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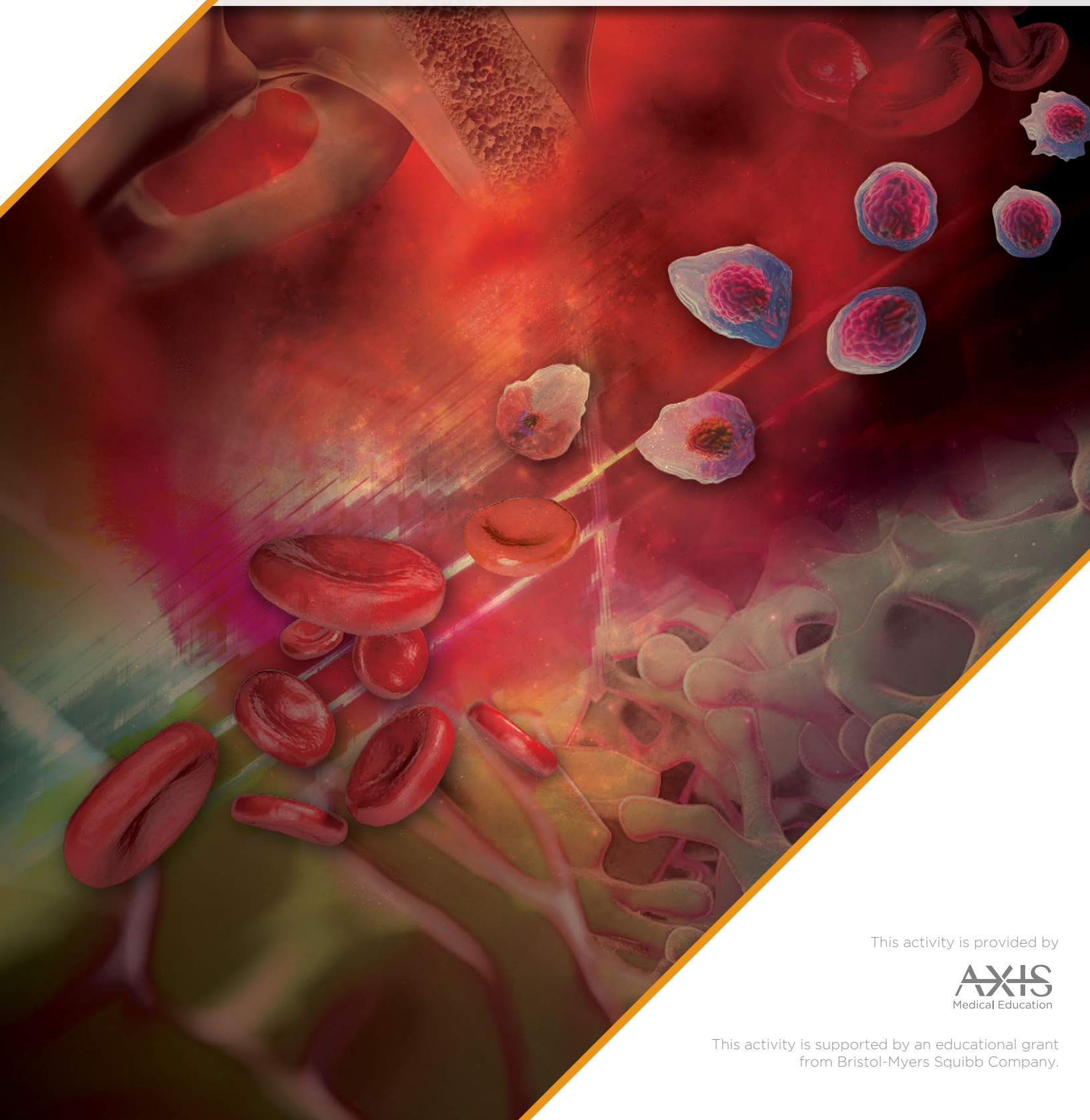
Taking Command of the Treatment of ESA-Refractory, Transfusion-dependent LR-MDS

This transcript has been edited for style and clarity and includes all slides from the presentation.



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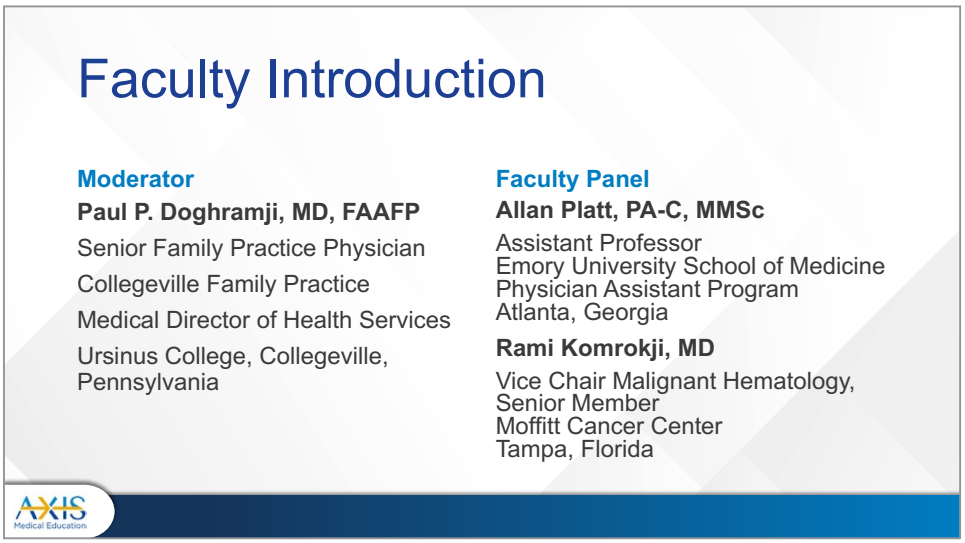
Taking Command of the Treatment of ESA-Refractory, Transfusion-dependent LR-MDS

Paul P. Doghramji, MD, FAAFP, Allan Platt, PA-C, MMSc and Rami Komrokji, MD

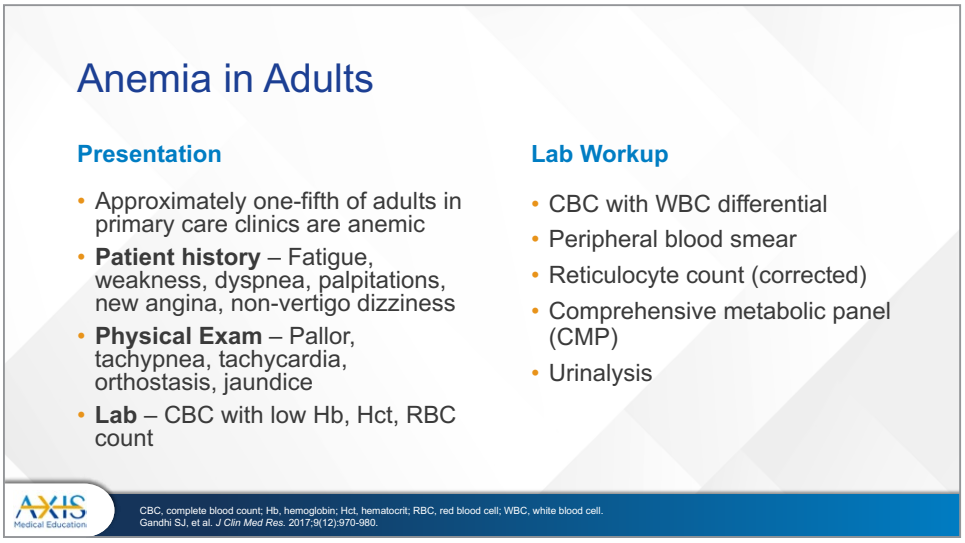
Dr. Doghramji:
This is CME on ReachMD, and I'm Dr. Paul Doghramji. I'm joined today by Dr. Rami Komrokji and PA Allan Platt to discuss ESA-refractory, low-risk MDS.

Dr. Komrokji:
Hello. It's really a pleasure to join you as well.

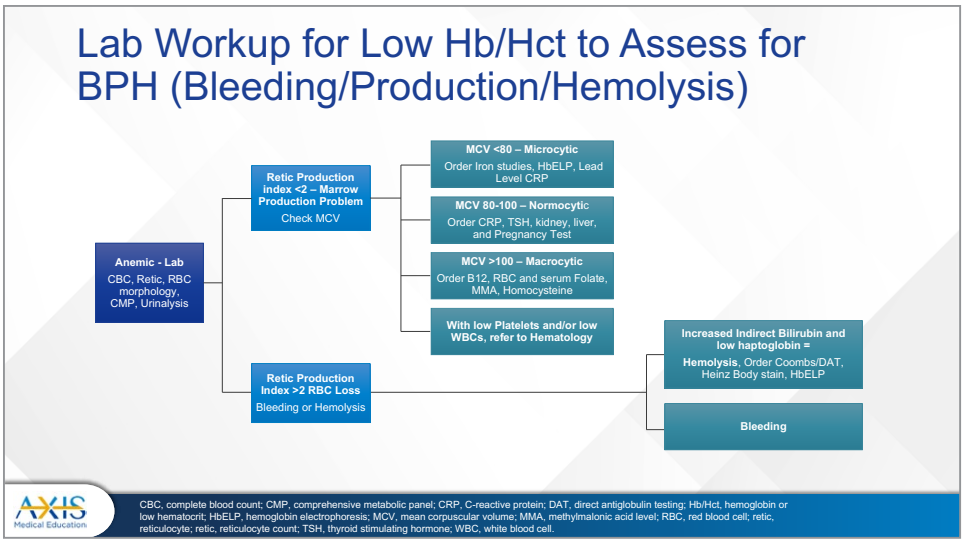
PA Platt:
Glad to be here.



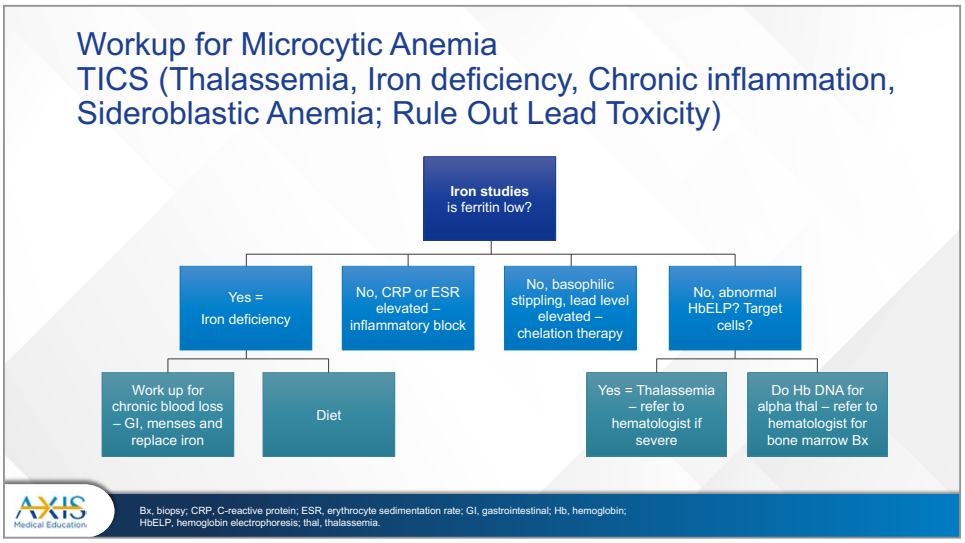
Dr. Doghramji:
And we're here to discuss ESA [erythropoiesis-stimulating agent]-refractory, low-risk MDS [myelodysplastic syndrome]. So, let's begin. PA Platt, to begin our session, can you first describe the diagnosis of anemia and when to refer a patient to a hematology specialist?



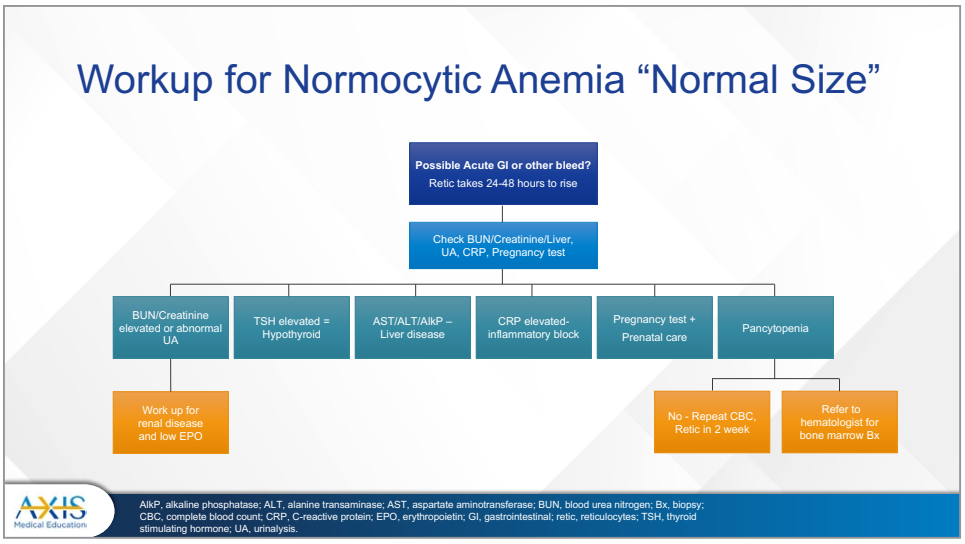
PA Platt:
Absolutely. It's very common in primary care – 20% of your adult patients are anemic. Usually, that's picked up on a routine CBC [complete blood count] when you're doing a physical exam. However, people can present with non-vertigo dizziness, weakness, fatigue – and those should all be indicated to check for anemia. On physical exam, you want to check their vital signs. If they're unstable, that person needs to go to a hospital base where they can be worked up and maybe even be typed and crossed for a blood transfusion, but if somebody's stable, you can use peripheral tests to make pretty much 90% of the diagnosis. So, start with a CBC with a white cell differential. You'll need a peripheral blood smear, you'll definitely want a reticulocyte count that's corrected, a metabolic profile, and a urinalysis. Based on that, it's going to guide your whole work-up.



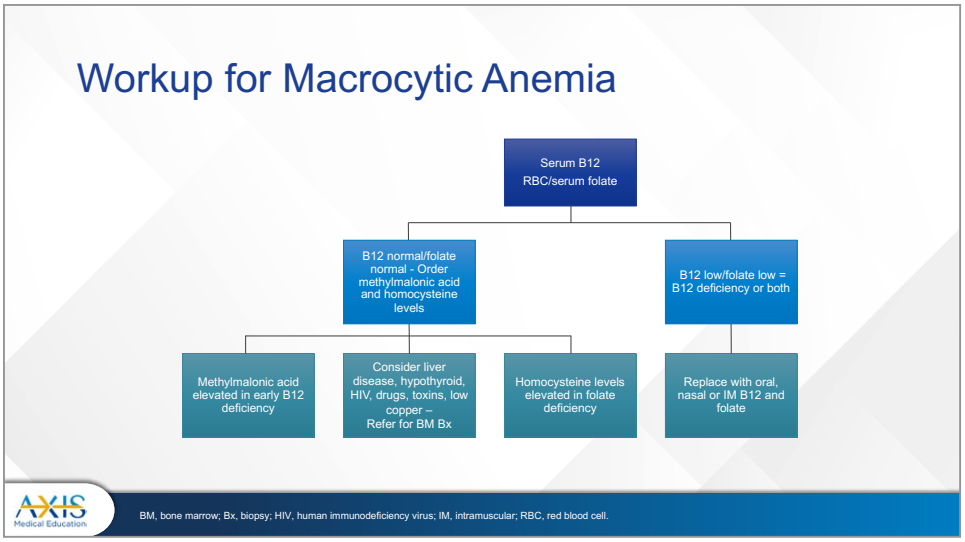
- I have a flow chart that will guide you based on the results that you just obtained from those basic labs, and if you do see a low white [blood cell] count and either/or a low platelet count with anemia, that should be pretty much referred to hematology immediately, something drawing at the bone marrow level. However, if that's not present, you just have a pure anemia, you want to go on the reticulocyte count. Once it's corrected, if it's under 2, the bone marrow's not producing. It's a production problem. If it's over 2, you're losing blood either from bleeding or hemolysis, and there's total work-ups for pursuing that. If it's a low-production anemia, the next step is to look at your CBC and look at the size of the red cells. That's MCV – mean corpuscular volume – microcytic, normocytic, or macrocytic, and each of those should have targeted tests to make the diagnosis.



- For the microcytic chain, you want to look at iron studies primarily. Iron would be the most common, and basically, the ferritin level tells you what your storehouse iron is. You also want to consider electrophoresis looking for thalassemia, and a lead level looking for lead toxicity, and a C-reactive protein looking for inflammation. Those are the 4 big differentials for microcytic.

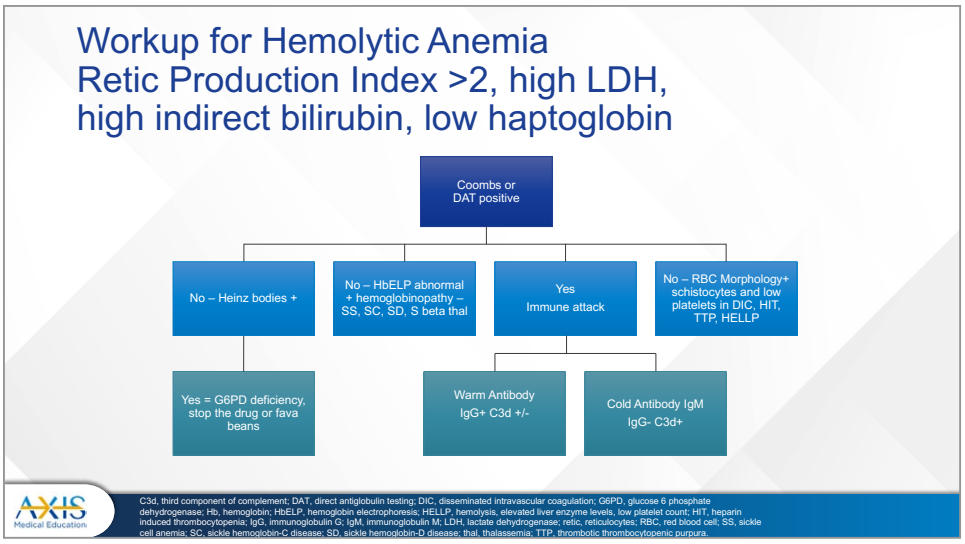


- For normocytic, you’re going to look at your metabolic profile because kidney disease/liver disease are all big in this category with low EPO [erythropoietin] from the kidney if it’s renal failure. Get a TSH [thyroid stimulating hormone] and a CRP [C-reactive protein] looking for inflammation.



- For macrocytic, you definitely want to do a B12 and a RBC [red blood cell] folate level to check for B12 and folate deficiency. That’s going to be your most common in that category. If you can’t figure it out with these peripheral tests, then basically you’re going to send your patient to hematology because the next step is a bone marrow biopsy if you can’t figure it out with the peripheral tests.

  So, the microcytic differential – thalassemia, iron deficiency, chronic inflammation, and sideroblastic, rule-out lead toxicity first, but that may be MDS. For the normocytic side, if you can’t figure it out with the peripheral test, again, you’re referring to hematology. For the macrocytic, if it’s not B12 or folate deficiency you’re definitely going to send the patient to hematology, and their next step will be a bone marrow biopsy.



- Hemolytic work-up – again that's pretty much a hematology referral unless you have just G6PD deficiency, which would be picked up on a Heinz body stain, and that would be just removing the offending agent.

- **Dr. Doghramji:** Alright. Well, low-risk myelodysplastic syndrome, or LR-MDS, is an acquired bone marrow disorder that manifests with symptomatic anemia. Erythropoiesis-stimulating agents, or ESAs, are the first-line treatment, but not all patients with LR-MDS respond to ESAs, and many become refractory to ESAs. Dr. Komrokji, would you expand on the utility of ESAs and identification of ESA failure?

Scope of the Problem

- MDS is the most common myeloid neoplasm and one of the most common causes of anemia in elderly patients
- Lower-risk MDS constitutes almost half of MDS cases
- One-third of patients will progress to higher-risk/AML
- Lower-risk MDS remains a major source of morbidity and mortality, primarily due to cytopenia complications
- Majority of patients are anemic, and more than half become RBC TD over time
- Isolated thrombocytopenia and/or neutropenia are rare but concomitant cytopenia with anemia is common
- Limited treatment options and unmet need for large number of patients
- All currently available therapies have response rates of approximately 30% and response durations of 1-2 years

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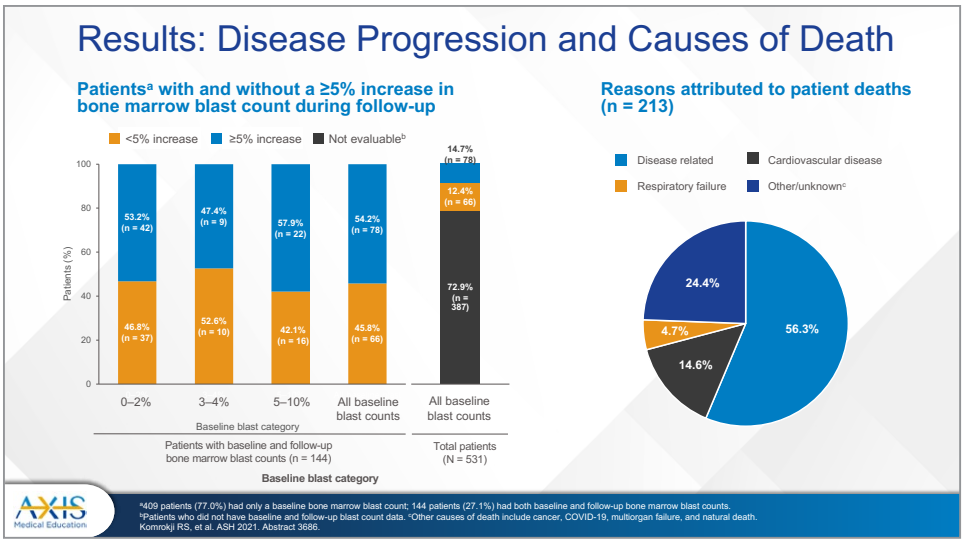
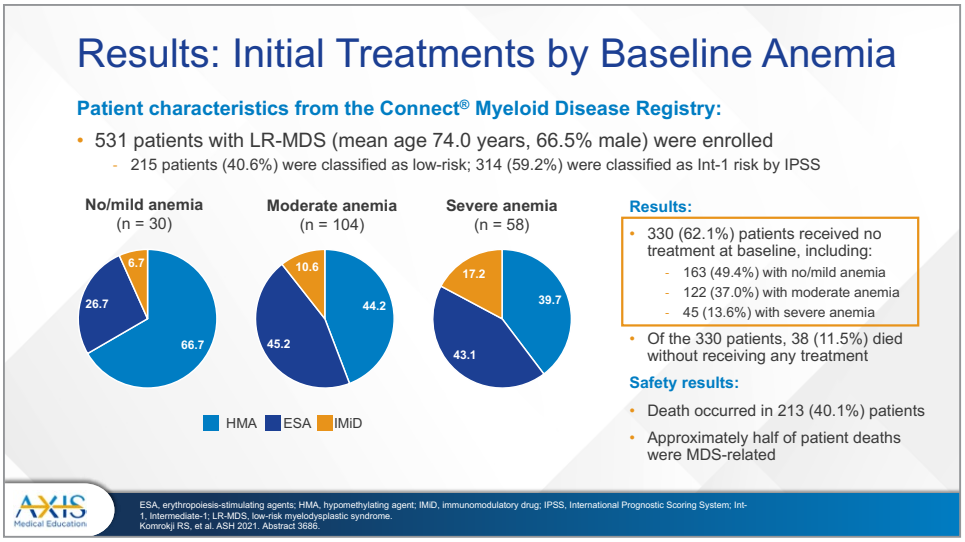
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; RBC, red blood cell; TD, transfusion-dependent.
Volpe VO, et al. *Clin Lymphoma Myeloma Leuk.* 2023;23(3):168-177.

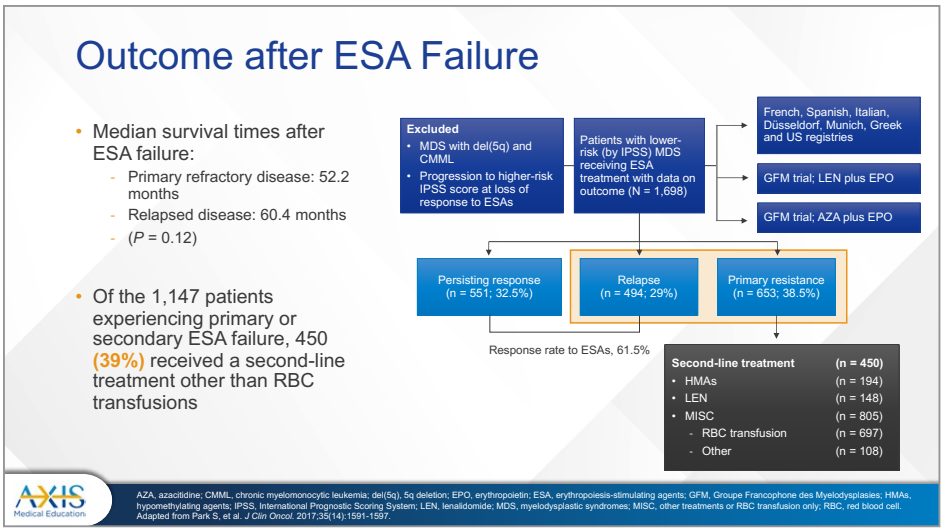
Dr. Komrokji: Absolutely. Thank you. So, I think just to set the background to summarize the scope of the problem, myelodysplastic syndromes are the most common myeloid neoplasm we deal with. It's one of the top 5 causes of anemia in elderly, as stated, and a majority of the patients are actually what we call a lower-risk MDS, which means less likelihood to progress to acute myeloid leukemia. However, a majority of those patients unfortunately will die from complications related to the disease, anemia, and its complications. Anemia is the most common cytopenia we encounter in lower-risk MDS. Almost 90% of the patients are anemic at time of diagnosis, and over time, more than half of the patients will become transfusion-dependent, needing blood transfusions every 2 weeks or sometimes more often. Isolated thrombocytopenia or neutropenia are less common to encounter. However, the coexistence sometimes dictates the choice of therapy. We have limited treatment options, and there is a huge unmet need for those patients. All the current available therapies we had in the past had roughly around 30% chance, and they work around probably a year or two.



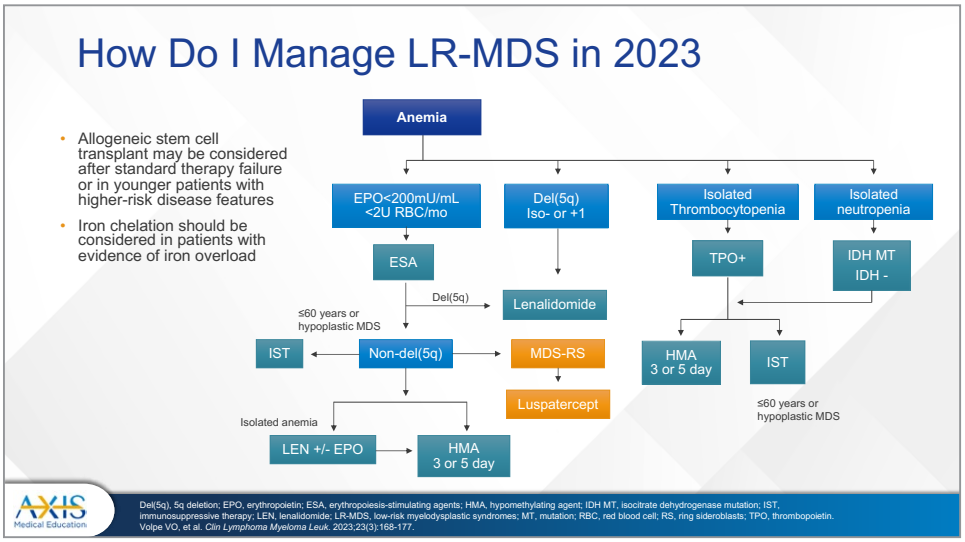
- When we look at patients with lower-risk MDS, actually most of them stay as lower-risk MDS. One-third of those patients may eventually progress to acute myeloid leukemia or higher-risk MDS, but when we look at the cause of mortality and morbidity, more than half of those patients, it's directly related to the anemia and the manifestations of the cytopenia. The second most common cause of mortality and morbidity among lower-risk MDS patients are cardiovascular events, which probably also correlate with their anemia and the interplay between the anemia and the other comorbidities, particularly [the] majority of MDS patients are in their 60s and 70s.



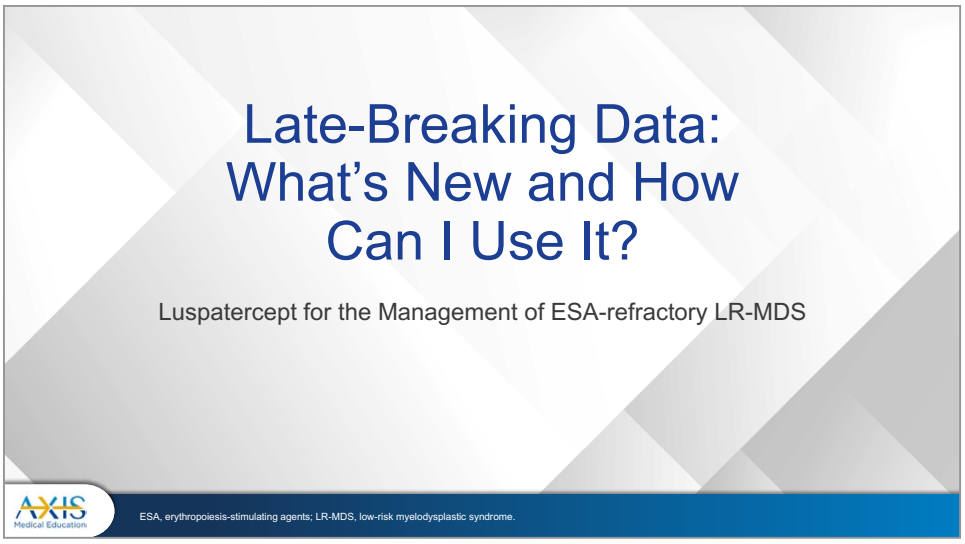
- We also have looked at the severity of their anemia, and there's correlation between the severity of anemia and outcome obviously, but unfortunately, even patients that we label as moderate or severe anemia are undertreated in general, many of those patients just receiving blood transfusions or erythroid-stimulating agents.



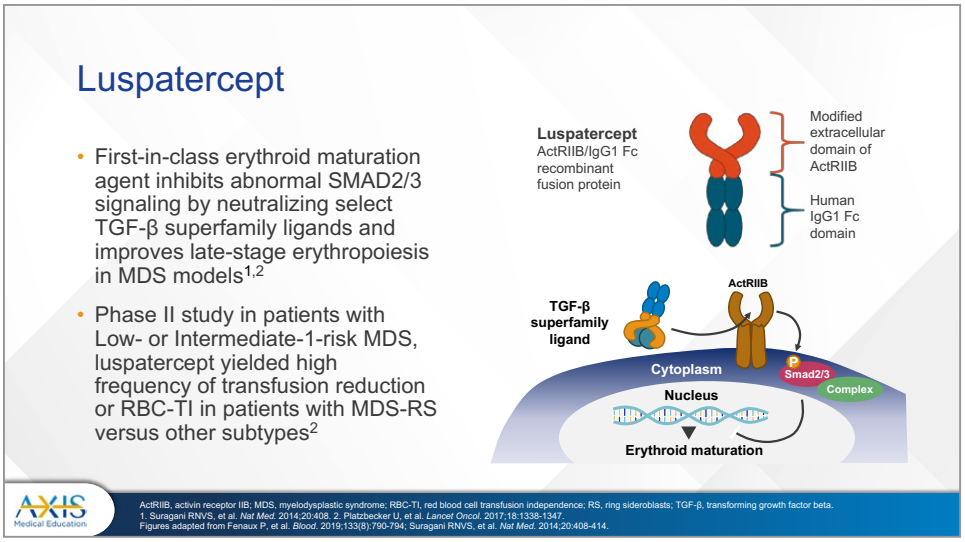
Now, erythroid-stimulating agents are a reasonable first step for management for the patients that are mostly anemic. There are different formats of erythropoietin – short-acting, nowadays there are biosimilars, there is long-acting darbepoetin. It's really a matter of dosing which ones to use. However, one could predict the chances of response easily by checking the endogenous serum EPO levels of those patients, and those patients that have less than 500, and some studies reserve to less than 200 endogenous serum EPO level, who are not heavily transfusion dependent, receiving less than 2 units every month, may have good chance of response. However, if a patient has endogenous serum EPO level more than 500, or they are receiving more than 2 units of blood every other week or monthly, then those patients have less than 10% chance of response. So, we typically recommend starting somewhere equivalent of 40 to 60,000 international unit of erythropoietin. This is different dosing than used in renal failure. We try that for somewhere around 6 to 8 weeks. If there is a response, we continue. If not, then we start thinking of moving to the next step. In general, around 40% of the patients will respond to erythroid-stimulating agents for a duration of a year, year and a half. There are around 40 to 50% of the patients [that] we call as primary resistance that will not have a response from the get going. Unfortunately, we see a lot of patients that had not had a good response to erythroid-stimulating agents, and they continue with that. In general, patients have to have either transfusion independency or an increase in their hemoglobin of one a half grams that's also seated with the improvement in the quality of life of patients to call that a response to erythroid-stimulating agents, but once they stop working, or if they do not work, then that's usually an indication to start thinking of [the] next treatment option.



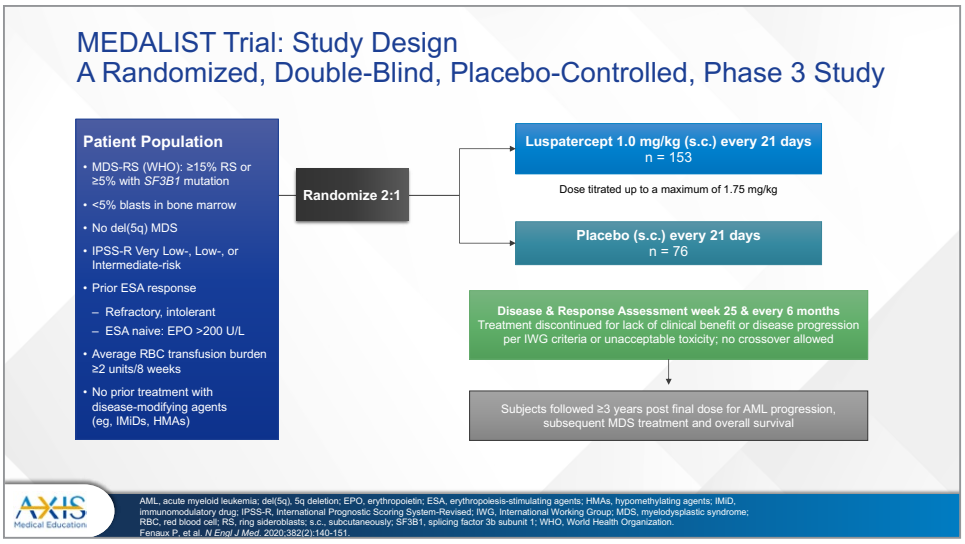
We do have some options, and now our armamentarium had been expanded with newer therapies like luspatercept, there is a drug approved called lenalidomide for patients with deletion 5q, luspatercept particularly for patients with ring sideroblasts, and also we use hypomethylating agents, azacitidine or decitabine, especially if patients have concomitant neutropenia or thrombocytopenia.

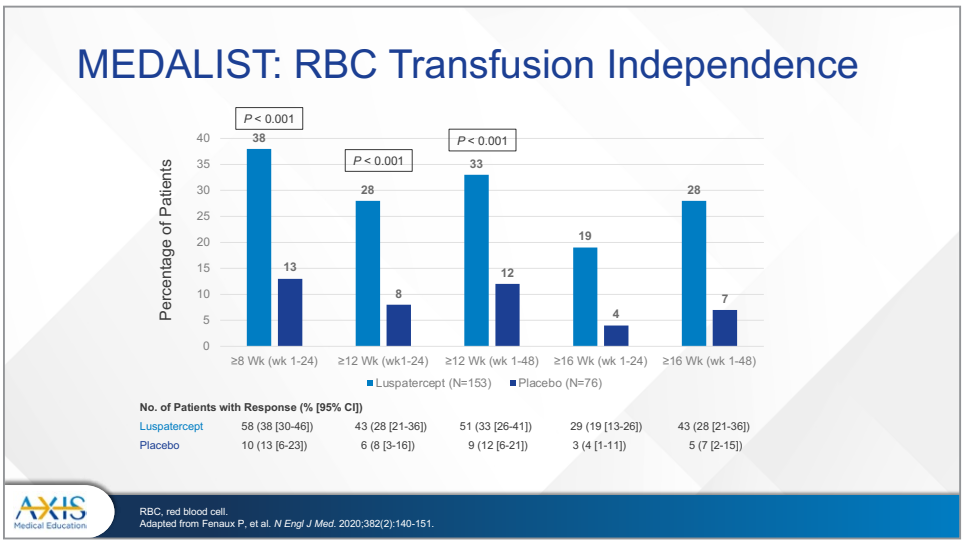


Dr. Doghramji:
Although advances have been made in the treatment of anemia in patients with MDS, there remains a significant unmet need for new and better treatment options for patients with ESA-refractory, transfusion-dependent MDS. One such option which you already mentioned is luspatercept. Would you discuss recent data related to luspatercept and its significance in the day-to-day management of ESA-refractory LR-MDS?



Dr. Komrokji:
Absolutely. Thank you again for the question. So, luspatercept was actually the first drug to be approved for MDS after almost a decade of not having any new therapies for MDS. Luspatercept is what we call [an] erythroid maturating agent. Erythropoietin works on early steps of erythropoiesis, promoting early erythroid differentiation. However, luspatercept works on the terminal erythroid differentiation. It's a fusion trap protein that neutralizes TGF-beta ligands, which turns [out] to be a negative regulator of the terminal erythroid differentiation. So, this drug will release the terminal erythroid differentiation blockage that we encounter in MDS.





- The drug was tested in several studies in phase 1/phase 2, and then in a large study called the MEDALIST where patients with lower-risk MDS with ring sideroblasts that were transfusion-dependent were randomized to receive luspatercept – it's an injection given subcutaneously every 3 weeks – versus placebo, and the study met the primary endpoint where around one-third of the patients had sustained transfusion-independency with luspatercept, and that led to the approval of the drug. One of the major important predictors of response was really the magnitude of transfusion burden at the baseline. So, the less the transfusion burden was, the patients were more likely to respond, and those response rates could approach as high as 70%.

MEDALIST: Adverse Events Occurring in ≥10% of Patients

Adverse event	Luspatercept (n = 153) n (%)		Placebo (n = 76) n (%)	
	Any grade	Grade 3	Any grade	Grade 3
General disorder or administration site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
GI disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal or connective-tissue disorder				
Back pain	29 (19)	3 (2)	5 (7)	0
Arthralgia	8 (5)	1 (1)	9 (12)	2 (3)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea	23 (15)	1 (1)	5 (7)	0
Cough	27 (18)	0	10 (13)	0
Infection or infestation				
Bronchitis	17 (11)	1 (1)	1 (1)	0
Urinary tract infection	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning, or procedural complication: fall	15 (10)	7 (5)	9 (12)	2 (3)

Adapted from Fenaux P et al. *N Engl J Med.* 2020;382(2):140-151.

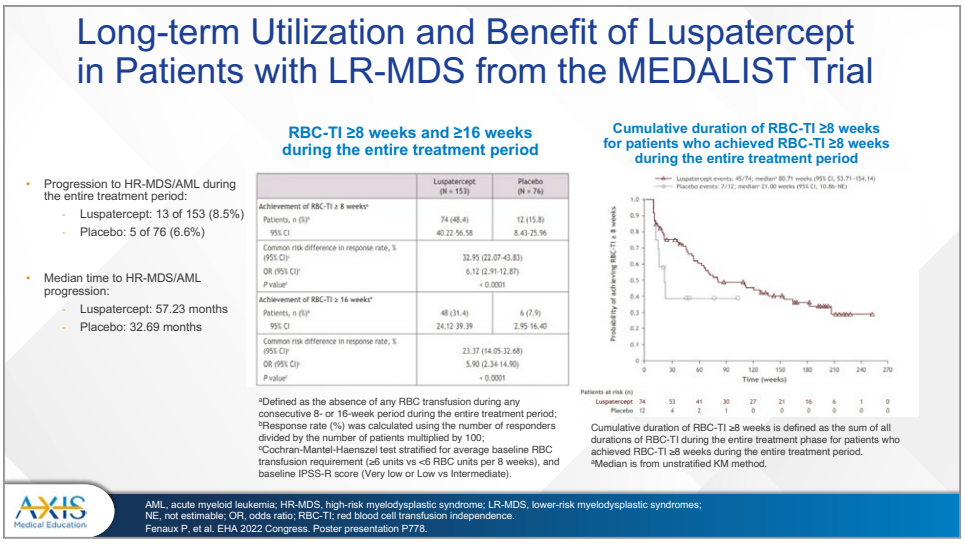
- The treatment, in general, is well tolerated. As I mentioned, it's an injection every 3 weeks. There was fatigue observed in patients, particularly during the first few cycles some GI toxicity, peripheral edema, but 95% of the patients were able to continue in treatment, no concerns of increased risk of AML transformation or transformation to higher risk.

Luspatercept FDA Approval

April 2020: luspatercept-aamt is an erythroid maturation agent (EMA) indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

FDA, U.S. Food and Drug Administration.
Reblozyl (luspatercept-aamt). Prescribing information. Bristol Myers Squibb; 2022.

- So, based on the data from this MEDALIST study, the FDA approved luspatercept for patients after ESA failure, lower-risk MDS with ring sideroblasts.

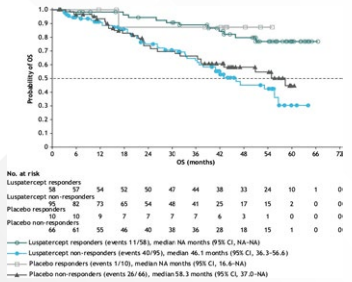


- Now, there had been updates on a longer-term follow-up on use of luspatercept. Dr. Pierre Fenaux presented that at the European Hematology Association in 2022 providing [a] longer update and the data still remains encouraging when we look at patients that had sustained transfusion independence, which means 16 weeks or more. Around one-third of patients with luspatercept enjoyed that transfusion independency, and when we look at the cumulative duration of response, it almost approaches 80 weeks. So, those patients will stop needing blood transfusion, and there were some patients that needed some blood transfusions for different events such as bleeding, hospitalization, etc., but when we look at the cumulative duration of response, it's almost approaching 81 or 82 weeks.

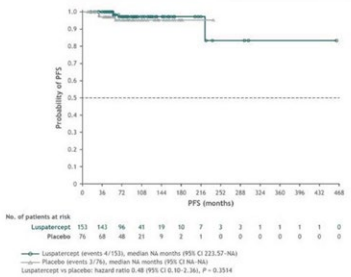
- There were also some interesting data presented at the last American Society of Hematology meeting of longer-term follow-up and the impact of such treatments on overall survival and progression-free survival.

Abstract 1174: OS and PFS with Luspatercept

OS with luspatercept:
Responders vs non-responders in the ITT population



PFS with luspatercept vs placebo



Luspatercept responders vs placebo responders: HR, 1.47 (95% CI, 0.19–11.46); *P* = 0.7088.
Luspatercept non-responders vs placebo non-responders: HR, 1.28 (95% CI, 0.78–2.10); *P* = 0.3355.
Luspatercept responders vs luspatercept non-responders: HR, 0.26 (95% CI, 0.13–0.52); *P* < 0.0001.
Data cut: January 15, 2022. OS was defined as time from randomization to death from any cause. Responders were defined as patients with an absence of any RBC transfusion ≥8 weeks during the first 24 weeks of double-blind treatment.

ITT, intent-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival.
Adapted from Santini V, et al. *Blood*. 2022;140(Supplement 1):4079-4081.

- Dr. Santini from the Italian group presented data on overall survival with luspatercept, demonstrating that responders enjoyed longer survival with the treatment. This also suggested that treatment of anemia is very important, and the elimination of the anemia and transfusion dependency could be an important factor in patients with lower risk.

Abstract 1174 Summary

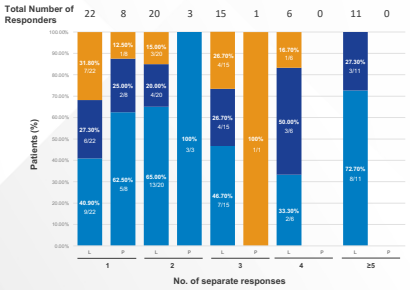
- Luspatercept was associated with increased 36-month OS probability for patients with IPSS-R very LR-MDS vs placebo:
  - 77.8% vs 16.7% (odds ratio 17.5; *P* = 0.0088)
- Luspatercept was associated with increased 36-month PFS probability in patients with a baseline serum EPO level of 100 to ≤200 U/L vs placebo
  - 97.3% vs 78.9% (odds ratio 9.6; *P* = 0.0238)
- Patients with LR-MDS with these baseline characteristics may derive greater survival benefit from luspatercept

EPO, erythropoietin; IPSS-R, International Prognostic Scoring System-Revised; LR-MDS, low-risk myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival.
Santini V, et al. *Blood*. 2022;140(Supplement 1):4079-4081.

- In the same presentation it was demonstrated that patients that had lower-risk disease using as a classification system we use for the International Prognostic Scoring System, that those patients with very low risk had a survival advantage with the treatment.

Abstract 3098:
Transfusion Independence and Response by Dose Level

RBC-TI ≥8 Weeks Response Periods Per Patient by Baseline Transfusion Burden



Responders at Different Luspatercept Dose Levels

	ITT population		LTB at baseline		ITB at baseline		HTB at baseline	
	L (n = 74)	P (n = 12)	L (n = 39)	P (n = 8)	L (n = 20)	P (n = 2)	L (n = 15)	P (n = 2)
Responders at dose level, n (%)								
1.0 mg/kg	55 (74.3)	9 (75.0)	37 (94.9)	7 (87.5)	12 (60.0)	1 (50.0)	6 (40.0)	1 (50.0)
1.33 mg/kg	28 (37.8)	3 (25.0)	13 (33.3)	2 (25.0)	9 (45.0)	0	6 (40.0)	1 (50.0)
1.75 mg/kg	31 (41.9)	3 (25.0)	14 (35.9)	1 (12.5)	10 (50.0)	1 (50.0)	7 (46.7)	1 (50.0)

HTB, high transfusion burden; ITB, intermediate transfusion burden; ITT, intent-to-treat; L, luspatercept; LTB, low transfusion burden; P, placebo; RBC-TI, red blood cell transfusion independence.
Adapted from Platzbecker U, et al. *Blood.* 2022;140(Supplement 1):6971-6973.

- Other [than] that, I also had looked at the predictors of response and the dose dependent relationship. Dr. Platzbecker from the German group presented this data at the last American Society of Hematology meeting as well, again demonstrating that patients that are not heavily transfusion-dependent, suggesting that we should start those treatments earlier at the time of ESA failure, had higher responses. The other important point [is] that a lot of patients will need dose escalation. Typically, we start with 1 milligram per kilogram subcutaneous injection every 3 weeks. After 2 doses, we go up to 1.33 and then up to 1.75.

Abstract 3098 Summary

- Patients who were low transfusion burden at baseline experienced more periods of RBC-TI response than intermediate and high transfusion burden patients
- Low transfusion burden patients were more likely to respond to lower doses of luspatercept, whereas almost half of intermediate and high transfusion burden patients responded to the maximum dose level
  - Rates of RBC-TI ≥ 8 weeks response at 1.0 mg/kg decreased with increasing baseline transfusion burden

RBC-TI, red blood cell transfusion independence.
Platzbecker U, et al. *Blood.* 2022;140(Supplement 1):6971-6973.

- So, there is a relation between the responses and the dosing. The low transfusion burden patients may respond to lower doses. However, the intermediate or high transfusion burden patients will often need higher doses to achieve the response.

Abstract 1757: Real World Data Replicates MEDALIST Study Results and Confirms Activity Among HMAs and Lenalidomide Treated Patients

- Seventy-three pts (67%) had MDS-RS subtype
- 91% were intermediate- or lower-risk MDS by IPSS-R
- ***SF3B1* mutation (MT) was detected in 71% (80/112).** The mean Hgb level was 7.90 g/dl and 47% were RBC HTB transfusion dependent.
- The median serum erythropoietin (EPO) level at time of referral was 122 U/L (19% >500 U/L) (n = 77)
- **Majority had prior erythroid-stimulating agents (ESA) (89%) with 29% hematological response to prior ESA**
- **59 pts (53%) had prior HMA therapy, and 42 patients (47%) had prior lenalidomide**

- **HI correlated with baseline RBC-TB**
- **Almost 55% of pts needed dose escalation:**
  - 62 pts received 1.33 mg/kg
  - 63 pts received 1.75 mg, among whom 40% (25 pts) demonstrated response to higher doses
- Based on RBC-TB:
  - 75% (6/8) NTD patients achieved HI with highest dose escalation
  - 40% (10/25) LTB pts achieved HI with dose escalation
  - 30% (9/30) HTB pts achieved response with dose escalation

% (n)	RWD (n = 114)	MEDALIST (n = 153)
Overall response • Hgb increase >1.5 g/dl in NTD or Hgb increase >1.5 g/dl with RBC-TI in RBC-TD • RBC-TI without Hgb 1.5 g/dl increase • >50% reduction in RBC-TB	**39.5 (45)** 27 (30/113) 5 (6/113) 7 (8/112)	38 (58)
Response in NTD: Hgb increase more than 1.5 g/dl	**69 (9/13)**	NA
Response in LTB • Hgb increase more than 1.5 g/dl and RBC-TI • RBC-TI without Hgb 1.5 g/dl increase • >50% reduction in RBC-TB	**46 (22/47)** 34 (16/47) 6 (3/47) 6 (3/47)	59 (52/87) RBC-TI
Response in HTB • Hgb increase more than 1.5 g/dl and RBC-TI • RBC-TI without Hgb 1.5 g/dl increase • >50% reduction in RBC-TB	**24 (13/53)** 9 (5/53) 6(3/53) 9 (5/53)	9 (6/66) RBC-TI

AXIS Medical Education

Hgb, hemoglobin; HI, hematological response/improvement; HMA, hypomethylating agents; HTB, high transfusion burden; IPSS-R, International Prognostic Scoring System-Revised; LTB, low transfusion burden; MDS, myelodysplastic syndromes; MDS-RS, myelodysplastic syndrome with ring sideroblasts; MT, mutation; NTD, non-transfusion dependent; pts, patients; RBC-TB, red blood cell transfusion burden; RBC-TI, red blood cell transfusion independent; RWD, real-world data; SF3B1, splicing factor 3b subunit 1.
Komrokji RS, et al. *Blood.* 2022;140(Supplement 1):4039-4041.

Abstract 1757 Summary

- Real-world data confirms clinical benefit and safety profile of luspatercept observed in the MEDALIST trial
- Responses are dose dependent with 1/3 of patients who were dose escalated responding
- Low baseline RBC-TB dependency and *SF3B1* MT correlated with higher response rates
- Luspatercept retained activity after HMA or lenalidomide failure; however, a trend of lower responses was observed correlated with RBC-HTB among those patients

AXIS Medical Education

HMA, hypomethylating agents; MT, mutation; RBC-HTB, red blood cell high transfusion burden; RBC-TB, red blood cell transfusion burden; SF3B1, splicing factor 3b subunit 1.
Komrokji RS, et al. *Blood.* 2022;140(Supplement 1):4039-4041.

So, now also we've shared our real-world data and experience after the approval of the drug. So, last year I also presented myself data on real-world experience with almost 114 patients treated with luspatercept, [what] was unique to this [is] I think the patients that had prior therapies, such as hypomethylating agents or lenalidomide, which was not part of the MEDALIST study, and indeed, we saw responses very similar to what was reported in the MEDALIST study, around 40% of the patients responding, transfusion burden being the most important predictor of response, needing to escalate the dosing, and we also observed that the responses were seen after exposure to hypomethylating agents and lenalidomide. However, those patients after hypomethylating agents failure or lenalidomide failure tend to have higher burden of their disease.

Abstract 389: Transfusion Outcomes During Luspatercept Treatment

	All patients (N = 76)
TB in the 8 weeks prior to luspatercept initiation. n (%)	
TI	1 (1.3)
Low TB	65 (85.5)
Moderate TB	10 (13.2)
High TB	0
TB conversion during first 24 weeks of luspatercept treatment, n (%)	
TI prior to luspatercept initiation	1 (1.3)
Maintained TI	1 (100.0)
Converted to increased TB status	0
Low TB prior to luspatercept initiation	65 (85.5)
Maintained low TB	5 (7.7)
Converted from low TB to TI	60 (92.3)
Converted from low TB to higher TB	0
Moderate TB prior to luspatercept initiation	10 (13.2)
Maintained moderate TB	0
Converted from moderate TB to lower TB	10 (100.0)
Converted from moderate TB to higher TB	0

TB, transfusion burden; TI, transfusion independent.
Adapted from Mukherjee S, et al. *Blood*. 2022;140(Supplement 1):944-946.

Abstract 389 Summary

- >90% of patients with low transfusion burden prior to luspatercept initiation achieved TI within the first 24 weeks of luspatercept treatment
- All patients with moderate transfusion burden prior to luspatercept had a decrease in level of transfusion burden within the first 24 weeks of starting luspatercept treatment
- This study suggests that initiating luspatercept for low or moderate transfusion burden may have a substantial impact on transfusion burden

TI, transfusion independence.
Mukherjee S, et al. *Blood*. 2022;140(Supplement 1):944-946. Fenaux P, et al. *N Engl J Med*. 2020;382:140-151.

- Dr. Mukherjee also presented data from real-world experience in the same meeting, again, showing the same data that patients that are low transfusion burden will have a very high chance of response in the real world. Patients that are high transfusion-dependent will most often need the highest dose of the luspatercept. However, both sets of data from [the] real world were actually showing that the same responses observed in the MEDALIST were observed in real-world experience.

Activity of Luspatercept and ESAs Combination for Treatment of Anemia in Lower-Risk MDS

Baseline characteristics (n = 28)	% (n)
Age (median)	72 (51-94)
Gender (male)	68(19)
Race (white)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dl	8 (6.6-9.4)
Platelets (mean) x10^9/L	259 (16-814)
ANC (mean) x10^9/L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n = 18)
RBC transfusion Burden	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Prior ESA treatment	89 (24)
Prior HMA treatment	42 (12)
Prior Lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

	% (n)
Overall response (n = 28)	36 (10)
Hgb increase more than 1.5 g/dl in NTD or Hgb increase more than 1.5 g/dl with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dl increase	14 (4/28)
>50% reduction in RBC-TB	4 (1/28)
Response in NTD (n = 3)	
Hgb increase more than 1.5 g/dl	33 (1/3)
Response in LTB (n = 13)	38 (5/13)
Hgb increase more than 1.5 g/dl and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dl increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n = 12)	33 (4/12)
Hgb increase more than 1.5 g/dl and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dl increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

Predictors of response included:

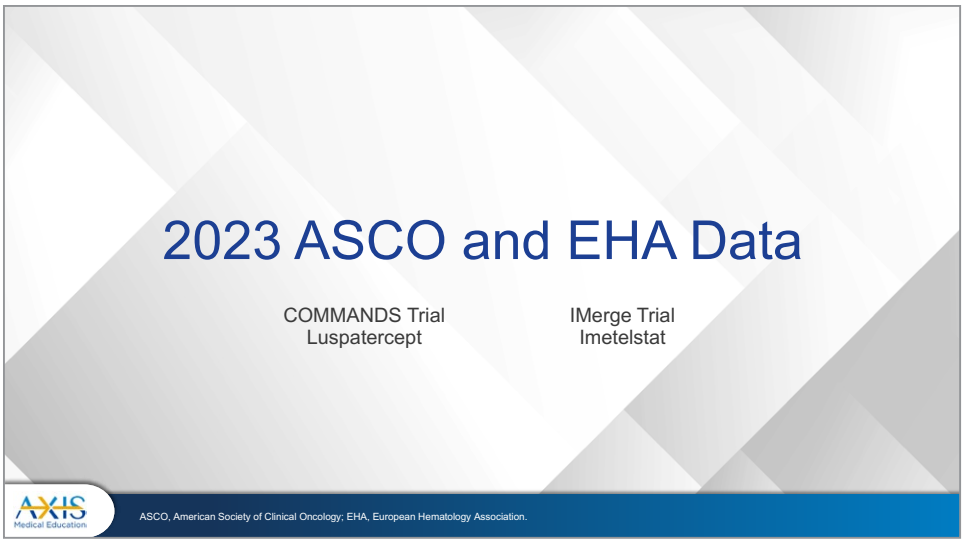
- Prior response to luspatercept monotherapy or frontline combination compared to primary luspatercept failure
- Endogenous serum erythropoietin levels <500
- *SF3B1* mutation
- HMA/Lenalidomide treatment naïve

AXIS Medical Education

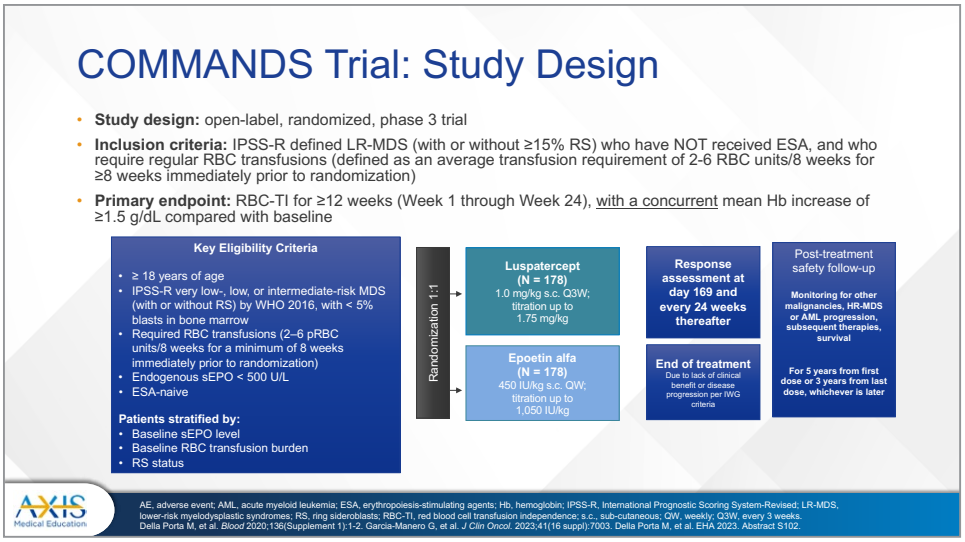
Del5q, deletion 5q; ESAs, erythropoiesis-stimulating agents; Hgb, hemoglobin; HMA, hypomethylating agents; HTB, high transfusion burden; LTB, low transfusion burden; MDS, myelodysplastic syndromes; MDS-RS, myelodysplastic syndrome with ring sideroblasts; MDS/MPN-RS-T, myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis; NTD, non-transfusion dependent; R-IPSS, International Prognostic Scoring System-Revised; RBC-TB, red blood cell transfusion burden; RBC-TI, red blood cell transfusion independent; SF3B1, splicing factor 3b subunit 1; WHO, World Health Organization.
Komrokji RS, et al. *Blood Adv.* Published online April 14, 2023. doi:10.1182/bloodadvances.2023009781

▶ Our group also had been interested [in] looking in combining luspatercept with erythroid-stimulating agents. So, as we said, erythroid-stimulating agents work on early stage, while the luspatercept works on the later stage of erythropoiesis, so it makes sense to combine them. So, we took patients that had ESA failure, had luspatercept treatment and had luspatercept failure, and we combined them, and, indeed, in around one-third of the patients, we observed that we can gain the response, suggesting there is some synergistic or additive activity having the combination, and that's now subject of several trials.

So, a lot of improvement and in this treatment option, a longer follow-up data demonstrating that the MEDALIST results were duplicated in real life, and this provides a new option for our patients with lower-risk MDS.



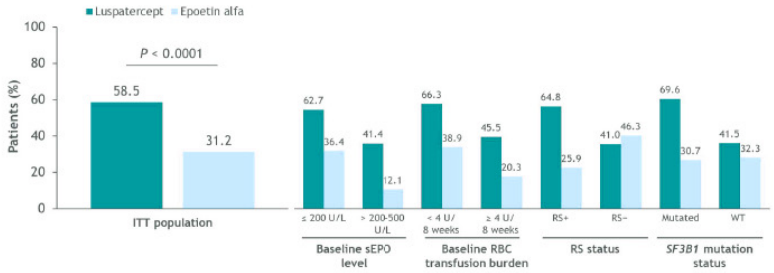
- The landscape for management of myelodysplastic syndromes, however, will be changing based on data presented at both ASCO 2023 and EHA 2023 meetings. There were two studies presented at those meetings. The COMMANDS study with luspatercept, just published in the Lancet Journal, and the IMerge study addressing the role of imetelstat in lower-risk MDS. So, I'll provide a brief overview of those trials, starting with luspatercept.



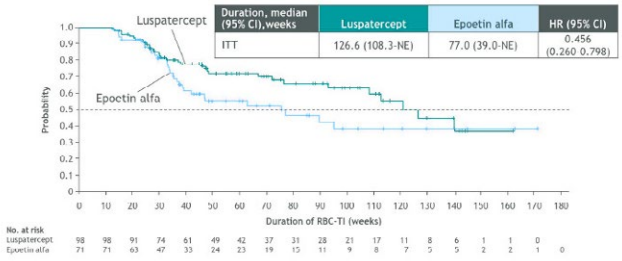
- This was the COMMANDS study where luspatercept was compared to epoetin alfa for treatment of anemia in erythroid-stimulating agent-naïve, lower-risk MDS patients requiring blood transfusions. This study was presented at both ASCO and EHA meetings this year. And the study included lower-risk MDS patients that were transfusion-dependent, between two to six units of blood every eight weeks, and no prior ESA treatment. And patients were randomized between receiving luspatercept similar to the dose administered in the MEDALIST trial, or erythropoietin. The primary endpoint was a robust red blood cell transfusion independence for 12 weeks or more, as well as a hemoglobin increase more than 1.5 grams per deciliter.

COMMANDS Trial: Primary Endpoint Luspatercept Superior to Epoetin Alfa

Achievement of primary endpoint in different patient subgroups



Duration of RBC-TI ≥ 12 weeks longer with luspatercept



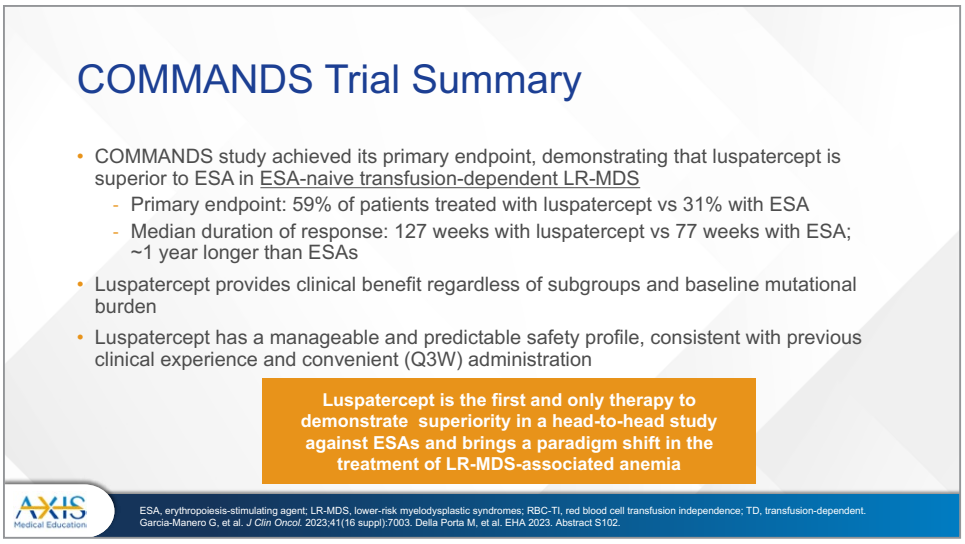
Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
ITT	126.6 (108.3-NE)	77.0 (39.0-NE)	0.456 (0.260 0.798)

Hb, hemoglobin; ITT, intent-to-treat; RS, ring sideroblasts; RBC-TI, red blood cell transfusion independence; sEPO, serum erythropoietin; WT, wild type.
Adapted from Garcia-Manero G, et al. *J Clin Oncol.* 2023;41(16 suppl):7003. Della Porta M, et al. EHA 2023. Abstract S102.

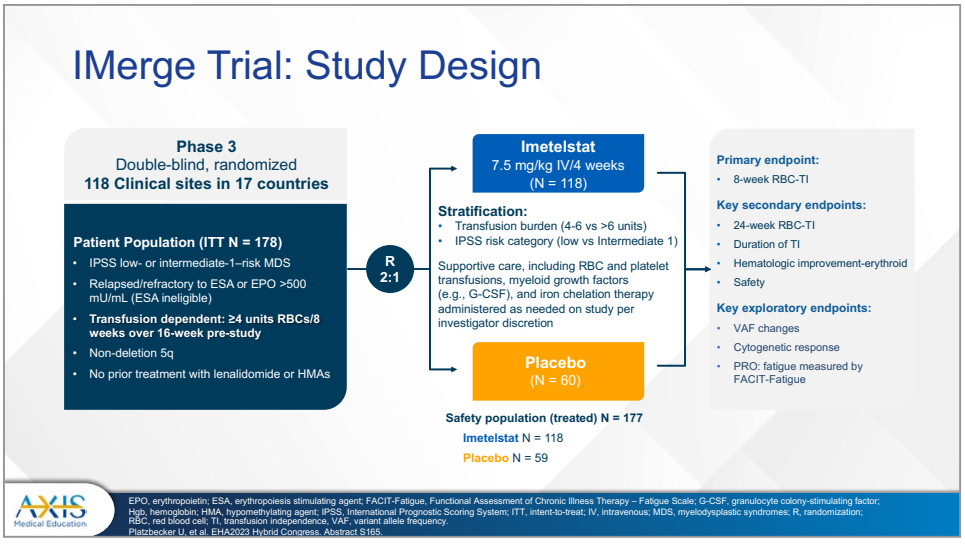
- The study met the primary endpoint, in the intent-to-treat analysis. The responses were doubled – almost 59% with luspatercept compared to 31% with erythroid-stimulating agents. When we looked at subsets, the luspatercept did better than ESA in most of the subsets. Of note, particularly in patients with endogenous serum epoetin between 200-500, the response to erythroid-stimulating agents was 12% versus 41%.

And, in addition to the higher rate of response, the durability was more pronounced, or doubled, with luspatercept, where the median duration was almost, around 127 weeks, compared to 77 weeks, which is historically what we expect with erythroid-stimulating agents. So, doubling the response rate, and doubling the duration of response.

In terms of safety profile, there were no new adverse events reported in the COMMANDS study that were not reported in the MEDALIST study. Fatigue, diarrhea, some edema were the most common. There was no signal of higher risk of progression to AML or higher risk MDS. There was no difference in the mortality between the two arms.



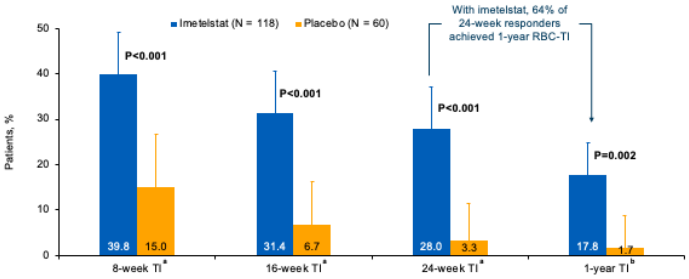
So, in conclusion, the COMMANDS study achieved its primary endpoint. It demonstrated that luspatercept is superior to erythroid-stimulating agents in ESA-naïve, transfusion-dependent lower-risk MDS, doubling the response – 60%, roughly versus 30%, and doubling the duration with a predictable and manageable safety profile. Hopefully this data will lead to moving luspatercept to the upfront management of patients with lower-risk MDS.



The next trial that will probably shape the landscape of management of lower-risk MDS was with imetelstat. This was also presented at ASCO by Dr. Zeidan and at the EHA meeting by Dr. Platzbecker. Imetelstat is a telomerase inhibitor. Telomerase is overactive in MDS cells, with telomeres being shortened, so the idea is affecting the MDS clone. With this in the phase 2, there was around 42% transfusion-independency reported, with durable responses. So, the phase 3 IMerge trial randomized patients that were lower-risk MDS. Those were patients had ESA failure or low chance of response to ESA. They were transfusion-dependent, and they were randomized into 2:1 fashion between imetelstat given once a month – IV infusion, versus placebo. And the primary endpoint was eight-week red blood cell transfusion independency.

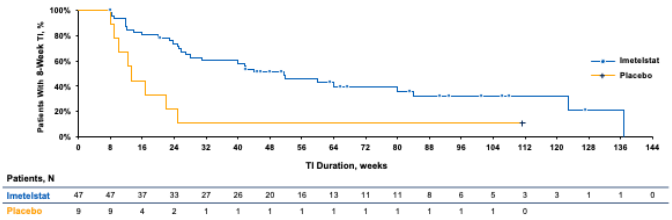
IMerge Trial: Primary Endpoint Imetelstat Superior to Placebo

Higher Rates of Longer-Term Duration of RBC TI Observed With Imetelstat vs Placebo, Including 1-Year RBC TI With Additional 3 Month Follow-up



Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)	HR (95%CI)	P-Value
Median duration of RBC-TI, weeks (95% CI)	51.6 (26.9–83.9)	13.3 (8.0–24.9)	0.23 (0.09–0.57)	<0.001



Significant and Sustained Increase in Hemoglobin Among Patients Treated With Imetelstat

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)
Median Hgb rise, g/dL (range)	3.6 (−0.1 to 13.8)	0.8 (−0.2 to 1.7)
Median Hgb peak, g/dL (range)	11.3 (8.0–21.9)	8.9 (7.9–9.7)

AXIS Medical Education

[a]Data cutoff: October 13, 2022. [b]Data cutoff: January 13, 2023.
RBC, red blood cell; TI, transfusion independence.
Platzbecker U, et al. EHA2023 Hybrid Congress. Abstract S165.

- The study met the primary endpoint, where around 40% of the patients became red blood cell transfusion-independent compared to 15% in the placebo. And when we assess the durable responses, more than 24 weeks, around one-third of the patients with imetelstat achieved that durable response.

  The median duration of response was around a year, compared to 13 weeks in the placebo. So again, many of those patients that achieved a response also have durable responses with imetelstat. The median hemoglobin increase was around 3.6 grams per deciliter. This is probably the second most increase in hemoglobin reported in MDS studies.

  In terms of safety profile, the most common adverse event was a grade 3 or 4 neutropenia or thrombocytopenia. Expected, seen typically in the second or third week, where patients will have an average of one or two weeks, cytopenia. Those were manageable by dose reductions and delays, and did not lead to higher rate of second-line neutropenia.

Higher Cytogenetic Response Rate Per IWG 2006 Criteria With Imetelstat vs Placebo

Cytogenetic Response	Imetelstat (N = 118)	Placebo (N = 60)
Patients with baseline cytogenetic abnormality based on central laboratory review, n (%)	26 (22)	13 (22)
Cytogenetic best response, n (%)		
Cytogenetic CR	5 (19)	1 (8)
Cytogenetic PR	4 (15)	1 (8)
Cytogenetic CR or PR criteria not met	5 (19)	5 (39)
Not evaluable	12 (46)	6 (46)
Cytogenetic CR or PR, n (%) 95% CI	9 (35) 17-56	2 (15) 2-45
% Difference (95% CI) *P* value	19 (-16 to 44) 0.216	

- Complete or partial cytogenetic responses were observed in 9 patients (35%) in the imetelstat group and 2 patients (15%) in the placebo group
- Among cytogenetic responders, 6/9 patients (67%) in the imetelstat group also achieved 24-week RBC-TI, none in the placebo group

CR, complete response; IWG, International Working Group; PR, partial response; RBC, red blood cell; TI, transfusion independence.
Santini V, et al. EHA2023 Hybrid Congress. Abstract S164.

IMerge Trial Summary

- Imetelstat treatment provides significant clinical benefit to a heavily TD LR-MDS patient population in need of novel therapy
- Treatment with imetelstat vs placebo led to:
  - Statistically significant and clinically meaningful efficacy with robust 8-week, 24-week, and 1-year TI rates and durable continuous TI
  - Almost one fifth of imetelstat-treated patients achieved continuous TI for ≥1 year, representing substantial relief from transfusion-associated complications
  - Higher cytogenetic response rate, which was associated with 8-week RBC-TI
  - Higher percentage of patients achieving ≥50% reduction in bone marrow RS cells (41% vs 10%)
  - Sustained reduction of SF3B1 VAF over time
  - Greater reduction of VAF in multiple genes, which correlated with clinical end points of TI response, longer RBC-TI duration, and increase in Hgb levels
- Safety results were consistent with prior reports
- VAF reduction and its correlation to clinical endpoints, including durable TI, support imetelstat's disease-modifying potential
- Imetelstat may alter the underlying biology of LR-MDS and can potentially modify the disease by reducing or eliminating malignant clones and improving ineffective erythropoiesis

RBC, red blood cell; RS, ring sideroblasts; TD, transfusion-dependent; TI, transfusion independence; VAF, variant allele frequency.
Platzbecker U, et al. EHA2023 Hybrid Congress. Abstract S165. Santini V, et al. EHA2023 Hybrid Congress. Abstract S164.

Also, in this same meeting, there was another presentation on the potential disease modification of imetelstat. Dr. Santini presented data on the cytogenetic and molecular responses with imetelstat in this study. So around one-third of the patients had a cytogenetic response, including almost 20% having a complete cytogenetic response. Also, there was observation in the reduction in deviant allele frequency in patients treated with imetelstat. In genes such as SF3B1, TET2, DNMT3A and ASXL1, where almost one-third of the patients had reduction in the variant allele frequency of those mutations – 50% or more. And there was a nice correlation between the reduction in the allele burden, as well as the hematological responses, in terms of transfusion independency and hemoglobin increase.

We also looked at different biomarkers, including reduction in the ring sideroblast, cytogenetic responses, reduction in the allele burden of the mutations mentioned, and all of those correlated with the eight-week transfusion independency, 24-week transfusion independency, as well as the hemoglobin increase. So, those data are really exciting, suggesting that the landscape of lower-risk MDS would change, with luspatercept moving to the upfront of the management, and imetelstat becoming [an] option for patients with lower-risk MDS after ESA or [luspatercept] failure. Thank you very much.

Dr. Doghramji:
PA Platt and Dr. Komrokji, thank you for reviewing this data, and exciting data, with us today. Unfortunately, that's all the time we have today. So, I want to thank our audience for listening in, and thank you, Dr. Komrokji and PA Platt, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Komrokji:
Thank you. It was my pleasure, and hopefully the audience will find this helpful.

PA Platt:
Thank you very much, too, for having us.

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About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

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