was 132 weeks or over 2 years.

In summary, imetelstat provided higher rates of longer term continuous TI compared to placebo. The significantly higher rates observed for at least 8 weeks continued to 24 weeks and through one year or longer. Critically, the study also assessed increases in hemoglobin levels, which is not only necessary for achieving TI but also demonstrates objective evidence of imetelstat treatment efficacy. Throughout the study, the mean change from baseline and hemoglobin values for all

patients was higher with imetelstat than placebo, and this difference was sustained over time. Hemoglobin measures within 14 days after transfusion were excluded from this analysis.

We saw particularly meaningful increases in hemoglobin among patients who achieved TI with imetelstat compared to placebo. Patients who achieved at least 8-week and at least 24-week TI on imetelstat had 3.6 grams per deciliter and 4.2-gram per deciliter rises in hemoglobin, respectively, and the 21 patients in the imetelstat group who achieved at least one year of TI had a median hemoglobin increase of 5.2 grams per deciliter.

Until now, I have shown you durable transfusion independence for these patients, accompanied by increases in hemoglobin values. This graph depicts the absolute mean change in RBC units from pretreatment for all patients. These data demonstrate that, overall, imetelstat-treated patients received significantly less transfusions over time than those on placebo.

Although TI is the ultimate goal for

assessing response in lower-risk MDS, the international working group developed criteria to describe additional measures of benefit. HI-E is commonly used in studies for these patients and updated 2018 IWG response criteria of at least 16 weeks reflects a more sustained transfusion burden reduction and TI. HI-E per IWG 2018 criteria was seen at a higher rate for imetelstat treatment compared to placebo. That at least 16-week TI rate for imetelstat was significantly greater than placebo and again demonstrated a 25 percent magnitude of benefit. Additionally, the percent of patients who achieved a 50 percent reduction in transfusion burden over 16 weeks was greater with imetelstat treatment than placebo.

Per protocol specified IWG 2006 criteria, which was in place when the study began in 2015, imetelstat benefit was seen with a hemoglobin increase of 1.5 grams per deciliter sustained over 8 weeks, despite not achieving statistical significance for the overall endpoint.

Presented here are the percent of patients

by subgroup achieving the primary endpoint of at least 24-week RBC-TI. Everything to the right of the midline at 0 favors imetelstat treatment and consistent clinical benefit with imetelstat has been demonstrated across subgroups. Magnitude of benefit and TI rates were comparable regardless of RS status, prior RBC transfusion burden, and IPSS risk category. This is important, as it demonstrates that imetelstat could fulfill an unmet need, as presented by Dr. Savona, including patients without ring sideroblasts and also patients who required more than 6 units of RBC over 8 weeks. These subgroups are known to be associated with worst outcomes. Subgroup analysis for the 24-week TI responders were similar to that of the primary endpoint.

The study evaluated other secondary and exploratory endpoints that support the TI response with imetelstat, including the patient-reported outcome of fatigue. This graph shows change in fatigue scores from baseline where a positive change means less fatigue and demonstrate that

patients treated with imetelstat therapy compared to placebo did not have a worsening of fatigue despite receiving fewer RBC transfusions. These and other PRO outcomes, as well as cytogenetic response data and exploratory mutation analysis, support the durable transfusion independence demonstrated by imetelstat and are described further in the briefing documents; CR and PR applicable for higher risk MDS patients with blasts greater than 5 percent, of which only 2 of 178 patients on this study were evaluable.

Overall, for efficacy, there was a statistically significant improvement in sustained and continuous transfusion independence with imetelstat compared to placebo. The pivotal phase 3 study met the primary endpoint, as well as the key secondary endpoint with a 25 percent magnitude of benefit seen for both endpoints. Additional data favoring imetelstat included long TI duration for TI responders and improvement in HI-E rates. Notably, improved TI rates were seen across all subgroups studied.

Turning to safety, I'll now present the clinical data supporting the well-characterized and manageable safety profile of imetelstat. Beginning with safety exposures, the median treatment duration on the study was approximately 34 weeks for imetelstat and 28 weeks for placebo. A median of 8 treatment cycles was received across both groups and 41 percent of imetelstat-treated patients received 13 or more cycles. We continue to monitor long-term use of imetelstat in our ongoing studies.

Overall, the majority of patients in either group experienced a treatment-emergent adverse event. The percent of patients experiencing a grade 3/4 or serious adverse event was higher in the imetelstat group compared to placebo, and more patients in the imetelstat group had an AE leading to discontinuation and dose reduction or cycle delay compared to placebo. One death occurred in each group during study treatment. Both were not related to study treatment.

Moving along to describe further the AEs,

overall, non-hematologic AEs were generally low in severity with asthenia and COVID-19 as the most common in either group. These events were generally balanced between groups in terms of frequency or severity, except for the events of asthenia and headache, which occurred more frequently in the imetelstat group.

Hematologic AEs, particularly thrombocytopenia and neutropenia, were the most frequently reported in the imetelstat group. Imetelstat therapy, which is active within the bone marrow, is expected to have on-target effects of cytopenias, and in a few slides I will describe these events in more detail. Overall, more serious adverse events occurred in the imetelstat group and many were reported as single events.

Although anemia was reported as an SAE in the imetelstat arm, all patients had anemia at baseline and transient decreases in hemoglobin occurred before response or late in treatment. Importantly, preferred terms occurred with similar frequency in both groups, and for early OS data,

recent data with a clinical cut of January 2024 showed a hazard ratio of 0.98, indicating no detriment to survival for imetelstat over placebo. We also continue to follow patients on this study for survival.

Most AEs leading to cycle delays and dose reductions in the imetelstat group were due to neutropenia or thrombocytopenia and were protocol mandated. The median time to dose reduction in the imetelstat group was 14 weeks or about 3 cycles, and although 50 percent of imetelstat-treated patients had a dose reduction due to an AE, less than 15 percent of patients discontinued treatment due to adverse events, suggesting that dose modifications enabled patients to continue treatment and derive benefit from imetelstat. This is further confirmed by a median dose intensity of 90.5 percent for patients treated with imetelstat.

The adverse events of special interest include neutropenia and thrombocytopenia and their clinical consequences, as well as hepatic events. Let's look at each in more detail. As mentioned in

the overview, grade 3/4 neutropenia was seen in 71 percent of imetelstat-treated patients and grade 3/4 thrombocytopenia in 65 percent of imetelstat-treated patients. These high-grade cytopenias occurred early within the first few cycles of treatment, and in fact were most frequent during the first 8 weeks when weekly hematology monitoring occurred. The median duration was less than 2 weeks and most resolved to grade 2 or less in under 4 weeks.

Given the incidence of neutropenia, infection events were closely monitored. Infections were more frequently reported in patients receiving imetelstat, though for grades 3/4 and serious events, rates were similar between treatment groups. Nine patients had an infection event concurrent with grade 3 or 4 neutropenia and these infections were mostly grade 1 and 2. Febrile neutropenia was reported in one patient in the imetelstat group. Overall, the risks associated with neutropenia were low and similar to placebo with respect to febrile

neutropenia and grade 3/4 or serious infections.

Given the incidence of thrombocytopenia, bleeding events were closely monitored. Bleeding events were more frequently reported in patients receiving imetelstat and most events were grade 1 or 2 hematoma or epistaxis. Nine patients had a bleeding event concurrent with grade 3/4 thrombocytopenia; however, importantly, none were grade 3/4 or serious. Overall, the risks associated with thrombocytopenia were low and similar to placebo with respect to grade 3 or 4 bleeding events.

While thrombocytopenia and neutropenia are common with imetelstat treatment, clinical risks of severe bleeding and severe infection are limited, and this is likely due to the short duration of cytopenias. Also, there was no long-term evidence of bone marrow aplasia or myelosuppression. Hematologists and healthcare professionals who will be administering imetelstat are experienced in managing cytopenias and the USPI will outline clear risks and monitoring.

We also monitored the use of supportive care, specifically growth factor and platelet transfusions, which were administered by investigators per medical judgment. Thirty-five percent of imetelstat patients were given growth factor with a median of three records of treatment per patient. Additionally, 18 percent of the imetelstat-treated patients received platelets with a median of one unit per patient. Platelets were given as a preventative measure rather than for the treatment of a bleeding event in most cases. The use of supportive care is infrequent per patient and does not contribute substantial clinical risk.

Turning to hepatic events, LFT elevations were observed in both imetelstat- and placebo-treated patients. Most were grade 1/2 in severity. ALP and AST elevations were higher in the imetelstat group. There were no grade 4 LFT elevations and no cases of severe hepatotoxicity or Hy's law were identified, as confirmed by the Independent Hepatic Monitoring Committee.

The overall risks with imetelstat treatment

are best summarized with a few key data points. The most common grade 3/4 adverse events with imetelstat treatment were neutropenia and thrombocytopenia, experienced by approximately 65 percent of patients. Importantly, these events were short-lived and reversible to grade 2 or less. Though 35 percent of patients received myeloid growth factor and 18 percent received platelet transfusions, these were administered per clinical discretion and choice, and most patients received treatment intermittently.

The most important clinical risk of grade 3/4 neutropenia and thrombocytopenia are high-grade infection and bleeding events. There were no severe bleeding events during periods of grade 3/4 thrombocytopenia and a low rate of high-grade infections during grade 3/4 neutropenia that was similar to what placebo-treated patients experienced. In summary, the safety profile of imetelstat is well characterized and manageable.

Thank you. I'll now turn the presentation to Dr. Komrokji.

Applicant Presentation - Rami Komrokji

DR. KOMROKJI: Thank you. My name is Rami Komrokji. I'm Vice Chair of the Malignant Hematology Department and Lead Clinical Investigator of the MDS program at Moffitt Center and Professor of Oncologic Sciences at the University of South Florida.

We see one of the highest volumes of MDS patients worldwide, with approximately 500 new patients per year and a database of almost 5,000 MDS-treated patients. I've spent my career working in this field and have run countless studies in MDS. Along with Dr. Savona, I was co-investigator on the imetelstat study, which was recently published in The Lancet Journal. I'm pleased to present my clinical perspective on imetelstat for the treatment of anemia in patients with lower-risk MDS.

As we heard, current treatment options are limited in this population. I'd like to share an example of a typical patient presentation. This patient is a 71-year-old gentleman who presented

with anemia and was diagnosed with lower-risk MDS, ring sideroblasts subtype, and his serum EPO level was greater than 500. By the time he presented to our center, he had a higher blood cell transfusion burden, receiving 6 to 7 units every 8 weeks. For this patient, the chances of an ESA response are around 7 percent.

My treatment goal is transfusion independence, and with luspatercept, the data showed that fewer than 10 percent of patients with high transfusion burden like this patient will achieve transfusion independence. Lenalidomide is not approved in this case and hypomethylating agents need low responses. They are often reserved for last choice, or in case of disease progression, or presence of other concomitant cytopenias, so clearly, patients like this have an unmet need. Dr. Savona illustrated the unmet need in lower-risk MDS, which accounts for 75 percent of these patients. Imetelstat addresses this need. Imetelstat demonstrated activity in lower-risk, non-del 5q MDS patients, both ring sideroblasts

positive or negative, and we observed responses with low and high transfusion burden, which is not the case for other agents.

As an MDS treating physician, I have a different perspective on some points made in the FDA briefing document. Let me take you through them. First, achieving transfusion independence is meaningful clinical benefit for these patients. Especially with imetelstat, this transfusion independence is durable for at least 16 and 24 weeks, and even longer than one year. In addition, duration of response is only clinically relevant in responders, as reported for lenalidomide and luspatercept.

When assessing the data in this way, we can see that imetelstat will provide long-term, continuous free transfusion periods, distinguishing it from other treatment options. In other words, almost two out of five patients will become red blood cell transfusion independent with a median of one year duration among a group of patients with an estimated median overall survival of three years.

And second, as a clinician, the increases in hemoglobin observed with imetelstat are meaningful because among all those drug tested and approved, this is the highest objective response observed in MDS studies after lenalidomide and deletion 5q.

The magnitude of benefit observed is even more important clinically in patients with high transfusion burden, where none of the approved therapies show benefit. With imetelstat treatment, my patients spend less time in my clinic and tell me they feel better and have more predictability and control of their lives and schedules.

Turning to safety, though all grade infection and bleeding rates are increased with imetelstat, I am reassured that the risk of grade 3/4 or serious infections and bleeding events are similar for imetelstat and placebo. Grade 1/2 infections and bleeding are generally self-limited and often don't require medical intervention. Additionally, febrile neutropenia events were uncommon, only one patient, and the use of supportive care in the study was acceptable when

looking at a per patient basis in line with supportive therapy used with other approved agents.

Looking at figures 5 and 7 in the FDA briefing document, the mean neutrophil and platelet levels of imetelstat-treated patients declined and anticipate plateau at grade 0 and grade 1. These levels do not put patients at risk for clinical consequences. The same degree of cytopenia is well known among responders to other treatments such as lenalidomide and deletion 5q. Those modifications are comparable to other treatment options. Furthermore, managing cytopenia is standard practice in bone marrow neoplasms such as lower-risk MDS.

This slide shows imetelstat adverse events compared to those associated with other common therapies in this patient population that result in cytopenias. The rate of neutropenia and thrombocytopenia reported with imetelstat, seen in light blue, are within the range reported with other agents. Lenalidomide is the most active therapy in MDS for deletion 5q subtype and is

associated with grade 3 or 4 thrombocytopenia and neutropenia, which leads to 84 percent dose reduction and interruption.

I'm comfortable managing the potential adverse effects with imetelstat and providing the supportive care required since dose modifications are commonly seen with other treatments for this patient population, and in my experience, dose modifications effectively help patients continue on treatment. Additionally, the monitoring proposed by the sponsor and implemented in the trial fits with my standard clinical practice.

In summary, the magnitude of clinical benefit and duration of transfusion independence seen with imetelstat is important, addressing the unmet need for transfusion-dependent anemia in lower-risk MDS patients. Given the safety profile that's familiar to hematologists and characterized by short-lived asymptomatic cytopenias, without an increased risk of severe bleeding or infections, the overall benefit-risk profile is favorable. In conclusion, I hope to have imetelstat as an

approved treatment for my patients as another option to help them achieve transfusion independence. Thank you, and I'll turn the presentation back to the sponsor.

Applicant Presentation - Faye Feller

DR. FELLER: Thank you, Dr. Komrokji.

The data we've shared today demonstrate that imetelstat offers a positive benefit-risk profile for patients with transfusion-dependent anemia due to lower-risk MDS. In the pivotal phase 3 study, imetelstat treatment met the primary and key secondary endpoints and resulted in statistically significant, clinically meaningful, and durable improvements in transfusion independence, as well as increases in hemoglobin and reduction of transfusion burden. The continuous transfusion independence seen with imetelstat is long and durable. TI has been the regulatory gold standard for approvals in this patient setting and FDA approvals have been granted, even in the recent few years in the absence of OS or other benefits.

The safety profile of imetelstat is well

characterized and manageable by MDS clinicians. Grade 3/4 neutropenia and thrombocytopenia were short-lived, requiring occasional growth factor or platelet transfusion support per patient, and most importantly without severe clinical consequences beyond what was observed in the placebo group. The remaining non-hematologic adverse events were infrequent and low grade.

We have heard from Dr. Savona and Dr. Komrokji that after ESA treatment, there is a high unmet need for lower-risk MDS patients who have transfusion-dependent anemia. We have also heard that the concerns expressed by the FDA over the cytopenias and associated events are not shared by the physicians who have used imetelstat in clinical practice. Therefore, taking into account all these considerations, Geron strongly maintains that the magnitude of clinical benefit is favorable and that the overall benefit-risk, given the unmet need, is positive. Thank you

DR. MADAN: Okay. We thank the speakers from Geron Corporation, and we will now proceed

with the FDA's presentation from Dr. Nina Kim.

FDA Presentation - Nina Kim

DR. KIM: Good morning. My name is Nina Kim, and I'm one of the hematologist/oncologist reviewing this application for the FDA. In my presentation this morning, I will discuss the issues identified by the FDA with regard to the efficacy and safety of imetelstat, for the treatment of transfusion-dependent anemia due to lower-risk MDS in patients who have failed to respond, lost response to, or are ineligible for erythropoiesis-stimulating agents, otherwise known as ESAs.

The members of the FDA review team are listed here. My presentation represents their collective input. In this presentation, I will first discuss concerns about the clinical meaningfulness of the results reported, including whether the magnitude and duration of red blood cell transfusion independence, or RBC-TI, provide a clinically meaningful benefit to patients in the intended population.

Next, I will discuss whether some of the secondary endpoints, such as hematologic improvement, complete remission and partial remission rates, and overall survival support the disease-modifying treatment effect. I will then discuss the patient-reported outcome data, as well as safety issues, including cytopenias, other risks, and dosing concerns. Finally, I will end by summarizing the data in a benefit-risk assessment.

As previously presented, the applicant conducted one study to support the proposed indication for imetelstat, Study MDS3001, also known as the IMerge study. This study was comprised of two parts. The first part was an open-label, single-arm, phase 2 trial, and the second part was a randomized, double-blind, placebo-controlled phase 3 trial.

Subjects in both parts of the study were adult patients with International Prognostic Scoring System, or IPSS, low- or intermediate-1 risk MDS who were relapsed or refractory to ESA or had an erythropoietin or EPO level greater than

500, predicting non-response to ESA. Subjects were required to have transfusion-dependent anemia, which was defined as requiring at least 4 units of red blood cells during any consecutive 8-week period over a 16-week baseline period of observation.

Notably, during the course of the phase 2 study, the applicant observed better 8-week RBC-TI rates in the subgroup of patients without deletion 5q and without prior treatment with a hypomethylating agent or lenalidomide, and so enrollment was restricted to this target population for phase 3. In phase 3, subjects were randomized 2 to 1 to receive either imetelstat or placebo infusions every 4 weeks. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary endpoint was 8-week RBC transfusion independence, defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks, starting from day 1 until subsequent anti-cancer therapy, if any. Notably,

there was no specific threshold for transfusion prespecified in the protocol. Supportive care, including transfusions and myeloid growth factors, could be administered as needed per investigator discretion and according to local standard practice.

In terms of key patient demographics on phase 3, there were no major differences between arms; however, it should be noted that the majority of patients were enrolled in the European Union with a comparatively small enrollment in North America of 25 patients, only 13 of which were from the United States, and the demographics are shown here.

In terms of baseline disease characteristics, there are a couple of important things to note. First, the majority of patients had prior exposure to ESA; however, relatively few patients had prior exposure to luspatercept, which was just recently approved for frontline treatment of transfusion-dependent anemia due to lower-risk MDS, and subjects with prior hypomethylating agent

or lenalidomide were excluded from the phase 3 trial, as previously mentioned.

Additionally, per eligibility criteria, patients were required to have an absolute neutrophil count of greater than 1.5 and a platelet count of greater than 75 at baseline, and when you look at the median neutrophil and platelet counts at baseline, these were normal; and this is something to keep in mind as we discuss the safety profile later, but first let's focus on efficacy.

Our review of efficacy focused on the phase 3 results of study MDS3001. The single-arm, phase 2 results were considered supportive. Now, the FDA acknowledges that the phase 3 trial met its primary endpoint of increased 8-week RBC-TI and also met the key secondary endpoint of 24-week RBC-TI; however, our analysis of efficacy focused on the question of whether these results represent a clinically meaningful improvement for patients receiving imetelstat.

It's important to note that the clinical meaningfulness of an 8-week RBC transfusion

independent period in the context of lower-risk MDS is uncertain. In recent years, the general consensus among MDS experts has been that only a 16-week or longer period of transfusion independence is clinically meaningful; therefore, the applicant evaluated alternative definitions of RBC-TI, reflecting greater durability. In addition to the primary endpoint of 8-week RBC-TI, they evaluated the rates of red cell transfusion independence lasting at least 16 weeks, 24 weeks, and one year, though only 8-week and 24-week RBC-TI were prespecified endpoints.

As shown here, the point estimate of the response rate decreased as the target duration of transfusion independence increased, with only about 14 percent of patients achieving transfusion independence for one year, with the lower bound of the confidence interval of 8 percent. As the applicant has presented in an updated analysis with an additional year of follow-up, the rate of one year RBC-TI was slightly higher, about 18 percent for imetelstat, but with a lower bound of the

confidence interval of only 11 percent.

Additionally, the applicant reported that the median duration of response was 52 weeks for imetelstat versus 13 weeks for placebo; however, this was only when looking at the longest RBC-TI interval for the subgroup of patients who achieved an 8-week RBC-TI response, not the entire study population. When looking at the entire study population, the median duration of the longest RBC-TI interval was substantially shorter, only 5 weeks for imetelstat compared to about 4 weeks for placebo, which is only a 1-week difference in median duration of transfusion independence, and this reflects the fact that the majority of subjects in the imetelstat arm did not in fact achieve an 8-week RBC-TI response.

CR and PR were also secondary endpoints, and an IRC was established for the phase 3 study to adjudicate whether response criteria were met per IWG 2006 criteria; however, the IRC was only instructed to adjudicate these endpoints for subjects with either baseline marrow blasts greater

than 5 percent at baseline or a CR, PR, marrow CR, or cytogenetic response per investigator assessment. At the time of the primary analysis, only 2 subjects, one in each treatment arm, out of the 178 subjects randomized actually had greater than 5 percent marrow blasts at baseline, and neither of these patients achieved CR or PR. But even when looking at CR and PR per investigator assessment, the CR and PR rates were zero in both arms at the time of the primary analysis, though it should be noted that about a quarter of patients in each treatment arm were simply deemed not evaluable by the investigator, mostly due to absent post-baseline marrow information.

Furthermore, there was no significant difference between arms in the key secondary endpoint of hematologic improvement in erythroid lineage, or HI-E, according to IWG 2006 response criteria. In fact, the erythroid response rate was 52 percent for the placebo arm, which is an exceptionally high response rate for subjects receiving no active therapy, and these results

suggest that a portion of hemoglobin rises, and corresponding periods of transfusion reduction may be at least, in part, due to natural fluctuations of the underlying disease rather than a direct treatment effect.

Of note, no subjects achieved a platelet response of the small proportion of patients with baseline platelets less than 100, and no subjects were eligible for a neutrophil response due to a requirement for an absolute neutrophil count of greater than 1.5 at baseline for study eligibility. And although the overall survival data are considered immature in the primary analysis, there were numerically more deaths in the imetelstat arm, 16 percent versus 13 percent for placebo, and the stratified OS hazard ratio was just over 1. With an additional 15 months of follow-up, the stratified OS hazard ratio is just under 1; however, there is still numerically more deaths observed in the imetelstat arm, 30 percent versus 25 percent.

The upper bound of the hazard ratio

95 percent confidence interval is 1.82, indicating that potential harm cannot be ruled out. Furthermore, it's important to note that incorrect stratification accounted for major protocol deviations in approximately 10 percent of patients in each study arm. Stratification errors were largely related to incorrect calculation of baseline transfusion burden by investigators. Additionally, there were only few events in some strata; therefore, the stratified hazard ratio should be interpreted with caution.

Notably, the unstratified OS hazard ratio is 1.11 with a lower 95 percent confidence bound of 0.61 and an upper bound of 2.03, again illustrating that potential harm cannot be ruled out; and this is important not only because OS is considered the gold standard efficacy and safety endpoint, but one of the arguments for therapeutically targeting transfusion-dependent anemia in subjects with lower-risk MDS is that a higher RBC transfusion density has been reported to correlate with a detriment in the overall survival. And so, by

increasing the rate of RBC transfusion independence, one would hope to confer an improvement in overall survival, and yet, in this study, there is no evidence of a trend toward OS benefit with imetelstat.

Furthermore, unlike growth factors such as ESAs, which artificially raise blood cell counts, imetelstat is purported to have a direct effect on the underlying MDS through telomerase inhibition, resulting in cell cycle arrest, apoptosis, or senescence of malignant cells, and yet these CR, PR, and OS results are not supportive of a substantial disease-modifying effect.

Now, what about mutation burden? The applicant reported that more subjects in the imetelstat group achieved a 50 percent or greater varying allele frequency, or VAF, reduction in SF3B1, with a trend toward VAF reduction and other mutations common in MDS such as TET2, DNMT3A, and ASXL1. Well, it's important to note that this was merely an exploratory endpoint. The study was not actually designed to show a difference in mutation

burden, and so there are issues with the methodology of data collection. Simply put, the NGS assay used in this study has not been designed for VAF tracking.

In addition, only a subset of patients had these mutations at baseline and at least one post-baseline assessment, making them eligible for this analysis. For example, only 78 of the 118 subjects treated with imetelstat, and 38 of the 60 subjects treated with placebo, were eligible for SF3B1 assessment; an even smaller subset of patients were eligible for the other mutation analyses. For example, the ASXL1 analysis is based on just 10 subjects in the imetelstat arm and 6 subjects in the placebo arm. Furthermore, samples were collected by peripheral blood, not marrow, and at relatively sparse time points, generally every 12 weeks and at the time of suspected response or progression.

Additionally, this analysis is based on maximal VAF reductions from baseline, which could have been achieved at any time point. Without

serial data at distinct prespecified intervals for all patients, it's difficult to examine associations between VAF changes and the dynamics of red cell transfusion independence. It's also unclear whether greater than 50 percent VAF reduction is clinically significant, as there was no a priori, well-justified rationale for the use of this cutoff and, of course, reduction in mutation burden is not a direct measure of clinical benefit. And so, despite there being a suggestion of activity here, the effect does not appear to be of sufficient magnitude to be clinically significant given the lack of a corresponding response or survival benefit, which brings us to patient-reported outcomes, which is a direct measure of how a patient feels or functions.

Notably, the applicant collected patient-reported outcomes in Study MDS3001, focusing on anemia-related symptoms such as fatigue using PRO instruments, including the FACT-AN and QUALMS measures; however, PROS were collected infrequently on day 1 of each treatment cycle.

Overall, the PRO data quality was good, meaning that most patients who received a PRO assessment completed it; however, due to attrition, less than half of enrolled patients provided a PRO response after cycle 8, which limits longitudinal interpretation of these results.

Furthermore, the applicant selected the proportion of patients who experienced deterioration in fatigue as the primary PRO endpoint of interest, and the results show that similar proportions of patients experienced deterioration of fatigue with no difference noted between imetelstat and placebo. Of note, FDA also examined categorical responses to fatigue questions in the first 6 months, and we noted that there were no major differences at baseline, nor major differences in each arm as cycles progressed. Similar results were observed with other patient-reported fatigue items that were administered to patients in Study MDS3001.

So overall, the FDA review team urges caution in any claims made by the applicant

regarding patient-reported fatigue. These results are purely exploratory, and the MDS3001 study was not designed to show a benefit in PROs; therefore, any positive results could be due to chance and not actually represent improvement in symptoms. This caveat aside, when the FDA review team examined these PRO results, we did not find evidence of a large or durable magnitude of improvement. Overall, the submitted PRO results are not compelling and cannot be relied upon to demonstrate benefit for imetelstat compared to placebo.

In summary, Study MDS3001 met the statistical objective for the primary endpoint of 8-week RBC-TI and secondary endpoint of 24-week RBC-TI. Although 8-week RBC-TI responders appear to have a substantially longer period of transfusion independence on imetelstat versus placebo, the longest RBC-TI interval was relatively short when considering all patients regardless of response status, at only 5 weeks for imetelstat versus 4 for placebo. Additionally, the HI-E, CR, PR, and OS results are not supportive of a

disease-modifying treatment effect, and the PRO analyses do not corroborate the treatment effect. With that in mind, we'll move on to the safety issues.

In considering whether to approve a potential new therapeutic agent, the efficacy of the medication must be balanced against the risks associated with taking the medication. Shown here is a summary of the adverse events associated with use of imetelstat compared to placebo.

Although almost all patients experienced at least one AE regardless of study arm, SAEs, grade 3-plus AEs, grade 3-plus AEs excluding the two most common events of neutropenia and thrombocytopenia, as well as AEs requiring dose modification, including treatment discontinuation, were more commonly observed in patients receiving imetelstat. Although only one death on study or within 30 days of end of treatment was seen in each arm, there were additional patients who received imetelstat and died of AEs which began during treatment but were not fatal until more than 30 days after the

last exposure to treatment.

In terms of the safety profile, adverse events, excluding laboratory abnormalities, observed more commonly in the imetelstat arm included infections, fatigue, arthralgias/myalgias, anemia, and hemorrhage. Adverse events of potential interest that occurred in fewer than 15 percent of patients but more commonly in the imetelstat arm included hepatic toxicity, fractures, pruritus, and bone pain.

This slide shows the most common laboratory abnormalities observed in patients receiving imetelstat compared to those receiving placebo. As you can see, cytopenias were very common with imetelstat. Although rates of anemia were similar between the two arms, the rates of leukopenia, neutropenia, and thrombocytopenia, both overall and grade 3 to 4 only, were more common in the imetelstat arm. Notably, the rate of grade 3-plus neutropenia was 64 percent higher and the rate of grade 3-plus thrombocytopenia was 57 percent higher with imetelstat compared to placebo.

This figure shows the mean value of neutrophils over time during the first 52 weeks of study participation by treatment arm. Note that the mean neutrophil count was similar between the study arms at baseline; however, in the imetelstat arm, the neutrophil count decreased rapidly after the start of treatment and did not recover to baseline levels at any time during treatment, despite a higher rate of use of myeloid growth factors.

This figure shows changes in platelet count over time during treatment with imetelstat. Again, the baseline platelet count was similar between arms, but mean platelet count decreased rapidly in the imetelstat arm, whereas it was stable in the placebo arm. The mean platelet count also did not recover to baseline levels during treatment, despite more common use of platelet transfusion in the imetelstat arm.

On an individual patient level, the median duration of each individual event of grade 3 or 4 neutropenia or thrombocytopenia was around 2 weeks

or less with imetelstat; however, the range was wide. There were subjects who had up to 16 weeks of grade 3-plus neutropenia and up to 13 weeks of grade 3-plus thrombocytopenia. You'll also notice that the total number of events was quite high in the imetelstat arm, suggesting that patients tended to have multiple events of grade 3-plus neutropenia and thrombocytopenia. And so, the total duration of time spent with grade 3-plus cytopenias was actually higher than the median alone would suggest.

Subjects treated with imetelstat also required more intervention for cytopenias such as myeloid growth factors and platelet transfusions compared to patients receiving placebo. For example, 35 percent of patients treated with imetelstat required myeloid growth factor at least once during treatment compared to only 3 percent of patients in the placebo arm. Furthermore, anti-infective medications were used more commonly in the imetelstat arm, with antiviral medications or antibiotics being used in 42 percent of patients

on the imetelstat arm and 34 percent on the placebo arm. Additionally, 18 percent of patients on the imetelstat arm required platelet transfusion during treatment , with one patient requiring 10 platelet transfusions.

Of course, neutropenia increases the risk of infection with a higher risk for longer or more severe infections. The investigators in the study were very diligent about giving growth factor support to patients who experienced neutropenia; nonetheless, a higher rate of infections was observed in patients who received imetelstat.

Although the rate of grade 3 to 4 infections was similar between the two arms, it should be noted that grade 4 infections were seen in 4 patients on the imetelstat arm versus only one on the placebo arm, and one death occurred due to infection in the imetelstat arm. The increase was particularly notable for viral infections. The overall rate of bacterial infections and infections where the pathogen was not specified were similar between the two arms.

Although no specific infection dominated the risk profile, we wish to highlight several specific infections which occurred at a rate of more than 5 percent in either arm or with a grade 3 to 4 rate of greater than 3 percent. For example, COVID-19, UTIs, and pneumonia were more commonly seen in the imetelstat arm of the study, and sepsis was not observed in the placebo arm but was observed in 4.2 percent of patients receiving imetelstat.

The table on this slide shows commonly reported hemorrhagic adverse events by treatment arm. Patients receiving imetelstat experienced more hemorrhagic events overall and slightly more grade 3 to 4 events. It's also notable that all events on the placebo arm were grade 1, with the exception of a single patient who experienced grade 3 to 4 GI bleeding, whereas 5 patients, or 4.2 percent, on the imetelstat arm experienced grade 2 events, as well as 2 patients with grade 3 to 4 GI hemorrhage and one with grade 3 hematuria. Thus, hemorrhage was more common and more severe in the imetelstat arm.

In addition to the highlighted safety issues, there were dosing issues noted during the course of our review. Specifically, there was a lack of adequate dose finding in the target population. Although other dose levels of imetelstat have been explored in myelofibrosis and solid tumors, only one dose has been explored in lower-risk MDS, and the question remains whether this is actually the optimal dose in MDS given the high dose modification rate with imetelstat observed in the MDS3001 study when compared to the placebo group. Combined with the fact that there were high rates and a positive dose exposure-response relationship for grade 3 to 4 thrombocytopenia, the data suggest that this may not in fact be the optimal dose.

As you can see here, there was a high dose modification rate with imetelstat as compared with the placebo group, including many more dose delays, dose reductions due to AE, infusion interruptions, and treatment discontinuations due to AE. This plot shows the percent of patients receiving 7.1,

5.6, or 4.4 milligrams per kg dose in each cycle. As cycles progressed, there was a higher percentage of patients receiving reduced dose levels in the imetelstat group, as shown on the top, compared to the placebo group, as shown on the bottom.

This figure shows the positive exposure-response relationship between the maximum plasma concentration of imetelstat, or Cmax, and the probability of grade 3 to 4 thrombocytopenia, suggesting that the starting dose and regimen of imetelstat may be further optimized; though it should be noted that this analysis is significantly limited by the fact that only one dose of imetelstat was studied in Study MDS3001.

In summary, use of imetelstat was associated with a higher risk of grade 3-plus AEs, SAEs, and AEs leading to treatment modification. The risk of cytopenias was much higher in patients receiving imetelstat and resulted in higher rates of infection and bleeding, as well as increased need for interventions to treat the cytopenias. Lastly, there is uncertainty regarding the best dose for

patients with lower-risk MDS, and so, overall, there are significant safety concerns with the use of imetelstat.

Now, for the benefit-risk assessment, it's important to note that many subjects experienced worsening grade 3-plus cytopenias regardless of response status. As you can see here, both imetelstat responders and non-responders had high rates of grade 3-plus neutropenia and thrombocytopenia. Importantly, 70 percent of imetelstat non-responders had grade 3-plus neutropenia and 69 percent of imetelstat non-responders had grade 3-plus thrombocytopenia on treatment; and so, there is a portion of patients treated with imetelstat who had significant cytopenias with no benefit.

Furthermore, many subjects required intervention for cytopenias during the course of treatment regardless of response status. As you can see here, both imetelstat responders and non-responders required myeloid growth factor or platelet transfusions during the course of

treatment. And again, it's important to note that 31 percent of imetelstat non-responders required myeloid growth factor while on treatment and 23 percent of imetelstat non-responders required platelet transfusion while on treatment. And so, there's a portion of patients treated with imetelstat requiring intervention for cytopenias with no benefit.

Furthermore, with a very effective and safe therapy, one would expect to see a much longer duration of treatment compared to placebo; however, this was not the case with imetelstat. In fact, patients treated with imetelstat had a median duration of treatment of 8 cycles, which was the same as placebo.

Seventy-seven percent of patients discontinued imetelstat treatment with median time to treatment discontinuation of 7.8 months. And although imetelstat is meant to be a long-term treatment, very few patients continued on treatment beyond 2 years, and the Kaplan-Meier plot shows similar treatment exposure for the imetelstat and

placebo groups. So why might this be? Well, when you look at the reasons for treatment discontinuation, you can see that adverse events and loss of RBC-TI response were more commonly cited reasons for discontinuing imetelstat compared to placebo, which brings us to our overall benefit-risk assessment.

Based on the results of this study, a patient receiving imetelstat has a 25 percent higher chance of achieving an 8-week or 24-week RBC-TI over placebo; however, this is in the context of requiring 2-hour infusion visits monthly; therefore, one must consider the amount of time spent in a healthcare setting getting an IV infusion, lab monitoring, and potentially other medical interventions, such as myeloid growth factor and platelet transfusions. Furthermore, there's been no demonstration of a CR, PR, or overall survival benefit and no clear improvement in patient-reported outcomes.

Potential risks of imetelstat treatment include a 64 percent higher chance of grade 3-plus

neutropenia and a 57 percent higher chance of grade 3-plus thrombocytopenia worsening from baseline. Additionally, there's a 32 percent higher chance of requiring myeloid growth factor and a 16 percent higher chance of requiring platelet transfusion at some point during treatment, as well as a 9 percent higher risk of infection and a 9 percent higher risk of bleeding. And it's important to note that these risks are regardless of response, so patients are at risk of toxicity regardless of whether they have an RBC-TI benefit. Furthermore, imetelstat is associated with a higher risk of fractures, arthralgias and myalgias, and possibly fatigue. Finally, there's residual uncertainty regarding the optimal dose of imetelstat.

Of course, it's important to keep in mind the patient population as well. These are patients with lower-risk MDS with estimated survival on the order of years, who would otherwise be receiving supportive care in the real world; and so, the acceptable risk profile may be different than, for

example, a higher risk MDS or AML population.

With that being said, we'd like to ask the panel to discuss the efficacy of imetelstat for patients with lower-risk MDS based on the results of the MDS3001 trial considering the safety profile. And the voting question will be, do the benefits of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-1 risk MDS who have not responded to, or have lost response to, or are ineligible for erythropoiesis-stimulating agents?

With that being said, I'd like to note that FDA recognizes the time and effort necessary to conduct cancer clinical trials. On behalf of all of my colleagues here at the FDA, I'd like to thank the patients and their families, as well as the investigators and research staff who participated in the research studies discussed today. Thank you, and that concludes my presentation.

Clarifying Questions to Presenters

DR. MADAN: Thank you, Dr. Kim.

We will now take clarifying questions to the presenters. Please use your raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon after you have asked a question. When acknowledged by the chair, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I see some hands raised up, so let me just move to the participants. It looks like, Dr. Vasan, you're first on the list here.

DR. VASAN: Hi. Neil Vasan, Columbia University. I'd like to ask some clarifying questions around the definition of this clinical meaningfulness, and specifically, this is the

applicant's slide CO-35.

It seems like one fundamental difference between the applicant's assessment of clinical meaningfulness and the FDA's is that the FDA states in the briefing document that the general consensus among MDS experts has been that only a 16-week or longer period of transfusion independence is clinically meaningful, and they cite a reference that is these IWG 2018 guidelines. I recognize that that was not the secondary endpoint of this trial -- it was the 2006 guidelines -- but I'd like some clarifying questions first.

Perhaps Dr. Savona could discuss what was the rationale for the changing of these guidelines from the MDS community, and then secondly, a question for the FDA is that, from the statistical point of view, these p-values are all significant, and so I'd like some thoughts from the FDA, or guidance from the FDA, about the relative merit of fulfilling these newer criteria.

DR. FELLER: Thank you. I'll turn the mic over to Dr. Savona.

DR. SAVONA: Well, thank you for the important question, Dr. Vasan. Just like in any field of oncology, this is a moving target. We over time learn in lower-risk MDS, it's been a very difficult place to develop new therapies for patients because achieving CR is not meaningful in patients who don't have increased blasts, so survival can be a long-term follow-up and can be difficult to show, and we've struggled to find the right criteria by which to support a clinical benefit.

We've worked through transfusion reduction and hematologic improvement. The thing that really sticks out and has been associated with longer term better outcomes is transfusion independence, and in 2006, the criteria defined transfusion independence, as you note here on the slide. We looked at studies over time and determined that this is really less robust, when you count up the transfusions that occur over time, than the criteria imposed by the proposed IW 2018 criteria, so this is kind of the moving target.

I think the study's designed at a point where that new criteria is just getting hold, so the primary endpoint is built around this 2006. But I think the important thing, just like IPSS, is to go back and reclassify, as was done here on this slide, to illustrate that this is an effective therapy in the most robust manner by which we measure transfusion dependence, which is the 16-week TI.

DR. VASAN: And just to clarify, the definition of the new HI-E guidelines are those two parameters, the 16-week TI and the transfusion reduction by 50 percent at 16 weeks?

DR. SAVONA: One or the other, yes.

DR. VASAN: One or the other. Okay. Thank you.

Then if I could hear from the FDA as well.

DR. NORSWORTHY: Hi. Yes. This is Kelly Norsworthy, the Deputy Division Director, FDA. I'll be helping to moderate the Q&A from the FDA side. I'd like to ask Dr. Nina Kim to address this question. Thank you.

DR. KIM: Hi. So regarding the p-values, I think it's important to note that only the HI-E per IWG 2006 criteria was a prespecified key secondary endpoint that was included in that testing hierarchy with multiplicity adjustment and alpha allocation in this study. HI-E per IWG 2018 criteria was an ad hoc analysis as per the applicant's clinical study report, so the results including any of those p-values should really be interpreted with caution.

Furthermore, I think it should be noted that the 42 percent HI-E rate with imetelstat per IWG 2018 criteria reported by the applicant was calculated by taking the number of patients with low transfusion burden at baseline who achieved an HI-E response, and adding this to the number of patients with high transfusion burden at baseline who achieved at least a minor HI-E response, which was defined as an at least 50 percent reduction in RBC transfusion burden over a minimum of 16 weeks.

So if you look at the actual breakdown of the HI-E rate according to baseline transfusion

burden -- I believe we have a backup slide on this; it's slide 50 that can be pulled up. Well, while it's being pulled up, if you look at the actual breakdown, you can see that the results for patients with low transfusion burden at baseline are marginal. So there were 22 percent of patients who received placebo that actually achieved an HI-E response compared to 33 percent for patients who received imetelstat, and for patients with high transfusion burden at baseline, there's a bit more of a spread between the imetelstat and placebo arms, but the major HI-E response rate is only 31 percent.

But again, I want to emphasize that the HI-E per IWG 2018 criteria was not a prespecified endpoint with multiplicity adjustment or alpha allocation, so again, these results really should be interpreted with caution.

DR. VASAN: Thank you.

DR. FELLER: Would it be possible for the applicant to raise a few points to address your question?

DR. MADAN: Briefly, yes. We do have other questions, but go ahead.

DR. FELLER: Thank you. Yes, we acknowledge that the prespecified endpoint was HI-E per 2006 criteria; however, the 2018 criteria was prespecified prior to analysis of the study results in our SAP, statistical analysis plan. So this was a preplanned analysis and was incorrectly attributed as ad hoc in our CSR.

Regarding the low transfusion burden, patients who achieved HI-E per the 2018 criteria, I'd like to ask Dr. Komrokji to come and address that point.

DR. KOMROKJI: Thank you. Rami Komrokji. First to clarify, 8-week transfusion independence is the entry gateway for a response. So it's not the duration of response. You have to be 8 weeks 56 days consecutively not needing blood to be assessed as a responder, and then you calculate the response from there, and the newer criteria looked at extending that to 16 weeks.

For the low transfusion burden, by

definition, by the new criteria of 2016, any patient that gets more than 3 units in 8 weeks, or the 8 per 16, is considered high transfusion burden. So there are none of the patients on the study by the eligibility criteria of 4 units or more that will be considered by the new criteria as a low transfusion burden. Thank you.

DR. MADAN: Okay. Thank you very much.

Our next question will come from Dr. Spratt.

DR. SPRATT: Thank you so much. This is for the applicant -- and be very direct with this, and you don't need to go over any of the data again that you've showed -- is do you have any of the PRO data or survival data for the patients that are transfusion free at the 8-week mark, where it seems to derive most of the benefit?

DR. FELLER: My very direct answer is yes, and I can show that here. If we can have the control of the screen, please?

We did do a responder analysis for all the PRO endpoints and PRO questionnaires that were assessed. That analysis supports or shows that

imetelstat-treated patients who experienced response in terms of transfusion independence were more likely to derive benefit, and I can pull that up here. Here you see the FACIT fatigue, which was our primary assessment by responders, so those patients who achieved TI, with one minor correction, not at 8 weeks but at for at least 8 weeks or longer. And we can see here that imetelstat responders had no worsening of fatigue compared with placebo.

I'd like to ask Dr. Savona to come and put this a bit more in context, but I'll also show another analysis. It's a more direct responder analysis that shows there's sustained meaningful improvement in fatigue that correlated with imetelstat response. You can see the blue bars represent imetelstat-treated patients, the darker blue are the responders, and the responders comprise 70 percent, or approximately 70 percent, of patients who had an improvement in fatigue.

DR. SPRATT: Thank you. I think this is actually sufficient. Do you have the survival data

like this as well?

DR. FELLER: We do have survival data by responder. It shows an improvement in survival for TI responders on imetelstat compared with placebo, and that's to be expected based on the literature.

DR. SPRATT: Thank you.

DR. NORSWORTHY: Hi. This is Kelly Norsworthy for the FDA. I'd like to call on Dr. Vishal Bhatnagar to comment on the PRO data shown. Thanks.

DR. BHATNAGAR: Hi. My name is Vishal Bhatnagar. I'm a medical oncologist and Associate Director for Patient Outcomes in the Oncology Center of Excellence. I'd like to just take the opportunity to respond to the exploratory analysis that the sponsor just presented, or applicant just presented.

Ideally, there would be an improvement in anemia that would be with large magnitude, and clinically meaningful, and durable. What the sponsor just provided was a 3-point or so difference, which they did not provide adequate

justification that this was a large magnitude of improvement in fatigue. I'd also like to reiterate that this was exploratory information, and to do a responder analysis on this would not necessarily be appropriate. Thank you.

DR. FELLER: For the applicant, can we respond to that as well?

DR. MADAN: Yes, go ahead.

DR. FELLER: Yes. We confirm that this is an exploratory analysis, and our major PRO objective hypotheses were to show that patients had no worsening of fatigue. For the definition of improvement in fatigue, we used an increase in the FACIT fatigue score by 3 points that was sustained for 2 consecutive cycles. Three points was verified in the literature and also on psychometric evaluation that was performed on unblinded data.

But more importantly, I'd like to ask Dr. Savona to come and to speak to what can be anticipated for patients with lower-risk MDS in terms of PRO outcomes.

DR. SAVONA: I respect and recognize the

difficulty with responder analysis, but talking about duration of response in people that don't respond is difficult, and I think it is a useful lesson to look at the responders and see what are the characteristics of those people that go along with their transfusion independence, and what we see is transfusion independence in this study. The patients who receive imetelstat had not only transfusion dependence but a greater rise in hemoglobin, sometimes back to normal with a hemoglobin rise of up to 5 points.

In those patients, their fatigue was less. That's not what we see in other newly approved agents that we're using now in the clinic, that actually cause more fatigue when we when we start to use them, insofar is it's so severe, we're not able to get past the first cycle in 30 to 40 percent of patients from their phase 3 study, and that's kind of ringing true in the community. And these patients, I'm sure they'll be questions about quality of life and the time spent in the clinic and so forth, but there's a demonstrable

improvement in how they interact with their healthcare team and the predictability of those appointments when they do respond.

DR. FELLER: One other point to note is that when we look at these responder analyses, also what's important to keep in mind is that patients do benefit temporarily from transfusions. So by assessing the patients who are transfusion independent, we keep in mind that they're no longer receiving the benefit of transfusions as the non-responders would.

DR. MADAN: Okay. Thank you very much.

I think we can move on to our next question from the panel, from Dr. Advani.

DR. ADVANI: Thank you. My question is, about 50 percent of the patients needed dose reductions. In the patients who had dose reductions, what was the TI rate? Was it similar to the ones who didn't need dose adjustments?

DR. FELLER: Yes, that is an important point. At the time of response, 75 percent of patients were receiving the 7.1 milligram per

kilogram dose. A smaller proportion of patients, only 23 percent -- if we could have the screen share; thank you -- of patients achieved response on the 5.6 milligram per kilogram dose.

DR. ADVANI: Thank you.

DR. MADAN: I believe, Dr. Rosko, you have the next question from the panel.

DR. ROSKO: Hi. Ashley Rosko. I guess my question is to the applicant. I don't want to underestimate the medicalization of these patients with lower-risk MDS. Essentially, these patients were coming in for a unit of blood every other week in order to be enrolled into this study. I want to know the data regarding healthcare utilization or the medicalization of these patients in terms of over the period of time, when it comes to whether or not they had to be hospitalized, if they were having neutropenia and the healthcare utilization rates for these patients during the duration of the study.

DR. FELLER: Indeed, that's a topic of some importance. Thank you for the question. When we

look at the number of red blood cell units saved, so that can be one measure of medical resource utilization, we see that patients who achieved transfusion independence on imetelstat saved a median of 38 units over the course of that transfusion independence compared with 11 units for patients receiving placebo. So that's one aspect in terms of the utilization of scarce blood supply.

Another aspect I can show are the rates of hospitalization, which similarly and not unexpectedly mimic those of the SAE rates and were a bit higher in imetelstat-treated patients; however it's notable -- and I'll bring it up on the slide in a second -- that the median duration of hospitalization for imetelstat-treated patients was shorter than for the placebo-treated patients, with 6 days compared to 25.5.

I'd like to ask Dr. Savona again to come to speak to the more intangible aspects of patient care.

DR. SAVONA: From the veracity of your question, Dr. Rosko, I'm sure this is very familiar

to you. The patients do have to come in once every other week, once a week, for infusions, and I've described in my presentation what that involves. As many of you in the panel are well aware, when you start any new therapy for MDS -- that includes lenalidomide, luspatercept, HMAs -- there are nuances and there's tweaking in the beginning, and they do have to come in more often as you are being careful to understand kind of what their response is going to be with respect to their ability to have normal hematopoesis; but once that's under control, these really are much more spaced out visits, and the important thing is that they're predictable.

When patients are in their 70s and 80s and coming from 6 to 8 hours away, they can come once every 2 weeks or once a month; it's on their calendar. If they have to come and get their blood checked and don't know when they're they're going to dive down and need a transfusion, that's a much different animal.

DR. ROSKO: Thank you.

DR. NORSWORTHY: This is Kelly Norsworthy, FDA. We'd like to respond as well. I'm going to call on Dr. Nina Kim. Thanks.

DR. KIM: Can we go to backup slide 59, please? So as the applicant presented, the total number of subjects who had at least one medical encounter, whether inpatient or outpatient, was slightly higher in the imetelstat arm, 56 percent versus 52 percent for placebo, and this was driven by a higher rate of hospitalization in the imetelstat arm.

But there's a major problem, really, with this medical resource utilization analysis. According to the SAP, protocol-mandated procedures, tests, and encounters were actually excluded from the analysis, meaning that infusion visits and transfusion visits, whether for red cells or platelets, were not included in these numbers, which I think is an issue because what we really want to know is whether patients on imetelstat may be trading RBC transfusion visits for infusion or platelet transfusion visits. And because both

infusion visits and transfusion visits were excluded, this data is of limited utility.

Could we go to the next slide, please? So the FDA actually did our own exploratory analysis of healthcare utilization, adding in infusion visits and transfusion visits for the imetelstat arm, and then just transfusion visits for the placebo arm since patients wouldn't be receiving placebo infusions in the real world. And as you can see, the total number of medical encounters per patient was actually higher for imetelstat responders compared to placebo responders, and for imetelstat non-responders as well compared to placebo non-responders.

Of course there are caveats with this analysis. We didn't account for the fact that patients on placebo would probably have some number of routine visits with their medical provider in the real world, and also subjects receiving placebo in this study were probably seen more frequently than they would be in the real world, which may have led to some differences in healthcare

utilization that are hard to quantify. So I think the most that we can say here is that there at least appears to be no major reduction in medical resource utilization with imetelstat based on this limited analysis, and it's actually possible that patients on imetelstat used more medical resources than those not on active treatment. Thank you.

DR. FELLER: The applicant would like to respond.

DR. MADAN: Yes, go ahead.

DR. FELLER: If we could put that slide back, please, for the -- sorry; control back to the FDA for the backup slide, if that's possible. If it's not possible, I'd just like to point out that in that slide, when we look at the per patient non-protocol mandated encounters, there's a slightly more higher rate for imetelstat responders and non-responders, but when compared to placebo, that difference is not quite there, and that is likely due to requiring more transfusions.

I think what drives a lot of the difference is that the duration of treatment when we look at

non-responders versus responders. In the real world, those non-responders would be continuing to have medical encounters, receive transfusions, and need to come in for medical resource utilization; whereas at what point, they'd be off the study, and we wouldn't capture that information. So we maintain that although we acknowledge that imetelstat treatment does necessitate close monitoring in the beginning of treatment as transfusion independence is achieved, patients can then space out visits. We also see that patients who are TI responders and achieve at least 8-week TI, which lasts a median of 52 weeks, they have a median treatment duration of 18 months.

DR. MADAN: Okay. Thank you very much.

DR. ROSKO: Thank you.

DR. MADAN: I think I'm next in the queue here, Ravi Madan, National Cancer Institute. I have a question for the sponsor, and it actually picks up a little bit on what was just discussed.

In the sponsor's presentation, the terms "RBC transfusion independence" and "transfusion

independence" were used somewhat interchangeably. Am I correct to assume, though, that it was always intended to be RBC transfusion independence and not transfusion independence when not labeled with RBC didn't include platelet transfusions?

DR. FELLER: That's an important point, and in most cases during the presentation when I spoke to transfusion independence, I did mean RBC-TI. We did also closely monitor platelet transfusions and did an analysis of patients who had both RBC-TI and platelet TI, and the analysis is quite similar to the first, with only -- I can pull it up -- a 39 percent 8-week TI rate and 27 percent 24-week TI rate. So receiving platelet transfusions did not deter from the rate of red blood cell transfusion independence and the magnitude of benefit maintain is maintained.

DR. MADAN: Right. So this is the percentage of patients, but what about the duration?

DR. FELLER: I am not sure that we have that analysis, but we'll be able -- I will check with

the team, and perhaps after the break, we can provide you with an analysis of the duration of platelet and RBC transfusion independence that were concurrent.

DR. MADAN: Okay. Thank you very much.

Our next question comes from Dr. Choueiri.

DR. CHOUEIRI: Hello, everyone, and I'm going to lower my hand, and thank you for the opportunity to be part of this panel. I have a question for the sponsor. The paper in Lancet was published in December 2023, so a couple of months ago recently. I have read this paper and details. There are a lot of things that I learned with the FDA now that were not present in the paper.

I understand I'm not part of the paper. I don't know if The Lancet asked you to put the additional information that is mostly negative information in terms of not meeting endpoint in the supplementary table or there's a limit on how many words in the document. But I think they need to be there, they have needed to be there, or they need to be in the future so that folks all around the

world decide, if this drug is to be approved, on how they use it. So I would like clarification why it's not there, and we learned about additional many, many endpoints because of what the FDA requested. That's one.

The second short question is we have seen loss of benefits with time -- that's fine -- of the drug. Are you working -- since this is a heme malignancy, you have access to tissue, and hopefully you have stored some tissue. It's a clean pathway. Are you looking at mechanism of resistance for the next generation of research or biomarkers of response that can enrich for responders?

Thank you very much, Chair Madan.

DR. FELLER: Thank you for your questions and your observations, and for reading our paper. I'd like to clarify if there are any specific endpoints you would like us to tackle, and then we can discuss why they were not included in The Lancet and were presented by the FDA.

DR. CHOUEIRI: Absolutely. I would like you

to tackle all the endpoints that were present in the FDA briefing for us that were not present in The Lancet paper, which was only a few months ago; and not one by one going -- that's going to take a whole day -- but in general.

DR. FELLER: In general, I think one analysis that may not have been included in The Lancet paper was the HI-E per IWG 2006 criteria, but it may be available within the supplement of that Lancet paper, or I may be wrong and it is in The Lancet paper. But those were the only endpoints that I know off the top of my head that were not included.

I can ask Dr. Komrokji to come, as he was a senior author on the paper. His recollection is a bit better than mine.

DR. KOMROKJI: Thank you. I'm Dr. Komrokji --

DR. MADAN: Just to be clear, we can probably keep this brief as an explanation because it's likely beyond the scope of this meeting.

DR. CHOUEIRI: Ravi, I just want -- if this

gets approved -- for the general practitioner in the U.S., or outside the U.S., to have access to all the data in one place and make their decision based on their milieu, their culture, the availability of drug, et cetera. And certainly if I'm a general practitioner, if I have access to all the extensive information that was well prepared by the FDA and all that, I may think differently than reading just the paper in Lancet. That's all.

DR. MADAN: That's a good point, then we'll hear that, and then get to your second question as well.

So go ahead, back to the sponsor. Sorry to interrupt.

DR. CHOUEIRI: Thank you, and thank you, Dr. Choueiri, for that question. I think it's important. The analysis presented by the FDA is not the classical academic or the way the standard is done in MDS. Duration of response is only calculated in responder, so we've never had any single study published that would report duration of response in somebody who had progressive disease

or non-responding. Similarly, in other endpoints, looking at the duration of response and the survival, and actually the other endpoints tested, it was not the standard way that's used in any MDS standard way of reporting, so that's why those analyses were done. This was an additional analysis done by the FDA, looking at it from their different perspective.

DR. CHOUEIRI: Okay. An actually, that's a very good response, and I'm satisfied.

DR. MADAN: Dr. Choueiri, can you remind them of your second question? I also forgot it.

DR. CHOUEIRI: My second question is this drug doesn't give you, for example, immune checkpoint inhibitor, some solid tumor responses that are durable for a long time and with time, especially at the one year follow-up 16 versus 3 percent, something like that. So this is not the solid tumor, this is a heme malignancy, and you have a lot of blood.

Are you -- this is my interest -- working on biomarkers of response, or more so, with time, at

acquired resistance hopefully for the next generation of drugs that will provide not marginal but more powerful clinical durability of response in the future? Thank you.

DR. FELLER: Indeed, we continue to collect data and have samples in which we looked at mechanisms of disease resistance, but I want to confirm that first, and then clarify another point that you mentioned.

If we could bring up slide CO-31 from our presentation, if you look towards the right hand of the slide, when we are quoting here an 18 percent response rate, these are patients who, at minimum, achieved one year TI, so the range of their TI response starts at one year and can go on further. Then when we look at the median duration of that TI response, it's 132 weeks, so we see really prolonged, durable responses over 2 years with these patients. In fact, we had a patient who was just dosed recently yesterday who had a 4-year period of transfusion independence.

DR. CHOUEIRI: Okay. That's important to

highlight. I skimmed over this quickly, but that's an important point. Thank you.

DR. FELLER: Thank you for the question.

DR. NORSWORTHY: This is Kelly Norsworthy with FDA. We'd like to just respond to the applicant's assertion that FDA's endpoints are atypical. I'll ask Dr. Nina Kim to comment. Thank you.

DR. KIM: Hi. So I specifically wanted to respond to Dr. Komrokji's statement that the duration of response is only clinically relevant in responders. So it is true that duration of response is usually calculated looking only at responders when the endpoint is a binary endpoint like CR, where you either achieved a CR or didn't. However, an RBC-TI response is different from a traditional CR response in that it's more of a continuum, because none of the patients in the study received transfusions every single day for the entirety of their time on study. All subjects actually had some duration of RBC-TI recorded, whether it was just a few days or several weeks,

independent of study arm.

So the the summary of interest is the median duration of the longest RBC-TI interval, so all patients should be included in this analysis rather than just a subset. In other words, it's informative to look at the duration of RBC-TI for all patients without already selecting for those who had a longer duration of response. Thank you.

DR. FELLER: I'd like to respond on behalf of the applicant and ask Dr. Komrokji to respond as well.

DR. MADAN: Yes, if we can keep it brief because we do have several other questions, so keep it on point, and we can do that.

DR. FELLER: Sure. I wanted to note that duration of response per responder was the prespecified endpoint within our protocol, and I'll ask Dr. Komrokji to address the other.

DR. KOMROKJI: Thank you, Dr. Kim. I definitely acknowledge that it could be meaningful to look at those, but what I meant, basically, CR, as we all know, is not an endpoint in lower-risk

MDS unless patients have more than 5 percent myeloblasts, and then in tradition, in all the other manuscripts, lenalidomide in the New England to the commands in Lancet, and all the studies that were published, none of those studies that looked at any medication had looked at duration of response among responders and non-responders, and I don't think even in solid tumors that's usually reported in that fashion.

I didn't mean by any way to say that this is meaningless. I think it gives you a different perspective, but our answer was why wasn't it included in The Lancet journal, and that's the reasoning. Thank you.

DR. MADAN: Okay. Great.

Just to update, we do have additional questions coming here from -- let me just go through the list so people know where they are. Oh, I lost the list, but, Dr. Garcia, you're next, please. Just go ahead and ask your question, please.

DR. GARCIA: Yes. Thank you. Thank you for

the opportunity to be part of this panel to ask a question. This question's for the applicant. I can appreciate the cytopenias in this patient population, and the mean level shown over time on the FDA slides 25 to 26 that Dr. Kim presented show that although there's concern for persistence, I did not appreciate decline over time, which I thought was encouraging, and they don't appear to be grade 3 or grade 4, which is also encouraging because grade 1 or grade 2 levels are not really of clinical concern or would warrant action as a clinical provider.

So my question is about the severity of these cytopenias long term, as the non-COVID infection rate on slide 29 were actually quite reasonable in the study that enrolled during the height of the pandemic. Can you help me to understand? Looking at slide 27 where the FDA showed the duration of cytopenias, I would like some clarification. Were the number of events from the same patients? And I ask that because in lower-risk MDS patients, there can be some overlap

with patients with bone marrow failure, so they are prone to cytopenias with any type of therapies.

So each event, my understanding from this slide, was considered a separate occurrence, so this might give the appearance of a high number of events if they're really from the same group of patients. And secondly, can the applicant comment on whether or not -- as you had mentioned, most of these grade 3/4 cytopenias occurred early in the treatment history. I am wondering for patients that are on long-term therapy beyond week 24, is the depth and frequency of grade 4 neutropenia, for instance, less frequent, because maybe if they get past the induction period, long-term responders might not have severe complications or issues as demonstrated in the AE tables.

DR. FELLER: The persistence of cytopenias is a very important topic; thank you for raising it. When we look at our data -- I could bring it up right here -- the median number of events per patient for grade 3/4 neutropenia and thrombocytopenia is one with a range of

zero to mid-teens. The mean is a little bit higher, but this is consistent with what you see in that overall trend over time graph, in that most of the grade 3/4 cytopenias do occur early in treatment when we are closely monitoring patients for the first 8 weeks of treatment.

I will say that we acknowledge that the cytopenias can recur, and whether this is due to disease fluctuations or imetelstat treatment is hard to tease out. I can show you the rate of grade 3 for thrombocytopenia in later cycles; so they do recur but, again, these are more like infrequent dips, and the platelet levels stay stable over time.

DR. NORSWORTHY: This is Kelly Norsworthy, FDA. I'd like to ask Dr. Dianne Pulte to comment as well. Thanks.

DR. PULTE: Thank you. Could we bring up slide 62, please? While that's being brought up, I just wanted to reiterate that one of the inclusion criteria, one of the requirements was that the patients have normal, or near normal, platelets and

neutrophils at the beginning of treatment.

Could you go to slide 63? This is a slide showing the changes in neutrophil and platelet count by cycle, and as you can see, there certainly is a higher rate in the first 1 to 3 cycles, but there's a persistent rate of grade 3 to 4 cytopenias, which occur particularly for platelets throughout the treatment. So there's really not a time after which patients can be said to have no or low risk of cytopenias.

In addition, since the number of CBCs which were obtained decreases after the first few cycles, it's possible that we're just not catching some of the cytopenias in the later cycles. It's difficult to a hundred percent say that there are fewer. Thank you.

DR. FELLER: The applicant would like to respond with some clarifications.

DR. MADAN: Okay. Yes, briefly, but go ahead.

DR. FELLER: I'll be brief. The enrollment criteria for the protocol was not a threshold of

normal platelets, or ANC, but patients were allowed to have grade 1 or 2 thrombocytopenia and neutropenia in the study, and this was in order to ensure that there be room for an expected drop in platelet and neutrophil count. And I apologize, but I did not mean to imply that the cytopenias don't recur or that patients are out of the woods, but I think when we look over time, we acknowledge that the lines of grade 3 and grade 4 are arbitrary lines, and patients can hover around those and dip up and down intermittently.

DR. MADAN: Okay. Great.

DR. GARCIA: That satisfies my question. Thank you.

DR. MADAN: Thank you, Dr. Garcia.

Okay. Our next question will be from Dr. Frenkl, and Dr. Hunter, you'll be up after that. So, Dr. Frenkl, go ahead.

DR. FRENKL: Well, thank you. My questions were answered in the context of other people's, so I took my hand down. Thank you.

DR. MADAN: I'm sorry. I did not recognize

that.

DR. FRENKL: That's ok.

DR. MADAN: Thank you.

Dr. Hunter, it seems like you're up, and, Ms. Powell, you will be next.

DR. HUNTER: Alright. Thank you. I appreciate the opportunity to be here on the committee this morning. So two questions, and the first was sort of partly answered relating to dose reductions and dose response effect, and getting at the dose that patients were on at the time of response. But a follow-up to that is, do you see an effect on response duration, and in particular in patients who had dose reductions? So getting at patients who respond, can they preserve response if their dose reduced after response?

Then the second question was more to healthcare utilization and how these patients do afterwards. Do you have data on the number of patients in each group that went on to a subsequent MDS therapy after study?

DR. FELLER: I acknowledge the questions,

and we do have data that shows that responses are really maintained once patients dose reduce. You can see that here, that the median time from dose reduction to the end of the TI is 46 weeks, so reducing the dose enables the minimization of further neutropenia and thrombocytopenia and allows patients to stay on treatment maintaining their response.

For your second question, we do have data regarding the number of subsequent therapy. Let's see if I can bring it up quickly. I do believe most, or at least half of patients, received subsequent therapy, but we could get back to you after the break with that.

DR. HUNTER: Alright. Thank you.

DR. MADAN: Thank you.

Ms. Powell, you have the floor for a question.

MS. POWELL: Yes. Of course my computer doesn't want to act right. Let's see. My name is Joan Powell, and I'm an MDS patient, and I've been a patient since 2014, and I started out with

Epogen, Procrit. When would a patient begin this process of this new therapy? Most of us that start out as an MDS patient start out with Epogen or something like that, Procrit. Who would make that determination that we could switch over to this new therapy? Thank you.

DR. FELLER: To clarify, this is a question directed at the applicant, and, Ms. Powell, thank you for your participation today. I would like to ask Dr. Savona to come and speak to when a patient would be considered for imetelstat therapy.

DR. SAVONA: Thank you, Dr. Feller, and thank you, Ms. Powell, for being here and your question. I think it's just an important level set to remember this study is entirely in ESA refractory patients. I have patients, some probably like you, that respond to ESAs for several years, and that's a great thing. Responders tend to respond, and depending on where they fit on that pie -- remember that pie graph we showed -- if they had ring sideroblasts, they were high transfusion burden and so forth. Our next treatment would

vary. If they were a 5q minus patient, they might go on lenalidomide. If they were a low transfusion burden, a ring sideroblasts patient, they might go on luspatercept, and I can bring the slide up and show you. But imetelstat would be used in the other scenarios, which are kind of marked in pink here.

Does that satisfy your question?

MS. POWELL: Yes, it does. Thank you.

DR. MADAN: Thank you, Ms. Powell, and thanks for being on this panel and bringing your valuable perspective.

I think our next request for a question is from Dr. Kim of the FDA.

DR. NORSWORTHY: That no longer applies. Thank you.

DR. MADAN: Okay. Well, if that is the case, then I think we are done with our clarifying questions portion of the presentation, so we will now break for lunch. We will reconvene at 1:15 p.m. Eastern Time. Panel members, please remember there should be no chatting or discussion

of the meeting topics with other panel members during the lunch break. Additionally, you should try to reconvene around 1:05 p.m. Eastern Time to ensure you're reconnected by 1:15. Thank you.

(Whereupon, at 11:58 a.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Open Public Hearing

DR. MADAN: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. 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 each 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 applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or expenses in connection with the presentation at this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you

do have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can only help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today in this open public hearing is that it is conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank you in advance for your cooperation.

And with that, we will start with speaker number 1. Please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing, and you will have 5 minutes to speak.

Thank you.

DR. BUCKSTEIN:

Hi, everyone. I'm Rena Buckstein from Toronto, from the Sunnybrook Odette Cancer Centre. I have no financial relationships with the applicant, Geron, or imetelstat. I work as a clinical investigator/hematologist for the last 24 years, and my disease focus for the last 15 years has been myeloid cancers, specifically MDS, which is my research focus.

I run a national MDS registry, where we collect detailed disease characteristics, as well as patient-related factors and patient-related outcomes, and have learned over the years the importance of anemia and transfusion dependence and how they impact negatively on quality of life, as well as families because there's a huge burden to the families who have to bring their often elderly parents for a cross-match on a separate day and then a transfusion on another day; so it's very burdensome to the patient, as well as the family.

We have a limited repertoire of treatments

for low-risk MDS, particularly in Canada. We have ESAs, erythropoietic-stimulating agents, which don't work very well in transfusion-dependent MDS patients, and we know that up to 50 percent will become red blood cell transfusion-dependent. We have luspatercept approved in the relapse setting after failing in ESA, but only for patients with ring sideroblasts, which comprises the minority of the MDS patients that we treat.

I participated in the imetelstat RCT. I had 3 patients on the study, one of which two were unblinded and one was not unblinded, and I'm going to speak to my experience with the unblinded patient who I know was getting active drug. The other unblinded patient of mine was receiving placebo. So I'll just quickly describe her story, which is, I think, a very typical and emblematic patient who needs this treatment.

She was 81 at the time. She had been diagnosed with MDS with multilineage dysplasia without ring sideroblasts. Eighteen months before I saw her, she had been treated with ESA for her

red cell transfusion dependence and had remained transfusion independent for about 16 months, but when I saw her, she was starting to need transfusions more regularly than she had before and was receiving 2 units per month.

She participated in the study and was randomized. She started in October of 2021, and then within one month, she got 2 units of blood, and that was in November; and then after that, she remained red cell transfusion independent for 25 months on treatment. In fact, her hemoglobin rocketed up to 139 by the 7-month mark and she maintained amazing blood counts until we started seeing declines in September 2023, which was 23 months where her hemoglobin had dropped to 108; and, unfortunately, she began to require transfusions again in January of this year and was taken off study. Even though she has not progressed in her bone marrow, interestingly, she's now developed MDS with ring sideroblasts, and for the first time where we have the NGS back, at least done locally, we know that she has an SF3 beta 1

mutation.

So why do I think this is an incredible agent and something to be considered? One, we have, as I mentioned, very few drugs for this space, and transfusion dependence is a terrible way to live, and it's associated with iron overload and complications. Being transfusion-dependent correlates with inferior survival and certainly worst quality of life. In the experience of my 81-year-old patient who had comorbidities, it was very well tolerated, with the exception of having to come in once every 3 weeks. She was an outpatient and was functioning at a very high level in her home as the homemaker, with very good energy level and quality of life.

I like that the drug works in non-MDS-RS, which comprises the majority of our patients, and I like that it has a specific activity, excellent activity, in patients with high transfusion burden, which we see less activity with luspatercept. And I also like the fact that it has anti-clonal activity, as evidenced by a correlation between the

decline in the spliceosome mutations that were measured, as well as response, so its mechanism of action is exciting in that it may potentially even change the disease trajectory of low-risk disease. With the exception of lenalidomide, we have no other agents that do so or that we know that do so. So I was very impressed with the length of response my patient had, the very high hemoglobin she achieved, and its excellent tolerability.

DR. MADAN: Thank you very much for your comments.

Speaker 2, please turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have --

MS. IRARCA: Hi. Sorry.

DR. MADAN: Go ahead.

MS. IRARCA: Hi. I'm Tracey Irarca. I am the Executive Director of the MDS Foundation, and I'm here with my colleague, Ashley Moncrief, who will share my time with me. We do work with Geron. We partner on educational programs. That's what

you had asked us to disclose.

I just want to start by saying that this November will mark my 20th year at the MDS Foundation. I started working in patient correspondence, and it was out of convenience, not a career choice at first. The part-time hours were perfect, it was close to home, but the minute you speak with your first MDS patient, you're pretty hooked. You want to do everything that you can to help. They hear that their new found disease has no cure, and they rightfully panic. I recall spending time on a call with an angry patient just asking me to define the word "terminal." He had read that he was terminal, and he wanted me to say what that meant.

Eventually, I started traveling and meeting in person our patients, their families, and healthcare providers. As my interests and knowledge grew, I became board secretary of the foundation and listened to our board members, experts in the field, talk about the future science in MDS, and they for the first time were saying

that it was promising. We didn't have many options, so hearing that from those experts was something that we could then relay to our patients.

So eventually, working full time by now, I began working with our industry partners, where I witnessed firsthand the change from including patients as an afterthought, to putting patients and their families at the forefront of the research. We started bringing patients and their caregivers to pharma companies and having them share their MDS journey with the researchers who were working on their disease. We attended as well as advocates. We talked about why advocacy partners are so vital to ensuring that the research into MDS treatment includes what the patients actually need and want, and not just what we all think they want.

I watched that research grow into something that has the opportunity to give our patients choices and hope. This job never disappoints. There are ups and downs in the research, of course, but the excitement of a promising future always

wins out, and our goal remains to continue offering our patients choices and hope. During a recent low-risk MDS roundtable, we heard direct from patients how MDS has a significant progressive impact on the physical, psychological, and social aspects of their day-to-day life. Because of the chronic fatigue, they plan their lives around their MDS. They make big decisions like altering retirement plans or moving closer to treatment centers.

We hear that MDS takes over your life. They experience down days and depression. They incorporate naps into their day-to-day routine now. And people don't understand it because they don't look sick, but they can't keep up with people like they used to, their family and their friends, and because of this, sometimes they lose friends, which leads to feelings of loneliness and isolation.

Now though, patients are being empowered to have educated conversations with their healthcare teams about their choices. They're grateful to be part of shared decision making, but they need

options. As Rena mentioned, we don't have many options. Treatment options give patients greater flexibility to live happy lives rather than having to plan their lives around the blood counts and what it means to have a terminal illness. So thank you very much for allowing me this time to speak. Ashley will now talk more about the treatment burdens facing MDS patients.

MS. MONCRIEF: Hi. As Tracey said, my name is Ashley Moncrief. I'm the the Director of Patient Care for the MDS Foundation. I have been a nurse in malignant hematology for 11 years, and five of those years are dedicated to clinical research. My main take away, I want to start by saying that low risk does not equal low impact. High risk receives a lot of attention, as the life expectancy can be measured in months. The urgency is certainly appropriate, but it should not detract from the impact of the disease on lower-risk patients. The life expectancy for low-risk patients can be measured in years. The increase in time is so important, but it is our job as

healthcare professionals to ensure quality is equally as important. Why? Because it matters to patients.

In a survey conducted by the foundation, in partnership with Clinical Care Options, 56 percent of those surveyed listed maintaining quality of life as their most important treatment goal. It ranked higher than prolonging life and managing symptoms, so take a minute to consider the implications of transfusion dependency.

According to a recent study published in ASH, outpatient transfusions for myelodysplastic syndromes, up to 90 percent of patients with MDS will require transfusions at some point. Patients with MDS require lab work to monitor for anemia and determine that need. It can take anywhere from 1 to 24 hours to get these results, depending on the facility, and then a type and screen must be done, and then you have to calculate the time for the transfusion itself, which can take up to 4 hours per unit, depending on the patient's tolerability. It may even require an observational

admission if they can't give the blood in the outpatient clinic. You also have to consider the impact on caregivers and families, as some patients are not well enough to transport themselves. So caregivers pay the price of time away from their daily lives and patients pay the price of giving up their self-control.

So imagine having to do this multiple times per month, or even per week. Imagine having to do this while experiencing the manifestations of severe anemia, weakness, overwhelming fatigue, shortness of breath; it can be unbearable. As a nurse, I have seen patients leave without getting transfused when they're overwhelmed by the process. We didn't even have time to touch on the long-term consequences of transfusion dependency like iron overload, the multiple needle sticks, and the economic burden.

Imetelstat offers hope to patients who desperately need it. There are limited treatment options for MDS patients -- six to be exact -- and then for patients who qualify for imetelstat, the

options are even fewer, as growth factors have been exhausted. There are no words to express the impact of decreasing the transfusion burden for MDS patients. Time not spent in an infusion chair is time spent living, really living. Patients may have MDS, but MDS does not have to have them. Thank you.

DR. MADAN: Thank you both for your comments and staying on time. It's very helpful and informative. Thank you.

Speaker number 3, please unmute and turn on your webcam.

(No response.)

DR. MADAN: Speaker number 3, please unmute and turn on your webcam.

(No response.)

DR. MADAN: Okay. Perhaps we have technical issues and we can come back to speaker number 3 later.

MS. LUNSFORD: No, I'm here.

DR. MADAN: Oh, you're here. Great. I'm very happy that it's --

MS. LUNSFORD: Yes. It's called two thumbs on two buttons at the same time.

DR. MADAN: Oh, no need to worry about it. You're on now. That's all that matters.

MS. LUNSFORD: Okay.

DR. MADAN: Please introduce yourself and go ahead and get started. You'll have 5 minutes. Thank you.

MS. LUNSFORD: Thank you.

Good afternoon. My name is Cynthia Lunsford. I'm 72 years old and I live with my husband in Trophy Club, Texas. I receive a stipend from Geron for fuel and lunches during my treatments. My husband Kenny [ph] and I are both retired, he from over-the-road trucking business, and myself from GE Healthcare medical software implementation. We have a beautiful blended family of 4 children, 13 grandchildren, and one great-grandson. Kenny is battling CKD and lost one of his kidneys three years ago. He's thankfully holding at stage 3 with an 8-pound tumor hanging on for a free ride right now. I am his primary

caregiver.

The diagnosis of MDS was delivered to me on December 20, 2021, and I'll never forget that day. I was told, just matter of factly, that I had 5 to 7 years and be prepared for multiple blood transfusions, and there are some other things that could be tried, but 5 to 7 years would be it. Until I started feeling the effects of myelodysplastic syndrome, I was very active in AKC dog agility competition with my furry best friend, and we were working hard to secure a position in the national competition. I was also active in my church, until I simply didn't have the strength to even get out of bed to attend Sunday services.

Aranesp was received for 5 months that proved to be completely ineffective for me. I was then given luspatercept from August of '22 to February, that returned less than really acceptable results. It helped some I think. As a layperson, I can't get into other areas. Blood transfusions did increase in frequency, roughly biweekly, which made it challenging to get my husband to his

multiple doctor appointments and infusion sessions, as well as my own.

I moved to UT Southwestern Medical Center under Dr. Yazan Madanat's care in November of '22. When presented with the opportunity to participate in a clinical trial for lessening the need for so many blood transfusions, I didn't have to ponder very long before applying for the trial and make the hour-plus drive each way for treatments and weekly labs. I began the trial April 5th of last year, unknowingly placed in the placebo group; wouldn't you know it? By the end of May, after a dramatic weight loss of more than 60 pounds, frequent blood transfusions, extreme weakness and fatigue, I truly believed the Lord was calling me home, and I was completely at peace and ready to go. This was not a life I wanted to live. The trial records were then unblinded, and I immediately began receiving the drug imetelstat on June 5th. Within 6 weeks, my life completely turned around. My hemoglobin and other blood values started returning to normal levels, and it's

now been over 8 months since my last blood transfusion.

Today, thanks to God, my family, the MDS Foundation, Dr. Madanat and his staff, and the Geron Corporation, of course, I feel vibrant and so very much alive. I am fully able to support my husband and the rest of my family. My church activity is back, and I started training with a young sheltie for agility work just recently. I'm also thrilled and honored to be here today to share my back-to-life story with you. I would appreciate you take from my story, as you consider your decision, the number of other MDS patients a chance like mine to extend their time with fulfilling quality of life, and I thank you for your time.

DR. MADAN: Thank you very much for sharing that with us.

Speaker number 4, please unmute your computer and turn on your webcam.

DR. ROBOZ: I have done both. Am I here?

DR. MADAN: You are.

DR. ROBOZ: Okay.

DR. MADAN: Thank you, speaker number 4. Please introduce yourself, and you may begin. Please also state any organization you're representing for the record. You will have 5 minutes. Thank you.

DR. ROBOZ: Will do. Thank you very much for the opportunity to present a few thoughts and comments today. My name is Dr. Gail Roboz. I'm a professor of medicine and director of the Clinical and Translational Leukemia Program at Weill Cornell Medicine and the New York Presbyterian Hospital in New York City. I have not been compensated in any way for my participation in this hearing, but I have served as a consultant in the past for Geron. I've spent my career actually focused on the development of novel therapies for patients with MDS and acute leukemia, and I've been treating MDS patients in my clinic for the last 25 years, and my presentation follows a very wonderful presentation that you just heard from a patient.

As you've heard, patients with MDS are generally divided into lower and higher risk

groups. Patients with high-risk MDS are at imminent risk of dying of their disease, either with or without transformation to acute leukemia. Benchmarks for therapeutic success in these patients are remission and improved overall survival. Patients with low- and intermediate-1 risk disease aren't at immediate risk of dying or leukemia transformation, but they are still in trouble. Their biggest clinical problem is generally progressive bone marrow failure and transfusion dependence, and if you talk to MDS patients, and as you've just heard, they know to dread this complication. Even at the time of their first red blood cell transfusion, many of my patients have asked, sadly and fearfully, "Is this the beginning of the end? Am I going to have to spend the rest of my life sitting here and getting transfusions?"

Simply put, what patients with lower-risk MDS generally need is treatment that improves erythropoiesis. That treatment needs to result in higher levels of hemoglobin and fewer transfusions,

and while we do have approved treatments for transfusion-dependent MDS patients, the difficult reality is that most of these patients cycle through most or all of our options, and either don't respond at all or lose their response after just weeks to months on treatment, and come back asking for something else.

So with this background, it's no surprise that I, along with doctors and patients in the MDS community, am enthusiastic about the prospect of having imetelstat as a treatment option. As a clinical trialist in the myeloid malignancies field, I have followed the development specifically of this agent for many years and have thoroughly reviewed the data, both from the pivotal trial and from earlier studies.

As you saw in the data presentation, imetelstat doesn't work for everyone -- nothing that we have in MDS does -- but the many responding patients enjoy a prolonged period of transfusion independence. Furthermore, these patients didn't just squeak by a clinical trial threshold to avoid

needing a transfusion; they had improvements measured in grams of additional hemoglobin. If a patient comes into a clinic with a hemoglobin of 7.9, he may get sent home without a transfusion but he's going to feel a lot better if his hemoglobin is 10. And I realize in prior presentations, the scale of the measurements may be different in different areas, but the magnitude of these differences, again, are measured in grams.

Even heavily transfusion-dependent patients were able to achieve significant responses to imetelstat, and usually it's these patients who are the most in need that are the least likely to benefit from the other choices we have available, for example, the ESAs. We all know there's no free lunch in medicine, and so it is the case here, too. The excellent responses with imetelstat come with a price, and that price is myelosuppression in some patients.

Doctors who treat MDS and acute leukemia are used to it; that most of our effective new therapies for these diseases typically cause

cytopenias. Actually, to be honest, when we're evaluating new therapies for MDS and leukemia, we're skeptical about ones without myelosuppression will actually work. We're used to talking to patients about neutropenic and thrombocytopenic precautions, and we're used to it that our therapy might need schedule delays or dose reductions.

Patients treated with imetelstat only rarely had significant complications from neutropenia or thrombocytopenia, and these issues were typically seen early in the treatment course, and they were addressed with changes in dose and schedule. And the fact that so many patients were able to continue treatment for multiple ongoing cycles confirms that the cytopenias were actually a manageable problem.

Imetelstat also had a favorable extramedullary toxicity profile as evidenced by the patient-reported outcomes, data suggesting that the ongoing treatment was tolerable and did not have a negative impact of quality of life that made them stop taking it. Furthermore, as expected, if you

look at the responding patients, those patients had improvements in fatigue and other measures of quality of life, as we would expect and as you have heard from a patient.

MDS is complicated, and it's challenging, and somehow even our most sophisticated instruments don't capture the spectrum of benefits that individual patients will experience during their period of transfusion independence. That said, the data presented for imetelstat are concordant with my clinical experience. Most of my transfusion-dependent MDS patients can tell you their hemoglobin without even getting labs checked; they feel it.

Responding patients like the ones you saw on the swimmer's plot and in the open hearing, they look better, they feel better, they function better, and they're generally thrilled not to need transfusions. Of course, what all of these patients really want is for us to hurry up and cure MDS and get rid of their transfusions forever, but until that time, I hope they will have access to

imetelstat. Thank you for the opportunity to participate in this meeting.

DR. MADAN: Thank you for sharing your expertise.

Speaker number 5, please unmute and turn on your webcam.

MS. SANTINI: Hello. Good afternoon, and thanks for --

DR. MADAN: Please go ahead and introduce yourself, and please state your name and any organization you're representing for the record.

MS. SANTINI: Yes, of course.

DR. MADAN: Thank you. You will have 5 minutes. Thank you.

DR. SANTINI: I was just thanking for this opportunity. My name is Valeria Santini. I'm a hematologist working at the University of Florence in Italy, and I've been working in this hospital for 30 years. My present role is coordinating clinical research studies in MDS and elderly AML, and I'm also the chair of the Scientific Committee of the Italian foundation for the study of MDS,

FISiM, and the Italian registry. I do not have to disclose any economical relationship for this open public hearing, and I have been, in the past, part of the advisory board for Geron.

My clinic is a center of excellence for treatment of MDS in Italy, and I receive referrals from the entire country. I have been PI of more than 50 phase 2 and phase 3 international clinical trials, and I'm focused on MDS and elderly AML, as I mentioned. The majority of patients with MDS we follow are patients, as you just heard, who belong to the lower-risk prognosis, but they have, in more than 50 percent of the cases, anemia, symptomatic anemia, that may require, from diagnosis or later on, transfusion. And some of these patients have a burden of transfusion that is 1-2 red blood cell transfusions per week or more, and of course with the decrease in their quality of life.

Because these low-risk patients have real long overall survival, they're having prospective years of transfusion with dependence from caregivers and from hospitals and very limited

freedom of moving and traveling, all situations that affect their daily life. These patients are frequently demanding to be enrolled in experimental studies, being exhausted by the transfusion routine and the oscillation in hemoglobin levels that indeed provokes symptoms.

My role in the imetelstat trial was the PI of my center. We enrolled the first patients during the pandemic in 2020; I must confess, in a particular difficult condition. At that time, patients were very eager to participate in the study, especially because of the restriction and obstacle to perform transfusions. The patients tolerated very well the infusion of the drug. We did not experience a non-hematological adverse event related to the drug, and regarding myelosuppression, we observed few and transient events of thrombocytopenia and neutropenia.

Among our patients, one is still now in response. He is the oldest one. He is now 82. He has transfusion independence, and he has had it for more than 3 years, approaching 4 years of treatment

now. This particular patient was re-challenged after an interruption of treatment for a short period because of a femur fracture and immobilization, and he responded well. All the patients that we treated with imetelstat had an age above 70, but one. Transfusion independence was an important achievement, rendering them again free and independent from caregivers, so that especially the one who maintained transfusion independence, he has now 12.6 gram hemoglobin and is living at present a complete, normal life.

For those who had a shorter period of transfusion independence, of course the advantage was less pronounced, but it was meaningful, also because to them it was the signal that we may somehow alleviate their chronic condition because they suffer not only of fatigue and malaise, but also the chronic need to ask for help from someone else, and the number of low-risk MDS patients with such problems is quite relevant. Overall, my experience in treating elderly patients with imetelstat was positive. Treatment was manageable

and very well tolerated.

Coming back to the myelosuppression, I observed that it was transient and it was grade 3/4 for neutrophils and platelets, especially in the patients who responded for more than 3 years, but it was resolved within the 4 weeks of the cycle, usually. We did not observe infection or admission to hospital for sepsis, nor severe bleeding. Thus, the myelosuppressive effect has to be considered when choosing to treat with this agent, but it's clearly overweighting the disadvantages.

The effectiveness in the long term of imetelstat is really impressive, and the possibility to have also a disease-modifying effect is also quite important and intriguing. The availability of this drug is, in my opinion, of great importance for the future of our low-risk MDS patients, especially the ones with high transfusion burden who do not have options for achieving transfusion independence. Thank you.

DR. MADAN: Thank you for sharing your experience.

So we'll move on to speaker number 6. Please go ahead and unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing, and you will have 5 minutes.

DR. SILVERMAN: Okay. Sure. Thank you very much, and thanks for the opportunity to to speak today. I'm Lou Silverman. I'm the Director of the Translational Research Center for the Myelodysplastic Syndrome here at the Icahn School of Medicine at Mount Sinai in New York. I have been conducting clinical trials in MDS for about the last 30 years and led the trials that brought azacitidine to FDA approval for patients with myelodysplastic syndromes. I have no financial relationships with Geron to disclose, particularly as it relates to this meeting.

The data for imetelstat, that demonstrates a significantly higher rate of durable transfusion independence compared to placebo, represents sufficient clinical benefit, in my view, to grant FDA approval. The cytopenias, though significant,

are similar to the AE profiles of other agents used in both low-risk and high-risk MDS, and when monitored appropriately are manageable to successfully mitigate any safety issues. Red cell transfusion requirements are common in patients with lower-risk MDS and negatively impact outcome. Reduction in transfusion requirement is an important objective in treating these patients. Increasing red cell transfusions are associated with worsening overall survival and increased risk of transformation to acute leukemia. This is independent of the iron overload that develops, need for chelation, impaired quality of life, and reduction of physical functioning.

Imetelstat is associated with significant transfusion independence, particularly at week 16 and 24, compared to placebo, with a median duration of response at 51 weeks. Patients with high transfusion burden, and thus at greater risk for compromised survival, are more likely to benefit from imetelstat. Currently, as you've heard, treatment options remain limited for lower-risk

patients with MDS and include lenalidomide, luspatercept, ESAs, as well as the hypomethylating agents, both azacitidine and decitabine, are both approved for lower-risk and higher-risk disease.

All of these agents can produce transfusion independence in a proportion of their target populations and are associated with an improvement of quality of life and reduction in symptoms, but none of these drugs that are approved by the agency improve overall survival in low-risk disease. Clinical benefit in lower-risk disease in particular has been controversial to define, with shifting response criteria and opinions over the last several years.

Transfusion independence is agreed upon as an objective endpoint and affords clinical benefit to patients, as you've heard described. The clinical benefit results from severing the umbilical to their transfusion center, improved physical functioning, increases in daily activities, resumption of normal work and family life, and reduced need for chelation therapy.

Transfusion independence is often associated with improvements in quality of life, as reflected in the imetelstat studies, and in some of our prior studies, quality of life actually improved prior to improvements in blood counts in patients receiving benefit from respective therapies for their MDS.

Cytopenias are associated with some of the approved MDS therapies. The HMAs are associated with significant cytopenias in up to 50 percent of patients, including patients with low-risk disease, and lenalidomide is often associated with neutropenia.

In randomized trials with azacitidine, an increased risk of infection and bleeding was seen in the control group compared to the azacitidine-treated group, despite the treatment-related cytopenias that were associated with the treatment, signaling that the risks may often be related to the cytopenias derived from the MDS and bone marrow failure rather than treatment when monitored appropriately. Treatment-related cytopenias in patients are common and can be

effectively managed, and even treatment-related cytopenias are manageable when appropriately monitored and can improve safety profiles of drugs.

As a brief vignette, a patient of mine recently presented with extreme fatigue, limited performance status and quality of life. An evaluation revealed the diagnosis of low-risk MDS with a hemoglobin ranging in the 6 and a half to 7 and a half range. Symptoms led to inability to work at a desk job, and the patient became disabled. ESAs and lenalidomide were not indicated or appropriate, and luspatercept was started.

The patient became transfusion independent with a modest increase in hemoglobin to 9, with improvement in quality of life, performance status, and the patient was able to return to a normal lifestyle and to work. The transfusion independence persisted for 16 months, after which symptoms and the red cell transfusion requirement resumed. Therapeutic options at that point were HMAs or investigational agents.

Imetelstat, if approved, would represent an

additional important therapeutic option with potential benefit for such patients. Imetelstat provides a credible clinical benefit of durable transfusion independence with a median duration of almost a year and a manageable safety profile. It offers additional therapeutic options for patients with poor prognosis, transfusion-dependent, lower-risk MDS with limited treatment options, and addresses a critical unmet need for this patient population.

DR. MADAN: Great. Thank you very much for your insights.

DR. SILVERMAN: Thank you.

DR. MADAN: Thank you.

We'll now hear from speaker number 7. Please unmute and turn on your webcam.

MS. SEKONI: Hello.

DR. MADAN: Hello.

MS. SEKONI: Hi. How are you?

DR. MADAN: Fine, thanks. How are you doing today?

MS. SEKONI: I'm well, thank you.

Good afternoon. My name is Daneen Sekoni.

DR. MADAN: Just real quick, please go ahead and introduce yourself and make sure to state any name or any organization you are representing, and you will have 5 minutes. Please go ahead.

MS. SEKONI: Thank you. Yes, thank you.

My name is Daneen Sekoni. I'm Vice President of Policy and Advocacy at the Cancer Support Community, an international nonprofit organization that provides support, education, and hope to those affected by cancer. Thank you for the opportunity to be here today to provide comments regarding approval of the new drug application for imetelstat for treatment of anemia and transfusion-dependent MDS patients. My comments today reflect our mission to uplift and strengthen people impacted by cancer by providing support, fostering compassionate communities, and breaking down barriers to care.

As the largest provider of social and emotional support services for people impacted by cancer, we have a unique understanding of the

cancer patient experience and have learned a great deal from those we support. As our oncology psychosocial researchers and others have shown, enhancing cancer patients' sense of control can positively impact their psychological well-being. When people living with cancer have more control over the best treatment options for them, they feel stronger and more hopeful. Access to a full portfolio of treatment options, as well as supportive care solutions, helps arm them to make the best decisions for their personal situation.

Cancer Support Community provides services to all people with types of cancer, including those with rare blood cancer disorders such as MDS. MDS greatly impacts patients' and caregivers' daily lives, as treatment often involves many blood tests and transfusions. Having an additional treatment available that could potentially reduce transfusion dependence for a subset of MDS patients could mean significant gains in quality of life for patients.

While Cancer Support Community does not endorse any specific product, we do encourage, when

appropriate, the development and approval of effective treatments that give more options to patients, especially those that specifically improve physical and psychological aspects of their lives. The Cancer Support Community asked that the FDA include quality-of-life challenges faced by patients as clinically meaningful and relevant to your approval process.

According to Cancer Support Community's Cancer Experience Registry, an online, survey-based research study that incorporates the PROMIS, which stands for Patient-Reported Outcomes Information Measurement System and contains a national sample of 150 MDS patients, blood transfusion was the most common treatment reported. These respondents reported elevated symptoms of fatigue, anxiety, and pain, as well as deficits in physical and social functioning, and worst quality of life across multiple domains compared to the general population, and even in some domains compared to cancer patients with other types of hematologic and solid tumor cancers.

Having treatment options that could allow patients to become transfusion independent, while preserving adequate quality of life, would be life-changing for many MDS patients. Some MDS patients need transfusions as often as every week or 2 weeks, and these can take several hours to administer. The time-consuming nature, symptom burden, and side effects of MDS treatment make caregivers a necessity, as even low-risk MDS patients with mild anemia report fatigue and decreased physical functioning.

We know that the patient experience is much broader than survivability and provider assessments of disease symptoms, treatment side effects, and physical functioning. Patient experience also includes the psychosocial impacts of a condition, therapy, and patient-reported outcomes. The Cancer Support Community encourages all sponsors to heighten the importance of collecting patient experience data throughout the approval process by consistently identifying, collecting, measuring, and considering the full breadth of patient

experience data to better understand what is actually meaningful to patients, as well as caregivers.

Today, we ask that you carefully consider the quality-of-life challenges of MDS patients, particularly those transfusion dependent and the need for a wider array of treatment options.

DR. MADAN: Thank you. If we could start to conclude, we're over the 5 minutes, please.

MS. SEKONI: Yes.

We urge you to support improving access to a broad range of treatment options that will encourage patients to be informed, empowered, and optimistic about their treatment. Thank you.

DR. MADAN: Thank you very much.

Okay. Speaker number 8, please unmute and turn on your webcam.

MR. URKEN: I apologize. My webcam's not working.

DR. MADAN: Okay. That's ok, sir. Do not worry about it. We'll still be able to hear you very clearly, but please -- I'm sorry. It looks

like -- oh, speaker 8.

FEMALE VOICE: That's speaker 8, I believe.

DR. MADAN: Okay. I think we switched speaker order, so speaker 9, we'll hear from you at the end.

MR. URKEN: Okay.

Speaker 8, if you could go ahead and introduce yourself --

MS. WHITE: Sure.

DR. MADAN: -- and state your name or any organization you represent, and you'll have 5 minutes. Thank you.

MS. WHITE: Alright. Great. My name is Kenan White. I am a 66-year-old female. I was diagnosed in 2018. I am simply a patient. I'm not representing any organization. So I am here basically to give you sort of a day in the life. I am currently on a third drug, and I would say that transfusions have become a part of my life.

I think the word "option" has been used a lot, and I think that's really what I wanted to start out with. I am extremely grateful for the

good care and the resources that I have been using, but it's not enough. I think what is important to understand is that this disease is incurable, and when I'm in an infusion room and I'm looking at people getting treatment, I realize that, God willing, they're going to be cured. What I [indiscernible - 5:03:04] unless I use the nuclear option, which I would consider stem cell.

So my life is spent dealing with this, and I think the women from the MDS society gave you a really good picture of what that's like, and I've heard quality of life over the past six years, and I'm really beginning to understand what that means. To live with an incurable disease with very few options -- and one of those is being transfusion dependent -- has, quite frankly, become a burden.

In my case, my veins are no longer adequate for a good draw. I've developed antibodies, which make securing my blood very difficult. I don't live in an area where I have a teaching hospital, and what that means for me is every 3 weeks go in for a draw, wait an hour, wait for the results, and

maybe I'm lucky, maybe I'm not. In some cases, the machine that actually determines the draw breaks because I'm in a small community, and the last time I was there, I was there for 6 hours because they had to drive the blood to an affiliate. In that case, I required a transfusion. The system that I found myself falling into means that could take a day; in some cases that can take 4 days because the infusion center closes [indiscernible - 5:04:52].

It's no way to live, quite frankly, and I fear that if I want to live the life that I want, and I have definitely made lots and lots of changes in order to accommodate this disease -- transfusion dependency is a nightmare for me, and right now it's getting more and more frequent, and I'm afraid I may end up being that person that's every 2 weeks. And if you think about the story I've told, having to wait at times for 4 days, that's a lot of loss of life in terms of experience. I'm alive, but it certainly isn't the life I was planning on leading, and I'm only 66.

So that's my plea, is to please listen. I

noticed that there weren't any other patients yet; I hope there will be more. But my story is not unique, and it's not an exaggeration. It is what life has become for me and many others, and I speak for them as well, so thank you very much.

DR. MADAN: Thank you for sharing that very personal perspective.

Now we have our last speaker. Speaker number 9, if you'll just unmute. I think you're having some issues with video, but we will still be able to hear what you're saying --

MR. URKEN: Great.

DR. MADAN: -- and that will be great. So just please state your name and any organization that you're representing, and you'll have 5 minutes. Go ahead.

MR. URKEN: Great. My name is Paul Urken. I'm not affiliated with anyone, except myself. I'm a Vietnam veteran living in St. Petersburg, Florida. I'm 75, married with four adult children and four grandkids. I'm retired from the dry cleaning industry. I was diagnosed in March of

2019 at the Bay Pines VA Hospital in St. Petersburg with myelodysplastic syndrome. Although the reality of this was quite a shock, it didn't come as a total surprise. The oncology department at the VA had been monitoring the decrease in my hemoglobin number for several years.

I first went to Moffitt Cancer Center in Tampa in December of 2019. The numbers were monitored and in conjunction with the VA started weekly Procrit shots in November of 2021. When they were no longer effective, we started luspatercept injections in June of 2022. I had 13 blood transfusions between April 2023, and the last one being September 7th of 2023. The travel time for each transfusion was 2 hours with transfusions taking about an hour and a half.

During this time, my stamina and energy were very low. Breathing and walking short distances was very difficult. I would get dizzy when standing up. Playing golf was out of the question. Biking activities with my wife were no longer possible. A trip to some national parks in 2022, I

was reduced to sitting in a car with scenic overlooks or short walks on trails before having to stop and rest. Trips to Denver to see my family and friends have been postponed.

The team at Moffitt started testing me in May of 2023 to qualify for the imetelstat trial. June 13, 2023 was day 1. After receiving 2 rounds of placebos, my first infusion of imetelstat was August 7, 2023. I can tell you honestly from my own experience that imetelstat has been a game changer in my life. At the beginning of September of 2023, my hemoglobin had dropped to a low of 6.6. By the end of December 2023, my hemoglobin number had jumped to 13.1, close to a normal range. This translates to more stamina and lots of energy. Recently, I was in Texas visiting my daughter and grandkids. I was able to attend many of their activities.

In the future, I look forward to playing some golf, if I can get my clubs to work, and I'm now doing 2-mile walks. That may not seem like much, but for me it's life changing because,

mentally, there's now hope. It's very uplifting. As you consider your decision today, I would ask that you remember my story and think of the other patients out there with MDS who desperately need an option like this. They need your help. Thank you.

Clarifying Questions to Presenters (continued)

DR. MADAN: Thank you, sir.

So with that, that will conclude the open public hearing portion of our meeting. We will now move to complete the clarifying question portion. Now, as I recall, no one from the panel had any questions, so unless that's changed -- I think we have one from Mr. Mitchell, but we also have a request from the sponsor to basically follow up with some data that they had told us they would present.

I think maybe we'll just have Mr. Mitchell ask his question, and then we can conclude the questions, and you can do your follow-up then.

Would that be ok with the sponsor?

(No audible response.)

DR. MADAN: Okay. Thank you.

Mr. Mitchell, this will probably be our last clarifying questions. I'll double check and make sure there are no other hands raised. Go ahead.

MR. MITCHELL: This is a clarifying question for both the FDA and for the sponsor, and I want to go to FDA's slide 12. As a layman, I need a little help here in evaluating how important slide 12 of the FDA's presentation is, especially in light of the fact that the FDA is pointing out that there were a lot of adverse events and serious adverse events -- oops. This is not the slide I'm after. Hang on a minute. I thought I was on slide 12. Hang on. It's the slide that shows the difference between the duration of response for the total population in the study versus those who had a response at 8 weeks.

Can the FDA help me find that slide?

DR. MADAN: Yes. I think that was slide 12 with the first presentation.

MR. MITCHELL: That's what I'm looking for.

DR. MADAN: Yes. I think that was the first presentation. I think it was shown towards the end

of the second presentation.

DR. NORSWORTHY: This is Kelly Norsworthy, FDA. It's slide 10, please.

MR. MITCHELL: So this slide is especially concerning given the FDA's presentation indicating there were a lot of AEs, and fairly serious AEs, among non-responders. When I put that together with this slide, it gives a whole different interpretation of the effectiveness of the drug we're looking at. So I would like both the FDA to talk about this slide, and the sponsor, because on one hand, I'm looking at quite a difference between 51 percent and 13 percent and what's happening with all the subjects in the study.

So can can both the FDA and the sponsor respond to how we should be looking at this slide, especially in relationship to the adverse events that are experienced by non-responders?

DR. NORSWORTHY: Thank you. This is Kelly Norsworthy for the FDA. I'd like to let the sponsor go first, and then we'll provide a response. Thank you.

DR. FELLER: Okay. Sure. You raise an important point; and just a note of thanks to all the presenters at the OPH, thank you for your time and your efforts.

So this slide presents not a percentage necessarily, but the duration of transfusion independence. The first row speaks to transfusion independence for all treated patients and shows imetelstat, 118 patients 5 weeks, and placebo 60 patients, almost 4 weeks with a difference of about a week. Of note, this is statistically significant when we apply statistical testing procedures to it.

The way the analysis was performed on our behalf was looking at the duration of transfusion independence of the patients who responded, and this was prespecified in our protocol to look at those patients who hit that 8 weeks without transfusions and how long did they stay without transfusions. And what we see in our data is 52 weeks, if they had hit the 8-week mark of being transfusion independent, that transfusion

independence persisted for a median of 52 weeks or about a year, compared with placebo, that was about 13 weeks.

I think another way to look at this data -- if we can pass the screen over to the sponsor -- is to see our swimmer's plot.

MR. MITCHELL: Right. I looked at it.

DR. FELLER: Okay. Great. I'm also going to ask Dr. Savona to speak to the clinical significance of assessing TI in responders versus all population.

DR. SAVONA: Right. Thank you, Mr. Mitchell, for the question, and thank you, Dr. Feller, for the opportunity to talk about this a little bit more. I think that anyone can look at this swimmer's plot and see these longer blue bars on the top of the patients who were treated, and 2 out of 5 patients who received imetelstat are responding.

Any of the drugs we have for patients with MDS, there are going to be patients who don't respond to the drug, and one of the things that's

different about a randomized-controlled trial than real practice is when it's double-blinded and randomized and controlled, you don't really know which drug you're getting, so you hang in there a lot longer, and if you're not responding, unfortunately, you're accumulating events, AEs and whatnot. But I think in real practice, these patients will get -- where you see these blue lines on the graph -- somewhere between 4 and 6 months just like with HMAs. We give 4-6 months, and if patients don't respond at that point, they're probably not going to respond, and we get rid of the drug.

So we get rid of the drug and patients who are not going to benefit, and therefore we get rid of the associated toxicities that come with that. The patients who do respond or are not having any toxicity will hang in there a little longer, more towards the 6-week end, to see if we can get a response out of them. And I think in practice, you're going to see more stories like the ones you heard from the patient from Florida who's able to

hopefully go golfing again soon.

DR. MADAN: Thank you.

I think we'll hear from the FDA.

DR. NORSWORTHY: Thank you. I'd like to call Dr. Nina Kim, clinical. Thanks.

DR. KIM: Hi. So I think we spoke earlier about the merit of looking at the duration of RBC-TI, looking at all patients and not just responders. Again, just to reiterate, even though we normally do think of duration of response looking at only responders, this is when we're looking at a binary endpoint like CR, where you either achieved a CR or didn't, and this RBC-TI response is different from that CR response in that it's more of a continuum.

So that being said, also I wanted to point out that we as doctors treat all patients and not just responders because we don't necessarily know who those responders will be, so we do think that there is merit in looking at the duration of response for all patients.

DR. MADAN: Thank you very much.

DR. FELLER: Can the applicant respond to the --

DR. MADAN: Yes, very briefly, because we are beyond the clarifying questions, and I know that you guys want to share some other data.

DR. FELLER: No. I just wanted to make a quick comment that this is somewhat of a binary endpoint because once patients achieve that 8-week TI, it's a yes or no whether they achieve the 8-week TI, just like achieving CR would be a yes or no. What we're reporting is another endpoint showing the duration of the response within those responders who check yes; just a clarification.

DR. MADAN: Thank you.

MR. MITCHELL: Thank you. That answers my question. Thank you.

DR. MADAN: Thanks Mr. Mitchell.

So the applicant would like to, I think, briefly address some things that came up earlier this morning in the clarifying questions. So again, since we are over time, if we could keep it to the point, that would be ideal.

DR. FELLER: Thank you for the opportunity. I will be very quick. There was a question about subsequent therapy. Thirty-three percent of imetelstat-treated patients received subsequent therapy; 42 percent of placebo-treated patients received subsequent therapy after discontinuing treatment on study.

There was another question regarding the duration of concurrent platelet and red blood cell transfusion independence. When we account for platelet transfusion independence, we lose one imetelstat responder, and the duration of response is 47.3 weeks or approaching a year, and placebo remains at 13.3 weeks. Again, this is within the responders. Thank you for the opportunity.

Questions to the Committee and Discussion

DR. MADAN: No, that was very informative and brief, but good. Thank you very much.

Okay. Great. So now I think we will move to the discussion portion of our presentation, and that's actually in some ways one of the more important aspects of this, of what we're doing

here. I think we will see the question for the committee on the screen.

So this will be the point of discussion for the committee now to consider. There's been a lot of discussion about approving this and everything, but we should remember here that the committee's focused on this discussion point and the voting question, and we'll take some good time here to do this as a group, and we'll do this in an orderly way. I'll try to lead an organized discussion here.

The question that the FDA would like the panel to review is to discuss the efficacy of imetelstat for patients with lower-risk myelodysplastic syndromes based on the result of the MDS3001 trial considering the safety profile.

We also have the fortune of having two experts in MDS, which I am not, Dr. Garcia and Dr. Hunter with us, so we'll probably lean into your expertise during this conversation. We also have Ms. Powell, who's a patient. But I think Mr. Mitchell, actually, allows us to really kick

off this discussion with the efficacy question, and I think that was something that I think the panel probably should discuss as well. And again, we'll rely on the expertise of the MDS experts on the panel.

But it is interesting that when you take a patient, you don't know if they're going to respond or not, and when you look at the median benefit in solids tumors, for example, we don't often just pick the responders and characterize the benefit in that population, although of course we're very happy when we do see responses.

So I think it would be worth hearing from the experts on the panel, the MDS experts on the panel -- again Dr. Hunter and Dr. Garcia -- your thoughts on this kind of median 1-week benefit in the context of the toxicity, and the context that essentially 60 percent of the patients treated with an agent that had twice as many AEs -- or SAEs I should say -- had a benefit that was measured in 1 week; and again, that was 60 percent of the patients not responding.

So let's start our discussion of the efficacy based on that, so thoughts from the panel, specifically our MDS experts maybe first.

DR. GARCIA: Do you want us to raise our hand? I'm sorry. I wasn't sure of the format.

DR. MADAN: Yes, you can go ahead.

DR. GARCIA: Okay. Jacqueline Garcia from Dana-Farber Cancer Institute. I'm an MDS and AML clinician. I would say I can definitely appreciate the cytopenias, but while they are numerically important, it was really gratifying to see that they did not result in complications. When you take a look at the infections that were reported, it looked like nearly the majority were viral infections, and as I had mentioned in my statement earlier, it has been really hard for any of us to conduct and help our patients during the pandemic, and for a lower-risk MDS where they're coming in frequently for transfusions, it was a laudable effort.

So I would say the long-term consequences of blood transfusions cannot be understated, and

seeing the 25 percent of patients that could have potential long-term benefits beyond the 24 weeks, and even up to a year, is really impressive. So I would say that I can appreciate the cytopenias. Many of the grade 3 or grade 4 events are transient, and I was impressed by the fact that it did not result in serious infections. The rate of sepsis is low.

In real practice, what we do is we sequence therapies, but if there are no options, you can't sequence them to anything, and we often move to hypomethylating agent early, and that definitely has serious cytopenias. Fever and neutropenia risk is much higher, nearly 25 percent, for the febrile neutropenia events. So I think that this represents an opportunity here, and I think the details were extremely helpful to understand whether or not this depth of cytopenias has resulted in something clinically significant to patients.

DR. MADAN: Okay.

Mr. Mitchell, I guess you had your hand

raised next.

MR. MITCHELL: I apologize. I forgot to lower my hand.

DR. MADAN: Okay. I think we'll go ahead to Dr. Hunter.

DR. HUNTER: Yes. I appreciate the opportunity. Again, I do lead a number of MDS clinical trials here at Emory, and that is my clinical focus and research focus here as well. To the point of the median duration, I think it's an interesting way and an important way to potentially look at it in this little population; that certainly has not been the standard in MDS, though. The standard has been to look at duration of response, and we do see a pretty significant duration of response that is clinically meaningful, in my opinion, a median of almost a year in these patients, which is definitely impactful.

Again, this is a previously treated population that has a very significant lack of available therapies, with half to two-thirds of patients not really applicable for lenalidomide or

luspatercept; luspatercept, again, the subset with higher transfusion burden patients not having very good outcomes regardless as well. So I think looking in that population and seeing the duration that's seen in responders is important.

I think transfusion independence is the standard of what to look for in these low-risk MDS patients. I think looking at things like CR and PR really are not applicable in this population; that applies to patients with over 5 percent blasts. So the lack of disease-modifying capacity that was reported, based on that, I think it's just not very appropriate, personally, in the low-risk setting where, really, those response metrics aren't even really applicable, and most patients aren't eligible for that type of response.

I think the transfusion independence is the benchmark that is used in these patients. It's been the benchmark that's used for other therapies in this setting. Luspatercept has picked up two approvals in the last several years and looking specifically at transfusion independence with

durations of 8 or 12 weeks, not even hitting that 16-week endpoint that was used in the 2018 IWG criteria that was, again, looked at as a secondary endpoint in this study.

So I think it is a clinically meaningful impact, I think, in my opinion, for these MDS patients who are transfusion independent and to achieve that rate of transfusion independence in that duration of transfusion independence in responders.

I think certainly cytopenias are always going to be a concern, but that's something that we live with in MDS. That's what we see in MDS. I think though we see those relatively high rates, the fact that they're largely short-lived and that we see duration of response maintained in patients who are dose reduced once they're responding, I think it potentially will help with that in the long run for these patients. And the fact that we don't see a dramatic increase in infection and bleeding risk, and relatively modest and mild grade infections and bleeding with really no increase in

severe bleeding or infections, I think is an impactful thing to think about here.

I think the other thing that is important is we're comparing to placebo here, and it's often brought up that these patients are going to be on supportive care otherwise, but in reality that's probably not the case. Many of these patients -- certainly in my practice and many other academic experts in MDS typically do reserve hypomethylating agents for last resort, especially in low-risk patients. But especially in community practice where the majority of these patients are treated, they're much quicker to initiate things like hypomethylating agent therapy, which similarly has high rates of cytopenias that are seen.

Also, as far as healthcare utilization, these are treatments that are given for 5 consecutive days of injections in a row every 4 weeks or 7 consecutive days in the standpoint of Vidaza. So I think that is also something I kind of consider here, and we did see it sounds like more of the placebo patients did go on to

subsequent therapies after that and something else to think about in the healthcare utilization standpoint here, so I'll stop there.

DR. MADAN: Just again, because I do think that Mr. Mitchell brought up a good point that I was considering as well and probably the panel here. Our questions really don't revolve around approval here, and it's hard to compare across trials, and what was done before isn't really relevant to the question we have today. But it strikes me as just being different, at least from solid tumors, like I said, where you take the best of the best and say that's the response rate, and then it has toxicity in the other 60 percent. So maybe we can have -- again, Dr. Garcia, your camera's on; if we can briefly address that, and then I'll move on from that point.

Dr. Hunter, if you want to briefly chime in on that perspective.

DR. GARCIA: Yes. To be brief and to better answer the original question, I would state that the reality is that patients in this category would

have otherwise gotten lenalidomide or HMA. And what is expected; there is neutropenia and thrombocytopenia. We would be getting weekly or biweekly labs, so the amount of interface and burden to patients is exactly the same.

So the fact that the placebo had that issue is probably a consequence of the fluctuations we see in MDS, so seeing the benefits at 16 weeks was reassuring because I think 8 weeks was too short, so that was very helpful for me to understand the value of these changes. But I would say the reality is, for next-line therapy after ESA or luspatercept, it will be regimens that do cause cytopenias, and that is the expectation in MDS. So as a clinician in this field, this is how we take care of our patients, whether they're on therapies or not. So if they're just continuing transfusion benefits, I'm still seeing them to get labs and symptomatic relief to the best we can.

The challenge is when we say supportive care, sometimes that means nothing because we don't have anything else. So when that was mentioned and

it's in all the different documents, I'm wondering what is it that I'm not giving because I would love to give that to my patients if there was actually something that supported them that provided real benefit. I think there is a lack of supportive care options that provide meaningful quality of life. The transfusion burden is extremely high, but I would say even HMA as an example, we often wait 4 to 6 cycles, which is 4 to 6 months, to see a benefit.

So we will often put a patient through the trials of cytopenias, knowing that the majority, the overwhelming majority, will not get a complete remission and only half will get some sort of clinical benefit. So we are willing to put most of our patients through it knowing that the majority will not benefit, and that's just because of the limited options.

DR. MADAN: Okay. Great.

So just a reminder during the discussion -- I apologize for not doing this myself, this is Ravi Madan, NCI -- just introduce

yourself with your name and your institution. Sorry about that.

Dr. Hunter, did you want to say something briefly before we move on?

DR. HUNTER: Yes, mostly the same things Dr. Garcia said, so I have nothing else significant to add. But I think it is probably a different way to think about our response and how it's defined here than what most of you in medical oncology are probably used to.

As Dr. Garcia mentioned, this has been the standard in MDS, and this is how other drugs have been studied and what the typical endpoints are, and it did meet those key primary and secondary endpoints. So to look at a different analysis, that duration, the total population, I think it is a clinically and potentially meaningful thing to look at, but it's not the standard of what we looked at with other drugs in this setting.

DR. MADAN: Okay. Great.

Now, we'll just make sure that when we speak again, we'll introduce ourselves with our name and

institution.

Dr. Spratt, you're next.

DR. SPRATT: Hi. Yes. Dan Spratt, University Hospitals, Seidman Cancer Center and Case Western Reserve University. Thank you, again, for all the speakers, and especially the patients; very informative. My gut instinct here when I see the term "efficacy," which is different than I think how the FDA defines it, I'm thinking of effective -- well, that's also different, effectiveness and efficacy, but in terms of is this helping patients have greater CRs, PRs, survival. But, obviously, efficacy is just the ability of a drug or intervention to produce a desired effect in ideal circumstances.

So it sounds like that it was discussed initially -- and I hope I'm not saying this incorrectly -- with the FDA at the outset that there's precedent of this endpoint, the 8-week transfusion independence endpoint; that this, as we heard from people, has clinical meaning, we heard from patients. For me as someone who's not an

expert in this space, it seems like this is not a direct measure of quality of life, which is actually the main thing I'm hearing from the patients and many of the speakers; that avoiding transfusions is really about quality of life, and it's not clearly a measure of quantity of life.

So this is sort of a very odd correlative, not surrogate endpoint, so I'm sort of left with that there are correlations clearly with both. But as the sponsor did state, I think very well, that in the real world, going to effectiveness, hopefully in practice people would -- and it would be great to hear from actually the experts who treat this -- have stopped after however long this intervention. You would have reduced toxicity and cost, and it does seem -- although I realize this wouldn't be approved in such a subgroup setting -- that there is quite a bit of signal and a greater signal of the measures of quality of life, although the data wasn't shown survival even, in those that reached that primary endpoint.

So I would say the efficacy is the strict

question posed here, and their primary endpoint, it was met. So I guess that's my interpretation. It would be great for the field, though, to come up with probably a better endpoint, that is a better capture, a true surrogate, to granularly capture what quality of life is for these patients, and hindsight's of course 20/20.

DR. MADAN: Okay. Thank you, Dr. Spratt.

Dr. Rosko?

DR. ROSKO: Hi. Ashley Rosko, Ohio State. So I bring to the lens of this as a hematologist and as a person who directs a multidisciplinary clinic for older adults, particularly for older adults with hematologic malignancies who come in with frailty and signs and symptoms. One of the things, particularly with the MDS population, is fatigue. So when I'm looking at this data in terms of being able to say, is what the applicant has presented here sufficiently robust? And I think, yes. I do think that if the metric was to have transfusion independence, that the data presented here shows that there is an 8-week transfusion

independence.

But importantly, there is also in my lens the most debilitating symptoms for patients with low-risk MDS is that the quality metric is transfusion independence as well. I know that they used health-related quality-of-life assessment tools that didn't show that there was a significant change here, but I think what patients want and what has been said here is, is it going to improve their quality of living or is it going to improve overall survival? And the metric here is transfusion independence, very unique to this disease, very unique to this modality in terms of being able to demonstrate that response, which has previously been used as the same metric for other drugs that have been approved in this area.

I know that the data that's presented here needs to stand alone, but luspatercept didn't have health-related, quality-of-life improvements either. But at the same time, I see the metric of quality living as transfusion independence, and the fact that 28 percent of these patients can have a

6-month transfusion period. Again, going back to the inclusion parameters for this patient population, they were coming in every other week getting a transfusion, and to be able to have the option, or potentially have the option, to have many weeks that are scheduled, where you could come in for a scheduled drug and have a better trajectory for living.

So knowing that you could come in, get hematologic blood labs and things like that, and then come in for an infusion for 2 hours versus waiting for half a day, or even a full day, to be able to get a blood product I think is meaningful. But at the same time, you don't want to take a drug and introduce that to a patient population and exchange one problem for the next. So I really wanted to get a better sense of what the neutropenia was. Are these things that clinicians can handle with having dose modifications?

So when I look at figure 5 of the FDA briefing document that was previously brought up, looking at the mean neutrophil count, I do think

these are things that clinicians are able to mitigate with dose reductions or changings in dose therapies. And not only that, when I look at the infections, what are the consequences of having the neutropenia? These are the main parameters and risks. I think about the grade 3/4 infections and whether or not they're hospitalized, and I'm not sure that that was clearly presented in terms of what are the outcomes of having neutropenia because that is certainly a complication of this drug. It looked like the infections, grade 3/4 infections, were similar within these patient populations or things that they could handle.

So I guess when I interpret the data, I interpret it in a way of saying that the metric of quality of life is transfusion independence, and that's what I see with the data that was presented here.

DR. MADAN: Dr. Rosko, thanks for your perspective. Just to bring balance to this question, though, because it's kind of in the context of the safety also, the added burden of

platelet transfusions and the growth factor shots that were required, can you just introduce how that would impact your thought process a little bit?

DR. ROSKO: Yes. I think that hematologists are no stranger to these cytopenias and no stranger to being able to administer Neupogen to be able to do dose delays and reductions, and these patients are being monitored in terms of hematologic, which is the main issues when it comes to thrombocytopenia and neutropenia. So I don't think the levels of neutropenia here are things that can't otherwise be mitigated.

Really, looking at some of the data in the FDA briefing document, looking at the mean neutrophil count over these durations of time, I felt like those are things that certainly need to be modified and certainly is something that needs to be taken into consideration when you're administering these therapies to be monitoring for, but I also think for patients to come in to get a couple of days of Neupogen or a day of Neupogen is better than necessarily for patients to be not

knowing if they're going to be spending a day or two getting a transfusion.

I speak in the context of our patients are coming to academic centers, they're getting blood work, and perhaps getting transfused the same day; but don't forget, most of these patients are out in the community and they're not being transfused. It's like a 2-day thing for patients to be able to get blood typing, and maybe they're alloimmunized, and all the other consequences that come into light. So I think when I'm looking at the consequences of it, to me, I feel like the benefits of having something or an option that potentially patients -- not everyone, clearly not everyone is responding, but a potential subgroup of patients certainly is.

DR. MADAN: Right. Okay, a very good perspective.

Dr. Kunz?

DR. KUNZ: Hi, everybody. Pam Kunz, Yale Cancer Center. I just have a comment and an observation. I'm not a hematologist, so really

come to this from the perspective of a solid tumor sort of clinician and clinician researcher, but I think my observation from the call, more so than really prior ODACs, is that there were really stark inconsistencies with how the applicant and the FDA presented the information. As a listener, they were very, very different, so I think, for example, really, the framing of the benefit, and the safety, and the PROs, and the healthcare utilization were almost polar opposites.

I think that it's very helpful to hear from the hematologists, but I think as a listener and someone who's voting today, I'd certainly welcome the hematologists to make other comments. That's sort of where I'm struggling.

DR. MADAN: Dr. Kunz, just to really clarify your struggle, I guess, your struggle is trying to understand where the balance is in between these two --

DR. KUNZ: Right, right, because I felt that the framing of the data was very, very different in terms of -- certainly the applicant stated that

there were efficacy benefits in terms of the RBC-TI, yet that was framed differently by the FDA. There was a debate about healthcare utilization, there was a debate about the PROs, and a debate about the safety. And I know that's the purpose of this, but I think that there's often more commonality than there is differences, and I think that's where I'm struggling. And I don't know that I need a response to that, but that's where I am.

DR. MADAN: I think that's a good representation. We'll try to come back to that after our next set of questions.

Dr. Vasan?

DR. VASAN: Yes. This is sort of marrying, I think, several people's comments and questions. One thing I'm struggling with is patients are transfusion --

DR. MADAN: Sorry. Dr. Vasan, just introduce yourself and your institution.

DR. VASAN: Oh, I'm sorry. Neil Vasan, Columbia University. One thing that's come out from this is that transfusion independence is not

just a disease marker, but it's also a quality-of-life metric. And so, if that's the case, obviously, with this drug, there's also an increase in other transfusions, in growth factor and in platelets. So patients perhaps are RBC transfusion independent, but they're not transfusion independent writ large. So I guess one question is how are we weighing these different types of transfusions?

To Dr. Kunz's point as well, I think one challenge is that, ideally, something would be reflected. There would be some bit of information in this, some bit of patient benefit that is reflected in some of these metrics. And I think that the FDA has really combed through these metrics in the PROs and healthcare utilization to try to find some variable that might be different and that might reflect that, and I think we're at variance right now, is that we can't really hang our hat on some discrete, real-world piece of data that shows there was some real-world benefit from this drug.

DR. MADAN: Right.

DR. VASAN: But I guess a question that would be either to Dr. Garcia, or Dr. Rosko, and any of the other hematologists, these different transfusions, again, it sounds like we're not weighing these RBC transfusions the same as a platelet transfusion. Is that correct? Is that how you think about it?

DR. MADAN: Yes. I think let's pause and go down our list of questions because this is important, and I'd like to just add on to that. I'm sorry. This is Ravi Madan, NCI. But in addition to Dr. Vasan's questions -- and if one hematologist on the call could answer this briefly, and if the others agree, then there's no need to chime in. But in addition to how you weigh an RBC transfusion versus a platelet transfusion, the exposure to frequent transfusions with RBCs are known, and is that also true with platelets?

Dr. Garcia, your camera's on, so go ahead.

DR. GARCIA: Thank you. I think platelet transfusions are just as important as red blood

cell transfusions, but from what I know about this drug and what I've read in all the documents, it was not the expectation for us to look for platelet improvement. And I think that's important, important because we didn't ask the other parameters of the patients' MDS to stay in standstill, and we also don't know how long these patients have been living with MDS.

By the time the patients who are eligible for the study got drug, they were already transfusion dependent and heavily so, so these patients, for the most part, I think the majority were not just recently diagnosed; they had already been living with MDS, so at least, I would imagine, several months to even a couple of years into their disease. So the expectation, the other counts wouldn't go down naturally with the natural history of MDS since this drug is not yet shown to be curative.

It was not my expectation when I was looking at the data or expecting that. So requiring transfusions is something that we do with people on

epo, people on luspatercept, people on lenalidomide, and decitabine, and supportive care might have just been more proactive because people are watching the counts.

DR. MADAN: So just to get to your point -- Ravi Madan, NCI -- from FDA slide 19, transfusions were 18 percent in the imetelstat group and 2 percent in the placebo group. So it doesn't seem to be as natural a drift. It does seem to be treatment related, based on that data at least. Any thoughts on that?

DR. GARCIA: I think that's a great point, but I don't think it's clear from the table 1 that's available, the MDS' were balances and how long people are living with it. So I don't know where they are in their disease course by the time they're coming; so they just met the platelet 75, and how many were there versus above 150? Where are people's starting point?

I think that might be helpful to know, but I would say it is not a surprise that it did not improve that. I'm not afraid of the extra

16 percent. It didn't seem to be a number that couldn't be overcome. It said the number of platelet transfusions, and I don't know if that decreases, like they suggested, maybe after the first couple of cycles, and if that was the case, that's reassuring that they're not grade 4 transfusion-required labs, but rather just something that you see early on and it goes away. That would be helpful I guess for clarification.

DR. MADAN: Right. I guess, though, we're assuming everybody is coming in at relatively the same spot because we make the same assumption with red cell transfusions. So we're kind of assuming everyone is coming in at the same spot, even though, of course, there's variation, but okay.

Great. I'm just struggling to understand this as a simple solid tumor oncologist, so I appreciate it.

Dr. Hunter?

DR. HUNTER: Yes. I was going to say roughly the same things as Dr. Garcia. I think with the platelet transfusion, the same thing to

keep in mind is that the median number of platelet transfusions was 1. So I think, as we saw, most of the cytopenias, especially the grade 3 and 4, tended to be relatively short-lived. So this isn't necessarily making someone dependent on platelet transfusions; it's more of a patient may need one somewhere along the way with treatment, and likely we're going to stop treatment quicker in patients in real world that are not on clinical trial if it's not working, which is probably going to eliminate some of that a little bit, too.

So I think the total number of -- any transfusion is important, because that affects quality of life and it affects healthcare utilization. I think they're equivalent in that sense, but I think eliminating red blood cell transfusion and then adding a median of 1 platelet transfusion in 18 percent of patients is not necessarily an equivalent trade-off of just substituting things.

And likewise with growth factor injections, again, I think it was something like 36 percent or

something that got growth factor injections. In my opinion, that's more depending on the physician. I don't usually use growth factor in my clinic for most MDS patients like this, especially if it's going to be a transient and short-lived neutropenia. It's not something that I would generally utilize anyway, so I don't think that's necessarily a trade-off in that sense either, if that makes sense.

DR. MADAN: Again, Ravi Madan, NCI. Just again, to look at the data, it was 35 versus 3 percent --

DR. HUNTER: Um-hmm.

DR. MADAN: -- so you've got to assume that, again, physician preference comes out in the wash there somewhere.

DR. HUNTER: Sure.

DR. MADAN: Okay. Great.

So that was very helpful. Again, your expertise is greatly appreciated on this discussion.

I'd like to move on. Dr. Nieva I think had

the next question or discussion.

DR. NIEVA: This is Jorge Nieva from the University of Southern California. Clearly this is a supportive care drug, not an oncology product, and it has some effect in modulating hemoglobin in this disease. They did a trial, they had a primary endpoint; they met their primary endpoint.

Now, the efficacy clearly doesn't apply to all patients and it applies to a subset, and there's no biomarker that identifies that subset a priori but, of course, toxicity is distributed among everybody. So the question here really is, can you trust clinicians and patients with the decision or do you think this drug is so problematic that you can't trust them with the decision?

But the good news here is I don't think we need to have a biomarker. I mean, the clinicians can continually evaluate the risks and benefits of the drug, and if it's not working, they can stop it if the drug's available on the market. And the data here I think are sufficient. I think there is

enough information here that they can make their own decisions.

Now, I do want to point out something that's not come up. There are some groups for whom the risk-benefit ratios are going to be outsized on the benefit part, and I'm going to begin with a religious minority group, members of the Jehovah's Witness faith for whom this drug may be really quite life-saving, and excluding it from the market would be really quite discriminatory. Additionally, people who are alloimmunized are a group for whom this drug really may have outsized benefits. And I think when OCE is making their decisions, they need to consider particular groups for whom red cell transfusion is just not an option, for whom basically this disease means death.

So I just want to bring up those two points and make sure that as we're evaluating the value of these medicines, we understand that these things do need to be individualized decisions for each patient. Thank you.

DR. MADAN: Thanks, Dr. Nieva.

I think it's also, again, just important to remember our question and scope of our question here today. Fortunately, we don't have to talk about community implementation or approval. We're just kind of having the discussion about the risk-benefit, which has sometimes a slightly different perspective here.

Mr. Conaway?

DR. CONAWAY: Yes. Mark Conaway, University of Virginia.

DR. MADAN: Dr. Conaway, sorry. Go ahead.

DR. CONAWAY: I thought I'd weigh in from a statistician's point of view on these responder analyses and the duration of response among responders only. As a general rule, these responder analyses are really difficult to interpret. They're really problematic. We have that graph where we're looking at 47 responders in one group versus 9. We don't know how those groups are different. When you look at everybody, at least you have the benefits of a randomized group,

so you sort of understand how they're the same or different.

I mean, I understand completely why you want to look at the duration of response among responders. When we looked at that graph that Mr. Mitchell had asked us to pull up, the responders were a mix of some long sustained blue lines with very few dots representing transfusions, and other responders were single, short blue lines in a sequence of transfusions, and those would both be counted as responders but are very different patient experiences.

So I understand why you'd want to look at how sustained and durable the responses are, but I think you can't really evaluate that without looking at the group as a whole. I just don't see how you can pull out those who responded to treatment and make any kind of inference between those two groups.

DR. MADAN: Thank you, Dr. Conaway.

I think Dr. Spratt is next.

DR. SPRATT: Yes. Just to discuss or

respond to some of the comments made -- Dan Spratt from Case Western, UH Seidman Cancer Center -- just quickly, Dr. Nieva brings up an excellent point, but I'd just like to add, all these patients I believe had to be transfusion dependent already for the Jehovah's Witness comment.

But I guess what Dr. Rosko had said, and others -- and again, there's precedent in this space. It just seems very odd to me, and we need some clarity here, that if the goal is quality-of-life improvement, really I think that needs to be directly measured. And just to say especially given there can be bias, and who does and doesn't -- and we just heard from one of the hematologists that when you give supportive agents is physician dependent -- I would just urge the field to move this into actually measuring quality of life. So that's I guess the final comment here.

The other thing -- sorry, real quick -- is that it might be helpful -- I know it wasn't presented. In other endpoints, I know the FDA has looked at, again, going back to solid tumors,

bladder intact free survival, where you have a quality of life, you keep your bladder, and in this case you avoid transfusions but you are measuring survival, it might be an interesting thing for the FDA to later look at, is transfusion-free survival as a composite endpoint given the survival signal was numerically a little worse, depending on the time point with the agent. Thank you.

DR. MADAN: Okay.

Dr. Hunter, I think I had you on the list, but your hand is down. I think that's because we already got your point.

Dr. Frenkl, and then maybe if we have time, we can come back to Dr. Spratt's point of survival, which really hasn't come up here. It wasn't really the focus of a lot of the data, but maybe we can come back to that after Dr. Frenkl's point.

DR. FRENKL: Thank you. I'd just like to maybe provide a little bit of industry perspective here, and that I also share Dr. Kunz's, I guess, difficulty with the framing. We heard loud and clear today, I think, from the public hearing, as

well as from Dr. Savona and Dr. Komrokji, that there's a definitive unmet need. And again, I think the patients really stressed, and it sounded like their quality of life was improved even though I know it wasn't measured in the study.

The phase 3 study did meet its primary and key secondary endpoints, and these endpoints have regulatory precedents that remain the benchmark and were agreed to in the end of phase 2 meeting. And again, I think we heard from Drs. Savona and Komrokji that this is their treatment goal, transfusion independence, and it's clinically meaningful. I just want to say, too, that I'm not convinced, maybe like Dr. Hunter, that the endpoints that the FDA referred to as indicators of disease modification should actually be a requisite for approval, nor were they required for prior approvals, and I think we've discussed those already and their relevance.

As an industry expert, and I've designed many studies and executed them, it's very difficult for the goal posts to change after they've been

decided on and agreed to; we're kind of stuck to all the prespecified analyses, and that's what the studies are very specifically designed to do. So again, I think we just have to take into consideration what conclusions we can actually draw from the study, and it's really limited to the prespecified endpoints that are powered for it.

I just want to say one more thing, is that I agree that I think the safety here has been very clearly defined and that the experts have shown that they can manage this in the clinic, and that it's a definite option for patients. And they can, after having an informed discussion between the patient and physician about all of those risks, decide if they want to take the risk themselves to be one of the 40 percent that respond and possibly have a long response. Thank you.

DR. MADAN: Thank you.

Okay. Dr. Spratt, your hand's up again.

DR. SPRATT: Trying to emulate an in-person discussion.

DR. MADAN: Just identify yourself.

DR. SPRATT: Dan Spratt, Case Western Reserve University. I don't accept that independence of blood transfusion can be the only focus. While it's clinically relevant if let's say the survival was statistically worse, that in and of itself, to me, is insufficient. I realize survival was not worse. I'm not saying in this specific setting it doesn't mean there's not efficacy -- I already said there is efficacy -- but I think just because the past bar and precedent maybe was what it was, it doesn't mean that now that trials have evolved, the landscape can't evolve with it.

DR. MADAN: That's a good point. And again, remember, some of this is beyond the scope of our discussion point. We're tasked with a very simple thing, and sometimes we're making it harder by talking about approvals, but the broader context is, to some degree, inescapable.

Dr. Choueiri?

DR. CHOUEIRI: Toni Choueiri, Dana-Farber Cancer Institute, Boston, Massachusetts. We're

digging into a lot of details. It's very important because I believe that Dr. Kunz said that this is not straightforward. But I would have loved to see -- and maybe the sponsor has that -- the number of transfusions per unit of time, of red blood cells, of platelets -- these are serious also to find -- of injections, of other injections, I don't know, or visits to the ER, and visits to the hospital or to an outpatient setting per unit of time in the placebo arm and in the therapy arm. That would have helped a bit.

I do think there is a decrease from what I've seen and read in the number of transfusions overall and visits, et cetera, but since the platelet transfusion is higher in the non-placebo, in the experimental arm, have we exchanged one transfusion versus another? I don't think the data was presented that granular. Those are very important issues, rather than considering healthcare utilization, in general, which is quite broad. Thank you.

DR. MADAN: Thank you.

Dr. Rosko, I think you might be the final discussion, as we're getting to our voting point. I also think if anybody wants to comment briefly -- and maybe you can, Dr. Rosko, since you have the last word and sorry to put this on you -- we didn't talk too much about it, but there's no survival signal here, and your thoughts on that as we kind of wrap up this and move to our voting question.

DR. ROSKO: Yes. Ashley Rosko, Ohio State. I don't know about the last word, but I just want to kind of respond to Dr. Choueiri's thoughts about healthcare utilization. I think we were trying to get a sense from both FDA's presentation and from the applicant's. I don't think the healthcare utilization was well measured in the fact that you needed to count the transfusion appointments, and you needed to count the appointments to be able to get the laboratory draws, and those weren't included in the analysis. I think the FDA was trying kind of say, here's what it would look like, we're estimating, from healthcare utilization.

I also think one of the ideas -- what is it like if a patient doesn't have access to this therapy? They went, again, from getting transfused every other week to now potentially having the option to be without this. With the drug, they could have a period of time potentially without needing blood transfusions, to what's the consequence of not having it. Will they go back to getting transfusion dependent, alloimmunized, LFT abnormalities, iron overload, and all of the burden that's associated with getting a transfusion? Which is why I do think transfusion independence is the quality metric here and why I think that there's efficacy, and it's meaningful for patients.

In terms of overall survival, I do think this goes back to Dr. Nieva's point about is this disease modifying. Well, the canary in the coal mine here is transfusion independence, but it's a tricky place to navigate for MDS, given the transformation to AML or needing other things. So I think that this is a difficult place to be able to see is it actually beneficial and is it actually

meaningful. And it has been this ability to not need transfusions, what I think is unique to this, in light of the very few other drugs that are available in this venue. Thank you.

DR. MADAN: Okay. Great. I think we're going to have to move to our voting question.

Dr. Lieu, we haven't heard from you. If you have something brief that you want to mention, please do, but we do have to move on. Go ahead.

DR. LIEU: Yes. I'll make this very, very quick. Just on the overall survival issue, just to Dr. Nieva's point of this being seemingly more of a supportive care product as opposed to disease modifying, I think it makes sense, number one, that there really wouldn't be a difference in overall survival, but because you're trading this transfusion independence for increasing growth factor support by 32 percent, by increasing platelet transfusion by 16 percent, you want to make sure that the neutropenia and the thrombocytopenia aren't causing us harm.

I think what the overall survival tells us

is that even though you do have these higher rates of neutropenia and thrombocytopenia, we're not necessarily harming patients with this agent either. So, to me, the lack of overall survival difference isn't very surprising, but in some ways a little bit reassuring, honestly.

DR. MADAN: Okay. Great.

So I will summarize briefly, and then we will move to the voting question. I think the discussion by the panel today really highlighted a difficult interpretation of the data here. I think there's very clear evidence that for those who do respond, there's a transfusion independence that can be gained that can be life changing. I think for people who don't treat heme malignancies regularly, it was more of a struggle to just focus on the best of the best who responded while also realizing that the broader group is exposed to toxicities that can result in growth factor support, platelet transfusions, and other reasons for doctors' visits.

Our heme colleagues really highlighted the

fact that this would be a game changer for a lot of their patients, at least the ones who responded, and I think it was a valuable discussion. I'd like to just kind of wrap up with that, so we have time for our voting discussion because I know we have people who are coming up on a hard stop.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the public, as well as the public comments. We will now proceed with the question to the committee and panel discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate unless at the specific request of the panel.

After I read the question, we will pause for any questions, or comments, or interpreting its wording so this may allow for time for people to get clarifying questions. So this is our voting question here, and I will read it, and we can ask the FDA to clarify if you guys have questions.

Do the benefits of imetelstat outweigh the

risks for the treatment of transfusion-dependent anemia in adult patients with International Prognosis Scoring System low- to intermediate-1 risk MDS who have not responded to, or have lost response to, or are ineligible for erythropoiesis-stimulating agents?

Is there anyone from the panel that wants to ask clarifying questions? Again, this is the specific question we're voting on, not necessarily FDA approval, so if anybody has any questions to clarify any components of the question, now would be the time to ask the FDA colleagues on the call to do that.

(No response.)

DR. MADAN: I don't think we have any hands up, so I think there's good understanding.

If there are no further questions or comments concerning the wording of the question, we will now move to the voting process.

I'm sorry; I read part of this wrong here, but we're now moving to the voting session. Voting members will use the Zoom platform to submit their

votes for this meeting. If you are not a voting member, you will be moved to a breakout room while the vote is conducted, so we will now move to the voting discussion.

After the chairperson reads the voting question, which I've already done, into the record, we will have a chance to clarify, which we already established that there is no need to do that. A voting window will appear where you will submit your vote. There will be no discussion during the voting session. You should select the button in the window that corresponds to your vote.

Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that voting is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members to the meeting room.

CDR BONNER: Hi, Dr. Madan. This is LaToya Bonner. Actually, I am reading the instructions for the vote, so I'll start now.

DR. MADAN: Oh, sure. Thank you.

CDR BONNER: No problem. Thank you. Thank you for reading it, and I'll read it over for you.

DR. MADAN: Yes, I went a little ahead. Sorry about that, a little too anxious. Go for it.

CDR BONNER: Alrighty.

Question 2 is a voting question. Voting members will use the Zoom platform to submit their votes for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct a vote. As the chairperson reads the voting question into the record and all questions and discussions regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select a button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will

announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the voting results will be displayed on the screen. I will read the vote results from the screen into the record. Afterwards, the chairperson will go down the list and each voting member will state their name and their vote into the record.

I saw that Ms. Powell had her hand raised.

Ms. Powell, do you have a question?

MS. POWELL: Yes. Joan Powell. So basically, something came on my screen that said meeting chat. Is that where I vote? This is my first time, so be patient.

(No response.)

MS. POWELL: Did did you hear me, Dr. Bonner?

CDR BONNER: Yes, I heard you very loud and clear. I don't see that chat here, but we should receive a prompt pretty soon, and I will let you

know. Thank you.

MS. POWELL: Alright. Thank you. Thank you.

CDR BONNER: This is Commander Bonner. Are there any questions about the voting process before we begin?

(No response.)

CDR BONNER: Since there are no further questions, we can proceed with the vote.

(Voting.)

CDR BONNER: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

CDR BONNER: For vote question number 2, 12 yeses, 2 noes, zero abstentions.

DR. MADAN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. You may also include a rationale for your vote. We will start first with Ms. Powell. If you would not mind telling us your vote and provide a rationale if you'd like.

MS. POWELL: Okay. I voted yes. As an MDS

patient, I believe that this drug will give us a better quality of life. The transfusions -- as some of my family members; I call people with MDS my family -- having a transfusion on a regular basis really interrupts your life, so this will give us more time to have a better life quality. Thank you.

DR. MADAN: Thank you, Ms. Powell.

Ravi Madan, NCI. I interpreted the question pretty strictly, as you may have guessed. As we heard today, even low-risk MDS patients are at high risk from their disease, but they shouldn't also be at risk from their treatments as well. And while a significant minority of patients clearly benefited from imetelstat, the majority of patients do not derive benefit, and that combined with the increased toxicity of the agents seen as infections, and bleeding, and platelet transfusions, and other supportive measures, it makes the data less clear to me that the risk totally outweigh the benefits for all patients treated. The data is very encouraging, however, in

a subset of patients who truly seem to benefit and it seems to be life changing.

I think it will be important for the applicant and the academic collaborators in the future to really better define who this population is with biomarkers or other clinical parameters, and with the selection process, they can bring the benefit to a vast majority of the patients treated with this intervention, and then probably more confidently deploy into the community.

Just from my perspective with the data as we saw today, unfortunately, at this time it's not convincing enough to demonstrate to me the risk for all patients are worth the benefits to the minority of responders. Thank you.

Dr. Vasan, you're next.

DR. VASAN: Neil Vasan, Columbia. I voted yes. So from my perspective, this trial met its primary endpoint and offers a new therapy for some patients who may have no other option, depending on their MDS classification, and I felt that the benefits of improvement in transfusion independence

outweighed the risks of cytopenias in a patient population and in a blood cancer oncology community that's well versed in these adverse events and their management.

The discussion today, both by ODAC and the patient community, has shown that transfusion independence as a quality of life entity is complex and multifaceted, and I think that this merits better clinical trial metrics and endpoints that I hope we can address as a field in the future. Thank you.

DR. MADAN: Thank you, Dr. Vasan.

We're going to go a little out of order just because Dr. Spratt is coming up against the time crunch. So, Dr. Spratt, would you go next?

DR. SPRATT: Yes. Dan Spratt, UH Seidman, Case Western. I voted yes. I think that it met the efficacy that has been both a precedent, as well as seems to be clinically meaningful to the patients and the providers that take care of these patients. To have this available and hopefully the physicians and subsequent guidelines to use this

agent could minimize the toxicity profile or improve that therapeutic ratio to obviously stop the agent in those not responding. Thank you.

DR. MADAN: Thank you, Dr. Spratt.

We'll go back to the order, I guess.

Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I voted yes, and I did so because the study met its primary endpoint on efficacy grounds and the toxicity appears to be manageable. While we don't know the subset of patients who are going to be responders, a therapeutic trial of the medicine will pretty easily sort that out for people in the community. Thank you.

DR. MADAN: Okay.

And Dr. Lieu?

DR. LIEU: This is Chris Lieu from University of Colorado. I voted yes. To me, this is primarily an issue of trade-offs. We have an agent that does not appear to modify overall survival or response rates, either in a positive or negative way, so the issue really comes down to

transfusion independence versus this increase that we see in neutropenia and thrombocytopenia that requires growth factor support, platelet transfusion, and the infusion of the drug itself. So, to me, this becomes truly a quality-of-life issue, and what we have heard from patients and providers is that the quality-of-life benefits outweigh the negative impacts of this agent, and I thought the comments from both Dr. Garcia and Dr. Hunter were extremely helpful.

So though I am concerned about the risks in this total trial population -- in other words, not just the responders -- I do believe it is more likely than not that there is a quality-of-life benefit here that is real.

DR. MADAN: Thank you, Dr. Lieu.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Ohio State. I voted yes. I think anemia has significant deleterious effects from the aging population with MDS. I think there is sufficient and robust demonstration of treatment efficacy with the study

drug. A subset of patients certainly have a higher benefit from transfusion independence, but I do think being free of transfusions in and of itself is a marker of quality of life. I do think also this study has brought to light being able to robustly characterize healthcare utilization to be able to better understand other metrics that impact patients significantly, too.

DR. MADAN: Thank you, Dr. Rosko.

Dr. Conaway?

DR. CONAWAY: Yes. Mark Conaway, University of Virginia. I voted no, even though the study met its primary outcome, but the magnitude of the benefit relative to the adverse event profile, with that, I thought that the benefits did not outweigh the risks.

DR. MADAN: Thank you, Dr. Conaway.

Dr. Hunter?

DR. HUNTER: Anthony Hunter, Emory University. I did vote yes, and I feel like there was certainly discussion regarding some of the other secondary endpoints, and duration, and things

like that, but clearly did meet both the primary and key secondary endpoints, which I do feel are not only agreed-upon endpoints, but certainly clinically impactful and significant ones that we use in this setting.

Certainly, there are some concerns regarding the cytopenias but somewhat reassured by the fact that this largely did not translate into higher risk, especially of grade 3 and 4 infections or bleeding events, and felt like this is fairly typical degrees of cytopenias that we see in the MDS population with the therapies and feel like that is something that's manageable. I certainly agree that continuing to improve on endpoints in this setting will be important in the long run for the field, as well as more robustly characterizing quality-of-life metrics in these types of studies.

DR. MADAN: Thank you, Dr. Hunter.

Dr. Mitchell?

MR. MITCHELL: Mr. Mitchell.

DR. MADAN: Mr. Mitchell. I apologize. Sorry.

MR. MITCHELL: I love being promoted.

DR. MADAN: Every time you're here.

MR. MITCHELL: I voted yes. I'm the consumer rep to the ODAC. I voted yes for reasons that others have stated. The study met the primary and secondary endpoints that were set forth, a priori. The cytopenias apparently are manageable. Transfusion independence, clearly, as the discussion went on, is a critical element for this patient population. And finally, the discussion from the clinicians on the committee was very helpful in putting the whole body of data into a context of what it is to treat these patients, so I voted yes.

DR. MADAN: Thank you, Mr. Mitchell.

Dr. Choueiri?

DR. CHOUEIRI: Thank you. I voted yes. This was kind of a narrow yes. I took in consideration the discussion of the heme and MDS expert, which was very helpful and overall balanced. I think, hopefully, the MDS community will continue to come up with meaningful endpoints

since overall survival may not be expected with new agents, including hopefully come up with definitions that are clinically meaningful, including metrics for quality of life for MDS specifically. I took in consideration the fact that this disease is mostly not curable and doesn't have many options, but I voted yes, and thank you.

DR. MADAN: Thank you, Dr. Choueiri.

Unfortunately, Dr. Kunz had the leave, but she was able to place her vote of yes into the record, and I will just read it for official purposes. Dr. Pamela Kunz, yes.

Okay. Dr. Advani?

DR. ADVANI: This is Dr. Advani from Stanford. I voted yes because, one, this is not a curable disease; there are very few options. The community of doctors who take care of these patients know how to manage these side effects. The neutropenia/thrombocytopenia seen with the other agents approved are used in this indication as well, and I thought the study met its clinical endpoint, which was transfusion independence. It's

really hard to show survival difference in a lower-risk patient, where the span is anywhere from 2 to 10 years. We don't see that in low-grade lymphomas as well, so that didn't bother me. I think people know how to manage these toxicities, and it did meet its study endpoint. Thank you.

DR. MADAN: Thank you, Dr. Advani.

Dr. Garcia?

DR. GARCIA: Hi there. Jacqueline Garcia, Dana-Farber Cancer Institute in Boston, Massachusetts. Thank you. I appreciate the access to details from both the FDA and company perspectives and the raw data beyond the published paper. The stories from the patients were extremely meaningful and impactful, and really mimic what I hear from my own patients for what they would like and what they want, and what's important to them in their time. I agree that transfusion dependence is a measure of quality of life for lower-risk MDS patients that is truly meaningful.

I was impressed by a couple of things in

particular; that the phase 3 study data was very similar to what we saw in phase 2. As a clinical investigator in MDS, we have not been able to recapitulate these types of translations to larger scale studies. They have not been faithfully recapitulated and confirmed, so I was grateful to see both a primary and secondary endpoint was met.

I was also an MDS investigator and a part of the discussions, and along with the FDA and other MDS experts who are looking forward to improving MDS outcomes based on study endpoints and how we design studies, I was grateful to see the use of the IWG 2018 hematologic improvement criteria, which I think are more meaningful than the original IWG with modern therapies.

I believe the safety can be addressed and overcome in an MDS clinic easily, and I was very impressed. I was not expecting how long the responses could be among the responders of this therapy, and I look forward to the correlates and biomarker data that might come out in the future. Thank you.

DR. MADAN: Thank you, Dr. Garcia.

I think today's discussion of imetelstat in MDS was very enlightening to the public, as well as to the committee. The committee in the end, the majority voted in favor of the benefits over the risks. It was acknowledged that this does come with side effects, but as a supportive measure, it liberated, perhaps, patients from the need for frequent transfusions, and the balance of the committee thought that in the broad components of the medical community, that the side effects could be handled. So I think that was how the day ended and the vote as well.

I'd like to thank, before I sign off here, the FDA for their details that they provided and the Geron Corporation for the very open access to their data and the responsiveness to the questions. I really appreciate the expertise on this panel, especially the MDS experts, and I really also am grateful for the open public hearing members, and patients especially, who shared their experiences, and I really think it did inform our discussion

significantly.

I think it was a productive day, and before we adjourn, I just want to make sure that the FDA doesn't have any final comments.

(No audible response.)

DR. MADAN: The FDA is speaking, but muted, just so you know. Go ahead.

(No audible response.)

DR. MADAN: Still not hearing you.

We'll just get the FDA mic unmuted, and we have support for that, for the final comments. Go ahead.

DR. NORSWORTHY: Hi. Kelly Norsworthy, FDA. I just wanted to take the time to thank all of the committee members and all the people in the open public hearing, especially the patients. We really appreciated hearing from everyone, so thank you for your time and valuable insights.

Adjournment

DR. MADAN: Thank you.

Okay. We will now adjourn the meeting for this afternoon. Thank you, everyone, for

participating.

(Whereupon, at 3:30 p.m., the meeting was adjourned.)