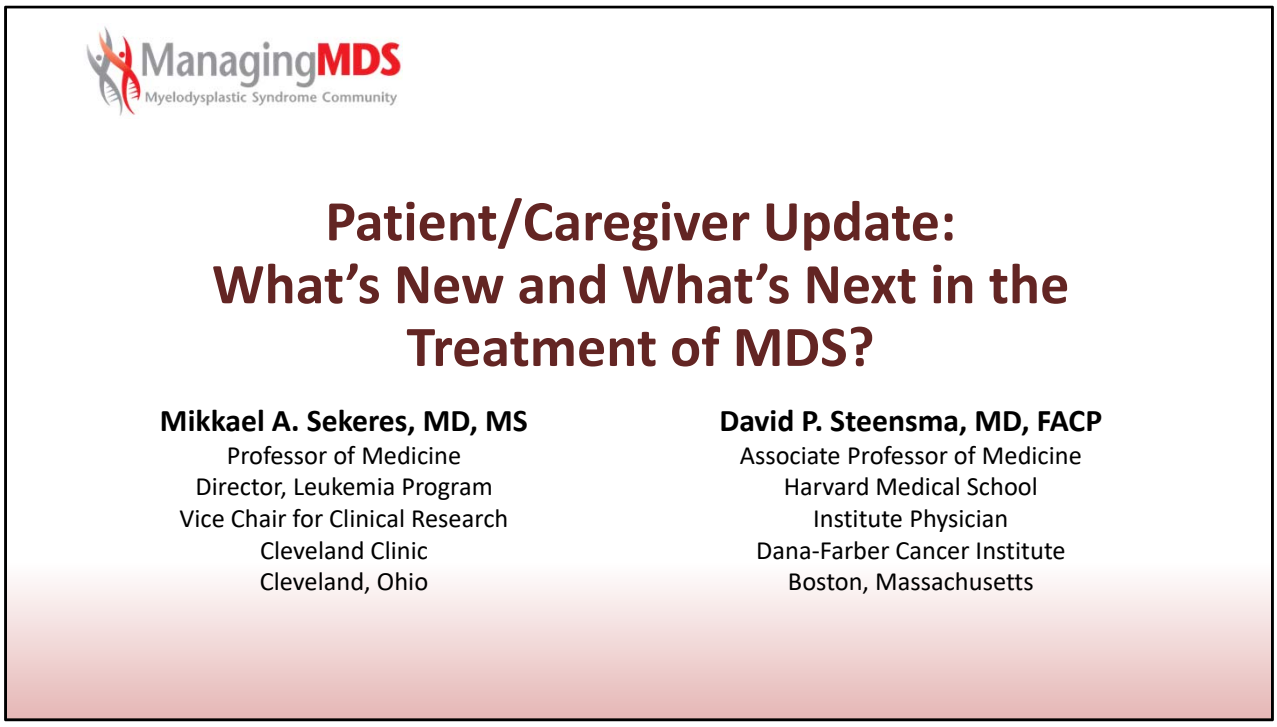
Patient/Caregiver Update:
What's New and What's Next in the Treatment of MDS?



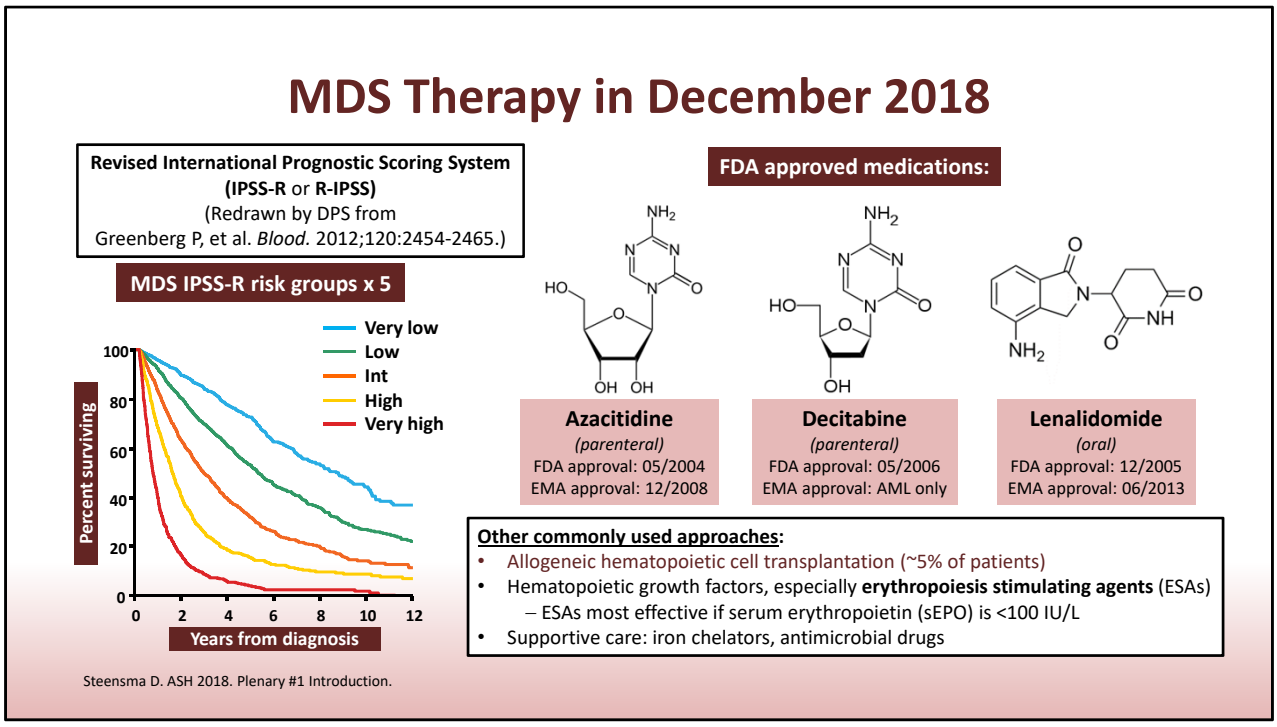
Dr. Mikkael Sekeres:
Hi everyone, and thank you for joining us, I'm Mikkael Sekeres. I'm Director of the Leukemia Program and Professor of Medicine at Cleveland Clinic in Cleveland, Ohio and today, I'm joined by my good friend, David Steensma.

Dr. David Steensma:
Hi, thanks Mikkael. Yes, I'm David Steensma from Dana-Farber Cancer Institute in Boston where I lead the clinical efforts in the myelodysplastic syndromes program.

Topics We Will Touch on Today

- Personalized risk stratification models beyond IPSS and IPSS-R
- Is there a benefit to treating iron overload in transfusion dependent MDS?
- Newer strategies for treating lower-risk MDS patients who are transfusion dependent
- Immunotherapies in MDS
- New strategies for treating high-risk MDS

Dr. Mikkael Sekeres:
We are pleased to be talking to you today about some of the current updates in MDS research most recently reported this past December at the 2018 American Society of Hematology Annual Meeting. We will be talking about a number of topics today. The first is prognostication models: in other words, the International Prognostic Scoring System, its revised counterpart, and some newer methods of determining prognosis in MDS, which is what we use as a default staging system. We'll also be talking about iron overload in people with MDS who are transfusion-dependent; newer strategies in treating lower risk MDS; immunotherapies in MDS; and newer strategies in treating higher risk MDS. I'm going to hand the mic over to my friend, David to give you a little background about MDS.



Dr. David Steensma:
MDS is a group of bone marrow failure disorders where the bone marrow is not making enough blood cells. These disorders also have a risk of progression to acute leukemia; they used to be called preleukemia. In order to assess that risk, and also to assess the patient's risk of a complication such as a severe infection that takes their life or severe bleeding event, we use a system called the Revised International Prognostic Scoring System. It was developed about seven or eight years ago and stratifies patients into five risk groups; from very low risk where most patients are going to live 8 to 10 years, to very high risk where most patients will unfortunately succumb from the disease within the first two years of diagnosis. There are only three drugs that are approved for MDS; azacitidine and decitabine which get used mostly for higher risk disease; and lenalidomide, which gets used mostly for a special subtype called deletion (5q) MDS. The most common treatments for MDS are red cell growth factors (or red cell boosters) called erythropoiesis stimulating agents (ESAs). This is epoetin and darbepoetin; you may know them as Procrit or Aranesp if you're getting these medicines. The only potential cure is an allogeneic stem cell – or bone marrow – transplant. Allogeneic means stem cells from a donor, a sibling or an unrelated donor or in some cases, a child; then in addition, many patients get supportive care. The problem with bone marrow transplant is that it's difficult to do for patients who are elderly or who have other medical problems, so only a minority of patients ever get transplant.

Now I'd like to turn it over to Dr. Sekeres to talk a little bit about what we're learning about these prognostic models and how artificial intelligence and machines can help us do a little bit better with predicting outcomes for patients than we can do now.

A Personalized Prediction Model to Risk Stratify Patients with MDS

- Patients with myelodysplastic syndromes (MDS) have heterogeneous outcomes that can range from months for some patients to decades for others. Although several prognostic scoring systems have been developed to risk stratify MDS patients, survival varies even within discrete categories, which may lead to over- or under-treatment. Deficits in discriminatory power likely derive from analytic approaches or lack of incorporation of molecular data
- Here, we developed a model that uses a machine learning approach to analyze genomic and clinical data to provide a personalized overall outcome that is patient-specific
- A personalized prediction model based on clinical and genomic data that outperformed IPSS and IPSS-R in predicting OS and AML transformation. The new model gives survival probabilities at different time points that are unique for a given patient. Incorporating clinical and mutational data outperformed a mutations only model even when cytogenetics and age were added

Nazha A, et al. ASH 2018. Abstract 793.

Dr. Mikkael Sekeres:
Thank you, David. We have been using the IPSS since 1997. That's how long it has been around and it works pretty well. Same with the revised IPSS. The original IPSS was based on information from about 800 patients. The revised IPSS is based on information from over 7000 patients, so it's really accurate but it has a couple of limitations. The first is that it's really accurate in people who never have received a drop of therapy for their MDS. Once somebody starts to get treated for MDS, the IPSS revised version (IPSS-R) loses its accuracy. The second aspect of it that isn't very accurate is that it only works at diagnosis. It is not very accurate when you try to apply it in real-time. For example, while the revised IPSS might be accurate in somebody at diagnosis who never receives therapy, if you were to try to use it in that same person two years later, it actually wouldn't be very accurate anymore. Finally, the revised IPSS and the IPSS don't include this new genetic information that we're getting which we refer to as either next-generation sequencing or genomics data. In other words, the genetics of the MDS cells themselves, whatever went wrong to cause the MDS. The vast majority of time, when we talk about genetics, we're not talking about something that you pass down to your kids or grandkids. We're talking about something that arose spontaneously within the bone marrow cells to cause the MDS, not something that's heritable.

The old way of classifying these took a bunch of information, ran some statistical analyses, and then pumped out some of the more important factors for determining prognosis. These boiled down to: the number blood counts that a person has that are low; the genetics of the MDS (there are some genetics that are relatively good risk and some that are relatively bad risk); and the percentage of blasts in the bone marrow. Blasts are immature white blood cells. We all have blasts, but if a person has 5% blasts or more, we consider that to be abnormal. Once that person has 20% blasts, we start to call that condition acute leukemia.

Patient/Caregiver Update:
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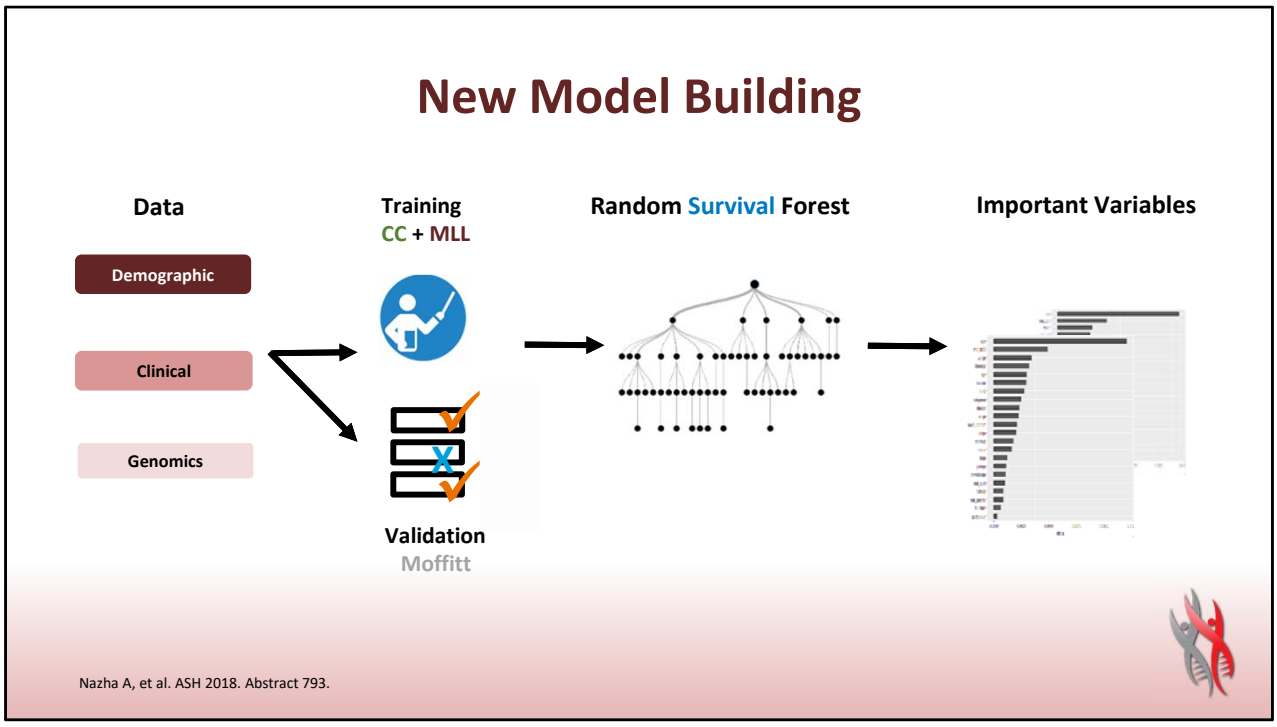
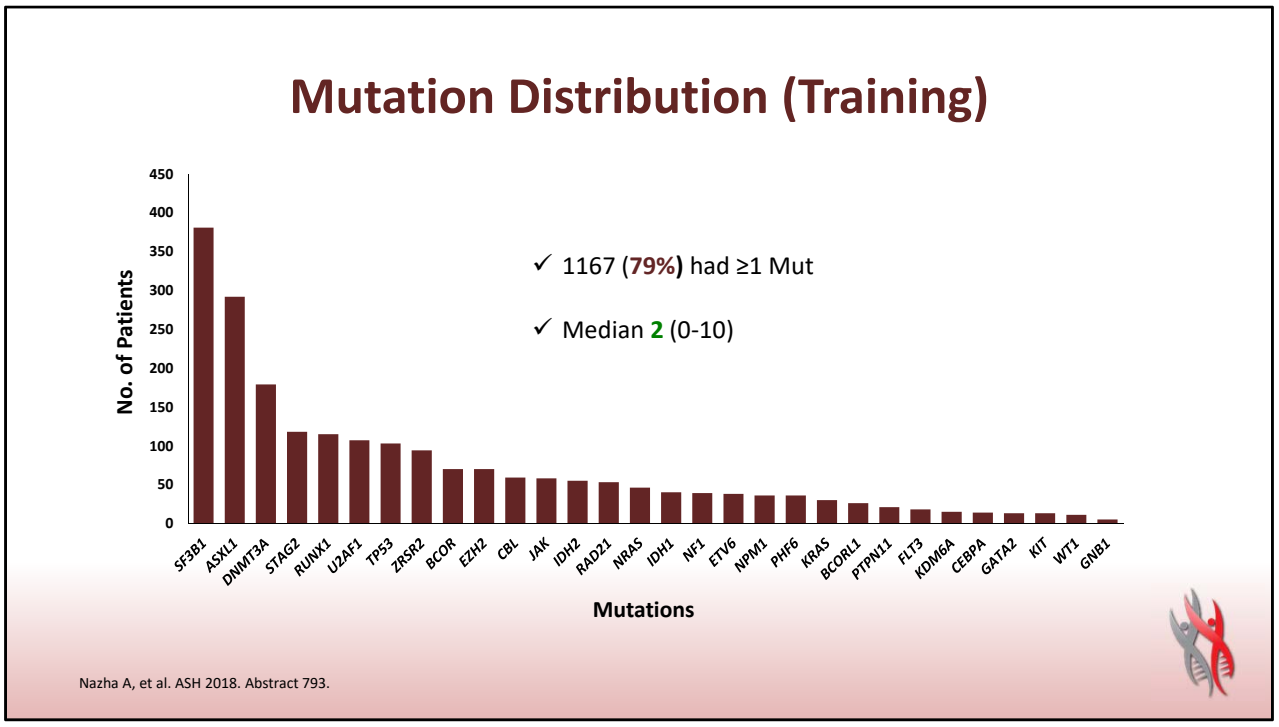
	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	(2)	3	4
Marrow blast proportion	≤2%	>2 - <5%	5 - 10%	>10%	
	0	(1)	2	3	
Hemoglobin	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	(1)	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	(0)	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	(0)	0.5	1		

Risk group	Points	% patients (n=7,012; AML data on 6,485)	Median survival, years	Median survival for patients under 60 years	Time until 25% of patients develop AML, years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermediate	(3.5-4.5)	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

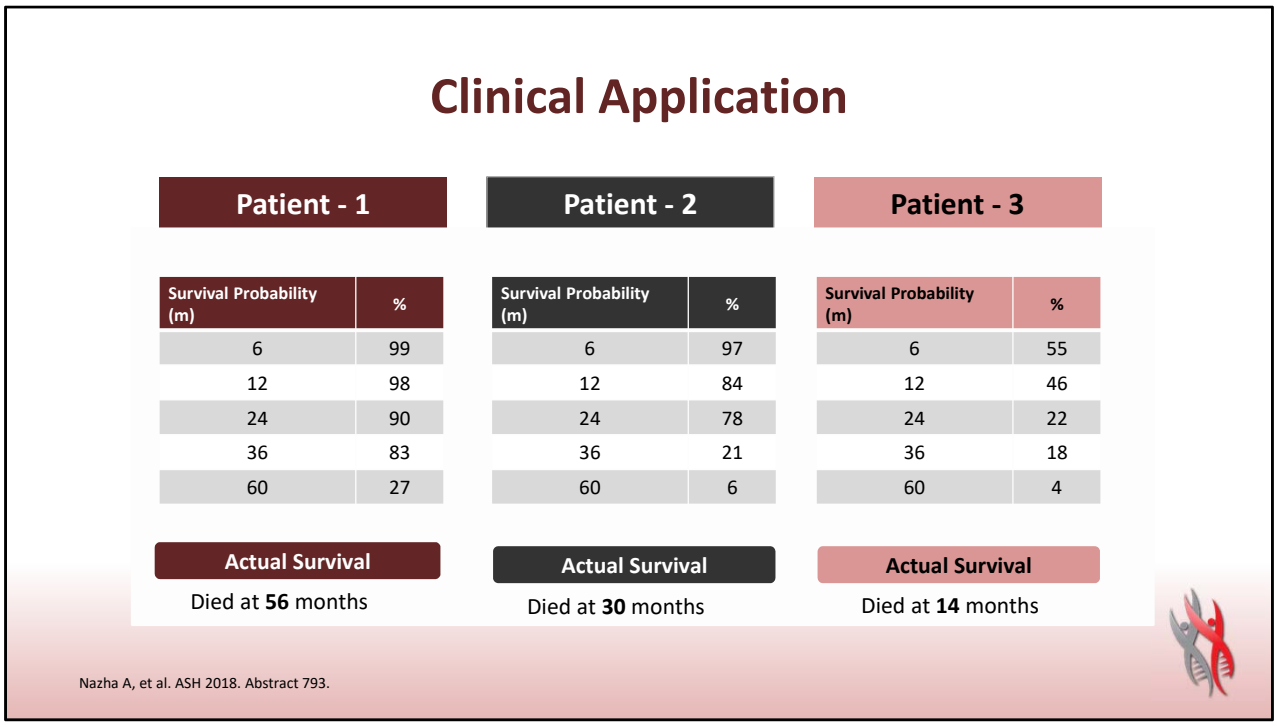
If you're trying to figure out what the prognosis is, you assign a point value to each one of these types of abnormalities that I just described. For example, somebody who has an abnormality of the gene on chromosome 8 in their MDS, that person would get a score of 2 under cytogenetic risk group. A person who has 3% blasts in the bone marrow, would get a score of 1. A person who has a hemoglobin of 8.5, that's a measure of anemia, would get a score of 1. Somebody who has a neutrophil count (those are the good guys among the white blood cells that fight bacterial infection) that's normal, let's say the neutrophil count is 2.0 or 2000, that person would get a score of 0. If a person has a normal platelet count, let's say platelets of 200,000, that person would also get a score of 0. We then add up those points; 2 for cytogenetics, 1 for blasts, 1 for hemoglobin, we'd get a total score of 4, and a score of 4 would place somebody into an intermediate risk category of the revised IPSS. This means that this person has a median survival of three years.



We can get much more sophisticated than that with things like machine learning and artificial intelligence. What we do now is get a lot of data about person's demographics (how old they are, their sex, all sorts of information), add to that some clinical parameters (what is their hemoglobin, what are their platelet counts or their blast percentage), and we fold into that the genetics of the disease. These are genetics at a much more refined level than what we call cytogenetics; we're looking at individual genes that we know occur abnormally in people with MDS. We put all of that into a computer that then goes through machine learning algorithms. We put the data in a training cohort where we teach the computer what's important, and then try to apply that in a total separate cohort of people. We come out with some important variables for predicting things like survival and likelihood of converting to leukemia.



This is an example of a lot of the genetic abnormalities that you can find, which have crazy names that are letters and numbers. Some of more common ones are SF3B1, ASXL1, DNMT3A, STAG2, TP53. We find abnormalities like these in over 90% of people with MDS. In this study, they were found in 79% of people who had one or more mutations. The typical MDS patient has two mutations.



We then apply this machine learning schema to three different patients who would have been predicted using the revised IPSS to have an average survival of three years. Well, it turns out there's a lot of heterogeneity in that intermediate risk group of the revised IPSS. One patient may live as long as 56 months. Another person may live as short as 14 months. We're increasingly going to be seeing systems like this in the future to be more accurate about our prognosis for our patients, and also to help determine the most appropriate therapy for people. David, I wonder how you use these prognostic scoring systems in your patients when you first see them?

Dr. David Steensma:
When I first meet a patient with MDS, I do try to risk stratify the patient using the existing tools, supplemented by the molecular data which we obtain on all patients that we see at our center for the first time. We always have to keep in mind though that, as good as these scoring systems are for the bulk of patients, in an individual case we really can't predict how they're going to do. They might have very good prognosis, looks like they're going to survive years and a few weeks later, they get a bad infection and it takes their life. They may be somebody who looks like they have a poor prognosis but they're one of the fortunate ones who respond, their disease responds very favorably to a treatment and they live for years and years. These are very important tools, and your colleague Dr. Nazha is using computational techniques to get better and better at how we're predicting how patients are going to do, but at the end of the day, there is always going to be some uncertainty and we have to be honest with the patients about that.

Dr. Mikkael Sekeres:
Yes, that's really well-stated. If you read in the newspaper, people are talking about the use of big data and data computation. This is an example of it: it's also entered the field of MDS to try to get more accurate at providing a prediction for an individual person. Yet we can use all the sophisticated computer technology we have in the world, but I always say to my patients, I would still look both ways when you're crossing Carnegie Avenue outside of our cancer center; anything can happen.

What is it that you think patients should be aware of, what basic factors should they ask their doctor for when they're diagnosed with MDS to determine their own prognosis?

Dr. David Steensma:
I think patients should understand where they fit, certainly, how many blasts they have in the marrow. It's important not to confuse marrow blasts with blood blasts because sometimes, there are blasts in the blood but it's really the marrow blasts that count. It is helpful to know what the chromosomes show too, because that can change with therapy. Most patients are very aware of their blood counts and that often is how they ended up seeing the hematologists or oncologist in the first place.

Dr. Mikkael Sekeres:
Great, thanks. David, I wonder if we can shift gears a little bit and talk about a study that looked at an iron chelation agent, in other words, a drug that's supposed to lower the iron levels in a person's body. This is one of the most common questions I get from my patients. Often people come to me more worried about their iron then they are about their MDS.

Dr. David Steensma:
Right, well patients with MDS are certainly at risk for having too much iron in the body and that sets up a reaction if a person has too much iron, that's very similar to rust. It's almost identical chemical process that can take place in the liver, or in late stages the heart, but just how much of a risk that is varies very much from patient to patient. One patient who's had 20 units of blood transfusions and another patient who has had 20 units of blood transfusions, their total body iron may be very different because they started from a different place, they absorbed iron differently, etc. There are medications that are available to get iron out of the body called chelators, but it has been controversial just how beneficial they are.

Patient/Caregiver Update:
What's New and What's Next in the Treatment of MDS?

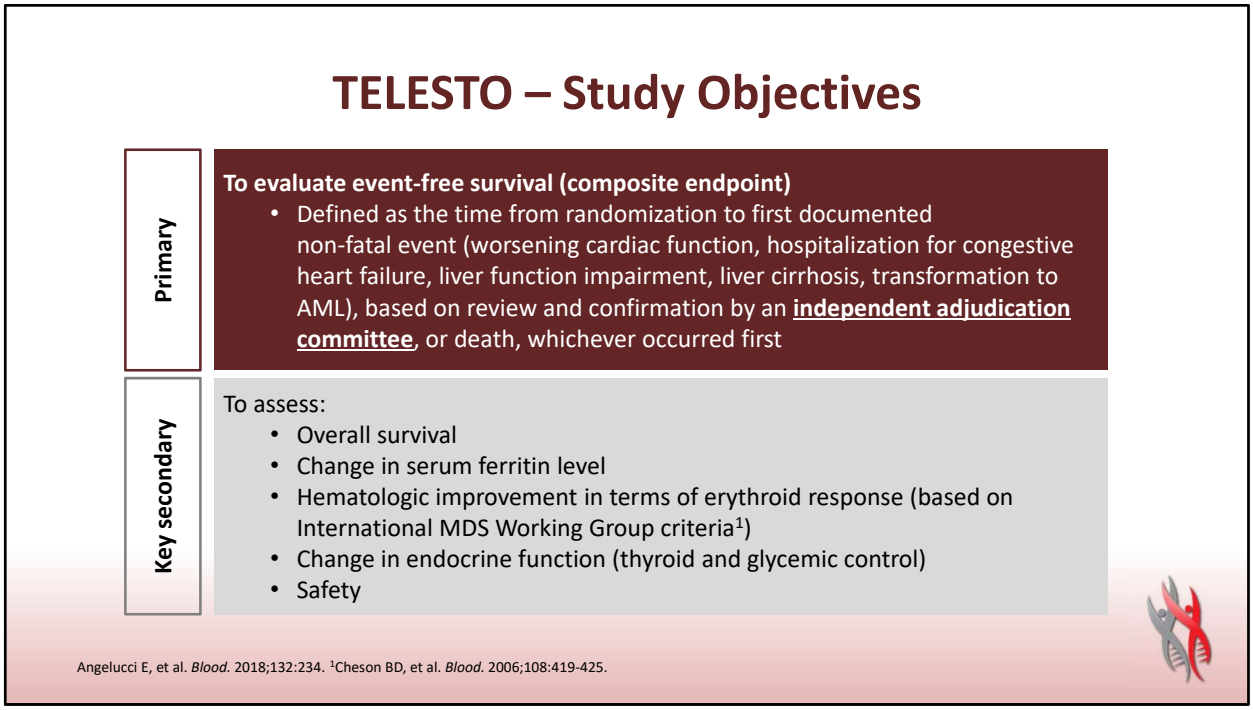
Safety and Efficacy, Including Event-free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients with Low- and Int-1-Risk Myelodysplastic Syndromes (MDS): Outcomes from the Randomized, Double-Blind TELESTO Study

- Although iron chelation therapy (ICT) has been shown to improve outcomes in lower-risk MDS patients, the studies were mainly retrospective analyses and registry studies[1-6]
- However, considerable debate remained on the clinical utility of ICT in this patient population, and the need for a randomized trial has long been recognized[7]

Aims	The TELESTO (NCT00940602) study prospectively evaluated event-free survival (EFS) and the safety of ICT with deferasirox versus placebo in patients with low/intermediate (Int)-1-risk MDS

Angelucci E, et al. *Blood.* 2018;132:234. [1]Delforge M, et al. *Leuk Res.* 2014;38:557-563. [2]Leitch HA, et al. *Clin Leukemia.* 2008;2:205-211. [3]Lyons RM, et al. *Leuk Res.* 2017;56:88-95. [4]Neukirchen J, et al. *Leuk Res.* 2012;36:1067-1070. [5]Remacha AF, et al. *Ann Hematol.* 2015;94:779-787. [6]Rose C, et al. *Leuk Res.* 2010;34:864-870. [7]Meerpohl JJ, et al. *Cochrane Database Syst Rev.* 2014:CD007461.

About 10 years ago, a group of international investigators got together and said okay, we're going to take patients who have lower-risk MDS – so we hope that they're going to survive for years – and they have received between 15 and 75 units of blood, but they still have good organ function. We're going to give them either deferasirox (which you may know as Exjade or Jadenu) or placebo, and we're going to see which patients live longer. Unfortunately, because many patients did not qualify for the study because they had such narrow enrolment criteria and also because many doctors either are proponents of chelation or skeptics, this study did not accrue very well.



Instead of looking at overall survival (how long people were going to live) the investigators had to enroll a much smaller population and look at what's called event-free survival, which is the time from enrollment in the trial until something happens: hospitalization for worse heart function, liver tests are worse, scarring of the liver (cirrhosis) is first detected.

Summary

- TELESTO is the first prospective, randomized study of ICT in patients with Low-/Int-1-risk MDS and iron overload
- Treatment with deferasirox led to longer EFS compared with placebo
- Exposure-adjusted AEs were similar in the two arms with the exception of non-severe increases in serum creatinine, with no new safety signals
- Considering the current treatment landscape, it is unlikely that a similar randomized trial will be performed

- ✓ **A 36.4% risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)**
- ✓ **TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS**
- ✓ **TELESTO provides evidence on the clinical benefit of ICT in lower-risk MDS patients with iron overload**

Angelucci E, et al. *Blood*. 2018;132:234.

When they did this, there was a benefit from the chelation, and it was pretty modest I have to say. The patients who had this composite endpoint of event-free survival, it was delayed by a few months and the events were reduced. The tradeoff was that people who got the chelator had increase in their creatinine, which implies a decrease in kidney function. Many of them had stomach upset or diarrhea and, of course, we know that iron chelation is expensive. I think we're left in a difficult situation where there some patients for whom chelation is likely beneficial, and there are some patients for whom chelation likely makes no difference and just adds cost and risk of side effects. We still don't know who those patients are, even after the study, and I think the fact that the study was so hard to do indicates that probably, there won't be another study of this, at least with the current chelator. What's your practice, Mikkael, with respect to which patients you offer chelation?

Dr. Mikkael Sekeres:
Yes, David, nice job presenting that study. This is always one of the more challenging conversations I have with a patient. No study prospectively (meaning in real-time), has ever shown that there's a survival advantage to giving a chelation agent compared to doing nothing in somebody with MDS. Chelation agents make complete sense in a child born with thalassemia or sickle cell disease: someone who's going to be getting transfusions for decades. In my patients, where the average age of diagnosis of MDS is 71 years, we should be so lucky that they're going to live decades to then experience the consequences of iron overload.

I will discuss chelation therapy in my patients who are heavily transfused, who have gotten for example, more than 50 packs of blood in their lifetimes, and those who have an appearance, it's almost a bronzy skin color that can occur when iron deposits in the skin. In those patients, I'm actually seeing the evidence that iron is there. If it's in the skin, it's probably in other organs and we'll initiate a discussion about chelation therapy. But I will tell you, in my own personal experience, it has been hard to keep these patients on these drugs because they don't like the side effects. That was actually seen in that study, wasn't it? The patients couldn't stay on the drug?

Dr. David Steensma:
Yes, 40% of them dropped out within the first year because of adverse events and side effects. In previous studies, both a European and a U.S. study, it was 50% who discontinued within the first year. Keep in mind that's 50% of people who are selected to participate in a study and met the criteria, so they were in theory a little bit better than the average patient with MDS in terms of other problems and other conditions. It is hard to keep people on that kind of therapy just because it's not easy to take.

Dr. Mikkael Sekeres:
David, thank you for that discussion about chelation therapy that is no easy nut to crack. There was a study on another drug that was presented at ASH. It was actually the number one abstract presented at ASH as a plenary presentation, and you had the privilege of introducing that plenary. I wonder if you could tell us about this new drug, luspatercept.

The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients with Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

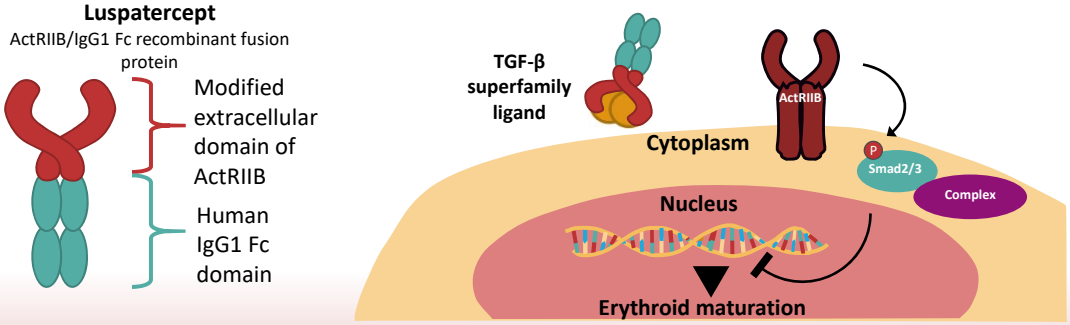
- Patients with lower-risk (LR)[a] transfusion-dependent MDS have a poorer prognosis, with greater risk of progression to AML and inferior overall survival compared to transfusion-independent MDS patients
- RBC transfusion-dependent LR, non-del(5q) MDS patients have a transient response to ESAs, with an attendant risk of iron overload and secondary organ complications
- Few treatment options exist for LR MDS patients who are either refractory to or become unresponsive to erythropoiesis-stimulating agents (ESAs)[1]

[a] IPSS-R-defined criteria
Fenaux P, et al. *Blood*. 2018;132:1. [1]Fenaux P, Ades L. *Blood*. 2013;121:4280-4286.

Dr. David Steensma:
Yes, so luspatercept is a drug that is attempting to answer an unmet need that we just described, which is that many patients with MDS continue to require transfusions and are failed by drugs such as Procrit or Aranesp, or they are not candidates for those drugs to begin with.

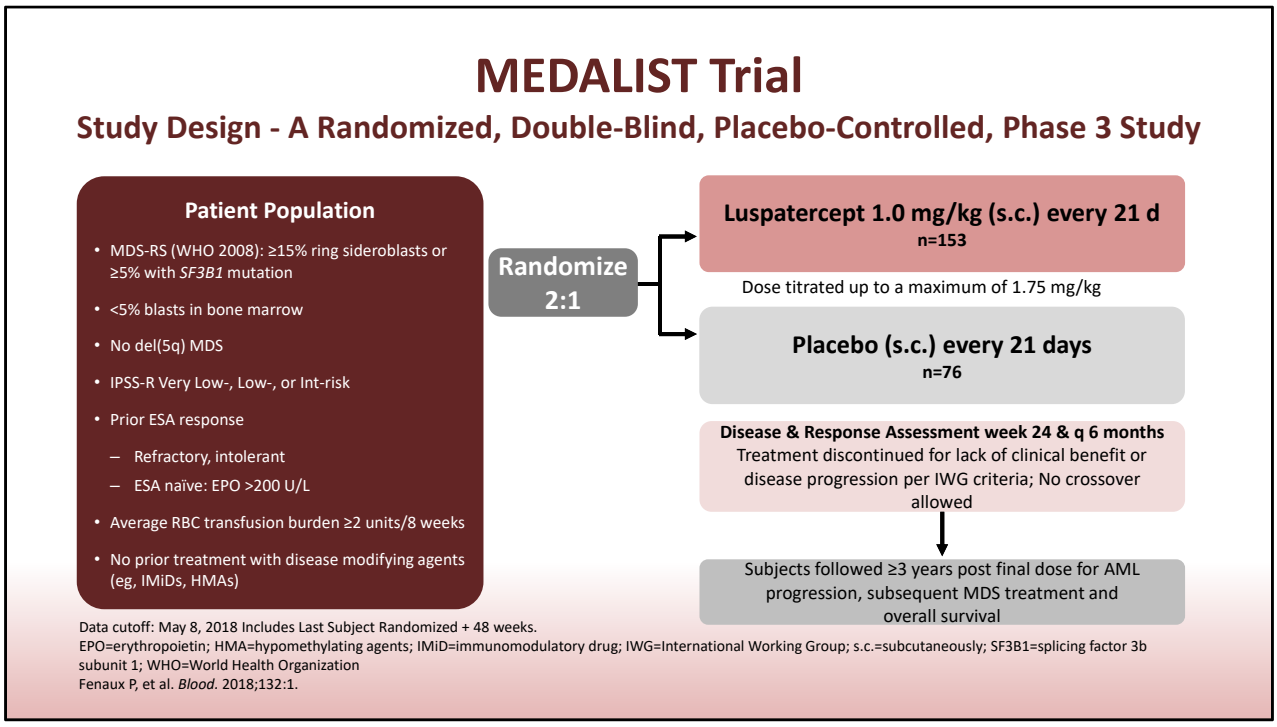
MEDALIST Luspatercept Trial

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion-reduction or RBC-TI in patients with MDS-RS (52%) vs other subtypes (30%)[2]



TGF-β=transforming growth factor-beta; ActB=activin B; ActRIIB=human activin receptor type IIB; IgG1 Fc=immunoglobulin G1 fragment crystallizable; LR=lower-risk; RBC-TI=red blood cell transfusion independence; RS=ring sideroblasts
Fenaux P, et al. *Blood*. 2018;132:1. [1]Suragani RN, et al. *Nat Med*. 2014;20:408. [2]Platzbecker U, et al. *Lancet Oncol*. 2017;18:1338.

Luspatercept is a treatment that's been developed for various forms of anemia including lower-risk MDS. It's an antibody that binds to molecules that are members of the family called TGF-beta, which inhibit red cell development. The idea is that by putting a brake on the brake, by inhibiting an inhibitor, you'll allow red blood cells to grow better than they would otherwise.



These were patients with lower-risk MDS who had ring sideroblasts, about 20% of MDS patients that's the finding in the bone marrow, and they had to have had at least two units of blood in the prior eight weeks. Two-thirds of them got luspatercept under the skin every three weeks and one-third got a placebo.

MEDALIST Trial: Study Endpoints

Primary endpoint:
- Red blood cell – transfusion independence ≥8 weeks (weeks 1–24)

Key secondary endpoints:
- Red blood cell – transfusion independence ≥12 weeks, weeks 1–24
- Red blood cell – transfusion independence ≥12 weeks, weeks 1–48

Additional secondary endpoints:
- HI-E (IWG 2006 criteria[1]) for any consecutive 56-day period
  Reduction in transfusion burden ≥4 RBC units/8 weeks[a] or
  Mean Hb increase of ≥1.5 g/dL/8 weeks[b]
- Duration of response
- Hb change from baseline
- Mean serum ferritins

[a] In patients with baseline RBC transfusion ≥4 units/8 weeks. [b] In patients with baseline RBS transfusion burden <4 units/8 weeks.
Hb=hemoglobin; HI-E=hematologic improvement-erythroid
Fenaux P, et al. *Blood*. 2018;132:1. [1]Cheson B, et al. *Blood*. 2006;108:419-425.

The primary endpoint that the study was measuring was: what proportion of patients in each group – in the luspatercept group and in the placebo group – became free of transfusions for at least eight weeks?

MEDALIST Trial
Demographics and Baseline Disease Characteristics

Characteristic	Luspatercept (n=153)	Placebo (n=76)
Age, median (range), years	**71 (40–95)**	**72 (26–91)**
Male, n (%)	**94 (61.4)**	**50 (65.8)**
Time since original MDS diagnosis, median (range), months	**44.0 (3–421)**	**36.1 (4–193)**
WHO Classification		
RCMD[a] or RCMD-RS, n (%)	**145 (94.8)**	**74 (97.4)**
RBC transfusion burden, median (range), units/8 weeks[a]	5 (1–15)	5 (2–20)
≥6 units/8 weeks, n (%)	**66 (43.1)**	**33 (43.4)**
<6 units/8 weeks, n (%)	87 (56.9)	43 (56.6)
Pretransfusion Hb, median (range), g/dL	**7.6 (6–10)**	**7.6 (5–9)**
IPSS-R risk category stratification[b]		
Very Low, Low, n (%)	127 (83.0)	63 (82.9)
Intermediate, n (%)	25 (16.3)	13 (17.1)
***SF3B1* mutation, n (%)**	**141 (92.2)**	**65 (85.5)[c]**
Serum EPO		
<200 U/L, n (%)	88 (57.5)[c]	50 (65.8)
≥200 U/L, n (%)	64 (41.8)[c]	26 (34.2)

[a] In the 16 weeks prior to randomization. [b] 1 (0.7%) patient in the luspatercept arm classified as IPSS-R High. [c] Data was missing for 1 patient.
RCMD=refractory cytopenia with multilineage dysplasia; RCMD-RS=RCMD with ring sideroblasts
Fenaux P, et al. *Blood*. 2018;132:1.

The study population was pretty typical. The average units of blood that patients had had in the eight weeks before enrollment was six units. Most of them had previously had Procrit or Aranesp and had been failed by those drugs.

MEDALIST Trial

Primary Endpoint Achieved: Red Blood Cell – Transfusion Independence) ≥8 Weeks

RBC-TI ≥8 weeks	Luspatercept (n=153)	Placebo (n=76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥6 units vs <6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
Fenaux P, et al. *Blood*. 2018;132:1.

37.9% of the patients in the luspatercept group and 13% of the patients in the placebo group – so a difference of 24% – met the endpoint of eight weeks of transfusion freedom.

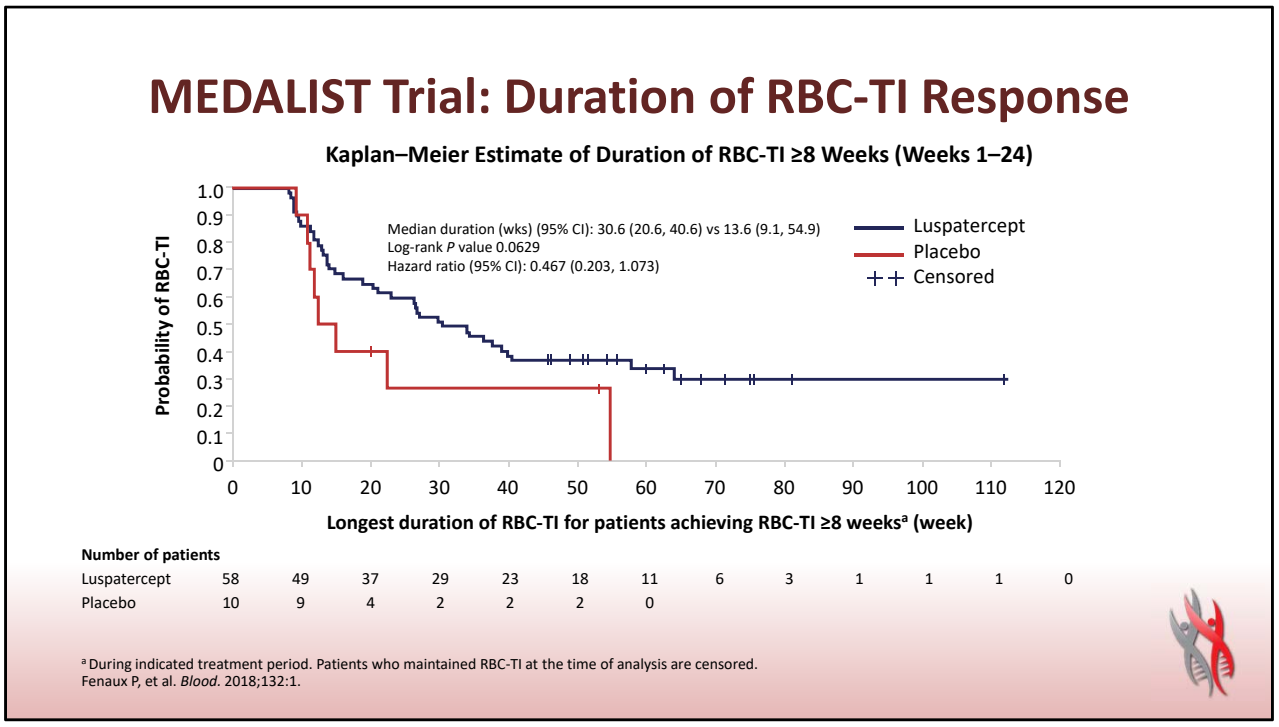
MEDALIST Trial

Key Secondary Endpoints: Red Blood Cell – Transfusion Independence ≥12 Weeks

RBC-TI ≥12 weeks	Luspatercept (n=153)	Placebo (n=76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

[a] Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥6 units vs <6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
Fenaux P, et al. *Blood*. 2018;132:1.

There was no separate group that seemed to benefit more than any other, and if one looked at how many were free of transfusions for at least 12 weeks, that was 28% versus almost 8%.



The median duration of transfusion independence when it happened was 30 weeks, about 7 to 7-1/2 months.

MEDALIST Trial

Secondary Endpoint Achieved: Erythroid Response (HI-E)

	Luspatercept (n=153)	Placebo (n=76)
Achieved HI-E[a] (Weeks 1–24), n (%)	**81 (52.9)**	**9 (11.8)**
Reduction of ≥4 RBC units/8 weeks (baseline transfusion burden ≥4 units/8 weeks)	52/107 (48.6)	8/56 (14.3)
Hb increase of ≥1.5 g/dL (baseline transfusion burden <4 units/8 weeks)	29/46 (63.0)	1/20 (5.0)
95% CI	44.72–61.05	5.56–21.29
P value[b]	<0.0001	
Achieved HI-E[a] (Weeks 1–48), n (%)	**90 (58.8)**	**13 (17.1)**
Reduction of ≥4 RBC units/8 weeks (baseline RBC transfusion burden ≥4 units/8 weeks)	58/107 (54.2)	12/56 (21.4)
Hb increase of ≥1.5 g/dL (baseline RBC transfusion burden <4 units/8 weeks)	32/46 (69.6)	1/20 (5.0)
95% CI	50.59–66.71	9.43–27.47
P value[b]	<0.0001	

[a] Defined as the proportion of patients meeting the HI-E criteria per IWG 2006 criteria[1] sustained over a consecutive 56-day period during the indicated treatment period.
[b] Luspatercept compared with placebo, Cochran-Mantel-Haenszel test.
Fenaux P, et al. *Blood*. 2018;132:1.; Cheson B, et al. *Blood*. 2006;108:419-425.

If you look at the proportion of patients who had an improvement in their hemoglobin regardless of transfusion, that was even a little higher than the luspatercept arm, 52%.

MEDALIST Trial
Safety: TEAEs and Serious TEAEs

TEAEs ≥10%, Incidence in any arm **by Category**	**Luspatercept** (n=153) TEAE ≥10%, n (%)	**Placebo** (n=76) TEAE ≥10%, n (%)
Fatigue	41 (26.8%)	10 (13.2%)
Diarrhea	34 (22.2%)	7 (9.2%)
Asthenia	31 (20.3%)	9 (11.8%)
Nausea	31 (20.3%)	6 (7.9%)
Dizziness	30 (19.6%)	4 (5.3%)
Back pain	29 (19.0%)	5 (6.6%)
Cough	27 (17.6%)	10 (13.2%)
Oedema peripheral	25 (16.3%)	13 (17.1%)
Headache	24 (15.7%)	5 (6.6%)
Dyspnea	23 (15.0%)	5 (6.6%)
Constipation	17 (11.1%)	7 (9.2%)
Urinary tract infection	17 (11.1%)	4 (5.3%)
Fall	15 (9.8%)	9 (11.8%)
Upper respiratory tract infection	15 (9.8%)	3 (3.9%)

Serious TEAEs ≥2%, Incidence in any arm **by Category**	**Luspatercept** (n=153) sTEAE ≥2%, n (%)	**Placebo** (n=76) sTEAE ≥2%, n (%)
Pneumonia	3 (2.0%)	2 (2.6%)
Urinary Tract Infection	3 (2.0%)	1 (1.3%)
Fall	3 (2.0%)	3 (3.9%)
Back Pain	3 (2.0%)	0 (0%)
Syncope	3 (2.0%)	0 (0%)

Overall for thromboembolic events were no significant differences between luspatercept and placebo arm.
Fenaux P, et al. *Blood*. 2018;132:1.

The drug was really well-tolerated. Most patients had very few side effects and there was no significant difference in side effects other than some fatigue between the luspatercept group and the placebo group.

MEDALIST Trial: Conclusions

- Luspatercept treatment was well tolerated and yielded a significantly higher proportion of patients who achieved RBC-TI or HI-E (major RBC transfusion reduction, Hb increase) compared with placebo in LR-MDS-RS patients (P<0.0001)
- Erythroid responses are durable, with 40% of patients achieving RBC-TI sustained at 12 months of treatment
- Luspatercept is a promising novel therapy for the treatment of patients with lower-risk MDS-RS with RBC transfusion-dependent anemia

Fenaux P, et al. *Blood*. 2018;132:1.

Overall, this drug was quite well-tolerated. We would have hoped that response rate would have been higher, but it did help, and I think the likelihood the FDA will approve this in the next 6 to 12 months is pretty high. We still have some work to do.

What were your impressions of these data, Mikkael? As you point out, this was at the plenary session which is a special session with no competing sessions, where the top six abstracts out of the six or seven thousand submitted to the meeting are presented. Clearly, the reviewers thought this was an important study from the global hematology standpoint.

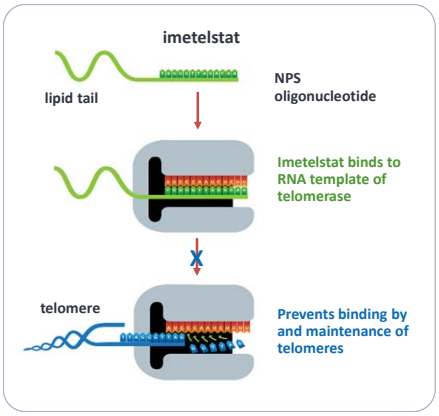
Dr. Mikkael Sekeres:
The fact that it was a plenary is a testimony both to the importance of the study (it was a large study conducted internationally and enrolled very quickly) but also, unfortunately, to the lack of available therapies that we have for MDS. We haven't had a drug approved with an MDS indication for over a decade, so this is probably the next up. We both anticipate that this will get approved later this year, third quarter or fourth quarter of 2019. It represents a step forward but not really a leap forward for MDS, as you indicated. Seeing about 4 out of 10 people get better on a drug is okay but we would have loved to have seen 7 or 8 out of 10 get better. What balances this is that it really didn't seem to have a lot of bad side effects, it was really well-tolerated. I anticipate that if it does get FDA approved, it will work its way into the treatment of a lot of MDS patients pretty quickly. David, do you have any sense about whether luspatercept is better than receiving erythropoietin or darbepoetin (Procrit and Aranesp)?

Dr. David Steensma:
That's a great question and that is being tested as we speak. There is a trial going on in which instead of a placebo control, as first-line therapy patients are getting either luspatercept or darbepoetin or epoetin in a clinical trial. I think that will help answer that question. Interestingly, that trial is not restricted to patients with MDS with a ring sideroblast subtype. It's a broader trial and it may be that this drug has efficacy in non-ring sideroblast patients. There were some patients treated in an earlier small trial without ring sideroblasts who benefited. In addition, the drug has been tried in some other conditions like that inherited disorder thalassemia you mentioned a few minutes ago, and that study was positive as well. I think this may be a drug that improves anemia in multiple conditions.

Dr. Mikkael Sekeres:
Yes, nicely stated. I wonder David if you wanted to mention briefly a trial that you were very involved in of a new drug called imetelstat.

Background: MDS and Imetelstat

- Patients with TD lower-risk MDS that has relapsed or is refractory to ESA therapy have limited treatment options
- Higher telomerase activity, expression of hTERT and shorter telomeres predict for shorter overall survival in lower-risk MDS
- Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomere lengths and active telomerase and has clinical activity in myeloid malignancies[1-3]
  - FDA granted Fast-Track designation for LR-MDS (Oct 2017)
- IMerge is an ongoing global phase 2/3 study of imetelstat in RBC TD patients with LR-MDS (IPSS Low or Int-1)
  - Part 1 consists of an open-label, single-arm design with single-agent imetelstat treatment
  - Preliminary results have been presented for the first 32 enrolled patients[4]

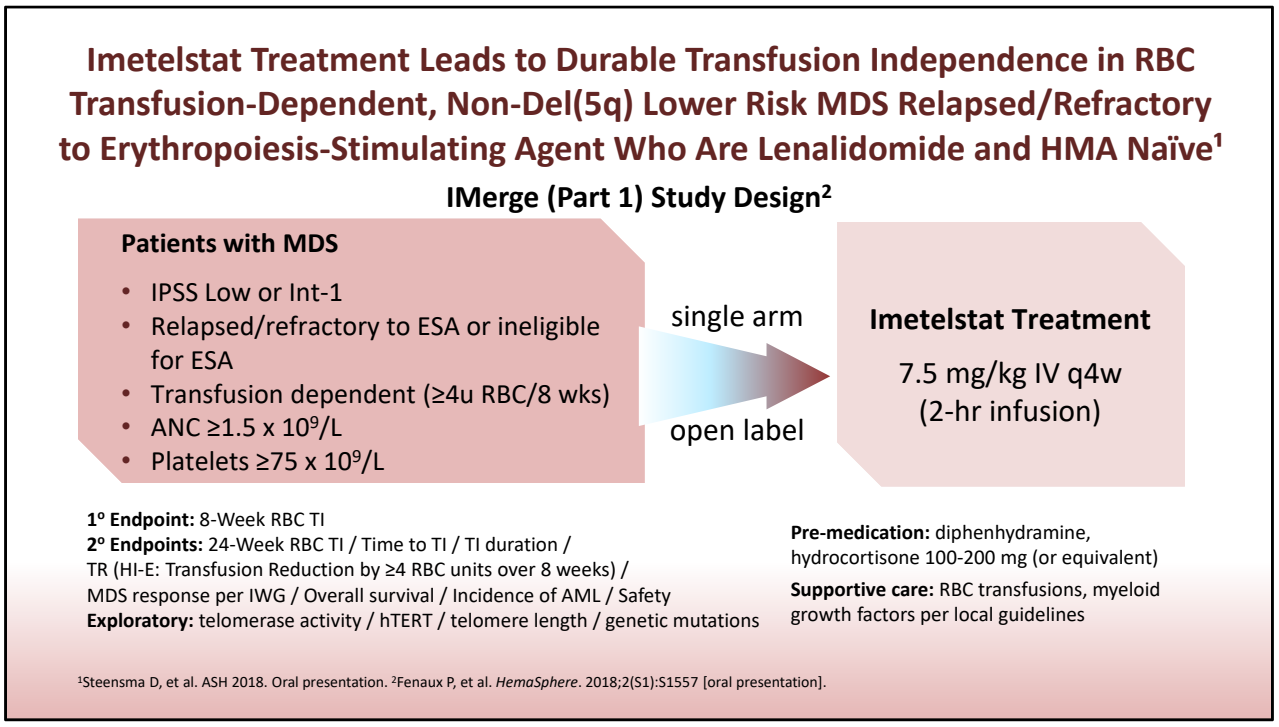


Htert=human telomerase reverse transcriptase;
IPSS=International Prognostic Scoring System;
Int-1= Intermediate-1; TD=transfusion dependent

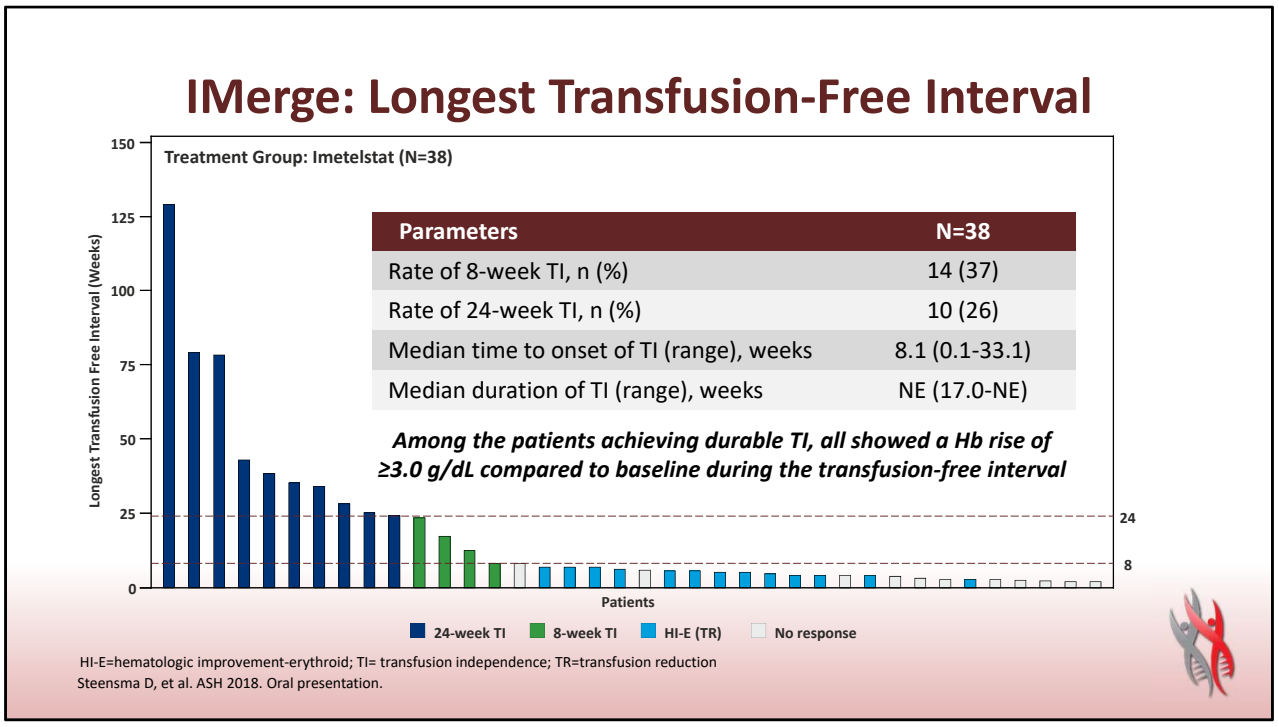
[1]Baerlocher GM, et al. *N Engl J Med*. 2015;373:920-928. [2]Tefferi A, et al. *N Engl J Med.* 2015;373:908-919. [3]Tefferi A, et al. *Blood Cancer J.* 2016;6:e405.
[4]Fenaux P, et al. *HemaSphere.* 2018;2(S1):S1557 [oral presentation].

Dr. David Steensma:
Yes, this drug is interesting in that it is also focusing on patients with lower-risk MDS who are getting transfusions. It's an inhibitor of an enzyme that puts the caps on chromosomes, called telomerase. In some patients with MDS, the cells activate this enzyme and when they should die because their caps are too short, this telomerase inhibitor helps them survive.

Patient/Caregiver Update:
What's New and What's Next in the Treatment of MDS?

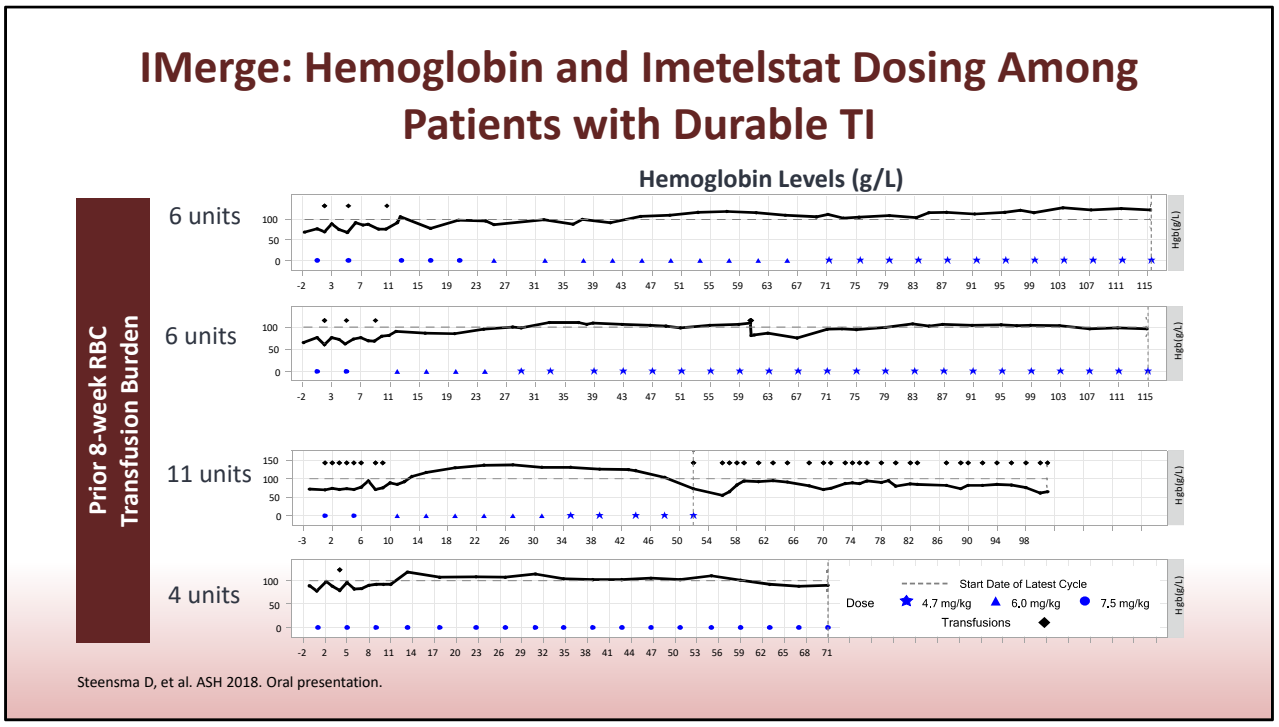


I presented data on 38 patients who had previously had epoetin or darbepoetin, were getting a lot of transfusions, and still have lower-risk disease. There was no placebo here. This was a phase II study so everybody got a two-hour infusion every four weeks.



The response rate in terms of the proportion of people who were free of transfusions for eight weeks, was identical to luspatercept 37%.

Patient/Caregiver Update:
What's New and What's Next in the Treatment of MDS?



Here you can see hemoglobin on the Y axis and time on the X, four patients responded nicely and were free of transfusions for over a year, so this is interesting.

Conclusions: Overall Efficacy and Safety

- Nineteen patients (50%) had dose reductions and 26 patients (68%) had cycle delays
- Reversible grade 3 LFT elevations were observed in 3 (8%) patients on study
- Side effects were limited, mainly cytopenias that were predictable, manageable, and reversible

Steensma D, et al. ASH 2018. Oral presentation.

I think one of the concerns that we have about this drug is that there were a lot patients in whom the white count and the platelet count were lower. That was reversible, but it still is a concern because that wasn't seen with luspatercept. This drug is in the phase III trial at this point being randomized against placebo, a very similar design to the MEDALIST trial of luspatercept we just talked about. It will be interesting to see where this fits.

So I'll turn things over to you, Mikkael, to talk a little bit about some other things that are going on for MDS. Particularly, there's a lot of interest in immune checkpoint inhibitors because of their efficacy in patients with solid tumors

Dr. Mikkael Sekeres:
Yes, I think the number one question my patients ask me is about lowering their iron levels. I think the number two question I receive is about immunotherapies, because we read so much about these in the newspaper or on Twitter or hear about them in the news. These drugs have really been remarkably effective in people with solid tumors like melanoma, like former president Carter, and also in certain types of lymphoma, so people have been anxious to see how well they work in disorders like myelodysplastic syndromes.

A Phase II Study of Nivolumab or Ipilimumab with or without Azacitidine for Patients with MDS

ICPI in MDS: Treatment

Cohort	Therapy
Cohort #1	Nivolumab 3 mg/kg IV q2 weeks
Cohort #2	Ipilimumab 3 mg/kg IV q3 weeks
Cohort #4	Azacitidine 75 mg/m^2 IV x 5 days q 28 Nivolumab 3 mg/kg IV on day 6 and 20
Cohort #5	Azacitidine 75 mg/m^2 IV x 5 days q28 Ipilimumab 3 mg/kg IV on day 6

Garcia-Manero G, et al. ASH 2018. Abstract 465.

There was a study that was conducted by the M.D. Anderson Group in Texas that actually assigned patients to one of four different trial arms. Patients either got the drug nivolumab as a single agent alone, or ipilimumab as a single agent alone, or they got these drugs in combination with azacitidine. They got the single drug if they had already received azacitidine, or its sister drug decitabine in the past; they got the combinations if they hadn't received either of these drugs in the past.

ICPI in MDS: Patient Characteristics

	Frontline		HMA failure	
	Nivo + AZA N=20	Ipi + AZA N=21	Nivo N=15	Ipi N=20
Age	66 [39.5-83.3]	72 [45.1-85.0]	78 [61.8-84.8]	69 [48.1-85.7]
Male	16 (80)	12 (57)	8 (53)	10 (50)
PS ≥2	1 (5)	5 (24)	2 (13)	3 (15)
WBC	5.1 (1.7-48.2)	3.4 (0.5-22.1)	1.8 (0.8-16.3)	2.0 (0.9-21.3)
ANC	2.2 (0.0-31.8)	1.9 (0.1-10.6)	0.4 (0.1-9.0)	0.7 (0.2-13.4)
Hgb	9.6 (7.3-14.6)	9.8 (5.2-13.3)	9.5 (6.5-11.2)	9.1 (6.5-13.8)
Plt	54 (6-224)	62 (2-319)	31 (12-282)	43 (2-189)
BM blasts	9 (1-18)	8 (1-18)	4 (1-13)	
Dx group				
MDS	13 (65)	17 (81)	14 (93)	16 (80)
MDS/MPN	6 (30)	4 (19)	1 (7)	4 (20)
AML	1 (5)	0	0	0

Garcia-Manero G, et al. ASH 2018. Abstract 465.

Patients who were enrolled on this study were pretty typical of those with MDS, with an age range of 66 to 78 years old on average. They were a mix of lower risk and higher risk MDS, and there was one patient who was enrolled who actually had leukemia.

ICPI in MDS: Response Rates

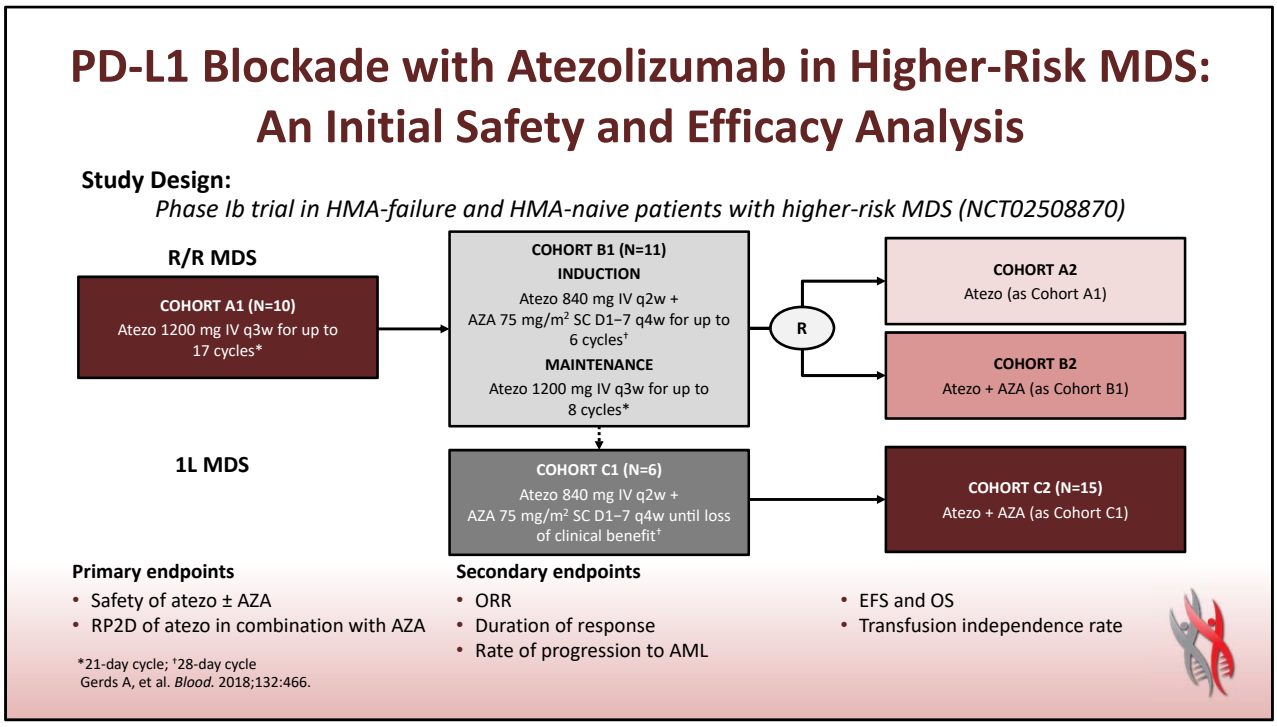
	Frontline		HMA failure	
	Nivo + AZA N=20	Ipi + AZA N=21	Nivo N=15	Ipi N=20
Response				
ORR	14 (70)	13 (62)	0 (0)	6 (30)
CR	8 (40)	3 (14)	0 (0)	0 (0)
mCR+HI	2 (10)	0 (0)	0 (0)	1 (5)
mCR	3 (15)	7 (33)	0 (0)	3 (15)
HI	1 (5)	3 (14)	0 (0)	3 (15)
SD	0 (0)	1 (5)	0 (0)	0 (0)
NR	5 (25)	5 (24)	15 (100)	13 (65)

- Not evaluable: 3 patients
- Median number of cycles: 4 (range 1-29)
- Median number of cycles to response: 3 (range 1-15)

Garcia-Manero G, et al. ASH 2018. Abstract 465.

When you look at the response rates on these drugs, they look pretty impressive for the combination arm. However, the overall response rate could be a little bit deceiving. When you look at the overall response rate for patients who got the nivo plus aza, it looks like it's 70%, and boy, that seems pretty high. There was one criterion for response that was included in there that isn't really a response that we value, because it doesn't translate into an improvement in somebody's life, and that's what's called a marrow CR. When we subtract that out of the response rates, the overall response rate actually drops to about 55%. That's still pretty good when you consider that the overall response rate to azacitidine alone is somewhere between 35% and 40%, But as David and I have discussed in the past, you tend to enroll healthier people to these studies so you tend to get slightly higher response rates than you would see in a general population, so that may not be that different.

When we look at the next arm of azacitidine and ipi, the overall response rate is 62%. Once again, we've got to subtract out a good portion of those patients who don't have a real response that we value and when you do that, the overall response rate comes down to 29%, worse than we would have expected with azacitidine alone. When we look at the patients who were treated just with nivo or just with epi, they really don't do too well at all. Those who got nivo alone actually nobody responded to the drug. Nobody got better on it. Those treated with ipi alone, only about 15% of people got better on it. So what I take out of this study is that, these checkpoint inhibitors, these immunotherapies aren't quite ready for primetime in people who have MDS.



There was another study that was presented by a colleague of mine, Aaron Gerds, looking at a different immunotherapy called atezolizumab also in people who have MDS. Once again, in this study, people got either the atezo alone if they had already received azacitidine or decitabine, or they got a combination if they were newly diagnosed and they have never been treated with azacitidine or decitabine in the past.

Response Rates in MDS (N=42)

N (%)	Cohort A1 Atezo (n=10)	Cohort B1 Atezo + AZA (n=11)	Cohort C1/C2 (1L) Atezo + AZA (n=21)
ORR (CR, PR, mCR, HI, mCR+HI)	0	1 (9)	13 (62)
HRR (CR, PR, HI, mCR+HI)	0	1 (9)	9 (43)
CR	0	0	3 (14)
PR	0	0	0
mCR	0	0	4 (19)
mCR + HI	0	0	2 (10)
HI	0	1 (9)	4 (19)
SD	7 (70)	6 (55)	3 (14)
PD	3 (30)	2 (18)	1 (5)
Not evaluable	0	2 (18)	4 (19)
mOS	177 days	361 days	NR

Study terminated early prior to completion of enrollment to all study cohorts

CCOD: 12 January 2018; NR=not reached

In this study, the overall response rate to atezo alone was 0% again. These drugs, it was reinforced, don't work alone in people who have MDS. Even in combination with the azacitidine, the response rate was 43%. Again, not much different than you would expect for azacitidine alone. My bottom line for these drugs is that they're not quite ready for primetime yet in MDS but people are still looking at them in a variety of studies.

Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with *TP53* Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

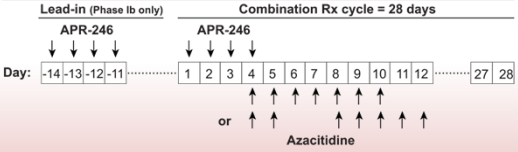
Study Design:

- TP53 mutant (mTP53) HMA-naïve MDS and AML (≤30% blasts)

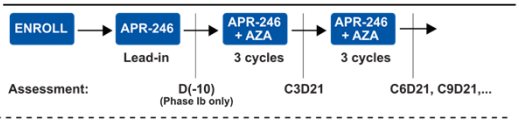
Dosing

Drug	Dose	Admin.	Duration
APR-246	Ph1b: 50 / 75 / 100 mg/kg LBM Ph2: 4500 mg fixed dose	i.v.	6 hr
Azacitidine	75 mg/m²	s.c. (or i.v.)	-

Dosing Schedule



Assessment Schedule

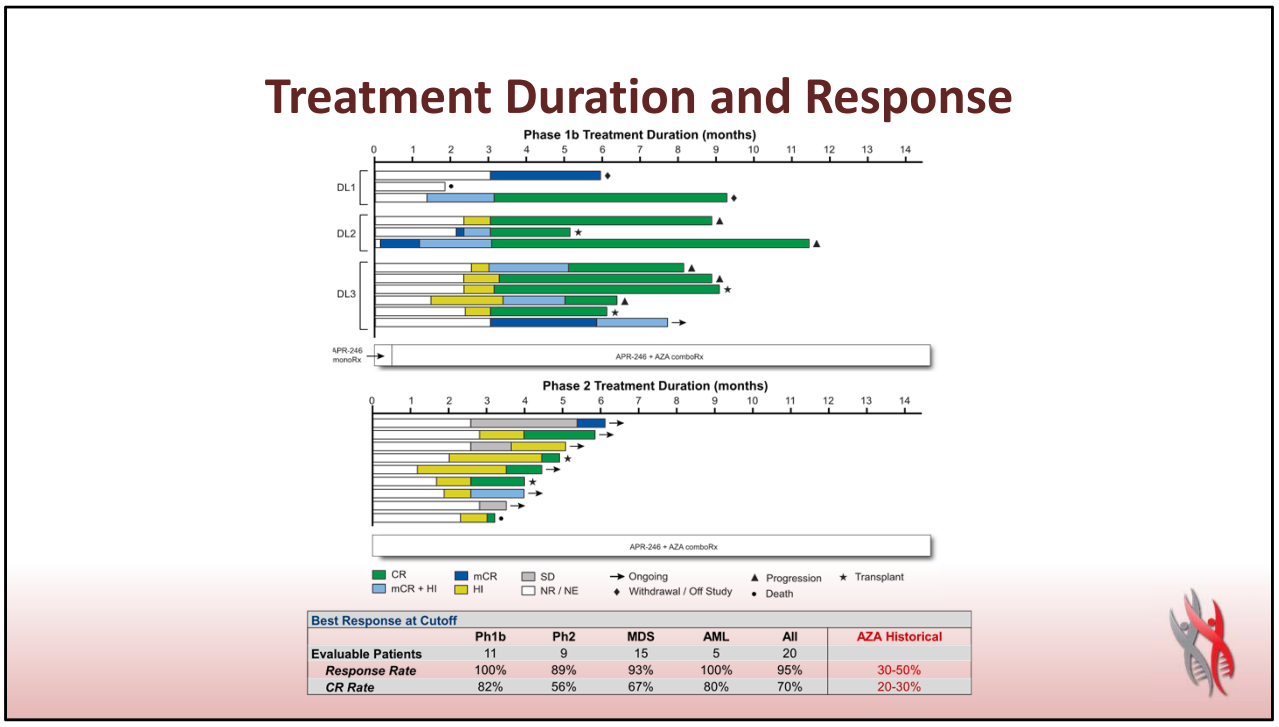


Endpoints

	Phase 1b	Phase 2
Primary:	Safety	CR rate
Secondary:	ORR, PFS, OS, *TP53* VAF	ORR, PFS, OS, *TP53* VAF

Sallman D, et al. ASH 2018. Abstract 3091.

There's another drug that was also looked at in an earlier phase study. This drug, it doesn't even really have a name yet, we call it a bunch of letter and numbers, APR246. This is specifically for people with higher risk MDS who have one of those genetic abnormalities; this one is the P53 abnormality. This is a particularly bad actor, and people who have this abnormality tend to not live very long and tend to not get better to drugs. In this study, the APR246 was combined with azacitidine. It was given for four days leading right up to the start of that azacitidine.



Best Response at Cutoff						
	Ph1b	Ph2	MDS	AML	All	AZA Historical
Evaluable Patients	11	9	15	5	20	
Response Rate	100%	89%	93%	100%	95%	30-50%
CR Rate	82%	56%	67%	80%	70%	20-30%

In this study, the overall response rate, believe it or not, was 95% out of 20 patients. Wow, that's actually really high; 70% of patients actually achieved a complete response. Now, David and I have participated in a lot of clinical trials at specialty centers and while we have seen higher response rates than we tend to see in our general population of folks who have MDS, those higher response rates, even in good studies, have been around 70%. We haven't seen 95% before. We're watching this drug APR246 pretty closely. It's now entering a randomized study in a much larger patient population and we're anxious to see if the response rates hold up as well in a larger patient population as it did in the first 20 patients. We're also anxious to see if those responses last a long time or if they just last for a short period of time.

High-risk MDS: New Strategies
Current and Ongoing Trials

- SGI-110 guadecitabine a next-generation oral HMA
- Pracinostat (HDACi) in combination with azacitidine (phase 2 interim analysis)
- Oral rigosertib in combination with azacitidine (phase 2 expansion study)
- ASTX727 – a unique fixed-dose combination of the hypomethylating agent decitabine, and the novel cytidine deaminase inhibitor, E7727 (cedazuridine) (phase 3)
- Venetoclax
- APR246

For information on clinical trials in MDS, visit
https://www.mds-foundation.org/clinical-trial-announcements/

There are other approaches that are in the wings for MDS. We have some new hypomethylating agents that are given either orally or IV or in combination with cytidine deaminase inhibitors, so they don't get degraded and hang out in the body for longer. My look at initial data from these drugs, they don't seem to be worse than existing hypomethylating agents. They may not be better either so we will see where their regulatory paths take us. We also continue to look at a variety of histone deacetylase inhibitors such as entinostat or pracinostat in combination with azacitidine. These have had disappointing results in the past but there are a dedicated few who still feel as if we can just get the right combination in regimen and doses, we'll see some advantage of that combination. The polo-like kinase inhibitor rigosertib which try to find a place in patients who have been exposed to hypomethylating agents in the past but did not quite meet a regulatory approval bar, has entered an oral formulation and is being used in combination with azacitidine. Another drug that we're looking at closely is of course venetoclax, the BCL-2 inhibitor. This has been approved for the treatment of "unfit" older adults with AML in combination with hypomethylating agents or low dose cytarabine. It is being explored in MDS, so far, we are not seeing the same response signals that have been seen in older adults with AML, but more to come on that with larger studies.

David, I wonder if there are any other new approaches that you've been following or that you think have some potential in the future?

Dr. David Steensma:
Well it's interesting to speculate why the immune checkpoint inhibitors really haven't been efficacious. I mean, the group who have been failed by HMAs, that's the group where we have the biggest unmet need and as we saw in all of these studies, the response rate was essentially zero in that subset. As you point out, you know, these are not benign agents and adverse event attribution is difficult. People are still thinking about how to deal with CAR T-cells in MDS and it's very challenging because of the lack of the specific antigen that has expressed on the MDS stem cells but not normal hematopoietic progenitors. As far as targeted agents, there are the IDH inhibitors; there are some data in MDS but having a targetable mutation is really quite rare. What we really need to do is figure out how to inhibit this spliceosome and do that effectively and there are several different trials going on looking at that; definitely some major unmet needs. The APR246 is really very exciting but I think as you point out, Mikkael, it's always hard with a trial that's not controlled to know what's hypomethylating agent alone versus the combination. Here, it really seems like a very high response rate, more than we have seen for hypomethylating agent alone so, a randomized trial just getting underway that should help answer that question.

I think the immunotherapies, for whatever reason, just aren't as active in MDS as we'd like. Maybe there's something we have to do to make patients' cells more sensitive those. The APR is very exciting. There are certainly other drugs in development (eg, venetoclax has some activity in TP53 mutant disease) but the response rate is really pretty impressive for a patient subgroup that is really quite high risk. TP53 mutations are one of the poorer prognosis mutations and those patients tend to have a lower response rate to conventional chemotherapies. They may have a good response to azacitidine and decitabine but it typically doesn't last that long. They don't do as well with transplants so, really an unmet need there. There are a few other drugs that are in development as well and hopefully, we'll have some new therapies for patients with MDS soon.

Conclusions

- Exciting new prognostic systems = increased accuracy
- Luspatercept anticipated approval (first in over a decade for lower-risk MDS and anemia)
- Newer approaches for higher-risk MDS

Dr. Mikkael Sekeres:
I sure hope so as well, we desperately need them. To summarize what we have covered today, the first is that I think we have some exciting new prognostic systems to be more accurate with an individual patient in predicting that person's survival and also, possibly, their ability to respond to certain drugs. We have a drug in luspatercept that we anticipate will be approved. It will be our first new approval for MDS in over a decade for people who have lower risk MDS and anemia. We have some newer approaches for people who have higher risk MDS that we think will be promising. On behalf of Dr. Steensma, I want to thank all of you for viewing this activity today and hope you have a good rest of the day.

Dr. David Steensma:
Thank you.