Dr. Sekeres: Good morning, everyone, and welcome to *Current and Emerging Treatments for Myelodysplastic Syndromes: The 2021 Landscape*. I'm Mikkael Sekeres, Chief of the Division of Hematology at the Sylvester Comprehensive Cancer Center at the University of Miami.

Dr. DeZern: Good morning, everyone. I'm Amy DeZern, speaking to you from Baltimore at the Johns Hopkins.

Dr. Sekeres: We're going to get started.

Faculty Disclosures

- **Dr. Mikkael Sekeres** has relevant financial relationships related to advisory activities from Bristol-Myers Squibb Company, Novartis AG, and Takeda Oncology.
- **Dr. Amy DeZern** has relevant financial relationships related to advisory activities from AbbVie Inc., Bristol-Myers Squibb Company, and Novartis AG, as well as relevant financial relationships related to the development of educational materials from Taiho Pharmaceutical Co., Ltd.

All of the relevant financial relationships listed for these individuals have been mitigated.

These are our faculty disclosures.

I'm going to be discussing genetics, risk stratification, and managing lower-risk MDS in 2021. Then I'll hand it over to my partner, Dr. DeZern, who will be discussing treatment of higher-risk MDS.

MDS Management: Agenda

- Patient
- Risk Stratification
- Ameliorating Anemia
- Tackling Thrombocytopenia
- Modifying Multilineage Dysplasia
- Conclusions

This is our agenda.

MDS Management: Agenda

- **Patient**
- Risk Stratification
- Ameliorating Anemia
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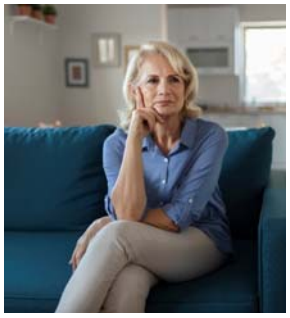
- Modifying Multilineage Dysplasia
- Conclusions

Let's get started by talking about a patient.

MDS Management: Patient



- 75-year-old woman with worsening fatigue
- WBC: 4500/uL with ANC 2100, no blasts
- Hgb: 7.8 g/dL with MCV of 102
- Platelet count: 174,000/uL
- Reticulocyte count: 0.4%
- Epo level: 80 mIU/ml
- A bone marrow biopsy shows hypercellularity (70%), dyserythropoiesis and 25% ring sideroblasts, and she is diagnosed with **MDS-SLD-RS (2% blasts)**
- Cytogenetics: normal; **NGS with *SF3B1* (VAF 26%)**

Our patient is a 75-year-old woman with worsening fatigue. She comes to our clinic with a white count that's normal at 4,500 and ANC of 2,100 also normal and no circulating blasts. Her hemoglobin though is low at 7.8 with an elevated MCV at 102. Her platelet count is normal at 174,000. Her reticulocyte count is inappropriately low for the degree of anemia at 0.4%. Her EPO level is high at 80 where the upper limit of normal is 25.

She undergoes a bone marrow biopsy and aspirate which shows a hypercellular bone marrow for her age at 70%, with dyserythropoiesis and 25% ring sideroblasts, and she is diagnosed with MDS with single lineage dysplasia with ring sideroblasts at 2% blasts. Her cytogenetics are normal. Our next-generation sequencing panel, however, reveals an SF3B1 mutation with a variant allele frequency of 26%.

MDS Management: Agenda

- Patient
- **Risk Stratification**
- Ameliorating Anemia
- Tackling Thrombocytopenia
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Let's talk about how we would risk-stratify such a patient.

How would you risk stratify this patient (risk of AML or death)?

A. Very Low Risk
B. Low Risk
C. Intermediate Risk
D. High Risk
E. Very High Risk

Please select your response below the video window and click the submit button to poll.

We'll start off by asking you: How would you risk stratify this patient?

In this case, we're talking about risk as her risk of transforming to AML or death.

A. Very low risk
B. Low risk
C. Intermediate risk
D. High risk
E. Very high risk

Please select your response

How would you risk stratify this patient (risk of AML or death)?

A. **Very Low Risk**

B. **Low Risk**

C. Intermediate Risk

D. High Risk

E. Very High Risk

The answer is I would casually rank her somewhere between very low risk and low risk, and we'll see formally where she would fall.

MDS: IPSS Classification

Calculation of prognostic score

Score	0	0.5	1.0	1.5	2.0
BM Blast %	<5	5-10		11-20	21-29
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Estimation of prognosis

Lower-Risk

Overall Score	IPSS Subgroup	Median Survival (Years)
0	Low	5.7
0.5-1.0	Intermediate-1	3.5
1.5-2.0	Intermediate-2	1.2
≥2.5	High	0.4

Greenberg P, et al. *Blood.* 1997;89:2079-2088.

We don't have a staging system in MDS. We use the International Prognostic Scoring System as our default staging system. It codifies what's clinically and intuitively fairly obvious. That patients who come into our clinic with a low blast percentage in their bone marrow like our patient, good risk cytogenetics, and an MDS good risk includes normal deletion 5q, deletion 20q and -Y, and an isolated cytopenia or no cytopenias, have a very good prognosis with a median survival that is measured in years.

On the other hand, somebody who comes into our clinics with high blast percentage, let's say 18%, poor-risk cytogenetics, and an MDS poor-risk per the IPSS includes complex set of genetics or chromosome 7 abnormalities, and multiple cytopenias, has a median survival that's measured in less than a year and a half.

MDS: IPSS-R Cytogenetics

Prognostic subgroup	Abnormality			n (%)	Overall Survival	
	Single	Double	Complex		Median (months; 95% CI) *P*<0.01)	HR (95% CI)
Very good	del(11q) -Y	-	-	81 (2.9)	60.8 (50.3-NR)	0.5 (0.3-0.7) +
Good	Normal del(5q) del(12p) del (20q)	inc. 5q-	-	1809 (65.7)	48.6 (44.6-54.3)	1.0 (0.8-1.3)
Intermediate	del(7q) +8 i(17q) +19 Any other Ind . clones	any other	-	529 (19.2)	26.0 (22.1-31.0)	1.6 (1.4-1.8) +
Poor	inv(3)/t(3q)/del(3q) -7	inc. -7/7q-	3 abn.	148 (5.4)	15.8 (12.0-18.0)	2.6 (2.0-3.3) +
Very poor	-	-	>3 abn.	187 (6.8)	5.9 (4.9-6.9)	4.2 (3.4-5.3) +

Schanz J, et al. *J Clin Oncol*. 2012;30:820-829.

The revised IPSS is sculpted around this cytogenetic risk classification schema that was published by Dr. Schanz in 2012. It makes things a little more complicated and I actually have to have this posted up on the wall in my workroom to remember all these different categories. Although I will say it basically puts the good risk categories in the very good and good risk. Once again, that's -Y, normal deletion 5q, deletion 20q, adds deletion 12p and deletion 11q which I will say are very, very rare abnormalities. It changes things a little, but not a lot.

MDS: IPSS-R Scoring

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	V. Good		Good		Intermediate	Poor	V. Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Lower-risk

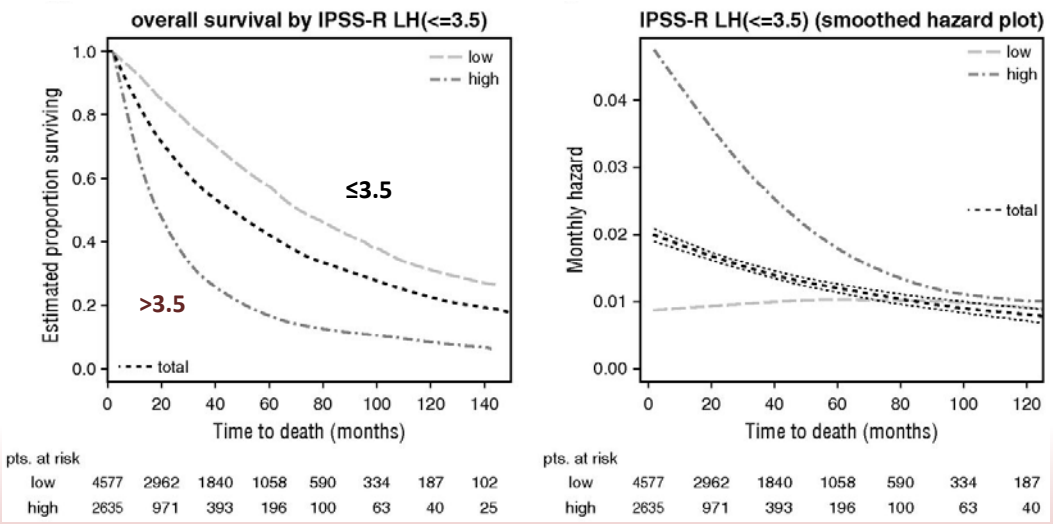
Prognostic Risk Categories/Scores

Risk Group	Risk Score	Median Survival (Yrs)
Very Low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very High	>6	0.8

Greenberg P, et al. *Blood.* 2012;120:2454-2465.

The revised IPSS now gives you a higher score for a very poor cytogenetics patients who have a paragraph long of abnormalities when you see them, even greater than 10% blasts and gives a different points score based on the degree of anemia, degree of thrombocytopenia, and an absolute cut point for the absolute neutrophil count.

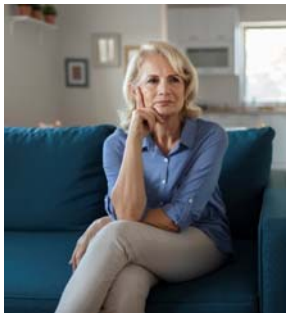
Updates in MDS: IPSS-R Scoring



Pfeilstocker M, et al. *Blood*. 2016;128:902-910.

To simplify it, patients who have an IPSS-R score of 3.5 or lower would be considered lower-risk, and those who have a score greater than 3.5 would be considered as having higher-risk MDS.

MDS Management: Patient – IPSS



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- Hgb: 7.8 g/dL with MCV of 102
- Platelet count: 174,000/uL
- Reticulocyte count: 0.4%
- Epo level: 80 mIU/ml

0

- A bone marrow biopsy shows hypercellularity (70%), dyserythropoiesis and 25% ring sideroblasts, and she is diagnosed with **MDS-SLD-RS (2% blasts)**

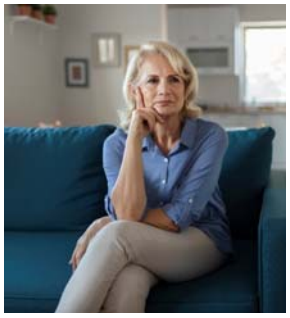
0

- Cytogenetics: normal; **NGS with *SF3B1* (VAF 26%)**

Total IPSS = 0

Let's go back to our patient using the IPSS. She would get a score of 0 for having an isolated cytopenia, score of 0 for having fewer than 5% blast, and a score of 0 for having normal karyotype, giving her a total IPSS score of 0 and placing her in the low-risk category.

MDS Management: Patient – IPSS-R



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- Hgb: 7.8 g/dL with MCV of 102
- Platelet count: 174,000/uL
- Reticulocyte count: 0.4%
- Epo level: 80 mIU/ml

1.5

- A bone marrow biopsy shows hypercellularity (70%), dyserythropoiesis and 25% ring sideroblasts, and she is diagnosed with **MDS-SLD-RS (2% blasts)**

0

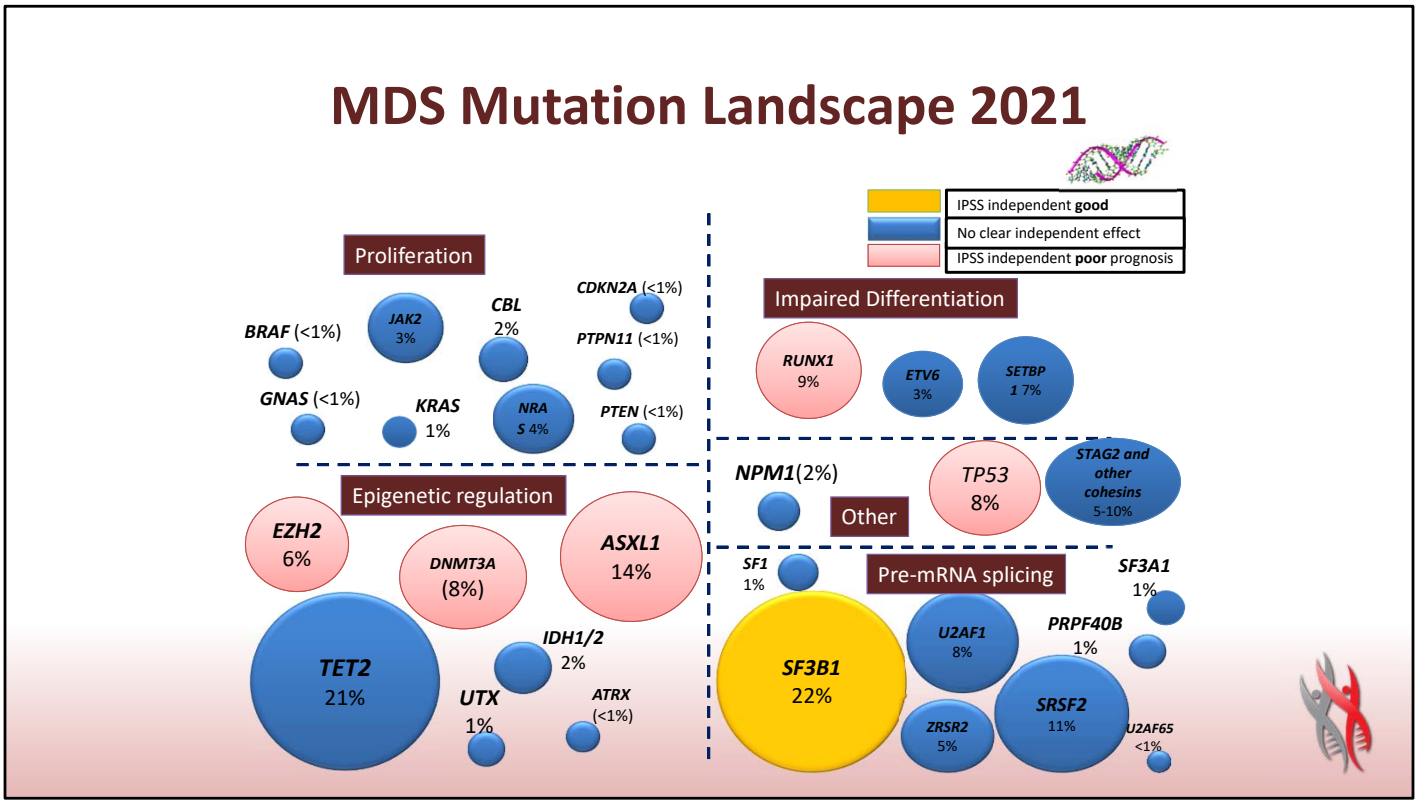
- Cytogenetics: normal; **NGS with *SF3B1* (VAF 26%)**

1

Total IPSS-R = 2.5

Using the revised IPSS, she would get a score of 1.5 for her degree of anemia, again, a score of 0 for having 2% blasts or fewer, and she would actually get a score of 1 for having a normal karyotype giving her a total IPSS-R score of 2.5 and placing her in the low-risk category once again.

Current and Emerging Treatments for Myelodysplastic Syndromes: The 2021 Landscape



MDS is more complicated than this. We know that there are a variety of molecular abnormalities that can be grossly lumped into those that are involved in proliferation, epigenetic regulation, impaired differentiation, pre mRNA splicing, and then others including p53 and NPM1. These two can be risk-stratified.

Which of these mutations is considered "good risk" in MDS?

A. PTPN11
B. NPM1
C. SF3B1
D. TP53
E. IDH1

Please select your response below the video window and click the submit button to poll.

Which leads us to our next polling question.

Which of these mutations is considered good risk in MDS?

A. PTPN11
B. NPM1
C. SF3B1
D. TP53
E. IDH1

Please vote.

Which of these mutations is considered "good risk" in MDS?

A. PTPN11

B. NPM1

C. SF3B1

D. TP53

E. IDH1

That is the correct answer.

Which of these mutations is considered "poor risk" in MDS?

A. PTPN11
B. NPM1
C. SF3B1
D. TP53
E. IDH1

Please select your response below the video window and click the submit button to poll.

Now, which of these mutations is considered poor risk in MDS?

A. PTPN11
B. NPM1
C. SF3B1
D. TP53
E. IDH1

Please vote.

Which of these mutations is considered "poor risk" in MDS?

A. PTPN11

B. NPM1

C. SF3B1

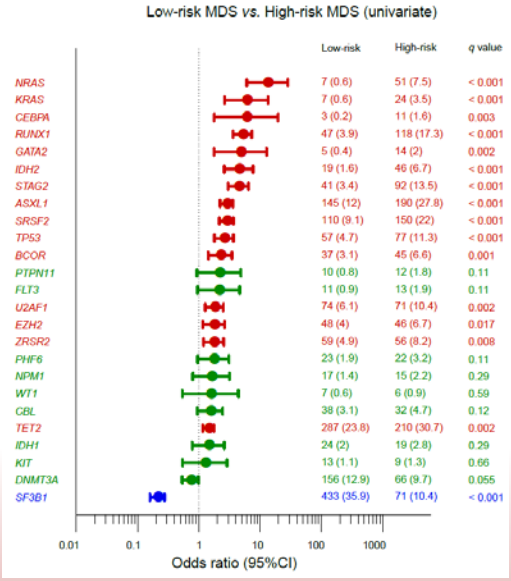
D. TP53

E. IDH1

The answer is TP53.

MDS: Mutation Risk

- Driver genes can be classified into molecular subtypes differentially associated with disease severity



Makishima H, et al. *Nat Genetics*. 2017;49:204-212.

Okay. This is a study that our group when I was in Cleveland, published in *Nature Genetics* in 2017 looking at the relative risk of different types of mutations. Driver genes can be classified into molecular subtypes differentially associated with disease severity. The abnormalities at that top tend to be associated with poorer-risk or high-risk MDS, they include RAS mutations, RUNX1, IDH2, ASXL1, TP53. The ones at the bottom start to get a little bit better risk, but the only truly good risk molecular abnormality in MDS is SF3B1, the abnormality that our patient has.

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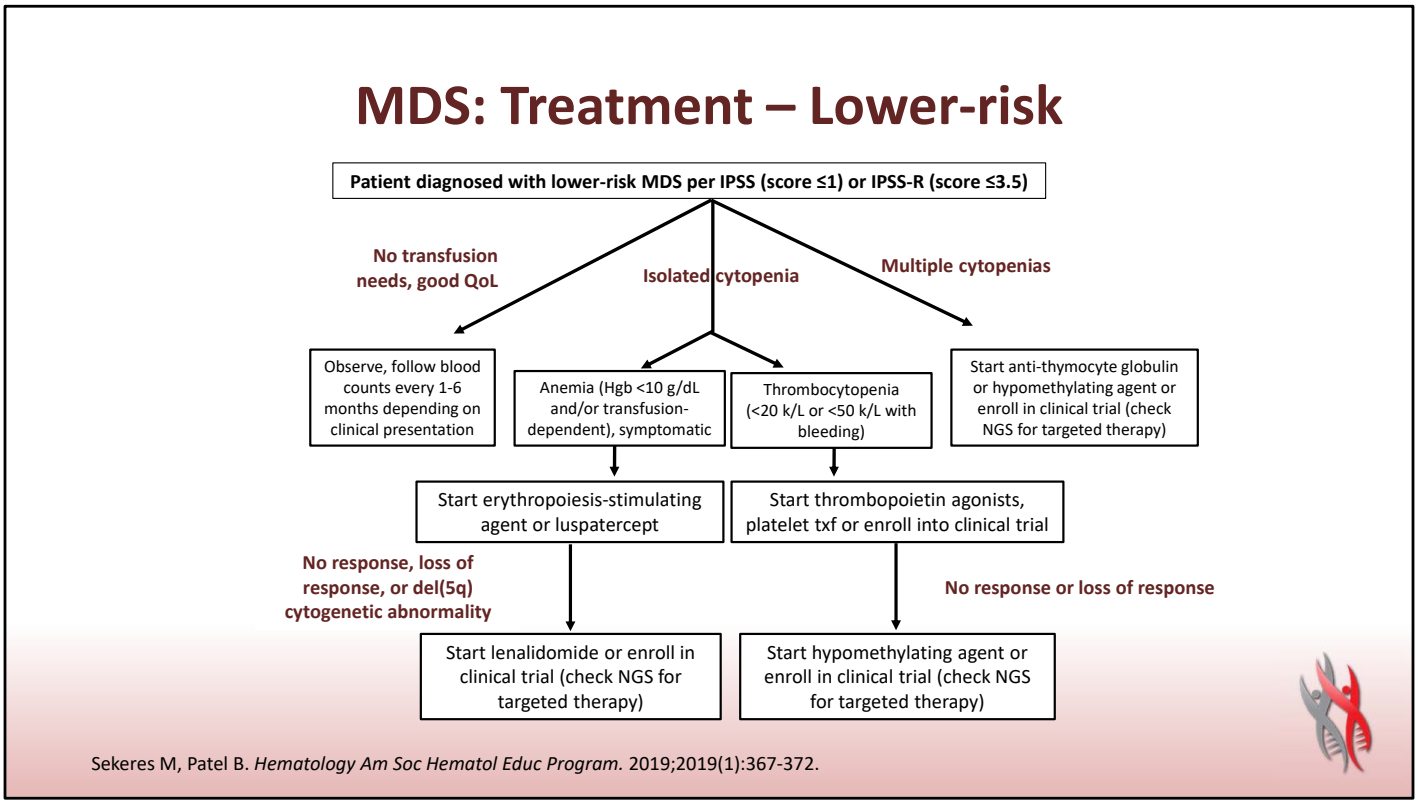
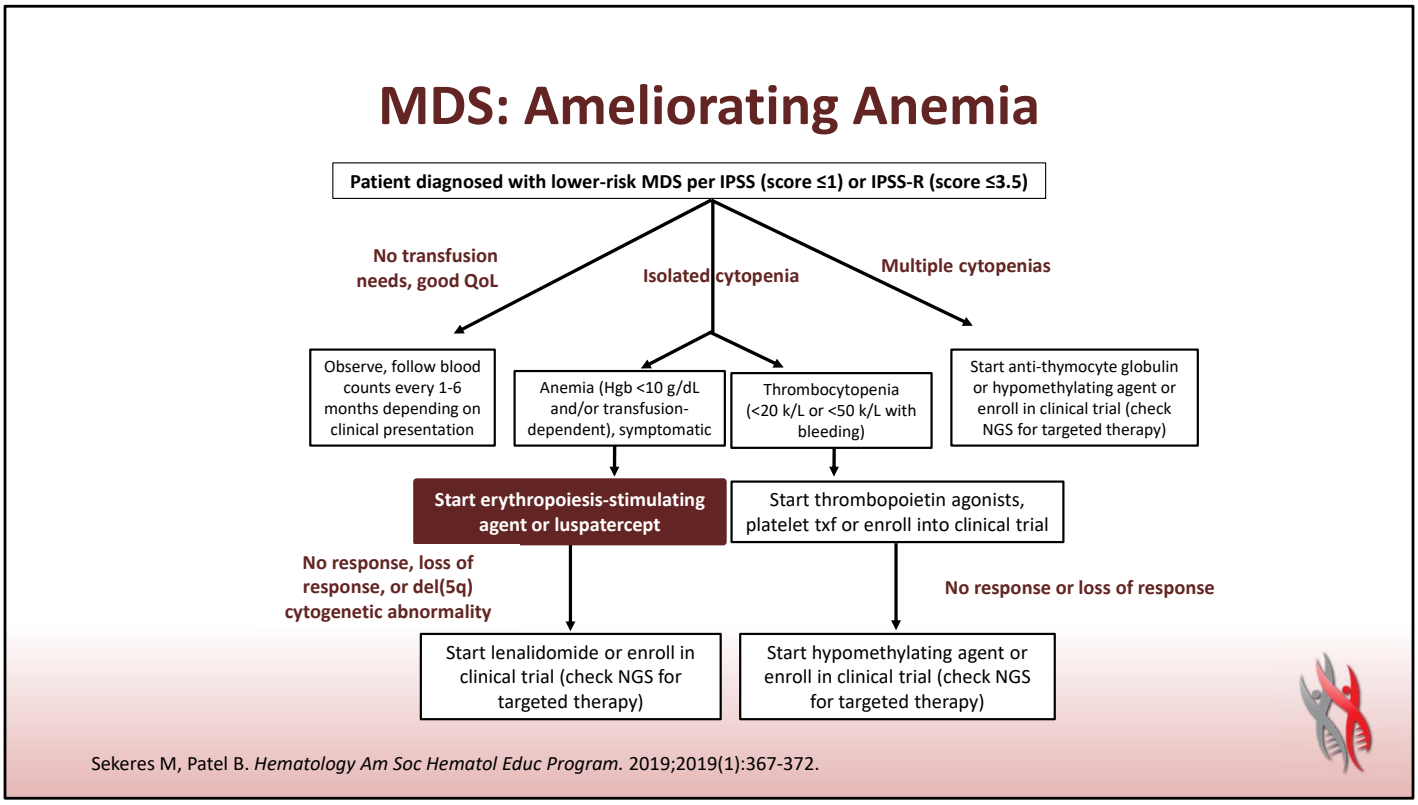
Let's talk about how we would treat her anemia.



Treatment for lower-risk MDS is broadly divided into the predominating cytopenia that a patient has when he or she presents. We have some patients who have no transfusion needs and a good quality of life. One of my patients literally once said to me, he described it as having mild displeasure syndrome. He didn't like to fight the traffic to get into Cleveland or Miami to see me but otherwise did not require any transfusions or in the interventions. These are folks we can follow.

Then we have patients where the predominating cytopenia is anemia, thrombocytopenia, or they really have more than one cell line that's down and that probably needs to be fixed.



Let's focus first on those who have an isolated anemia like our patient. The most widely used drug to treat MDS are erythropoiesis-stimulating agents.

What's the likelihood of response to erythropoiesis stimulating agents (epo, darbe)?

A. <10%

B. 15-40%

C. 40-60%

D. 60-80%

E. >80%

Please select your response below the video window and click the submit button to poll.

What's the likelihood that someone is going to respond to an erythropoiesis-stimulating agent?

This is all-comers with lower-risk MDS.

A. Less than 10%
B. 15% to 40%
C. 40% to 60%
D. 60% to 80%
E. Greater than 80%

Please vote.

What's the likelihood of response to erythropoiesis stimulating agents (epo, darbe)?

A. <10%

B. 15-40%

C. 40-60%

D. 60-80%

E. >80%

The answer is actually 15% to 40%. They don't work quite as well as we think they do, but they are easy to give.

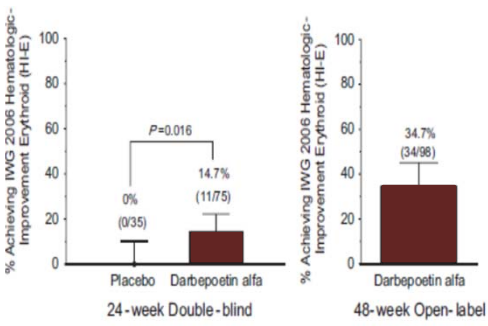
Lower-risk MDS: Ameliorating Anemia – ESAs

ESAs RR 15% - 40%

Response results

	Patients (%)	Response rate
Growth factors	100	39.5
EPO	57.3	39.4
EPO + GCSF	23.4	47.8
GMCSF	6.2	37.8
EPO + GMCSF	5.8	33.7
GCSF	3.0	47.0
IL3	3.0	17.0
IL6	1.3	38.1

N = 1587



N = 147 (2:1)

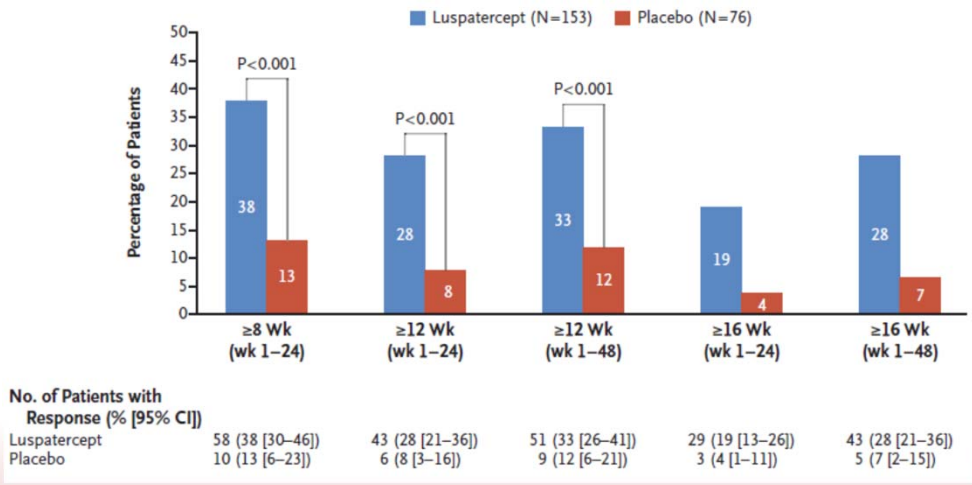
Golshayan A-R, et al. *Br J Haem*. 2007;137:125-132.; Platzbecker U, et al. *Leukemia*. 2017;31:1944-1950.

Why do I say 15% to 40%? We published a meta-analysis about a decade ago looking at 20 years of published literature of response rates to erythropoiesis-stimulating agents. In this study, we focused just on patients who had lower-risk MDS and standardized response to International Working Group response criteria. When we did that, we found that the response rate to erythropoiesis-stimulating agents as a whole was about 40%. That's out of almost 1,600 patients included in those studies.

More recently, a randomized trial was conducted in Europe, in which patients with lower-risk MDS were randomized to receive darbepoetin or placebo. On the study period, the response rate to darbepoetin was really only 15%, and that's during the initial 24 weeks. It was only with further follow-up that that rose to 35% in those patients who received darbepoetin. When I first meet with a patient, I will have a discussion with them about how the response rate is somewhere in the range of about 15% to 40%.

Naturally, those patients who come into our clinics who aren't yet dependent on red blood cell transfusions and who have a relatively low serum EPO level, and for MDS low means less than 100. Our patients who had an EPO level of 80 are more likely to respond to ESAs. Those patients who come into our clinics, though, who are already dependent on red cell transfusions and have a sky-high serum EPO level, and I've seen folks with EPO levels in the thousands, are highly unlikely to respond to exogenously administered ESAs.

MDS: Ameliorating Anemia – Luspatercept



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Independence from Red-cell Transfusion

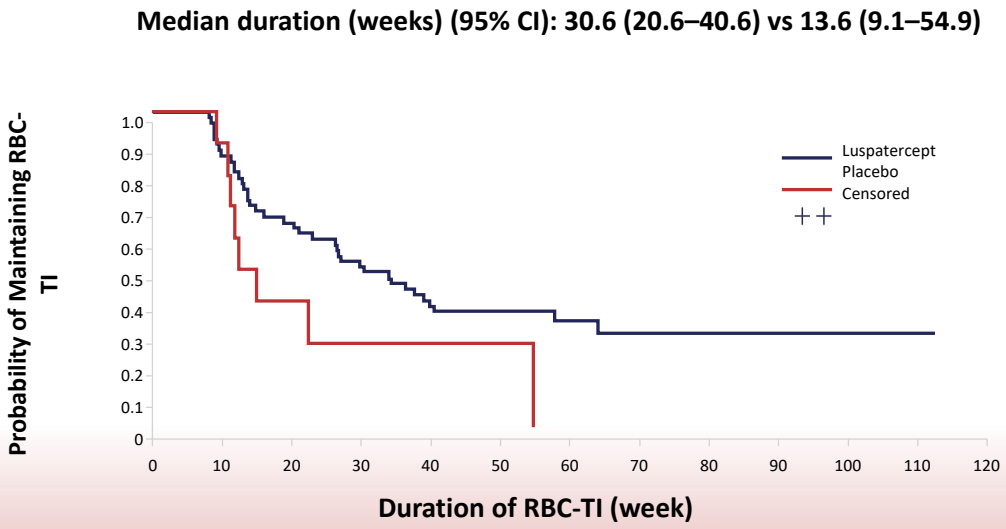
Fenaux P, et al. *N Engl J Med*. 2020;382:140-151.

There was another drug that was just approved in 2020 called luspatercept that works at late stages of erythropoiesis and probably through Smad2/3 signaling. This drug was approved based on a randomized trial in which patients were randomized 2:1 to receive luspatercept versus placebo. Patients on the study had to have lower-risk MDS, had to have already been exposed to ESAs or have a highly unlikely probability of responding to those ESAs, and had to be transfusion-dependent.

On this study, 38% of patients treated with luspatercept achieved transfusion independence lasting at least 8 weeks, compared to 13% in the placebo group. That 13% of patients receiving placebo technically had a response, emphasizes why it's just so important why we have randomized trials in MDS to demonstrate efficacy of a drug.

How is it that 13% of patients could have responded to a placebo? Well, it's just fortuitous. I think there are a couple of explanations. First of all, patients with MDS don't always have stable transfusion needs. They can wax and wane, but secondly, remember, our patients are older, and it may be that some of these patients happen to have some occult GI bleeding when they started the study, and that occult GI bleeding resolved fortuitously, as soon as they came onto the trial, making us think that they were responding to placebo. The absolute difference here was 25% in transfusion independence response rate. That response duration was a median of 31 weeks.

MDS: Ameliorating Anemia – Luspatercept



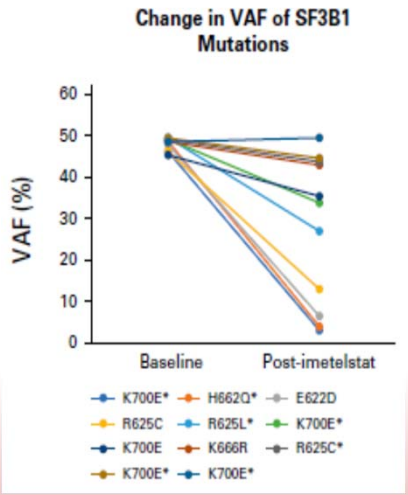
Fenaux P, et al. *N Engl J Med*. 2020;382:140-151.

I'll give a little bit of props to luspatercept here. Once a patient required a single blood transfusion, then that duration of response was stopped. But there were patients, and there were a few of them actually, who would go weeks without a transfusion or received one bag of blood and then go weeks afterwards on luspatercept. This a little bit undercounts the duration of response, but the data are the data, median of 31 weeks of response.

MDS: Ameliorating Anemia – Imetelstat

Imetelstat in HTB Lower-risk MDS

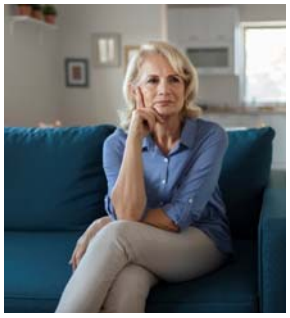
Parameter	Overall Population (n = 57)
8-week TI[a], No. (%)	21 (37)
Median time to onset, weeks (range)	8.3 (0.1-100.6)
Median duration of TI[b], weeks (range)	65 (17.0-140.9)
24-week TI[a], No. (%)	13 (23)
HI-E per IWG 2006, No. (%)	37 (65)
≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks	15 (26)
Transfusion reduction by ≥ 4 units/8 weeks	37 (65)
Response per IWG 2018, No. (%)	
Major response: 16-week TI	16 (28)
Major response: 8-week TI	21 (37)
Minor response[c]	28 (49)



Steensma P, et al. *J Clin Oncol.* 2020;39(1):48-56.

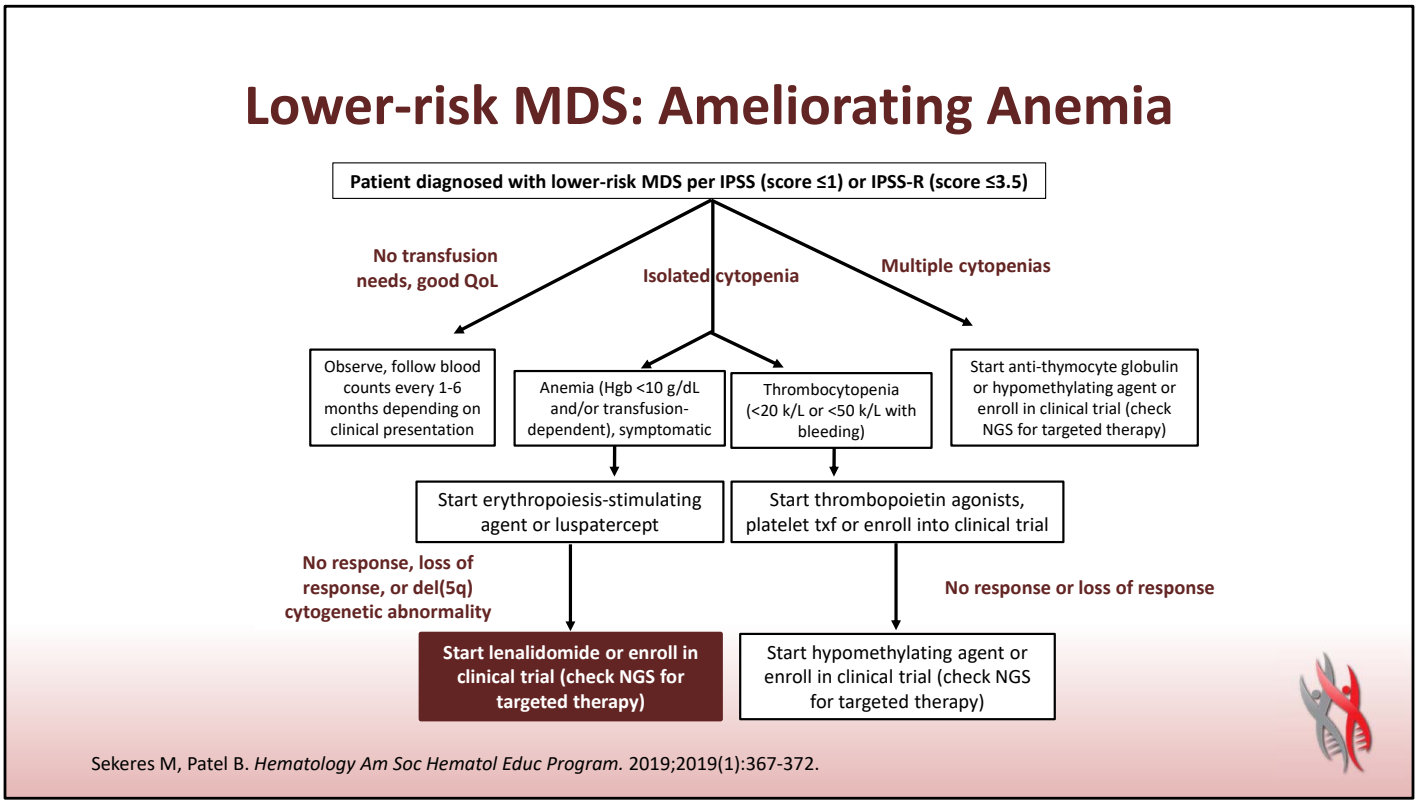
There is another drug, imetelstat, that works on telomerase inhibition that is being studied and now is in a randomized registration-type study. In the phase two trial that was published in *JCO* in 2020, last year, the transfusion independence response rate was 37%, eerily similar to what we just saw for luspatercept. The duration of transfusion independence actually was a little bit longer than a year. Interestingly, Dr. Steensma and colleagues showed that there was a decrease in the variant allele frequencies of SF3B1 mutations. Remember, that's the one that our patient has over time, demonstrating that imetelstat does have effects on the MDS clone. We will see if these results hold up in the randomized setting.

MDS Management: Patient



- Treated with darbepoetin 500 mcg q3w x 10 months with increase in Hgb from **7.8** g/dL to **9.4** g/dL
- Hgb then slips to **7.6** g/dL
- Repeat bone marrow essentially unchanged, but cytogenetics (previously normal) show **del(5q)**

Back to our patient. She's treated with darbepoetin, 500 mcg every 3 weeks for 10 months, and that is actually the dose that was studied in the US over a decade ago. She has an increase in her hemoglobin from 7.8 to 9.4 g/dL. Her hemoglobin then slips to 7.6 g/dL. This prompted another bone marrow biopsy and aspirate that was essentially unchanged, but her cytogenetics, which previously were normal, showed deletion 5q now.



This isn't an instance where you would consider starting lenalidomide or, of course, enroll patients onto a clinical trial.

What's the likelihood of response to lenalidomide for del(5q) MDS?

A. <10%
B. 15-40%
C. 40-60%
D. 60-80%
E. >80%

Please select your response below the video window and click the submit button to poll.

What's the likelihood that she's going to respond to lenalidomide for her deletion 5q lower-risk MDS?

A. Less than 10%
B. 15% to 40%
C. 40% to 60%
D. 60% to 80%
E Greater than 80%

Please vote.

What's the likelihood of response to lenalidomide for del(5q) MDS?

A. <10%

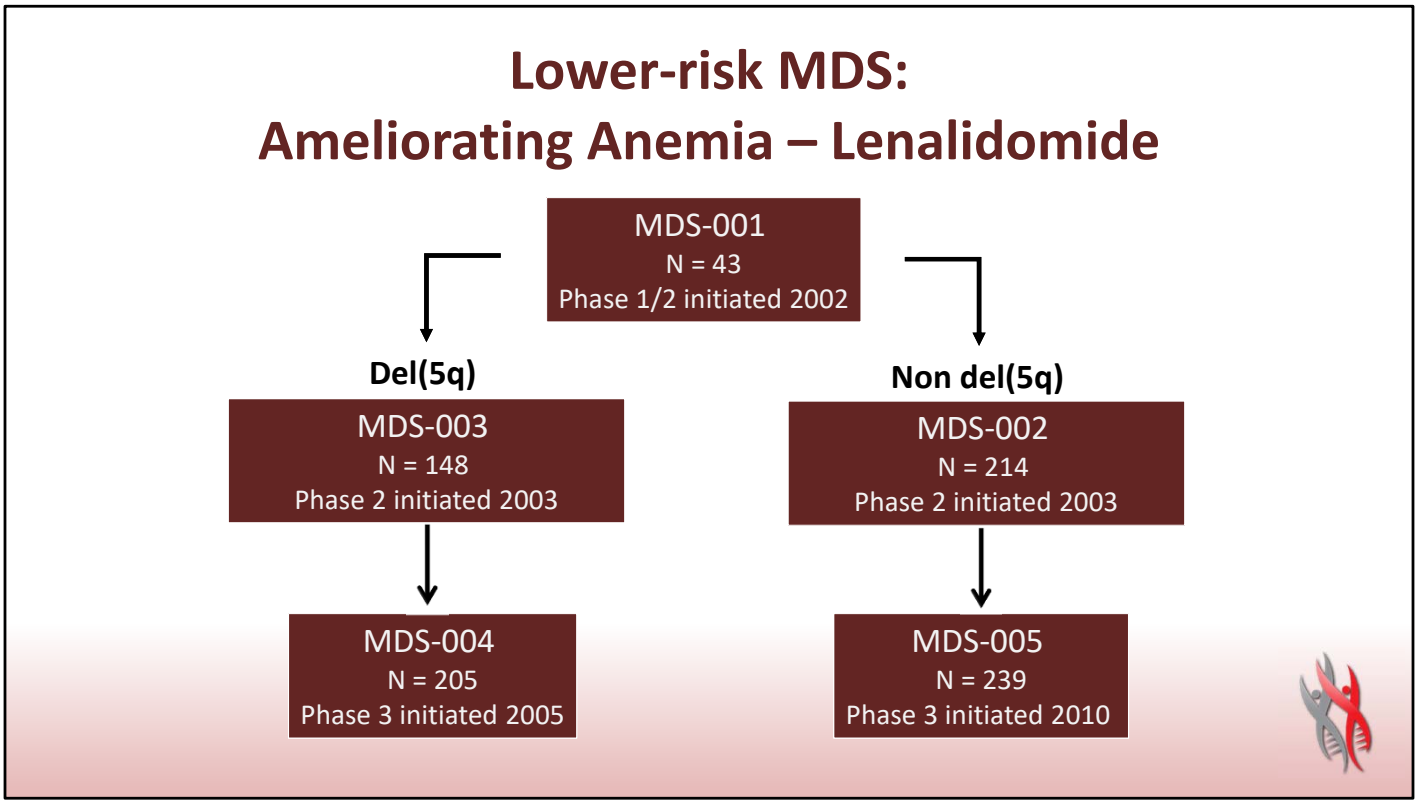
B. 15-40%

C. 40-60%

D. 60-80%

E. >80%

The answer is 60% to 80% in patients who have deletion 5q MDS.



There have been a number of trials that have looked at lenalidomide in treating lower-risk MDS, some that have included patients with deletion 5q, and some that haven't.

Lower-risk MDS: Ameliorating Anemia – Lenalidomide

Del(5q)

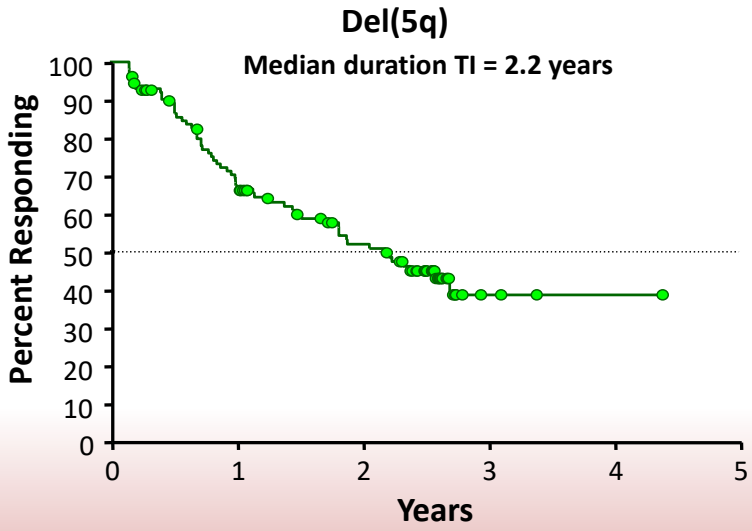
	RBC-TI, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
miTT population	**n = 51**	**n = 47**	**n = 41**
Protocol defined (≥26 weeks)	3 (5.9) [1.2-16.2]	20 (4.26) [28.3-57.8]	23 (56.1) [39.7-71.5]
IWG 2000 (≥8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]	25 (61.0) [44.5-75.8]
IWG 2006 (≥8 weeks)	3 (5.9) [1.2-16.2]	24(5.11) [36.1-65.9]	25(61.0) [44.5-75.8]

Fenaux P, et al. *Blood*. 2011;118:3765-3776.

Probably the best conducted in patients who have deletion 5q with lower-risk MDS for transfusion-dependent was this one conducted in Europe. Patients were randomized to receive lenalidomide at 10 mg, lenalidomide at 5 mg, or placebo. Those receiving lenalidomide at 10 mg had a transfusion independence response rate of 61%. In a previous phase 2 trial that led to lenalidomide approval in the US, that transfusion independence response rate was 67%. That's why we say the 60% to 80% range is probably correct.

When using lenalidomide in lower-risk MDS patients with deletion 5q, it's important to start at the higher dose, keep that going for a couple of cycles, and then consider lowering it to 5 mg daily or 5 mg every other day.

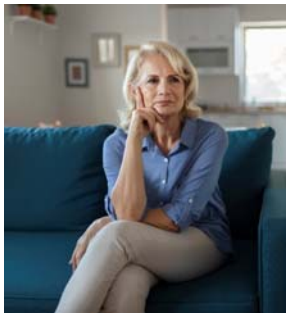
Lower-risk MDS: Ameliorating Anemia – Lenalidomide



List AF, et al. *Leukemia*.2014;28:1033-1040.

The response duration was 2.2 years, which is about as good as we get for lower-risk MDS. That, of course, is the median.

MDS Machinations: Patient



On lenalidomide

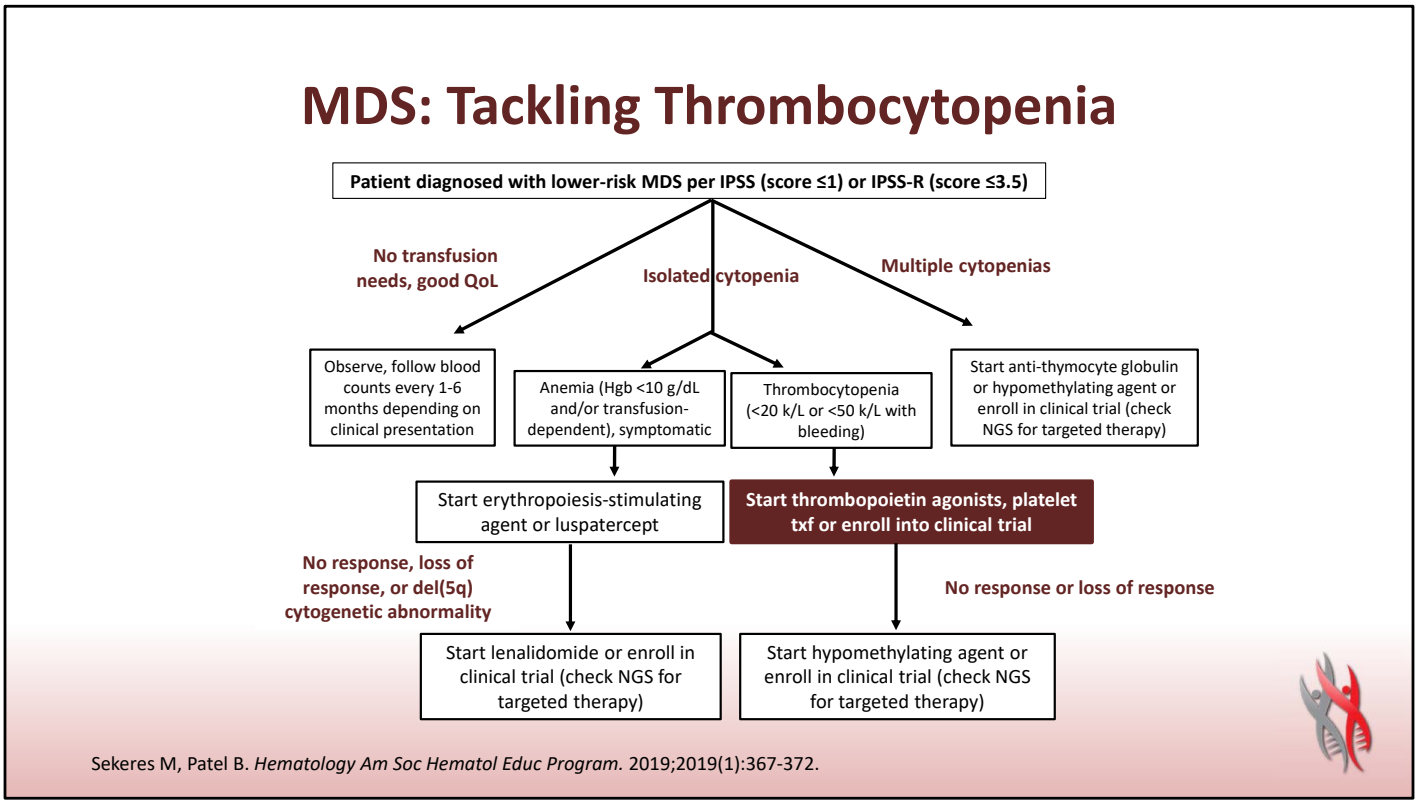
- Hgb improves to 11.7 g/dL x 22 months. Then, over the next few months changes in **laboratory results:**
  - WBC: 1800/uL with ANC 950, no blasts
  - Hgb: 7.8 g/dL with MCV of 106
  - Platelet count: 24,000/uL
- A bone marrow biopsy shows hypercellularity (80%), trilineage dyspoiesis, and she is diagnosed with **MDS-MLD-RS (2% blasts)**
- Cytogenetics: Del(5q); **NGS with *SF3B1*, ASXL1**

On lenalidomide, our patient's hemoglobin improves for 22 months, then her blood counts change again with a white count of 1,800 and ANC that's low at 950. Her hemoglobin is back down to 7.8 and her platelet count plummets to 24,000. Her repeat bone marrow biopsy continues to show hypercellularity, trilineage dyspoiesis. She has a low blast percentage, but now has MDS with multilineage dysplasia with ring sideroblasts. Her NGS shows evolution, now including an ASXL1 mutation.

MDS Management: Agenda

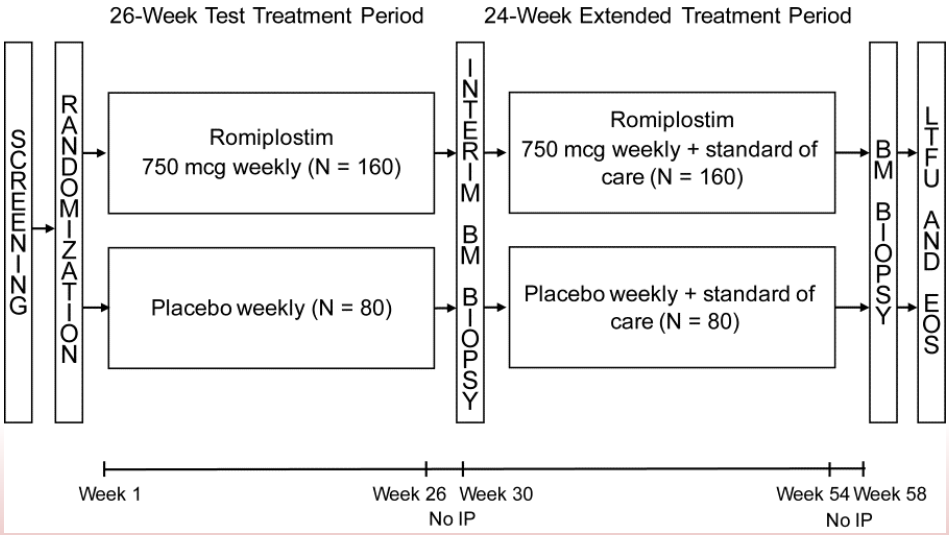
- Patient
- Risk Stratification
- Ameliorating Anemia
- **Tackling Thrombocytopenia**
- Modifying Multilineage Dysplasia
- Conclusions

What if we want to tackle her thrombocytopenia and treat her low platelet count to start with?



We would consider using thrombopoietin agonists, or, of course, enroll onto a clinical trial.

Lower-risk MDS: Tackling Thrombocytopenia



Giagounidis A, et al. *Cancer.* 2014;120:1838-1846.

Eltrombopag and romiplostim are the thrombopoietin agonists we most commonly turn to in hematology. This is the study of romiplostim that I think was the better of the two looking at these drugs in MDS. In the study, patients with lower-risk MDS and thrombocytopenia were randomized to receive romiplostim or placebo.

Lower-risk MDS: Tackling Thrombocytopenia

	Baseline platelets <20x10^9/L		Baseline platelets ≥20x10^9/L	
	Placebo (N = 43)	Romiplostim (N = 87)	Placebo (N = 40)	Romiplostim (N = 80)
CSBE (rate/100 pt-yr)	501.2	514.9	**226.4**	**79.5**
	RR = 1.03, *P*=0.827		**RR = 0.35, *P*<0.0001**	
PTE (rate/100 pt-yr)	**1778.6**	**1250.5**	179.8	251.8
	RR = 0.71, *P*<0.0001		RR = 1.38, *P*=0.1479	

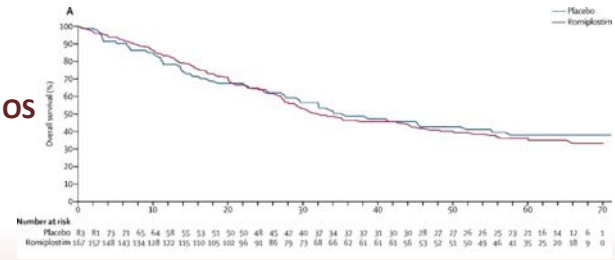
Giagounidis A, et al. *Cancer.* 2014;120:1838-1846.

The patients who received romiplostim had significant drop in clinically significant bleeding events and significant drop in platelet transfusion events. It appeared that the romiplostim was really working for these patients, and it did so in about 40% of patients. However, patients were enrolled onto this trial who had excess blasts. If you're an MDS nerd like me and Dr. DeZern, you know that you can be classified as having lower-risk MDS even with up to 10% blasts.

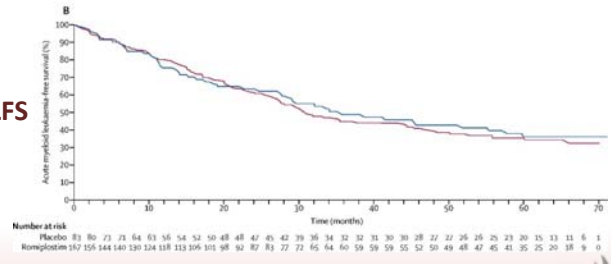
Lower-risk MDS: Tackling Thrombocytopenia

	Romiplostim	Placebo	HR	95% CI
Deaths	17.9% (30)	20.7% (17)	0.86	0.47, 1.56
AML	6.0% (10)	4.9% (4)	1.20	0.38, 3.84
AML-free survival	19.6% (33)	23.2% (19)	0.85	0.48, 1.50

OS



LFS



5 years of follow-up

Giagounidis A, et al. *Cancer.* 2014;120:1838-1846.;Fenaux P, et al. *Br J Haematol.* 2017;178:906-913.

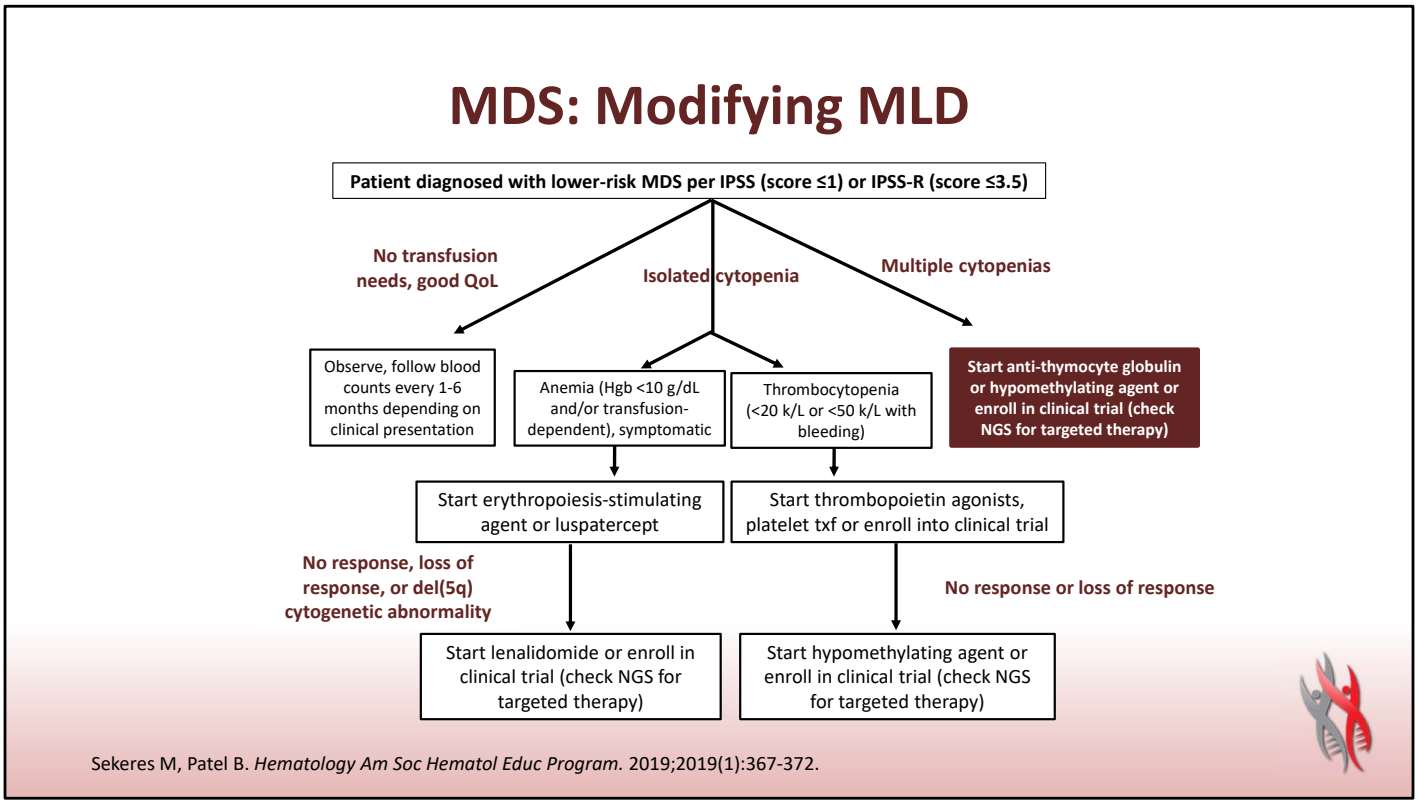
It turns out that a bunch of patients blasted off when receiving this romiplostim, which is a type of growth factor. A Data and Safety Monitoring Board stopped the trial prematurely when they found a 2.5-fold increase rate of transformation to AML in those receiving romiplostim compared to placebo.

You won't be surprised to hear that three-quarters of those patients who transformed had excess blasts to start with on the trial. The take-home point for this, I do use these drugs off-label in my patients with lower-risk MDS who have low platelet counts, but I never, never, never give them to anybody who has excess blasts. This does cause those blasts to increase and possibly go high enough to classify somebody as an AML.

MDS Management: Agenda

- Patient
- Risk Stratification
- Ameliorating Anemia
- Tackling Thrombocytopenia
- **Modifying Multilineage Dysplasia**
- Conclusions

What if we want to treat more than one cell line?



Then we would consider treating patients with a hypomethylating agent or even considering anti-thymocyte globulin.

Lower-risk MDS: Modifying MLD – HMA

- Regimens:
  - **DAC 20 mg/m^2 IV D1-3** every 4 weeks
  - **AZA 75 mg/m^2 IV/SC D1-3** every 4 weeks
- 113 patients with LR-MDS treated and evaluable for response
- Median duration of follow-up = 14 months (range: 2-30 months)
- Randomized follow-up study **NCT02269280**

Jabbour E, et al. *Blood.* 2017;130:1514-1522.

This is a trial we conducted with the MDS Clinical Research Consortium, in which patients received decitabine or azacitidine at their usual dose, but for a fewer number of days, only for 3 days instead of 5 or 7 days; 113 patients were enrolled with lower-risk MDS to this trial.

Lower-risk MDS: Modifying MLD – HMA

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabbour E, et al. *Blood.* 2017;130:1514-1522.

And we found that the overall response rate was 50% for these patients. Now, I'm discounting marrow CRs. We showed in a separate study that marrow CRs are no different than stable disease in MDS. Even with a 50% overall response rate, that's about 15% higher than we would expect for hypomethylating agents in lower-risk MDS, and the duration of response was about a year and a half.

Higher-risk MDS: HMAs: DAC/CED

Oral Cedazuridine/Decitabine Phase 2
In Int-1, Int-2, High, CMML

	Phase 2 overall (N=80)	
Type of response	**n (%)**	**95% CI**
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero G, et al. *Blood*. 2020:136(6):674-683.

Now a new oral version of decitabine/cedazuridine, has come onto the market. I know Dr. DeZern is going to talk about this in a little more detail later. I'm including it here because patients with intermediate-1-risk MDS were included in this trial, so they have lower-risk MDS. The overall response rate, remember, I subtract out those marrow CRs, was falling about in the range of what we would consider for IV decitabine. In interpreting the trial, we have to be careful because patients crossed over and actually received both drugs. This is really a trial to study. The PK levels in oral decitabine/cedazuridine compared to IV decitabine, those were equivalent.

Lower-risk MDS: Modifying MLD – ATG

	N (total)	% (95% CI)
All responses – intent to treat	9 (27)	33.3 (17-54)
HI-E	7 (18)	38.9
HI-E, major	6	
HI-E, minor	1	
HI-N, major %	3 (10)	30.0
HI-P, major	3 (13)	23.0
No response – intent to treat	18 (27)	66.7 (46-83)

Measure	Treatment Arm		*P*
	ATG=CSA (n=45)	BSC (N=43)	
No treatment, No. of patients	5	-	
Crossed over to ATG+CSA, No. of patients	-	14	
Hematologic response (CR+PR) by 3 months			
No. of patients	9	4	
%	20	9	
Hematologic response (CR+PR) by 6 months			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)			.009
No. of patients	14	4	
%	31	9	

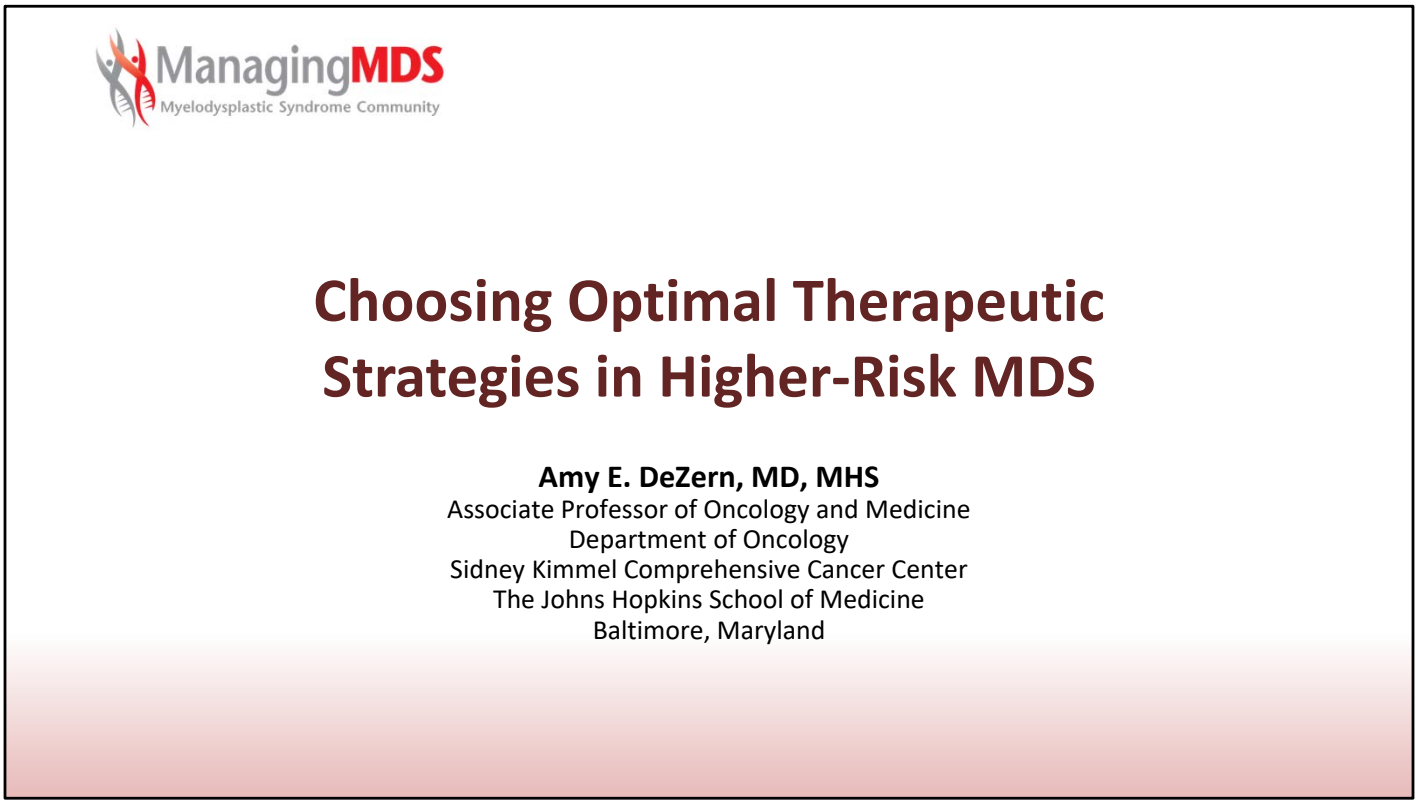
Komrokji R, et al. *Haematologica*. 2014;99:1176-1183.; Passweg J, et al. *J Clin Oncol.* 2011;29:303-309.

We also do treat patients with ATG because there has been some research showing that some of MDS may occur through T-cell mediated bone marrow destruction. In two separate studies, one conducted in the US, one conducted in Europe, the response rate to ATG was about one-third of patients, and the response duration was about a year to year and a half, and that's a median. This is something I consider for patients with multilineage dysplasia with lower-risk MDS. Of course, they have to be admitted to the hospital to receive this.

MDS Machinations: Conclusions

- **Biology** >> What we can do about it
- For lower-risk MDS, focus on what bugs patient most:
  - **Anemia**
  - **Thrombocytopenia**
  - **Lots o' penia**
- Goals of therapy should reflect goals of patient

Trying to wrap it all up, in MDS, I think our understanding of the biology has far exceeded what we can do about it, but we're gaining some ground. For lower-risk MDS, we focused on what bugs a patient most, that's anemia, thrombocytopenia, or what I call 'lots o' penia,' so multiple cytopenias. As always, our goals of therapy should reflect the goals of our patients.



With that, I'm going to hand it off to Dr. DeZern. Thanks so much.

Dr. DeZern: Thank you, and I'm looking forward to talking about higher-risk disease with you. As was alluded to in the first half of the presentation, we always think about what our goals are for our MDS patients. The goals can be slightly different for higher-risk compared to lower risk. Certainly, we're attuned to what may bug the patient, as Dr. Sekeres just mentioned.

Therapeutic Goals Are Constant for HR MDS Patients

- Decrease blasts
- Stabilize marrow function
- Gain trilineage improvement
- Lower risk of transformation to AML
- Move to definitive therapy or maximize benefit

EXPECTATION MANAGEMENT

In higher-risk disease, we are more focused on decreasing the blasts, stabilizing that marrow function, and hopefully seeing health improvement, not getting AML. Then deciding how we're going to move towards a definitive therapy, or maximize the benefit of the treatment we've chosen. I constantly reiterate to myself and our patients, and any trainees, that expectation management is incredibly key here.

How to Think About Each Individual Person Suffering with MDS

- Fit vs not fit
- BMT vs non BMT
- TD vs TI
- Unfavorable NGS vs OK
- Health literacy HIGH vs LOW
- Compliant vs NOT
- Patient factors vs disease biology
- Trial vs NOT
- Well diagnosed vs less well characterized

When patients ask me, "Is this good or bad?" I actually try to stay away from making value judgments. I'm honest that when we as providers are evaluating all patients, but in this case, higher-risk MDS patients, we have to think about a number of other features of that human being as we work through our therapeutic choices. Are they fit or not fit? Do we think they need a transplant or don't? Are they receiving transfusions, transfusion-dependent or TD, or are they transfusion independent?

Dr. Sekeres talked about next-generation sequencing with his first case, and we really do use that in our risk-stratification and prognostication. Sometimes for an individual patient, their health literacy becomes very relevant as well as their socio-economic status and what they're able to do with their treatments. These are always things that we have to think about as we're working through.

A Case

- Age 72 years
- Plays 18 holes 3x per week, walks course carrying bag
- PMHx: hypertension and lung cancer resected → no adjuvant therapy
- NOW: New transfusion needs, ANC 580, Plts 64
- Pancytopenic, dysplastic marrow, **8% blasts, 47, XY,+8**
- Heme NGS panel done:
  TET2 27.43% ***EZH2*** 27.43% ***ASXL1*****fs** 29.6%
  ZRSR2 91.3% ***STAG2*** 77.65%

I'm going to use a different exemplar case of this individual who is 72 years old and might be characterized as fit because he plays golf quite regularly and carries his own bag on the course. He has a unique past medical history of hypertension and lung cancer, but he has not had any previous chemotherapy. This would not be treatment-related disease, but he is transfusion dependent with a relatively low absolute neutrophil count of 580 and his platelets are 64,000. This is somebody who's truly pancytopenic, with dysplasia morphologically in his marrow evaluation, 8% CD34 positive blasts, and an abnormal karyotype, which is 47,XY,+8.

As I believe is standard, and you heard in the lower-risk section as well, he had a next-generation sequencing panel done, which has a number of molecular abnormalities. This is not an uncommon case, and this is a real person that I take care of.

What Treatment Option Do You Recommend?

A. Enrollment in a clinical trial
B. Supportive care alone
C. Lenalidomide with supportive care
D. Azacitidine or decitabine with supportive care
E. Targeted therapy with supportive care
F. Allogeneic stem cell transplant with supportive care

Please select your response below the video window and click the submit button to poll.

We'll begin with our first higher-risk audience response question.

What treatment option would you recommend?

A. A clinical trial
B. Supportive care with transfusions
C. Lenalidomide with supportive care
D. A hypomethylating agent with supportive care
E. A targeted therapy
F. An allogeneic stem cell transplant

Please select your response.

NGS May Help with Prediction of Therapy Response→ BUT Doesn't Really Guide Choice Yet

- ***TET2*** and ***DNMT3A*** may predict positive response after HMA therapy
  - Absence of *ASXL1* mutations also positive predictor
- Mutations of ***TP53*** are associated are enriched in MDS/AML with del(5q) and predict relapse, decreased survival
- ***TP53*** mutant clones may be initially sensitive to HMA therapy but HSCT outcomes remain poor
- Novel therapies in development for MDS (or approved for AML) may have targets (or molecular biomarkers of response) including ***IDH1/IDH2*** inhibitors, splicing factor inhibitors, ***FLT3*** inhibitors

Malcovati L, et al. *Blood.* 2011;118(24):6239-6246.; Walter MJ, et al. *Leukemia*. 2011;25(7):1153-1158.; Bejar R, et al. *J Clin Oncol.* 2014; 32(25):2691-2698.; Traina, et al. *Leukemia*. 2015.; Bejar R, et al. *Blood.* 2014;124(18):2793-2803.; Bally C, et al. *Leuk Res.* 2014;38(7):751-755.

We've talked about next generation sequencing. Dr. Sekeres showed us that lovely graft of the good risk, less good risk, and the unfavorable. The reality is, I think this is incredibly important to help us explain the biology of a patient's disease, higher or lower-risk.

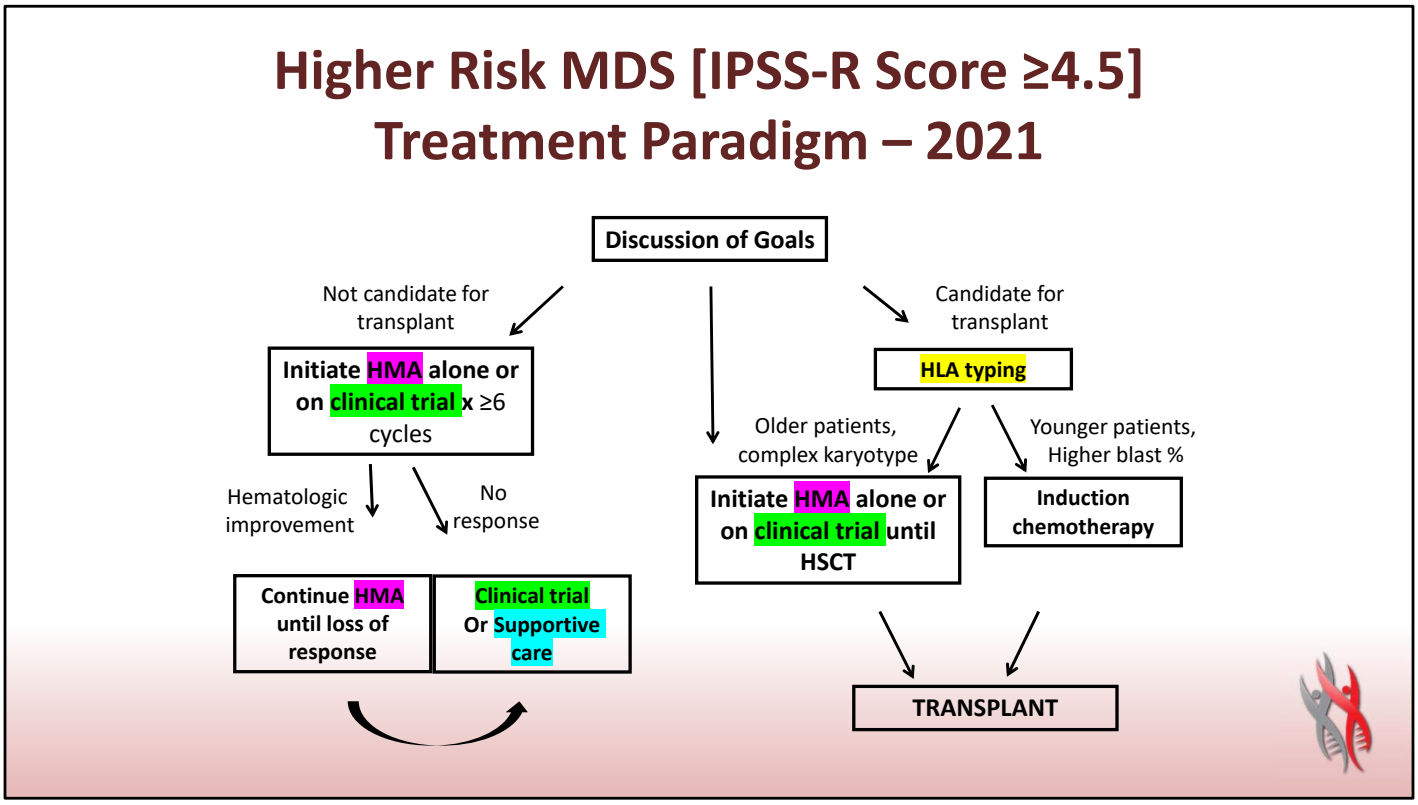
So far, there are limited options to truly guide therapy, especially in the higher-risk setting. I list here some of what is seen in the literature about TET2 and DNMT3A, which might predict a positive response after a hypomethylating agent paradigm. I think there's some nuances there that we won't get into for the sake of time. As was alluded to earlier, TP53 are most unfavorable, and something we're really trying to improve outcomes in. Then, certainly, one of our options for treatment is always consideration of targeted therapies. We are consistently looking for targeting as we do in AML patients in the MDS space.

Current Issues in the Treatment of HR MDS

- Hypomethylating agents only moderately improve survival
- Prognosis after HMA failure is poor
- Patients with complex karyotype/unfavorable molecular genetics have a very poor outcomes (even with BMT)
- Imperfect animal models
- We do not understand how to improve NORMAL hematopoiesis
- STILL TOO FEW THERAPIES

There are a number of issues, though, in the treatment of higher-risk MDS that I believe make it unique in what's so special about taking care of these patients. Unfortunately, our standard of care hypomethylating agents only moderately improved survival, and clinical trials as well as real-world analyses have shown that. Once a patient progresses through the hypomethylating agent, though, the patient does poorly, and the survival is quite short, as short as 6 months. Patients with complex karyotype and unfavorable molecular genetics still have worse outcomes, even if we use allogeneic bone marrow transplant.

Some of the reasons for this maybe because our animal models in the lab have limitations in terms of how we study the disease biology, and we still don't understand how to really improve normal hematopoiesis for our patients. The bottom line is, we just need more therapies to have greater options in our arsenal to help these patients with higher-risk disease.



Dr. Sekeres took you through the International Prognostic Scoring System, revised. For the sake of time, we will call our higher-risk patients, those who have scores by that metric of 4.5 or greater. Many of these highlighted options in the flowchart here were some of your options in the audience response question. Hypomethylating agents are the standard of care throughout the world for higher-risk patients. We must decide about clinical trials and HLA typing for consideration of bone marrow transplant.

This gets back to one of our earlier slides where we tend to put patients in a fit or non-fit transplant or non-fit box, but I think the lines of these distinctions are beginning to blur.

Path to Potential Cure → BMT!?

- Need to consider the expected survival with nontransplant therapy (IPSS-R, molecular markers, fibrosis, therapy-related disease)

But also

- Need to consider the likelihood of a successful transplant
  - MRD going in, TRM, donor source and risk of GVHD

The discussion of transplant is always a complicated but important one early in the course of a patient with MDS. I tend to phrase it to patients that it's a path to potential cure, and we really must consider if this is appropriate for our patient. Many patients, if not all patients, ask for the cure or want it, especially when they're diagnosed with higher-risk MDS. We really need to evaluate as best we're able with our early diagnostic testing and known prognostic variables, what the expected survival with the non-transplant therapy is, and how likely would a transplant be in the individual human beings sitting in front of us.

Factors to Consider

	Effect on non-HCT outcome	Effect on HCT outcome
High IPSS	+++	+
Therapy-related MDS	++++	++
Hypomethylating failure	++++	+
Molecular abnormalities	+++	++
High HCT-CI (>3)	++	++++
Low Karnofsky score (<80)	++	++++
Geriatric assessment	++	++++
HCT prognostic score	++	++++

There's a lot of factors in the literature, this table simply weighs some of them. Those with a high International Prognostic Scoring System (IPSS) tend to really not do as well without consideration of the transplant. Treatment-related disease also has limitations in terms of what we can do with our standard of care options. Certainly, if somebody has a high hematopoietic cell transplant, comorbidity index, or CI, with many other health care problems, they're less likely to do well with transplant. All of these factor into making our decision.

Allo vs Hypomethylating/Best Supportive Care in MDS (BMT CTN 1102)

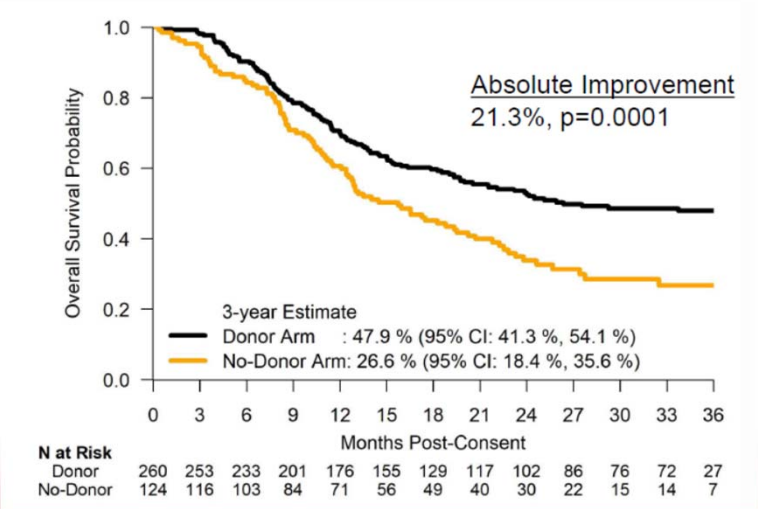
- Open-label, multicenter, biologic assignment study
- Assignment based on high-resolution typing to identify 8/8 HLA-matched related or unrelated donors
  - Mismatched, haploidentical and umbilical cord blood excluded
  - Donor arm subjects expected to undergo HCT within 6 months
- Subjects: **Randomized 260 = Donor; 124 No Donor**
  - Age 50-75
  - Primary MDS with intermediate-2 or high risk by IPSS
  - Candidates for traditional reduced-intensity transplantation
  - Transplant/non-transplant therapy per institutional standards

Nakamura R, et al. ASH 2020. Abstract 75.; Clinicaltrials.gov NCT02016781

Recently, there have been two trials, one in the US and one in Europe, which I'll speak about in a moment, who have tried to get at this particular issue. The first was a BMT CTN trial. It was an open-label multi-center study conducted in the US. That was really a biologic assignment study. Please understand the nuances of this, that it's not really randomizing an individual human being to get hypomethylating agent or a transplant. These patients were randomized based on fully match-related or unrelated donors.

There were 260 patients who had a donor and 124 patients who were not able to identify this particular flavor of donor. Some important features about the eligibility of this trial were these were patients a little bit more advanced in years, such as our case, ages 50 to 75. They did have MDS as their primary disease that was high risk by the International Prognostic Scoring System, intermediate-2 or high risk.

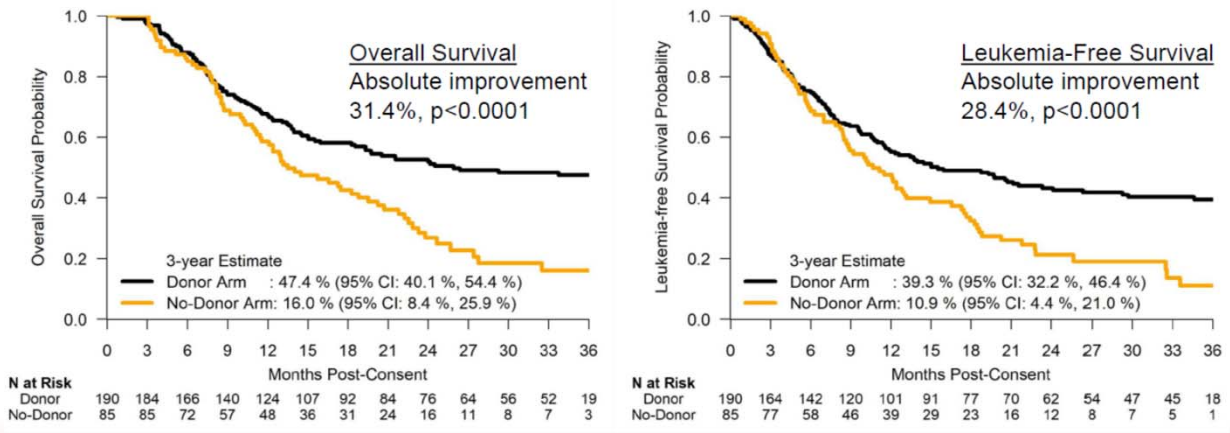
Primary Endpoint: 3-year Overall Survival



Sensitivity analysis: adjusted OS 48.0% vs 28.1%, *P*=.0004

The primary endpoint was three-year overall survival. What showed was that overall survival was improved by having a donor.

As-Treated Analysis



Nakamura R, et al. *J Clin Oncol.* 2021 Jun 9; Online ahead of print.

In the as-treated analysis, this absolute improvement for overall survival if they went to transplant was even greater at 31.4%. Also, an improvement in leukemia-free survival.

BMT in HR MDS Ages 50-75 Key Conclusions

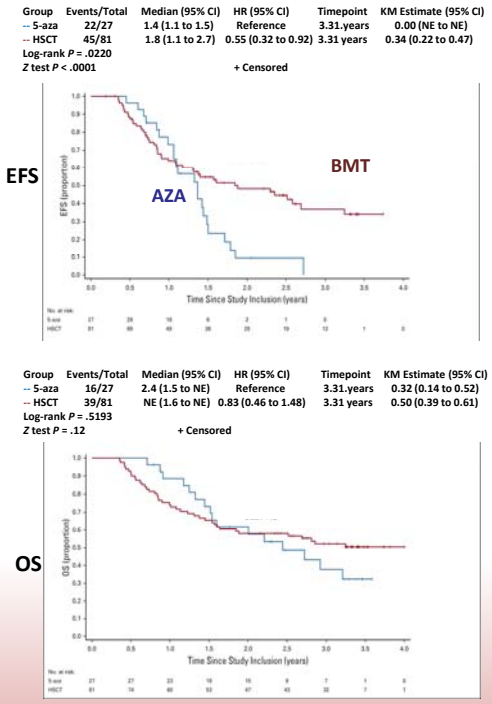
- Among HR MDS patients, having a suitable BMT donor leads to improved outcomes
  - Overall survival improved by 21%
- Leukemia-free survival improved by 15%
  - Subjects >65 (Medicare aged) had similar results to those subjects <65
- No decrease in quality of life compared to 'no donor' controls
- As-treated analyses suggest strong advantage for BMT vs non
- Early referral to an HCT center and coverage by Medicare is recommended

There are a lot of nuances to this trial, but I think it does show that part of the early "diagnostics and planning and discussions" for our higher-risk patients should consider HLA typing and early referral to a transplant center.

VidazaAllo Study

- Multicenter European study
- Comparison between AZA and AlloBMT in elderly patients with advanced MDS according to donor availability
  - Median age 63
  - RIC
  - Improved EFS for BMT >> AZA
  - Bridging with AZA to BMT -> increased dropouts because of progression, mortality, and adverse events

Kröger N, et al. *J Clin Oncol.* 2021 Jul 20; Online ahead of print.



This was more or less also shown in the VidazaAllo study which was a similar multicenter European study which compared azacitidine in transplant in older patients with again higher-risk MDS according to donor availability. Difference between the two arms was not quite as stark in this particular analysis, but there was still an improved event-free survival for transplant over azacitidine alone, which is why I think it's an important consideration for our higher-risk patients.

Always With the HMAs

Azacitidine Key Studies

Study	N	AZA Dose	Reference
AZA-001: Azacitidine vs CCR in Patients with Higher-Risk MDS (phase 3)	358	75 mg/m^2/d x 7d SC q28d	Fenaux, et al. *Lancet Oncol.* 2009;10:223-332.
Azacitidine in Patients with MDS: Studies 8421 (phase 2), 8921 (phase 2), and 9221 (phase 3) by CALGB (azacitidine vs observation)	309	75 mg/m^2/d x 7d SC q28d	Silverman, et al. *J Clin Oncol.* 2006;24:3895-3903.
Study of Alternative Dosing Schedules of Azacitidine in Patients with MDS (phase 2)	148	5-2-2 75 mg/m^2 SC 5-2-5 50 mg/m^2 SC 5 75 mg/m^2 SC	Lyons, et al. *J Clin Oncol.* 2009;27:1850-1856.

Decitabine Key Studies

Study	N	Decitabine Dose	Reference
Study of Decitabine plus Best Supportive Care (BSC) vs BSC (phase 3)	170	15 mg/m^2 (3 h q8h) 3 d IV q6wk	Kantarjian, et al. *Cancer.* 2006;106:1794-1803.
Low-Dose Decitabine versus BSC (EORTC) (phase 3)	233	15 mg/m^2 on days 1-3 of 6-wk cycle	Wijermans, et al. *ASH.* 2008 Abstract 226.
Alternative Dosing with Decitabine – MD Anderson (phase 2)	95	20 mg/m^2/d IV x 5 d 20 mg/m^2/d SC x 5 d 10 mg/m^2/d IV x 10 d	Kantarjian, et al. *Blood.* 2007;109:52-57.
ADOPT, Alternate Dosing for Outpatient Treatment (phase 2)	99	20 mg/m^2/d IV x 5 d	Steensma, et al. *J Clin Oncol.* 2008;26 Abstract 7032

Our patients usually and probably should not go straight to transplant. Certainly, all of you have seen many higher-risk presentations at this point about hypomethylating agents. Your reference, I simply list many of the key studies that have been done over the years which have brought azacitidine, mostly SubQ, and decitabine, mostly IV, as the standard of care throughout the world for higher-risk MDS.

HMA By Mouth!! Oral Cedazuridine/Decitabine

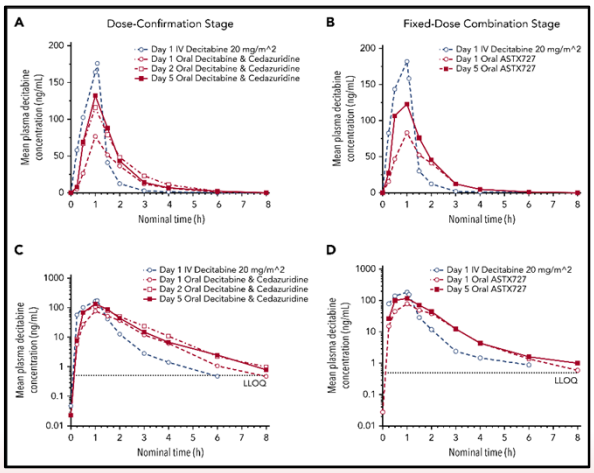
- Intravenous (IV) decitabine (DAC) is an approved therapy for MDS
- Oral bioavailability of DAC is low due to degradation in the gut by cytidine deaminase (CDA)

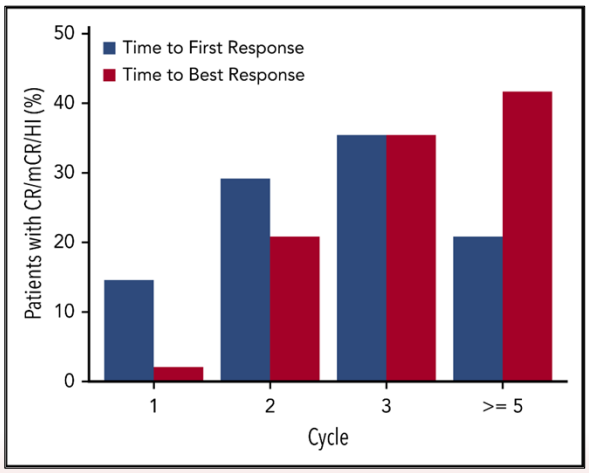
- MDS treatment requires continued treatment for long periods
- An oral decitabine would provide significant benefit
- Development of a potent safe CDA inhibitor should enable decitabine oral bioavailability

Garcia-Manero G, et al. *Blood*. 2020:136(6):674-683.

As was mentioned in the first half of the presentation, we also have an oral hypomethylating agent specifically for myelodysplastic syndrome at this point in time. It's oral cedazuridine which is an oral cytidine deaminase inhibitor which allows absorption of the oral decitabine component of the drug.

Oral Cedazuridine/Decitabine



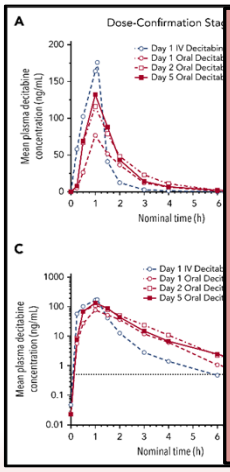


Approved July 2020 for Higher risk MDS and CMML

Garcia-Manero G, et al. *Blood*. 2020:136(6):674-683.

You saw some data earlier from the phase 2, there's also been a phase 3 that really showed that this is an equivalent drug taken by mouth to the IV levels that we can obtain for decitabine in our higher-risk patients. It was approved by the FDA in July of 2020 for higher-risk patients. This is an equivalent drug, and we won't spend a lot of time talking about the nuances of decitabine versus azacitidine today.

Oral Cedazuridine/Decitabine



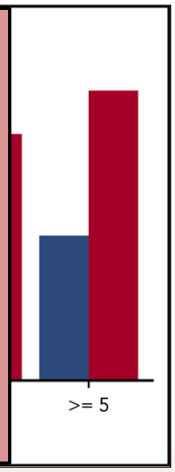
When I use:

1) Patients who desire oral

2) Patients truly stable on IV DAC and responding

3) Patients in whom it is not cost prohibitive (Taiho has zero co-pay/patient assistance programs)

4) Patients who I know will still come for labs



Approved July 2020 for Higher risk MDS and CMML

Garcia-Manero G, et al. *Blood*. 2020:136(6):674-683.

I do tend to use this on-label in patients who desire taking a pill. There are people who feel quite strongly about this, people who might have been previously stable on IV for their high- risk disease and responding. There are good copay programs because oral chemotherapies can be expensive for some of our patients. Then I cannot emphasize enough that even though it's a pill, the monitoring must be every bit as robust as that which we do for our IV patients. This is a more novel option that has been available for about the past year.

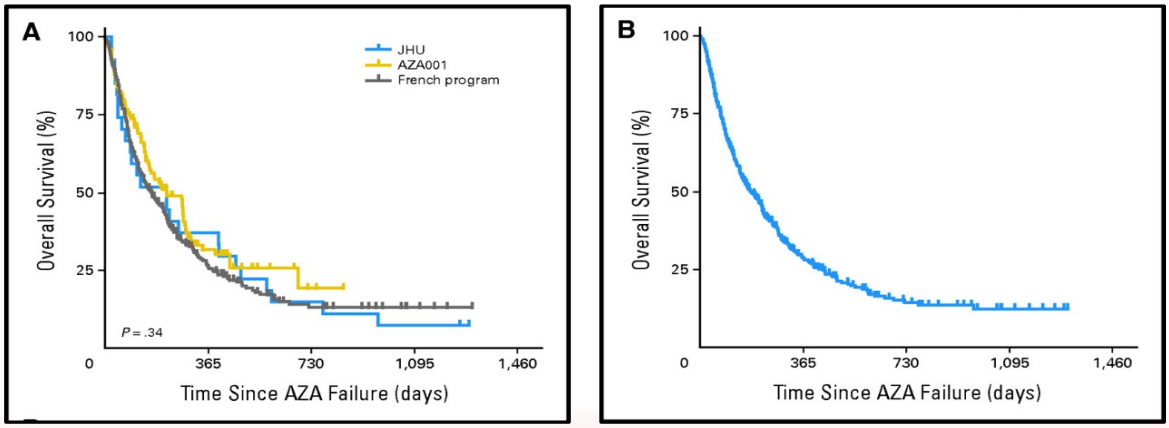
Optimize HMA Therapy

- AZA 75 mg/m^2 x 7 days *OR* DAC 20 mg/m^2 x 5 days *OR* decitabine/ cedazuridine 1 tab x 5 days
  - I tend to use IV over SQ
- Minimize delays = q28 days
- Prophylactic antibiotics
- Proactive transfusional support (with observation of antibodies)
  - Growth factors only when dire infection
- If it is working, don't stop or plan transplant

Something that is incredibly important, I believe, to tell patients about as well as think about for ourselves is if we're going to use standard of care, we must optimize that because we don't have so many options and we don't want to burn through it too quickly. If we're going to use azacitidine in true higher-risk MDS patients, we must use it as its appropriate dose at 75 mg/m ^{2} for 7 days or decitabine at 20 mg/m ^{2} for 5 days. The same goes for the oral.

Some people prioritize subQ azacitidine. I tend to use IV, but there's no right or wrong. The point is that the patient is getting that hypomethylating backbone at its appropriate dosing consistently. I minimize delays as best I can. The cycles start with day 29 of the previous cycle being day 1 of the next cycle. Prophylactic antibiotics to get through those periods of neutropenia, and then proactive transfusion support where possible. If this is working, don't stop it. Different than our solid tumor colleagues, this isn't for 6 cycles and done. This is continuous therapy. Planning of transplant, as I alluded to, is increasingly a part of the total therapeutic paradigm for our patient with higher-risk MDS.

Outcome of High-risk MDS After AZA Failure



Prebet T, et al. *J Clin Oncol*.;2011;29(24):3322-3227.

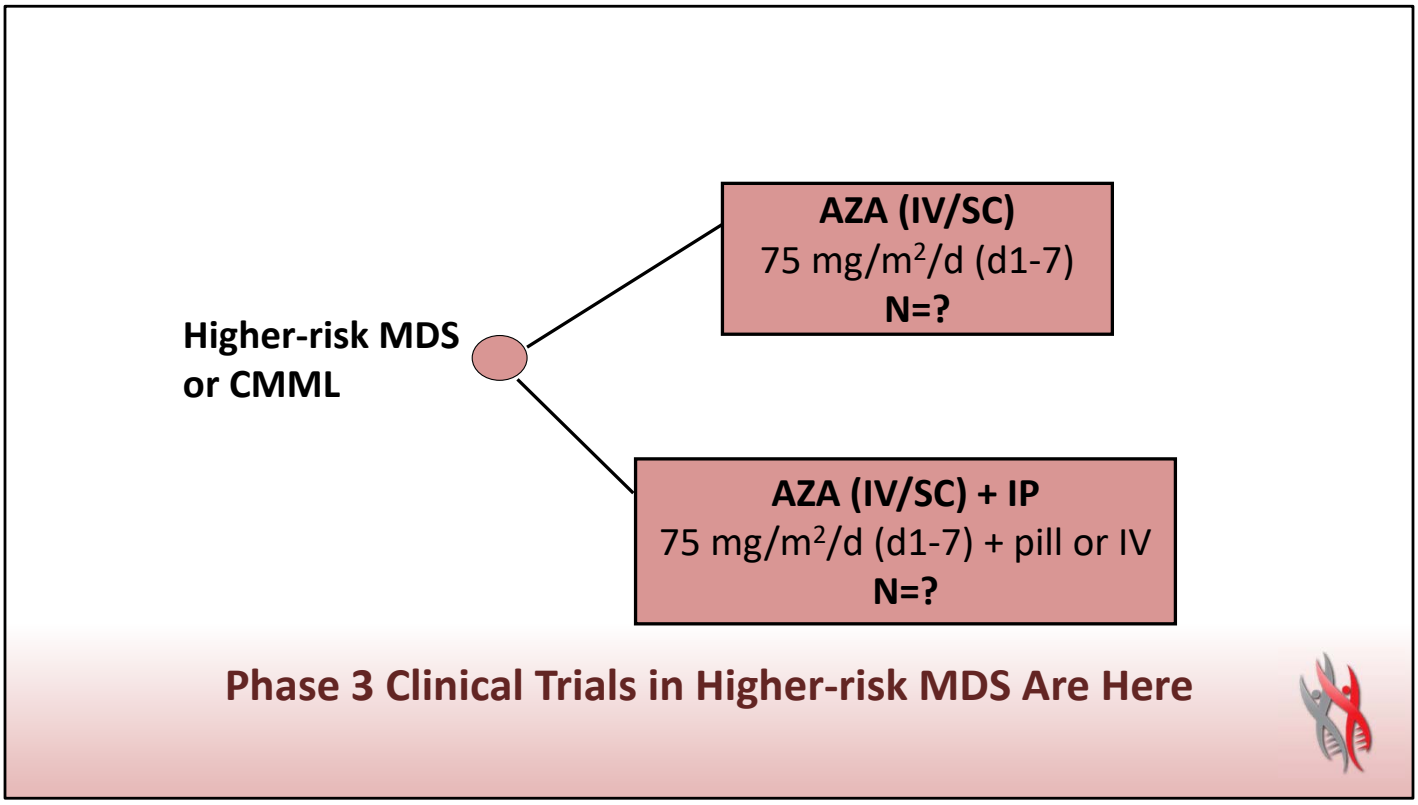
I mentioned one of the limitations in our field is the outcomes of patients after they've been failed by a hypomethylating agent. This is a paper that's a decade old that I find the data to hold that the patients really, unfortunately, have very limited time after they've progressed through this. I think that's increasingly why we need to find better therapies, and also perhaps offer transplants in appropriate patients more.

How to Get More

- Less conservative for individual and bold for field
- Target where can
- Treat like AML
  - Cytotoxic chemotherapy in younger, fit patients
  - CPX-351 in MDS pilot study for transplant eligible, higher risk patients with **MDS** NCT03572764
- **Clinical trials!!**

How else can we get more for our higher-risk MDS patients? I think sometimes I have a tendency to be conservative for an individual older patient, and I want to do that less and make sure that we're really offering all that we can. Certainly, we'll target a mutation where possible. It's a posity of higher-risk MDS patients that have an IDH1 or an IDH2. When I have those patients, I do offer them the therapies even off-label where accessible. Some younger patients can tolerate quite intensive AML-style therapies. There's a pilot of CPX-351 which is liposomal, daunorubicin, and cytarabine that could be considered. Then, of course, we'll spend the majority of the rest of our time talking about clinical trials because I believe this is how we can advance the field for our patients.

Current and Emerging Treatments for Myelodysplastic Syndromes: The 2021 Landscape



We're in a unique era in 2021 where we have quite a lot of phase three options for patients with higher-risk MDS. Certainly, there is a pattern that you'll see for how to design these studies. That gets back to what we know can work for our patients, which is a hypomethylating agent. The AZA-001 study published many years ago showed an overall survival benefit for azacitidine. This has never quite been replicated for decitabine, perhaps for statistical reasons as much as anything. That is why the backbone of all of these phase 3 trials is azacitidine dosed as I suggested at the full dosing and as monotherapy compared to azacitidine plus the investigational product.

Phase 3 HR MDS Trials →Accrued

- Pevonedistat (PANTHER) – accrued
  - NCT03268954
- Targeting of *TP53* with eprenetapopt – accrued
  - NCT03745716

A couple of these trials have already finished accrual. There was pevonedistat, which completed accrual, and there was eprenetapopt. Pevonedistat is a NEDD8 inhibitor, and eprenetapopt specifically targets TP53-mutated patients.

TP53 Targeting to Increase Response: Eprenetapopt

- Binds covalently to p53→ restores wildtype p53 conformation and activity→ triggers cell cycle arrest and apoptosis
- Phase 1b/2 in combo with AZA *J Clin Oncol*. Jan. 2021
  - Favor ORR and CRs
- Phase 3 results press released 12/2020
- Higher rate CR for COMBO 33.3% (95% CI: 23.1% - 44.9%)
- CR for AZA alone 22.4% (95% CI: 13.6% - 33.4%) (*P* = .13)
- 12/2020 Difference between the two arms did not meet the predefined threshold for statistical significance for CR
  - More analysis to come

Let's talk about eprenetapopt first. Quite a unique drug that binds to the P53 and restores to a wild-type confirmation. A pattern that has emerged over the years in higher-risk MDS is that phase 1 and 2 therapies are often quite favorable for our higher-risk patients. Then when we get to the phase 3 arena, unfortunately, we do not always see the statistical difference that we had hoped. In this case, even though there was a higher rate in the phase 3 for the combination of eprenetapopt with azacitidine, it did not meet the predefined threshold for statistical significance. I believe we may see some additional publications on this drug.

Pevonedistat in HR MDS Key Conclusions

- Pevonedistat: first-in-class inhibitor of the NEDD8-activating enzyme
- Longer EFS and encouraging OS with pevonedistat + AZA vs AZA was associated with:
  - Double the CR rate
  - Nearly tripled the median duration of response
  - Delayed transformation to AML
  - Increased rate of transfusion independence
  - Lower transfusion rates
- Exposure-adjusted AE rates were lower with pevonedistat + AZA, without added myelosuppression
- Phase 3 PANTHER trial fully enrolled
  - **9/2021: Difference between the two arms did not meet the predefined threshold for statistical significance for EFS = more analysis to come**

Published post ASH Abstract 653.; Sekeres M, et al. *Leukemia.* 2021;35(7):2119-2124.

In terms of pevonedistat, this was also studied. It was a first-in-class inhibitor. I mentioned earlier it's a NEDD8 activating enzyme and it showed an encouraging longer event-free survival and overall survival with the combination compared to monotherapy. Again though, at the phase 3 level the difference between the two arms didn't quite meet the predefined threshold. I think we're learning in the field how important it is to maximize on combination arms that azacitidine backbone, stay on time, and make sure we choose combinations that do not have combined toxicities so that the patients are able to tolerate both agents.

Phase 3 HR MDS Trials →Accruing

- Magrolimab
- Tamibarotene
- Venetoclax

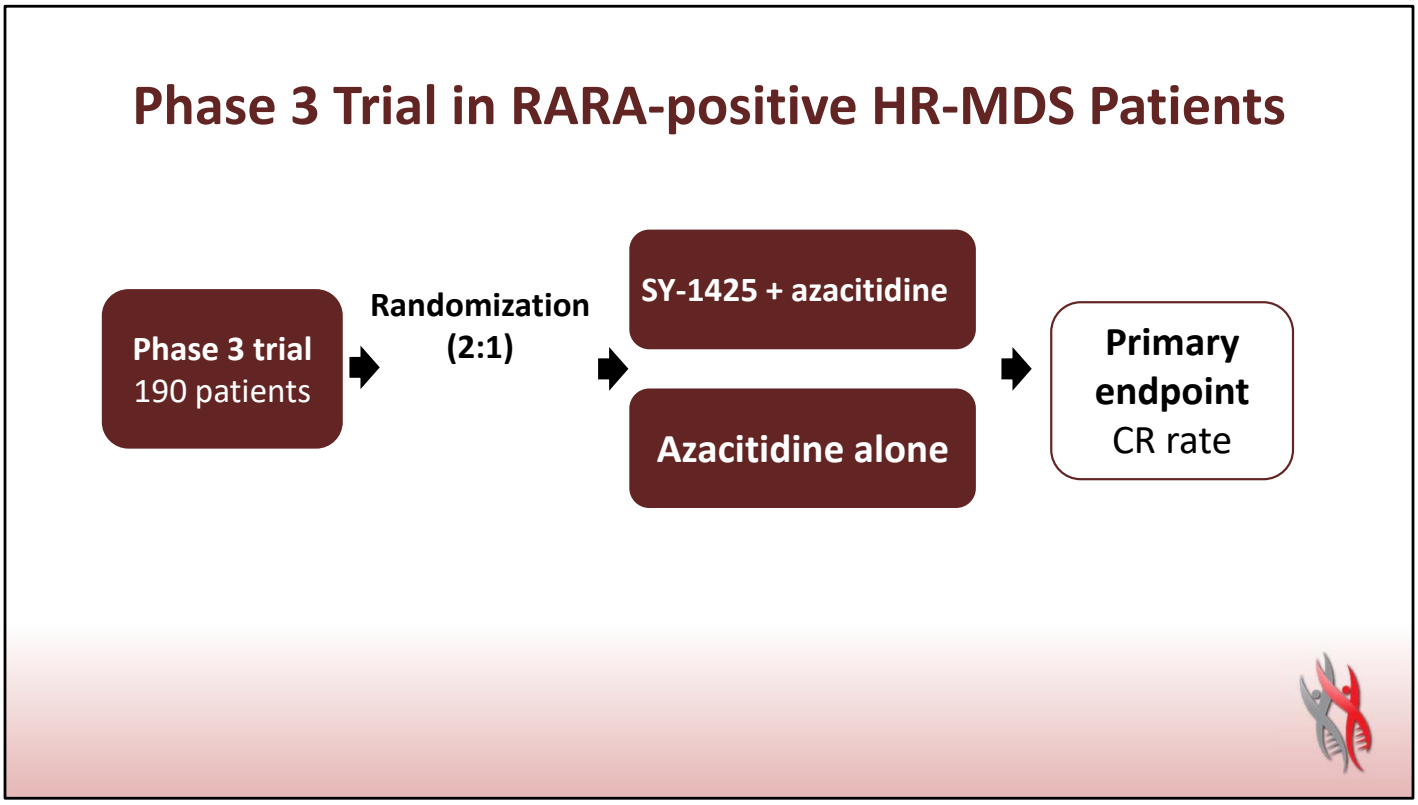
Let's talk about some of the accruing trials in the phase 3 space. Many of you in the audience response question said you would pick a clinical trial for our higher-risk patient. I also think this is very important for consideration for these patients.

SY-1425-301 Trial for RARA-positive HR-MDS → Biomarker Driven

- Subset of HR-MDS patients characterized by overexpression of the *RARA* gene
  - Novel blood-based biomarker test identifies patients for treatment with SY-1425, with typical 2- to 3-day turnaround time
  - Approximately 30% of HR-MDS patients are RARA-positive
- Preclinical synergy of SY-1425 + AZA
- Early data of SY-1425/AZA demonstrated high CR rate and rapid onset of responses in RARA-positive newly diagnosed unfit AML

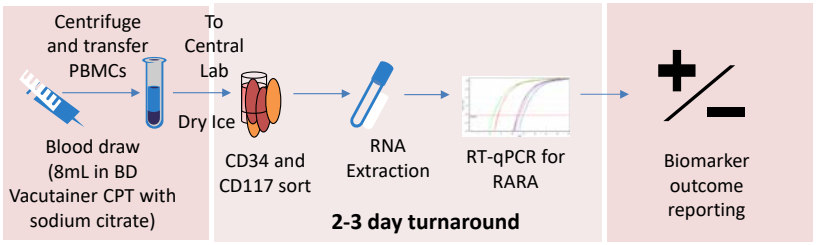
Stein E, et al. ASH 2020. Abstract 114 .

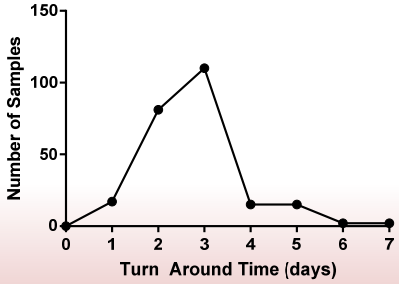
The first is Tamibarotene, also called SY-1425. This is a biomarker driven study which makes it a little bit different from the other two, I'm going to speak about. There are subset of higher-risk patients who are characterized by the overexpression of the RARα gene. Enrollment on this particular trial uses a blood-based biomarker test to identify patients in whom we believe that tamibarotene or SY1425 is more likely to help. There has been preclinical data in AML and higher-risk MDS patient samples that's shown a synergy between these two combinations.



This is one of the options that our higher-risk patients will have in phase 3 and it's organized just as the other phase threes are, with the combination compared to azacitidine alone, with a primary endpoint of complete response. I will mention that tamibarotene or SY-1425 is a pill with reasonable toxicity.

RARA-positive Patients Identified With Peripheral Blood-based Clinical Trial Assay





30% of AML and HR-MDS patients are RARA-positive
(>350 screened patients)

Vigil E, et al. ESH. 2017.; de Botton S, et al. ESH. 2019.

Patients could enroll with this blood-based assay and about 30% of higher-risk MDS patients are currently believed to be positive for it.

TIM-3 is an Inhibitory Receptor Expressed on Immune and Leukemic Cells

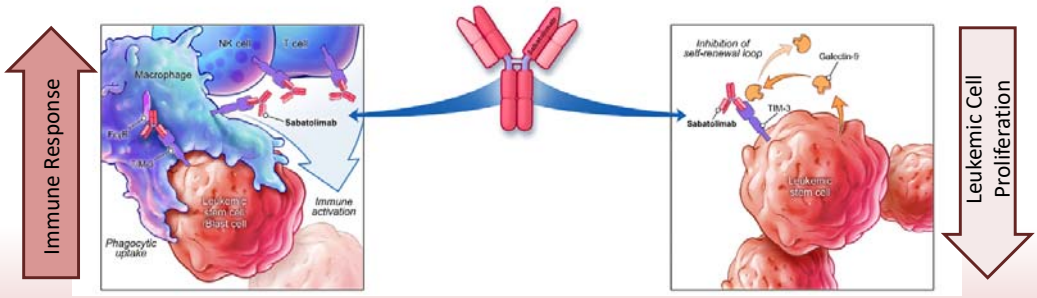
Dual Targeting by Sabatolimab

Targeting Immune Effectors

- Binds TIM-3 on immune cells, enhancing anti-leukemia immune activation[1,2]
- Enhances phagocytic uptake, facilitating cell-mediated killing of LSCs and blasts[1-3]

Targeting Leukemic Cells

- Directly targets LSCs through high-affinity binding of TIM-3[2]
- Blockade of TIM-3 on LSCs may inhibit TIM-3/galectin-9–driven self-renewal[1,2]



FcγR, Fc gamma receptor.

1. Acharya N, et al. *J Immunother Cancer* 2020;8(1):e000911. 2. Sabatos-Peyton C, et al. Poster presented at SITC 2020 [Abstract 439]. 3. Borate U, et al. Oral presentation at EHA 2020 [Abstract S185].

Let's talk about another way we could approach a higher-risk patient in the phase 3 setting with TIM-3 inhibition. Now, TIM-3 is interesting, and the drug here is called sabatolimab. TIM-3 is an inhibitory receptor on two flavors of cells in our MDS patients. This is a dual mechanism of action, where for the immune effects in higher-risk MDS, it targets those immune cells to enhance anti-MDS immune activation and enhance the phagocytic uptake of those adverse cells. It also directly targets the leukemia stem cells through binding of TIM-3.

Sabatolimab in HR MDS/AML

- The combination of sabatolimab + HMA continues to show promising ORRs in patients with vHR/HR-MDS (64.1%), ND-AML (41.0%), and CMML (54.5%)
- Encouraging durability was observed in vHR/HR-MDS and ND-AML, with an estimated 6-mo duration of response of 83.9% and 78.8%, respectively

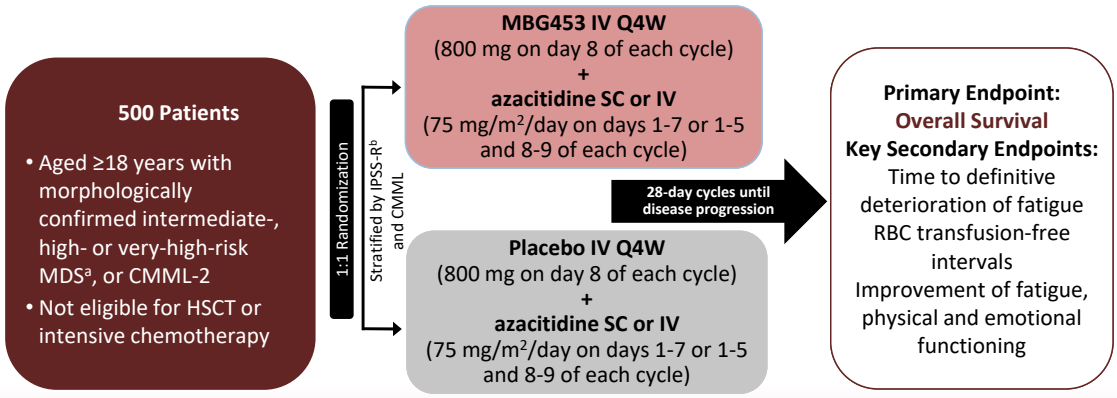
STIMULUS Clinical Trial Program		
STIMULUS-MDS1	Phase 2 study of MBG453 + HMA in higher-risk MDS	NCT03946670
STIMULUS-MDS2	Phase 3 study of MBG453 + azacitidine in higher-risk MDS	NCT04266301
STIMULUS-AML1	Phase 2 study of MBG453 + azacitidine ± venetoclax in unfit AML	NCT04150029

Brunner A, et al. ASH 2020. Abstract 657.

This has again been studied in earlier phase trials and what was presented last year at ASH was that the combination has very promising overall response rates in patients with very high-risk and higher-risk MDS. We're looking forward seeing more about this combination and this trial is probably going to open in the next 6 or 8 weeks.

Phase 3 STIMULUS MDS-2: Study Design

Phase 3, randomized, 2-arm, parallel-group, double-blind, placebo-controlled study



OS, overall survival; Q2W, every 4 weeks; SC, subcutaneous.
[a]Defined according to the IPSS-R criteria: very high risk (>6 points), high risk (>4.5-6 points), or intermediate risk (>3-4.5 points) with ≥5% bone marrow blasts.
[b]IPSS-R prognostic risk score (intermediate, high, very high).
Novartis. Data on file (CMBG453B12301 Protocol; November 15, 2019). ClinicalTrials.gov Identifier: NCT04266301

Then this is the similar design that we talked about for that particular combination.

AZA VEN in HR MDS Key Conclusions

- Ven + AZA demonstrates efficacy, including response durability, and an acceptable safety profile for patients with HR-MDS
- The recommended dose of Ven is 400 mg for **Days 1–14 of a 28-day cycle** when combined with AZA (75 mg/m^2, Days 1–7)
- Clinically meaningful improvements in dyspnea, fatigue, and global health status/QoL were observed, whereas physical functioning was maintained throughout treatment
- Patients who achieved CR reported a moderate to large maintained improvement in dyspnea and fatigue and a moderate to large improvements were maintained in overall global health status/QoL
- A further phase 3 study (VERONA[1]) will open soon for patients to evaluate safety and efficacy in Ven + AZA in newly diagnosed patients with HR-MDS

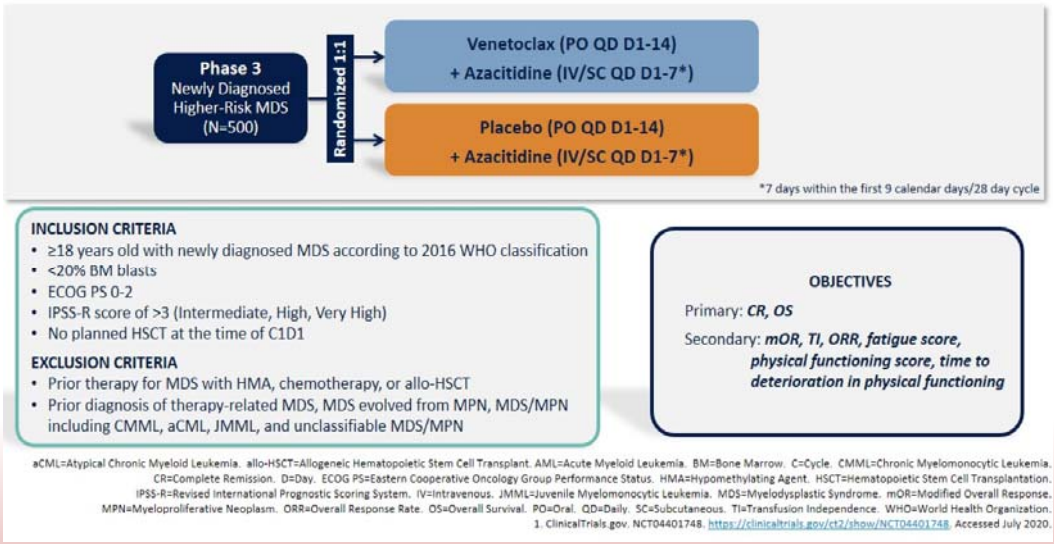
AZA, azacitidine; CR, complete remission; HR-MDS, higher-risk myelodysplastic syndrome; QoL, quality of life; Ven, venetoclax

[1]NCT04401748. Available at: https://clinicaltrials.gov/ct2/show/NCT04401748. Accessed November 3, 2020.;
Garcia J, et al. ASH 2020. Abstract 656.

Let's talk about azacitidine and venetoclax, this is called VERONA trial. Certainly, we're borrowing a bit from our AML colleagues. There are many who believe, probably appropriately, that biologically higher-risk and very high-risk MDS are quite akin to AML. It's simply a difference of more or less than 20% blasts. We know that azacitidine and venetoclax in AML through the VIALE trial has been very efficacious.
This combination is a natural thing to study with this similar design in higher-risk MDS. Now, something I can't emphasize enough is that in higher-risk MDS, after some earlier studies, the venetoclax is dosed in a fewer number of days compared to our AML patients. The recommended dose is 400 for days 1 through 14 of a 28-day cycle. This VERONA study, which again is azacitidine monotherapy compared to azacitidine in combination with venetoclax is just opening up to evaluate in patients with higher-risk MDS.

Venetoclax in MDS – Clinical Data:

M15-954 – Study Design and Endpoints



The endpoint here is going to be complete response as well as overall survival. Probably you're really seeing a theme that these have been studied in earlier phase and now we're doing the registration style phase 3. A lot of options for patients with higher-risk MDS looking for clinical trials.

Magrolimab Key Conclusions

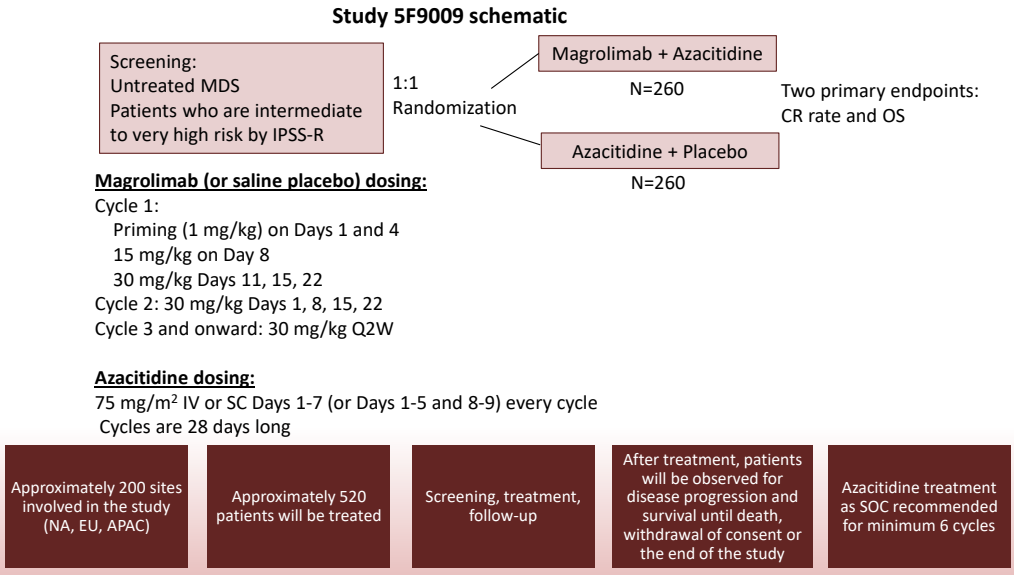
- Magrolimab is a first-in-class antibody targeting the macrophage checkpoint CD47
- Magrolimab is well tolerated with AZA, with no significant immune-related AEs and showing improvement in cytopenias on therapy
- Regardless of *TP53*-mutation status, encouraging efficacy is observed with magrolimab + AZA in untreated AML patients unfit for intensive chemotherapy
- The preliminary median OS in *TP53* wild-type (18.9 months) and *TP53* mutant (12.9 months) is promising in this treatment setting in terms of historical treatment
- Given the high unmet need in this population, a randomized phase 3 trial of magrolimab + AZA vs venetoclax + AZA in frontline *TP53*-mutant AML patients is planned
- Phase 3: magrolimab + azacitidine versus azacitidine + placebo in untreated participants with myelodysplastic syndrome (MDS) (ENHANCE)

Sallman D, et al. ASH 2020. Abstract 330.

The last option is magrolimab. Now, this is different than the other drugs that we've spoken about so far. This is a first-in-class antibody therapy targeting the macrophage checkpoint CD47. It has been looked at in higher-risk MDS, as well as AML in earlier phase studies and it has good tolerance in combination with azacitidine without a lot of immune-related adverse events, which is often a concern when we're using antibody therapy. Something that was mentioned a lot in the earlier phase presentations is this seems to be equally efficacious in patients who have TP53-mutated disease.

Now, I think this is probably a pathway issue, and it's not that TP53 patients respond better. It's that all-comers could respond to this particular agent. The enhanced study, which is the phase 3 of magrolimab plus azacitidine compared to azacitidine with a placebo is open and enrolling now.

Magrolimab Study Design and Schema



It has the exact same schema that I've showed you with, again, two primary endpoints, a CR rate and overall survival. It's a large study with a one-to-one randomization.

Next Steps: P3 Summary

	Sabatolimab TIM3 Inhibitor	Syros SY-1425 selective (RARα agonist = Tamibaterone)	Magrolimab CD47mAb	Venetoclax Bcl2-inhibitor
Next steps	Phase 2 and 3 ongoing	Phase 3 ongoing	Phase 3 starting	Phase 3 planned
Population	Intermed High Very high CMML-2	RARα + Intermed High Very high	Intermed High Very high	Intermed High Very high
Planned "n"	500	190	520	500
Randomization	1:1	2:1	1:1	1:1
Dosing of IP (with SOC AZA)	IV q4 weeks	Oral D8-28	C1:D1,4,8,11,15, 22 C2: D1, 8, 15, 22 ≥C3 Q2W	Oral D1-14
Endpoint	OS	CR	CR and OS	CR and OS

That was whirlwind of potential trial options for a patient such as our case. Just to show you, these are the things that are coming or already online in a tabular format. We've talked about the TIM-3 inhibitor sabatolimab. We've talked about the RARα agonist tamibarotene. We've talked about the anti CD47 monoclonal antibody magrolimab, and then the BCL-2 inhibitor venetoclax. These are all happening right now with different dosing schedules, quite the same in population and you can see fairly high numbers looking at overall response and complete response rates.

How to Decide Referrals and Trial Choice

- No right or wrong…except not to offer the trial option
- Geography matters
- Timing matters
- BMT candidacy later
- Gut…doctor's or patient's
- Endpoints vary in trial

How do we decide between all of these? There's not a fantastic algorithm and sincerely there's no right or wrong, except not to offer the patient the option of a clinical trial. They have to think about where they live, if they can get to the clinic and then understanding what the patient and the doctor wants.

Returning to Our Friend

- Age 72 years
- Plays 18 holes 3x per week, walks course carrying bag
- PMHx: hypertension and lung cancer resected → no adjuvant therapy
- NOW: New transfusion needs, ANC 580, Plts 64
- Pancytopenic, dysplastic marrow, **8% blasts, 47, XY,+8**
- Heme NGS panel done:
  TET2 27.43% ***EZH2*** 27.43% ***ASXL1*****fs** 29.6%
  ZRSR2 91.3% ***STAG2*** 77.65%

We'll go back to our case. He's doing well and I think any of these could be options for him.

What Treatment Option Do You Recommend?

A. Enrollment in a clinical trial
B. Supportive care alone
C. Lenalidomide with supportive care
D. Azacitidine or decitabine with supportive care
E. Targeted therapy with supportive care
F. Allogeneic stem cell transplant with supportive care

Let's revisit our previous question and see if I've changed anybody's mind a little bit about what's out there at the time.

Now, based on seeing all the data, what would you think about as a treatment option for our patient?

What Treatment Option Do You Recommend?

A. Enrollment in a clinical trial
   - **So many options in 2021!**
   - **Offer it!**

All right, so many options. I'm glad you're willing to offer it.

What Treatment Option Do You Recommend?

B. Supportive care alone
   - Always part of every higher-risk MDS discussion for me

Supportive care alone is always an important part of the conversation, but I think we agree there's more to be done.

What Treatment Option Do You Recommend?

C. Lenalidomide with supportive care
   - Less of a role here with pancytopenia, increased blasts and no del(5q)

This patient did not have a deletion 5q as was described in the first half of the presentation, so lenalidomide doesn't make sense.

What Treatment Option Do You Recommend?

D. Azacitidine or decitabine with supportive care
   - Standard of care!

Standard of care is never wrong. We just want to offer patients something more with a trial.

What Treatment Option Do You Recommend?

E. Targeted therapy with supportive care
   - His molecular profile did not have targetable options

His particular molecular profile did not have a targeted option.

What Treatment Option Do You Recommend?

F. Allogeneic stem cell transplant with supportive care
   - Never say never…probably not upfront but referral for HLA typing is very reasonable

Then back to the candidacy for transplant, I never say never anymore. Certainly not upfront transplant in a patient with 8% blasts, but referral for HLA typing based on the BMTCTN1102 or the VidazaAllo study is very reasonable for a patient such as this.

Dr. Sekeres: I want to thank everyone for participating today. I especially want to thank my co-host, Dr. DeZern. It's always a pleasure to give presentations with you. I always learn so much from you as well.