ManagingMDS
Myelodysplastic Syndrome Community

Treatment Protocols for Patients with Symptomatic Low-risk MDS

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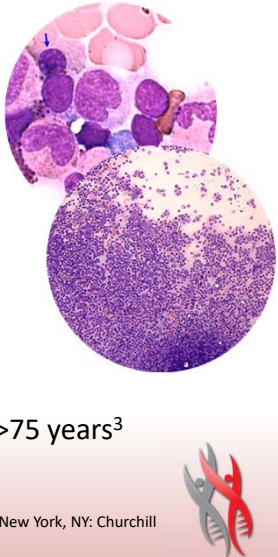Moffitt Cancer Center
Tampa, Florida

Hello, and welcome to *Managing MDS*. I'm Dr. Rami Komrokji, Section Head for Leukemia and MDS at Moffitt Cancer Center. And today, I'll be discussing treatment protocols for patients with symptomatic lower-risk MDS.

Treatment Protocols for Patients with Symptomatic Low-risk MDS
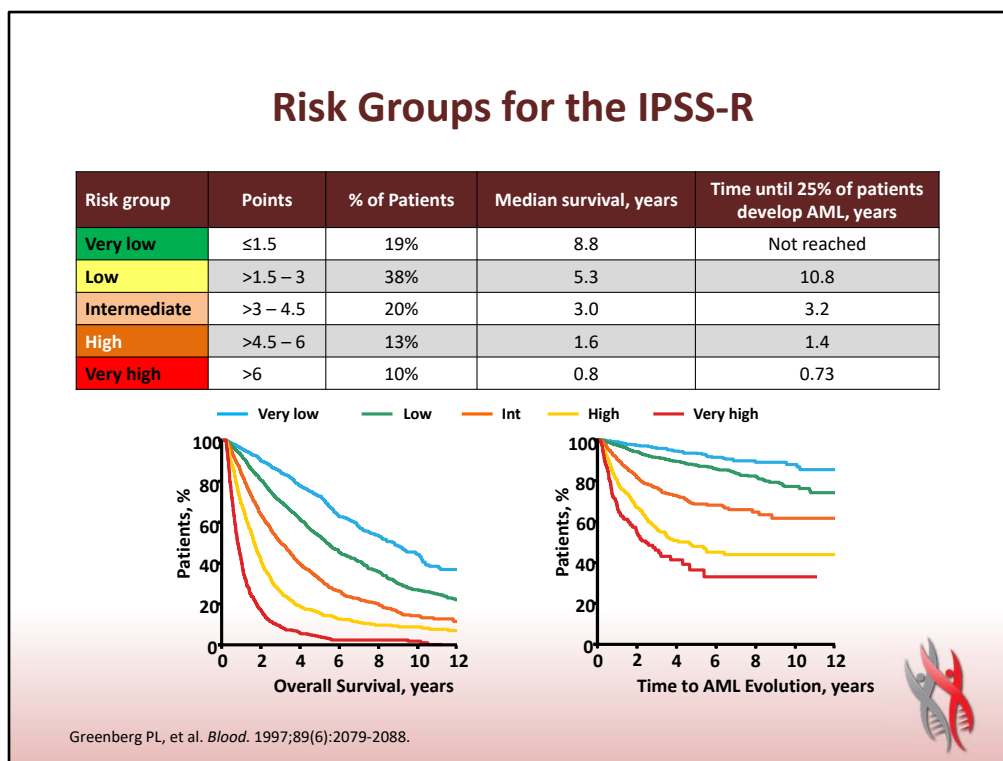
Myelodysplastic Syndromes (MDS)

- A group of malignant hematopoietic neoplasms characterized by[1]
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000[2]
  - In US (true estimates ≈37,000-48,000)
- Median age: 70 years; incidence: 34-47/100,000 >75 years[3]

1. Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, eds. *Clinical Oncology*. New York, NY: Churchill Livingstone; 2004:2849-2881. 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.
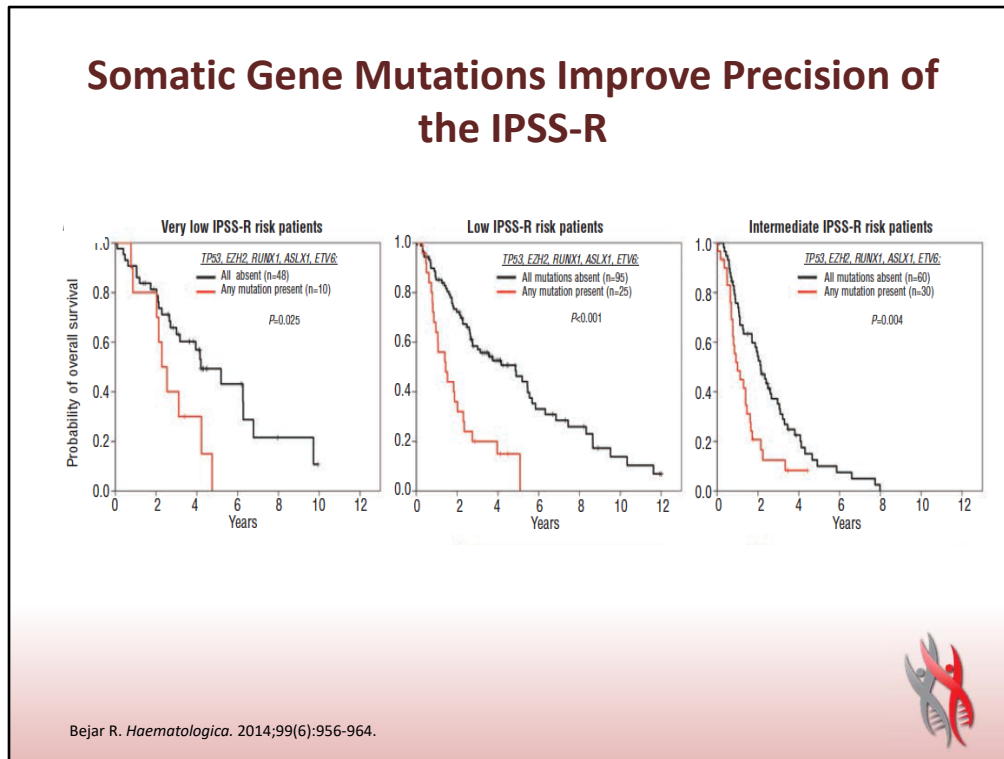
As you know, myelodysplastic syndromes are a heterogeneous group of neoplastic stem cell disease characterized by bone marrow failure with a resultant cytopenias and related complications, demonstrating evidence of clonality in most of the patients nowadays, and the hallmark of the name, the presence of dysplasia. It's important to know that MDS is a disease of elderly with average age of 70. It's probably one of the most common myeloid malignancies. Roughly around 30% of MDS patients will eventually progress to acute myeloid leukemia. However, unfortunately, around 50% to 60% of the patients will die from complications of the disease, namely related to cytopenias unrelated complications.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Risk Groups for the IPSS-R

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤1.5	19%	8.8	Not reached
Low	>1.5 – 3	38%	5.3	10.8
Intermediate	>3 – 4.5	20%	3.0	3.2
High	>4.5 – 6	13%	1.6	1.4
Very high	>6	10%	0.8	0.73

Greenberg PL, et al. *Blood.* 1997;89(6):2079-2088.

After establishing the diagnosis, our first step is usually risk stratification. Because with that, we tailor the treatment accordingly. And the most accepted or used widely nowadays is the revised IPSS, where we generate a score based on the blast percentage, the cytopenias, and the cytogenetics. And patients are grouped in one out of five risk groups from very low, low, intermediate, high, and very high. And you can see here, the median survival will vary from 8.8 years for somebody with very low risk to less than a year, unfortunately, in somebody who is very high risk.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Somatic Gene Mutations Improve Precision of the IPSS-R

Bejar R. *Haematologica.* 2014;99(6):956-964.

What we do also currently is we integrate some of the data from somatic gene mutations. This was work done by Rafael Bejar a few years ago, where they published in the context of the IPSS, presence of any of those five gene mutations will upstage patient's risk. This was also looked in the revised IPSS. I always discuss with my fellows and team that it's important to spend time establishing the diagnosis for MDS and risk stratification

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Therapeutic Objectives for Patients with MDS

MDS Type	Treatment Goals
Lower risk **(2/3 of patients)**	• Achieving RBC-TI • Hematologic improvement • Improving QoL • ? Overall survival and AML transformation
Higher risk	• Overall survival and AML transformation • Altering disease's natural history (eg, CR/PR, OS, cytogenetic responses, disease transformation, progression-free survival) • Improving QoL

Cheson BD, et al. *Blood.* 2000;96(12):3671-3674.; Cheson BD, et al. *Blood.* 2006;108(2):419-425.

because the treatment is going to be tailored based on that. And at the end, we try to classify patients in either a lower-risk MDS or a higher-risk MDS. And in the lower-risk MDS, which compromise probably majority of the patients, our goal is improving cytopenias, achieving red blood cell transfusion independency, and improving quality of life for patients. I do think that we indirectly may impact the overall survival for those patients because the mortality in lower-risk MDS is complex and it's usually an interaction between the patient's cytopenias and other comorbidities. For example, patients with severe anemia, it may exacerbate coronary artery disease. So by improving patient's count, we may impact the survival indirectly for those patients. In higher risk, as we just showed, that those patients have unfortunately a median survival typically less than a couple of years. The goal is really to improve the survival, prevent AML transformation, and we start thinking immediately of allogeneic stem cell transplant, which is the only curative option for patients with higher-risk MDS.

Red Blood Cell Transfusion in MDS

- Upon diagnosis of MDS 30-50% are red blood cell transfusion dependent (RBC TD)

- RBC TD is defined by requiring ≥2 units PRBC every 8 weeks for 3-4 months

- RBC transfusions remain an important supportive care option for many MDS patients

- Leuko-reduced RBC transfusions are recommended for MDS patients

Malcovati L, et al. *J Clin Oncol.* 2007;25(23):3504-3510.; Malcovati L, et al. *Clin Lymphoma Myeloma.* 2009;9:S305-S311.

Now in lower-risk MDS, as I mentioned, the main problem remains always the cytopenias, predominantly anemia, which is the most common. Almost 90% of the patients with MDS will have anemia, and at one point during the disease course, almost 50% plus will become red blood cell transfusion dependent and patients will be needing blood transfusions on a regular basis. By definition criteria for clinical trials, transfusion dependency is defined as requiring more than two units of blood every eight weeks, and that is persistent over three to four months. And obviously, red blood cell transfusions or occasionally platelet transfusions remain a mainstay for treating patients with myelodysplastic syndrome.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Erythroid Stimulating Agents (ESA)

- Use in lower-risk MDS patients

- First step for managing anemia

- No difference between epoietin and darbepoetin (dose equivalence)

- Start with an 8-12 weeks trial, if no response consider adding G-CSF weekly

- Epoietin starting dose is 40,000 units weekly and may be escalated to 60,000 weekly

- Among responders, average duration of response 12-18 months

Usually when we are treating lower-risk MDS the most common indication is treating anemia. The first question was, do the patients need treatment or not? If patients have mild cytopenias asymptomatic, I think it's very reasonable to observe those patients. However, most of the patients will become symptomatic with anemia, less often with thrombocytopenia or neutropenia, so in most of the times we are treating anemia. Erythroid-stimulating agents are typically the first step, erythropoietin or darbepoetin dose equivalent. We typically try those for 8 to 12 weeks. If they are working, we continue. If not, then we move to the next step. Among responders, the average duration of response is typically somewhere between a year to a year and a half.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

When Would You Give Erythropoiesis-stimulating Agents (ESAs)?

RA, RARS, RAEB

- Score > +1 → Good response (74%, n=34)
- Score −1 to +1 → Intermediate response (23%, n=31)
- Score < −1 → Poor response (7%, n=29)

Treatment response score

Epo level U/L	<100	+2
	100–500	+1
	>500	−3
Transfusion U RBC/month	<2 units/m	+2
	= or >2 units/m	−2

Hellström-Lindberg E, et al. *Br J Haematol*. 2003;120(6):1037-1046.
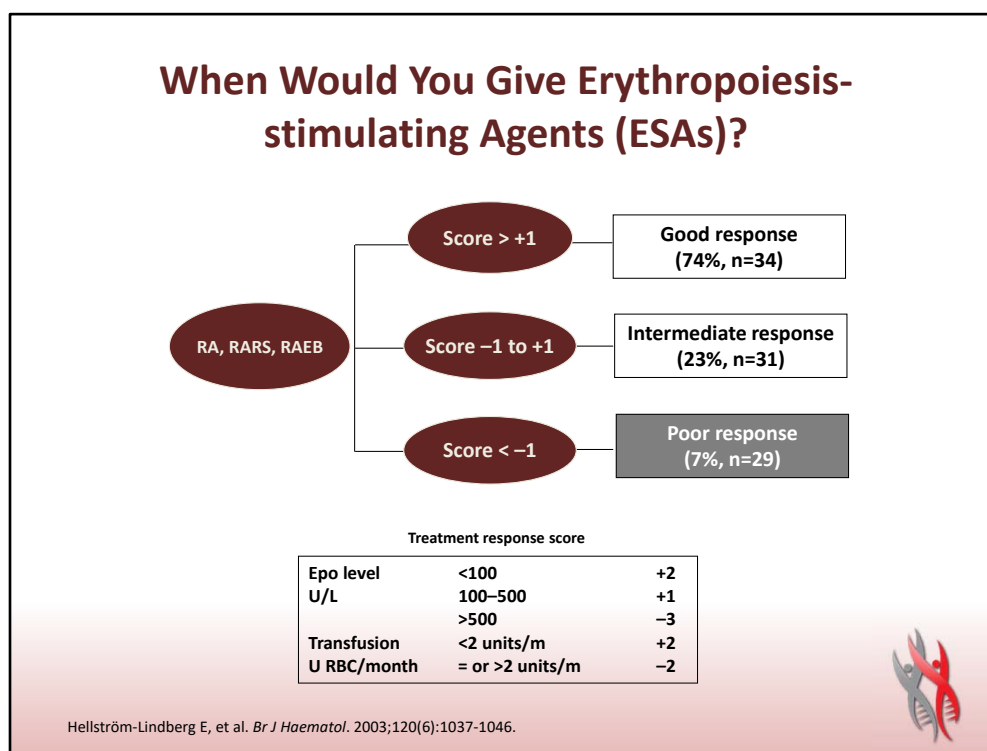
We can use the simple model published many years ago by Eva Hellstrom trying to predict responses to erythroid-stimulating agents, looking at the endogenous serum EPO levels on patients as well as the transfusion dependency or burden. For those patients that have endogenous serum EPO level more than 500 or they are receiving more than two units of blood per month, we can see that the response rate is probably going to be less than 10% with erythroid-stimulating agents. And one would argue that one could move to the next step without even a trial of ESA or a simple trial of ESA and then moving forward.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Outcome After ESA Failure

Excluded
MDS with del(5q) and CMML
Progression to higher-risk IPSS score at loss of response to ESAs

Patients with lower-risk (by IPSS) MDS receiving ESA treatment with data on outcome (N = 1,698)

French, Spanish, Italian, Düsseldorf, Munich, Greek, and US registries

GFM trial: LEN plus EPO

GFM trial: AZA plus EPO

Persisting response (n = 551; 32.5%)

Relapse (n = 494; 29%)

Primary resistance (n = 653; 38.5%)

Response rate to ESAs, 61.5%

Second-line treatment (n = 450)

HMAs	(n = 194)
LEN	(n = 148)
MISC	(n = 805)
RBC transfusion	(n = 697)
Other	(n = 108)

Park S, et al. *J Clin Oncol.* 2017;35(14):1591-1597.

And this is worked by Sophie Park that we were part of that we looked at what happens after ESA failure. So roughly in real life and real-world experience, around 60% of the patients will have some response to erythroid-stimulating agent. However, a majority of those patients subsequently will lose the response. There is obviously primary resistance in 40% of the patients almost. When we look at the outcome for those patients after ESA failure, typically it's poor with a median survival of around five years and higher rate of AML transformation, particularly among patients with primary resistance. And it's important to note that in this study, less than 50% of the patients after ESA failure proceeded to get any other second-line treatment in this study.

Treatment Protocols for Patients with Symptomatic Low-risk MDS
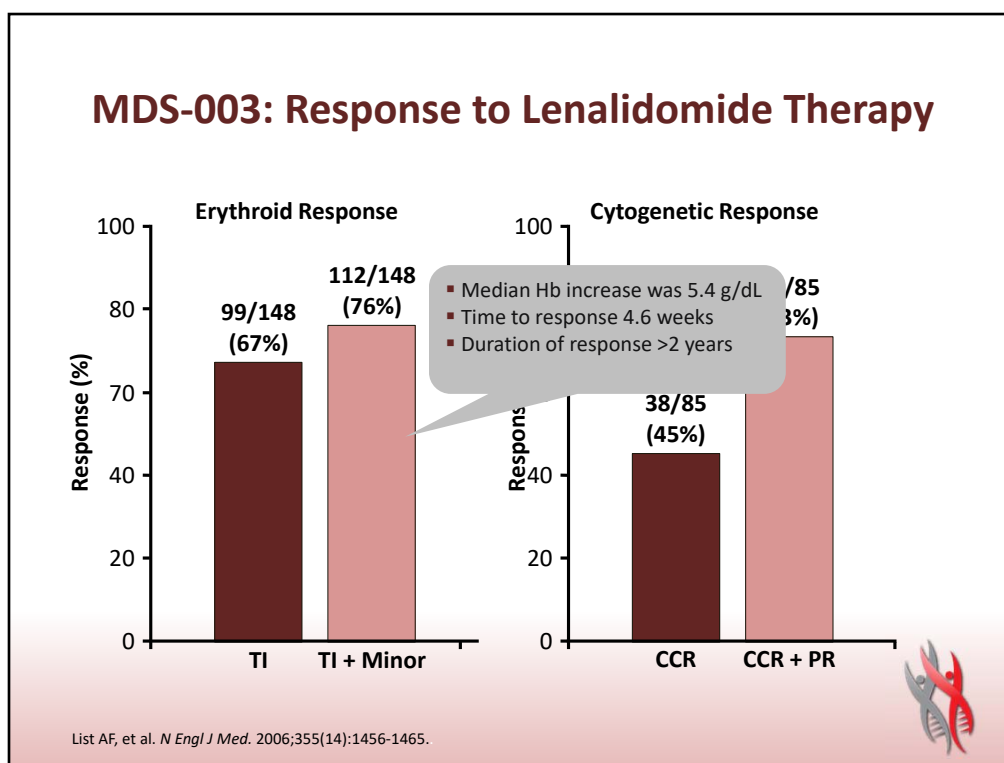
Lenalidomide in MDS

- Lenalidomide is standard of care for lower-risk MDS with del 5 q
  - Transfusion independence by IWG (67%)
  - 90% of patients respond within 3-4 month and duration of response is almost 3 years
  - MDS-004 supports 10 mg as appropriate starting dose
    - Higher TI for 10 mg
    - Greater proportion of cytogenetic responses vs 5 mg (41% vs 17%)
    - No significant differences in hematological toxicity
- MDS-001, MDS-002 and MDS-005 provided evidence that lenalidomide could be a choice for anemia treatment in lower-risk non-del(5q) patients with adequate platelets and neutrophil count

Fenaux P, et al. *Blood.* 2011;118(14):3765-3776.; List AF, et al. *N Engl J Med.* 2006;355(14):1456-1465.; List AF, et al. *N Engl J Med.* 2005;352(6):549-557.; Raza A, et al. *Blood.* 2008;111(1):86-93.; Sekeres MA, et al. *J Clin Oncol.* 2008;26(36):5943-5949.

Now, lenalidomide is approved by the FDA for treatment of deletion 5q lower-risk MDS, and I think it's become the standard of care; 67% of the patients become transfusion independent, 90% will respond within three to four months with durable responses. We start typically with 10 mg dose then lower the dose because we see higher hematological improvement and better cytogenetic responses. One should be aware that early on cytopenia on therapy is very predicted and that actually it correlates with the response, so majority of the patients will need dose holding and then adjustment. Lenalidomide can also be used in the non-del 5q setting in selected cases for patients with isolated anemia with no neutropenia or thrombocytopenia.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MDS-003: Response to Lenalidomide Therapy

Erythroid Response

Cytogenetic Response

- Median Hb increase was 5.4 g/dL
- Time to response 4.6 weeks
- Duration of response >2 years

99/148 (67%)

112/148 (76%)

38/85 (45%)

List AF, et al. *N Engl J Med.* 2006;355(14):1456-1465.

Those are the results from the MDS-003 that originally established with lenalidomide for del 5q, again showing 67% of the patients becoming transfusion independent completely. Almost half of the patients achieved a complete cytogenetic response with a median hemoglobin increase of 5.4 grams.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MDS-005: RBC-TI ≥8 Weeks

Significantly more LEN patients achieved RBC-TI ≥8 weeks vs placebo (*P* < 0.001)

The median duration of response was 32.9 weeks (95% CI 20.7–71.1) among RBC-TI ≥8 weeks responders with LEN

Santini V, et al. *Blood.* 2014;124(27):409.; Garcia-Manero G, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19(4):213-219e4.
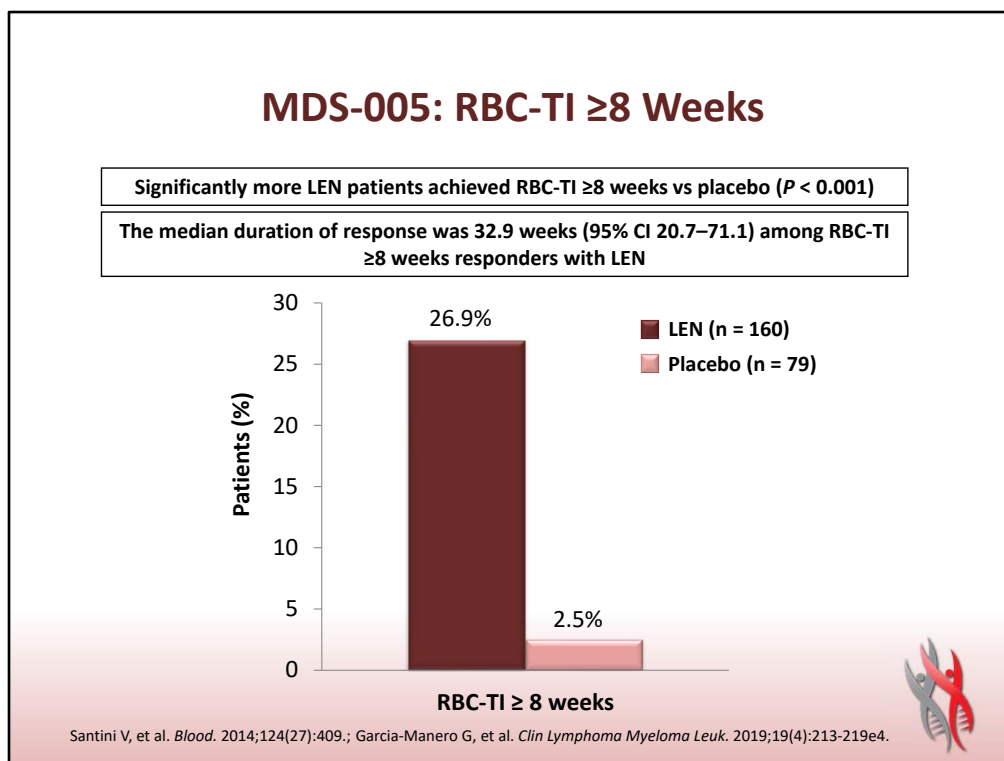
This is a work from Valeria Santini looking at use of lenalidomide in non-del 5q lower-risk patients. You can see that around 26% or 27% of the patients became red blood cell transfusion independent. It's not as high as in deletion, but it's probably on par with what we expect of responses with other agents used in lower-risk MDS.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Phase 3 Intergroup Study of Lenalidomide + Epoetin Alpha After ESA Failure [ECOG 2905]

Randomize [n=250]

→ Lenalidomide 10 mg/day x 21d → IWG MER Continue

→ Lenalidomide + Epoetin α → NR Cross-over LEN Arm only

Week: 0 — 16

- Eligibility: Low/Int-1 IPSS, ESA failure or low response profile, Hgb <9.5 g/dL
- Stratification: Serum EPO (> vs <500 mU/ml), prior ESA (EA vs DA vs none)
- Epoetin alfa 60,000 units SC weekly
- Primary endpoint (EP): MER
- Secondary EP: Time to MER, MER duration, LEN cross-over response, candidate response biomarkers (CD45 isoform profile)

List A, et al. *Blood*. 2016;128(22):223.

And this is what we've done in the context of SWOG and the US Intergroup looking at combination of lenalidomide/erythropoietin in comparison to lenalidomide.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Response Analysis

Response & Cohort	Arm A (%) LEN	Arm B (%) LEN+Epo	*P* value
ITT Analysis [n=163]	N=81	N=82	
MER	9 (11.1)	21 (25.6)	*P*=0.025
Minor ER	15 (18.5)	13 (15.9)	*P*=0.68
Overall ER	24 (29.6)	34 (41.5)	*P*=0.14
Arm A Crossover MER	N=34	7 (21%)	
Week 16 Evaluable [n=117]	N=56	N=60	
MER	8 (14.3)	20 (32.8)	*P*=0.029
Minor ER	13 (23.1)	13 (21.3)	*P*=0.83
Overall ER	21 (37.5)	33 (54.1)	*P*=0.09

List A, et al. *Blood*. 2016;128(22):223.

And we observed higher responses with the combination in terms of hematological improvement

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Duration of MER

Log Rank Test p=0.37

Treatment	TOTAL	FAIL	CNSR	MEDIAN
LEN	9	5	4	13.0
LEN+EPO	21	9	12	25.4

List A, et al. *Blood.* 2016;128(22):223.
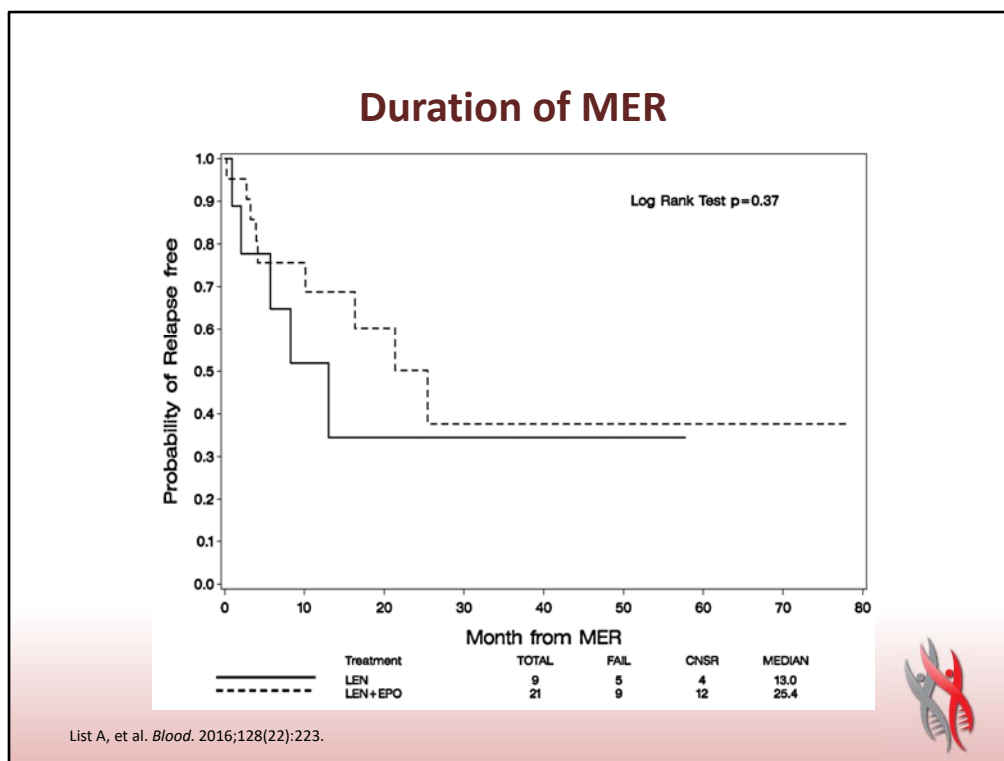
and probably more durable responses. In patients with non-del 5q, it's reasonable to combine both lenalidomide and erythroid-stimulating agents. Again, we select those patients that are purely anemic with no major concomitant neutropenia or thrombocytopenia.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

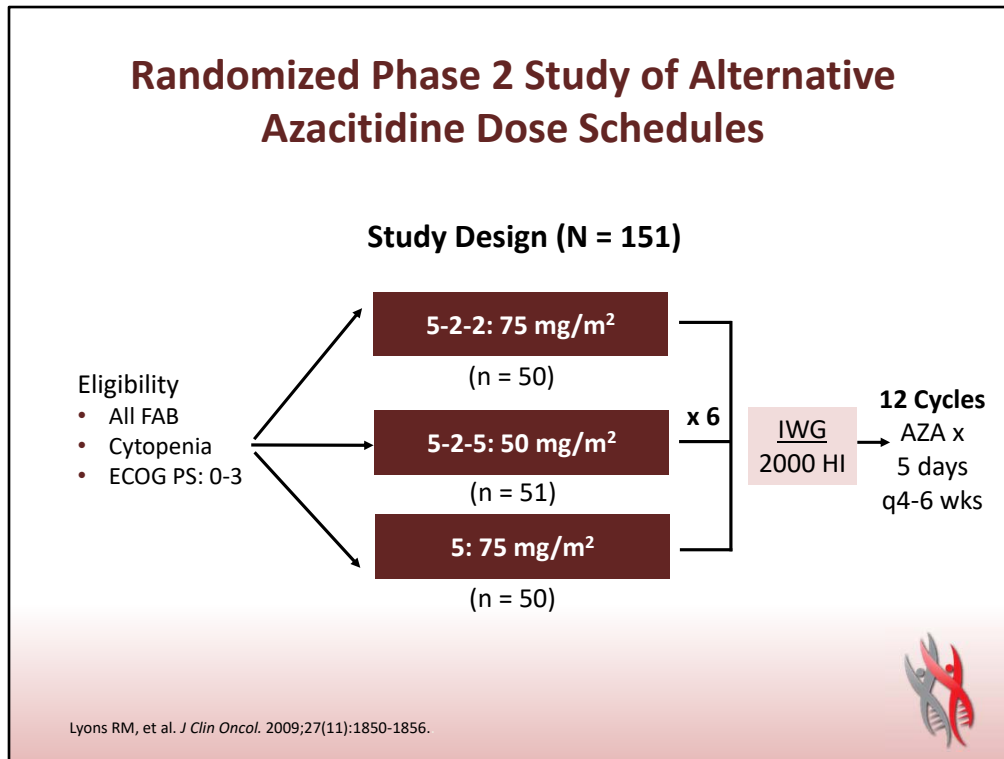## Sequential Use of Lenalidomide and Azacitidine in Lower-risk MDS

	LEN Response Rates (HI+)	AZA Response Rates (HI+)
LEN 1st line **n = 37**	38% (n=14)	38% (n=14)
LEN 2nd line **n = 26**	12% (n=3)	35% (n=9)
P value	0.04	0.69

Zeidan AM, et al. *Clin Lymphoma Myeloma Leuk.* 2015;15(11):705-710.

We also try to look at sequence of therapy. After ESA failure, if patients have isolated anemia, should we go for lenalidomide or hypomethylating agents? Because in the United States, hypomethylating agents are approved and used for lower-risk MDS contrary to the practice in Europe. We looked at use of lenalidomide as first-line or second-line after ESA failure and we observed that higher responses are seen if lenalidomide was used after ESA failure, 38% versus 12%, while the responses to azacitidine did not matter whether it was used as a first-line or second-line. Typically, if I have a patient with isolated anemia and I'm thinking of using lenalidomide, I will use lenalidomide prior to hypomethylating agents.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Randomized Phase 2 Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

| 5-2-2: 75 mg/m^2 |
| (n = 50) |

| 5-2-5: 50 mg/m^2 |
| (n = 51) |

| 5: 75 mg/m^2 |
| (n = 50) |

x 6

IWG 2000 HI

12 Cycles
AZA x 5 days q4-6 wks

Lyons RM, et al. *J Clin Oncol.* 2009;27(11):1850-1856.

Now, hypomethylating agents still remain to be used in lower-risk MDS. This is worked by Dr. Lyons published several years ago trying to look at the schedule of hypomethylating agents in lower risk and established that five days of hypomethylating agents are adequate in lower-risk MDS with around 30% to 40% hematological improvement

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Alternate AzaC Dose Schedule Study:
Frequency of Major HI in Evaluable Patients (N = 139)

Lineage HI in Evaluable Patients, n/N (%)	5-2-2 (n = 50)	5-2-5 (n = 51)	5d (n = 50)
Erythroid$_{Ma}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	**12/24 (50)**	**12/22 (55)**	**15/25 (64)**
Platelet$_{Ma}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
Neutrophil$_{Ma}$	4/23 (17)	4/23 (17)	9/24 (38)
Heme AEs > grade 3	**33/50 (66)**	**24/48 (50)**	**17/50 (34)**
AE Tx delay	**34/50 (68)**	**30/48 (63)**	**17/50 (34)**

Lyons RM, et al. *J Clin Oncol.* 2009;27(11):1850-1856.

and toxicity was similar between the 5:5 or 5:2 regimen and five days. So most people have adopted the five days regimen. Some other studies have suggested lower responses a little bit with hematological improvement, but I think it's fair to say somewhere around 30% to 40% hematological improvement is observed with hypomethylating agents in lower-risk MDS.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Low-dose HMAs in LR MDS: Response Rates

Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	P Value
ORR	70	49	.03
CR	37	36	.90
mCR	9	5	NR
HI	24	8	NR
SD	26	44	NR
PD	4	8	NR
CCyR	25	6	.12
PCyR	36	19	.02
CCyR + PCyR	61	25	.02

Response, * %	Decitabine (n = 70)	Azacitidine (n = 39)	P Value
Blasts ≥5%	n = 21	n = 11	
ORR	100	36	<.001
CR	52	18	.06
Blasts 5%	n = 45	n = 27	
HI -- ≥1 lineage	38	48	.29
HI – all lineages	22	26	.72
TI at response	32	16	.20

- Strongest predictors of response included BM blasts ≥5%, MDS/MPN or CMML diagnosis, high MFA LR MDS score, and IPSS intermediate-1 risk

*Median treatment cycles (range): 9 (1-41).
Jabbour EJ, et al. *Blood*. 2016;128(22):226.; Jabbour EJ, et al. *Blood*. 2017;130(13):1514-1522.

Within the context of the MDS Consortium pioneered by our colleagues at MD Anderson, we've been trying to look at a shorter course of hypomethylating agents. This is worked by Elias Jabbour published in *Blood*, looking at three days azacitidine or three days decitabine showing equivalent to historical data hematological improvement in patients with lower risk, and we just finished accrual to a randomized study between five days azacitidine, three days decitabine, or three days azacitidine. And if the study shows non-inferiority with a shorter course, one would move probably to three days regimen of hypomethylating agents in lower-risk MDS.

Now typically, I use hypomethylating agents in lower-risk MDS patients after ESA failure if they are purely anemic or for those patients that have concomitant neutropenia or thrombocytopenia that will preclude use of lenalidomide in those patients. Also, some would suggest that if there are higher-risk features or certain somatic mutations, one may use hypomethylating agents in lower-risk MDS.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Immunosuppressive Therapy (IST)

- One course ATG +/- CSA
- Positive variable for IST response
  - Age is the strongest variable for response
  - HLA-DR 15 status
  - Short duration of disease
  - Low transfusion burden
  - Trisomy 8
  - Hypoplastic MDS
  - PNH clone
- Negative predictors of response
  - Bone marrow fibrosis
  - Del 5q
- Responses are durable and trilineage responses are observed

Saunthararajah Y, et al. *Blood*. 2002;100(5):1570-1574.; Sloand EM, et al. *J Clin Oncol*. 2008;26(15):2505-2511.;
Sloand E, et al. ASH 2004. Abstract 1431.

Immunosuppressive therapy ATG cyclosporine is often underutilized treatment. There are several studies trying to predict who are going to be the good responders. Some institutions preserve the use of immunosuppressive therapy only for hypocellular or hypoplastic MDS, and the NIH studies and Moderna turned out that age is probably the strongest predictor of outcome or response to immunosuppressive therapy for patients less than the age of 60. Shorter duration of disease, lower transfusion burden were all predictors of better response.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Somatic Gene Mutations (SGM) as Biomarkers for Response to Immunosuppressive Therapy (IST)

- NGS for 49 SGMs performed on DNA from 66 patients with IPSS Low/Int risk MDS treated with ATG ± CsA
- ORR was 42% (n=28) by IWG 2006 criteria
- 50% had at least one and 22.5% had ≥2 SGM
- Absence of SGM was associated with higher response to IST (70% vs 40%), P=.16 with a mean duration of response of 12 months without SGM vs 9 months with SGM, P=.09
- Presence of *SF3B1* mutation was associated with IST nonresponse (11% *SF3B1* mut vs 68% WT, P=.01)
- Rate of AML transformation in patients with non-*SF3B1* SGM was higher than those without SGM, P=.023 with a corresponding reduced OS
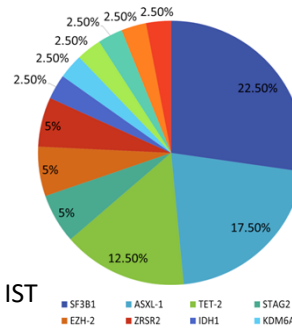
Komrokji RS, et al. ASH 2015; Abstract 1664a.

This is our work trying to look at somatic gene mutations prediction for response to immunosuppressive therapy. Overall, as you can see, we observe around 40% responses. And we observed that if patients had presence of SF3B1 mutation, that was a negative predictor for response, only 11% responded or one out of nine patients. In our practice, we do think of immunosuppressive therapy, particularly for younger patients early in the disease. In absence of presence of ring sideroblasts or SF3B1 mutation, we will think of using ATG cyclosporine. Durable and trilineage responses can be attained using immunosuppressive therapy.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Prevalence of Thrombocytopenia in MDS

- The estimated prevalence of thrombocytopenia in MDS, defined as a platelet count <100 × 10^9/L ranges from **40 to 65%**

- 5-10% of MDS patients can present as isolated thrombocytopenia and be misdiagnosed as idiopathic thrombocytopenic purpura

- In the MDACC chart review, 968/2410 of MDS patients (40%) died without progression to AML, where **10%** died from hemorrhagic complications

- In the Düsselforf MDS Registry, signs of bleeding were present in 19%
  - 20% of patients in this cohort became platelet transfusion-dependent during the course of disease and **13.3%** of patients died from bleeding complications

Kantarjian H, et al. *Cancer*. 2007;109(9):1705-1714.; Neukirchen J, et al. *Eur J Haematol.* 2009;83(5):477-482.

Now focusing on thrombocytopenia or overt thrombocytopenia is observed probably in 40% to 65% of the patients, more commonly in higher-risk MDS patients. Around 5% to 10% of the patients with MDS will present with isolated thrombocytopenia. The impact of thrombocytopenia in MDS was studied in two registries from MD Anderson and the Dusseldorf registry showing that probably it accounts unfortunately for 10% to 15% of the mortality from bleeding complications. And in addition to that, it probably dictates the choice of therapy, so presence of thrombocytopenia will, for example, preclude using lenalidomide in those patients, and hypomethylating agents or ATG cyclosporine become the only options.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

How I Treat Thrombocytopenia in MDS

- Lower-risk MDS
  - Pancytopenia
    - ATG/CSA in younger patients early disease
    - HMA
  - Isolated thrombocytopenia
    - Eltrombopag
- Higher-risk MDS
  - HMA
  - AHSCT
  - Palliative TPO stimulants in severe thrombocytopenia post HMA failure

This is how I treat thrombocytopenia in MDS. In higher-risk MDS patients, obviously, we go with hypomethylating agents, we consider transplant. In lower-risk patients if they are very young below age of 60 early in the disease, we tend to use ATG cyclosporine. For the others, we use hypomethylating agents, and for subsets of patients with lower-risk MDS isolated thrombocytopenia, there is probably a role for using eltrombopag the thrombopoietin stimulant.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Eltrombopag for Treatment of LR-MDS

Randomization 2:1

Week 24

Patients
(N = 174)

Eltrombopag + standard care (n = 116)

CR and R

Eltrombopag + standard care

Placebo + standard care (n = 58)

Standard care

Dose start: 50 mg with increases every 2 weeks up to 300 mg daily.

Oliva EN, et al. *Lancet Haematol.* 2017;4(3):e127-e136.
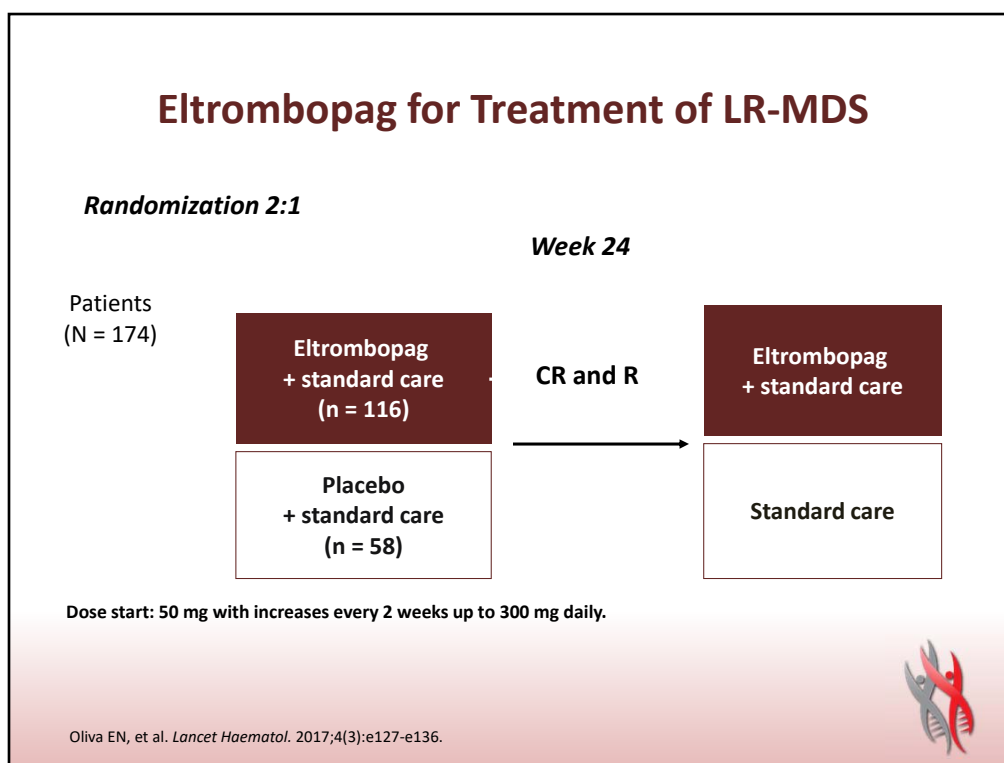
And this is based on this study from our colleagues from Italy, where they randomized lower-risk MDS patients with thrombocytopenia in 2:1 fashion between eltrombopag and best supportive care, and they defined CR or complete remission by achieving platelets more than 100.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Oliva EN, et al. *Lancet Haematol.* 2017;4(3):e127-e136.
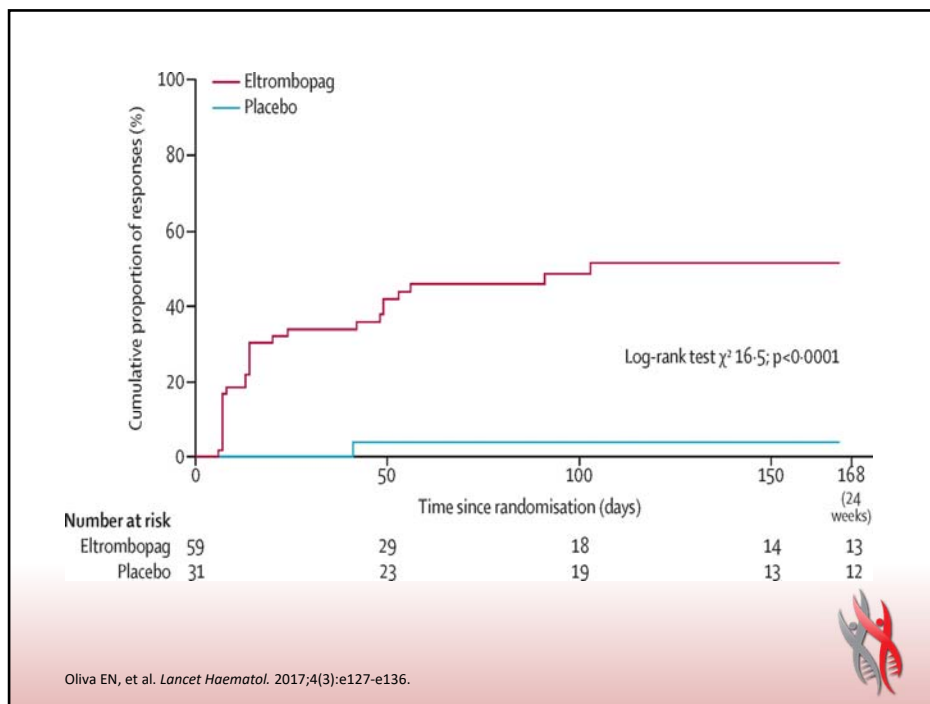
And around 40% to 50% of the patients achieved a complete platelet response, and there was no signal of increased fibrosis of leukemia transformation in this study. So, it's reasonable in selected patients with isolated thrombocytopenia to think of eltrombopag as treatment for those patients.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

TELESTO: Phase 2, Randomized, Double-Blind Study

Screening
35 days
(two visits ≥14 days apart)

Randomization 2:1
Stratified by IPSS (Low or Int-1) and geographic region (Asian or non-Asian)

Deferasirox (N = 149)
10–40 mg/kg/day based on dosing guidelines

Placebo (N = 76)

Final assessment
LPFV plus 3 years of treatment*

*Patients who experienced a nonfatal event were discontinued and followed up for 28 days; patients were then followed up every 3–6 months (for evaluation or survival)

Key inclusion criteria:

- Hematologically stable IPSS Low- or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
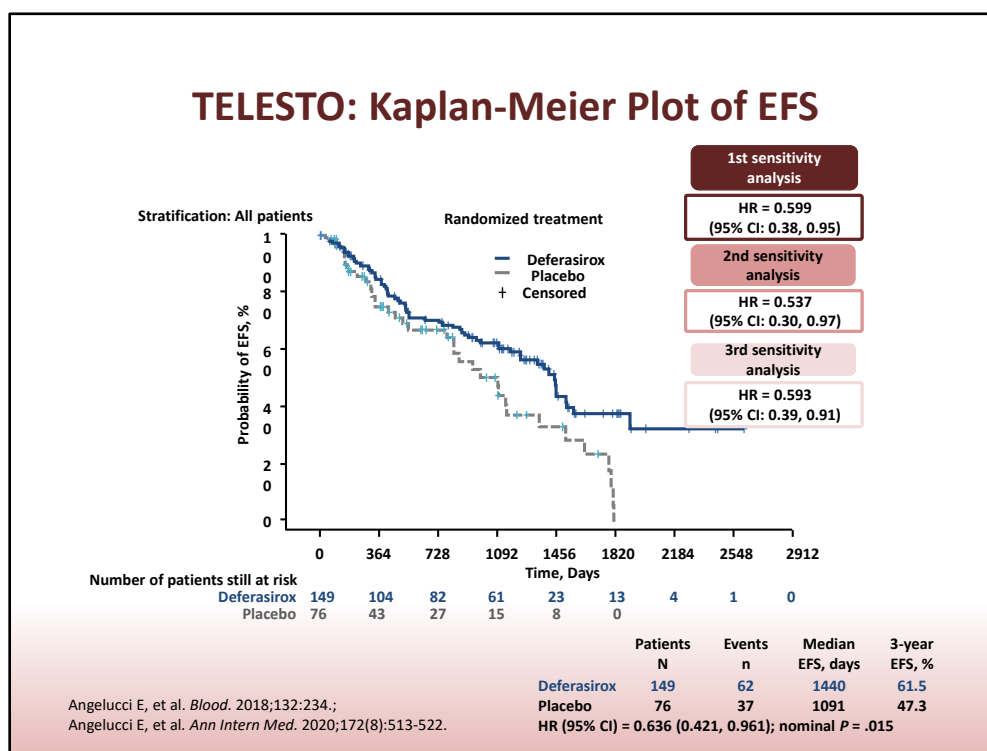- Serum ferritin >1000 ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF ≥50% by echocardiography
- ALT or AST ≤3.5×ULN, total bilirubin ≤1.5×ULN, no previous diagnosis of liver cirrhosis; CrCl ≥40 mL/min
- ECOG performance status ≤2

Angelucci E, et al. *Blood.* 2018;132:234.; Angelucci E, et al. *Ann Intern Med.* 2020;172(8):513-522.

The other topic to discuss in lower-risk MDS is role of iron chelation. I think we know that red blood cell transfusions are associated with iron overload. Typically, once the patients get 15 or 20 units of red blood cell transfusion, they do have evidence of excess iron or iron overload, which is detrimental. And several studies have documented worse outcomes with higher ferritin levels as well as evidence of iron overload in MDS patients. The question always had been the benefit of iron chelation. Several retrospective studies suggested benefit of iron chelation in terms of survival. The TELESTO study that was presented a couple of years ago now tried to randomize patients between iron chelation with deferasirox versus placebo. The study was powered originally for overall survival. But because of poor accrual on the study as patients were not allowed to be receiving active therapy, a composite endpoint was changed to be the primary endpoint, lumping up hospitalization as well as evidence of end organ damage.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

TELESTO: Kaplan-Meier Plot of EFS

Stratification: All patients

Randomized treatment
- Deferasirox
- Placebo
- + Censored

1st sensitivity analysis
HR = 0.599 (95% CI: 0.38, 0.95)

2nd sensitivity analysis
HR = 0.537 (95% CI: 0.30, 0.97)

3rd sensitivity analysis
HR = 0.593 (95% CI: 0.39, 0.91)

Probability of EFS, % (y-axis: 100, 80, 60, 40, 20, 0)

Time, Days (x-axis: 0, 364, 728, 1092, 1456, 1820, 2184, 2548, 2912)

Number of patients still at risk

	0	364	728	1092	1456	1820	2184	2548	2912
Deferasirox	149	104	82	61	23	13	4	1	0
Placebo	76	43	27	15	8	0			

	Patients N	Events n	Median EFS, days	3-year EFS, %
Deferasirox	149	62	1440	61.5
Placebo	76	37	1091	47.3
HR (95% CI) = 0.636 (0.421, 0.961); nominal *P* = .015				

Angelucci E, et al. *Blood.* 2018;132:234.;
Angelucci E, et al. *Ann Intern Med.* 2020;172(8):513-522.

And the brief answer is basically the iron chelation did show a decrease in the composite endpoint in terms of less hospitalization, less liver and cardiac events. My take on iron chelation obviously there are some different camps, some advocate using iron chelation, some don't. I think it's one of the options that we should consider for lower-risk MDS patients, especially in the context of presence of the iron overload. I think we should individualize that decision. Obviously, the benefit is overcoming the excess iron overload and the complications related. The disadvantage is probably some adverse events observed with all of those iron chelation. I discuss the option with patients. For those patients, the NCCN guidelines recommend considering iron chelation for patients with serum ferritin more than 2500. The MDS Foundation discusses using iron chelation for patients more than 1000. I think it's something to keep in mind and discuss with patients and consider, particularly if patients have gone through all options of treatment, and they are bound to red blood cell transfusions, or in occasions where patients had a good response to therapy where we can take that window as an opportunity to get rid of the excess iron.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Refractory Anemia with Ring Sideroblasts and RARS with Thrombocytosis
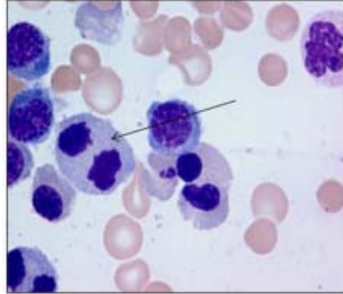
A- Wright Giemsa stain demonstrating Dyserythropoiesis (arrow).
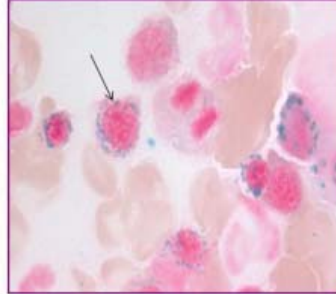
B- Prussian blue stain demonstrating Ring sideroblasts (arrow).

- Ring sideroblasts (RS) are erythroid precursors in which after Prussian blue staining (Perls reaction) there are a minimum of five siderotic granules covering at least a third of the nuclear circumference
- The iron deposited in the perinuclear mitochondria of RS is present in the form of mitochondrial ferritin

Patnaik MM, Tefferi A. *Am J Hematol* 2015;90(6):549-559.

I want to focus a little bit on patients with ring sideroblasts. As you know, sideroblasts in Greek means iron deposit. Ring sideroblasts are erythroid precursors with perinuclear iron deposition thought to be due to a defect in the mitochondrial transfer, and, as you know, there is an MDS subset with ring sideroblasts, whether they are single lineage dysplasia or multilineage dysplasia. Ring sideroblasts are not peculiar to MDS, they can be seen in other conditions. But obviously, we do have a subtype of MDS with ring sideroblasts and it's probably the most common cause for ring sideroblasts in others to be observed. Historically, probably MDS with ring sideroblasts accounts for around 15% to 20% of all the MDS cases, associated with favorable outcome in terms of overall survivor less likely to progress to acute myeloid leukemia. However, those patients do present with ineffective erythropoiesis and become transfusion dependent over time.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Spliceosome Mutations Are Enriched in MDS Patients

MDS Without RS (n=155)
RARS/RCMD-RS (n=73)
CMML (n=88)
AML/MDS (n=162)
De novo AML (n=151)
MPN (n=53)

Yoshida K, et al. *Nature.* 2011;478(7367):64-69.
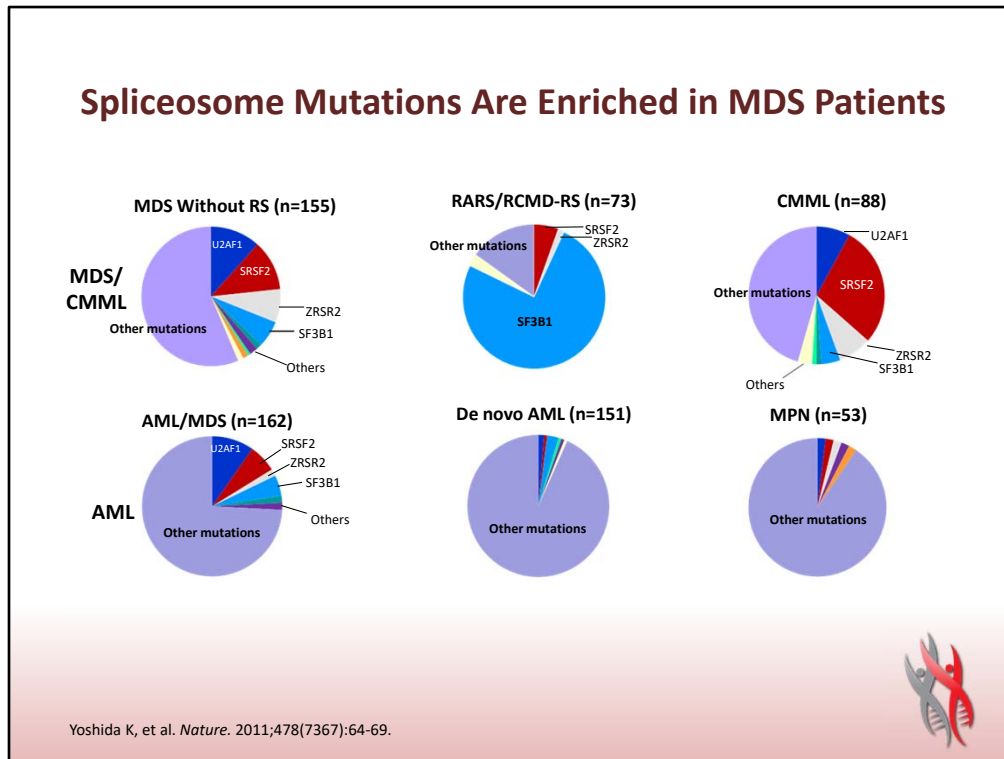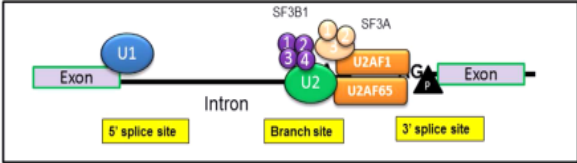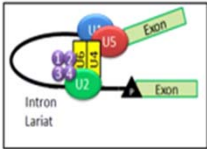
And we know that splicing mutations are enriched in patients with MDS, particularly the SF3B1 where we see a phenotype/genotype association with ring sideroblasts where around 80% to 90% of patients with ring sideroblasts will demonstrate SF3B1 mutation.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

SF3B1

- SF3 splicing factors help tether the U2 snRNP to the pre-mRNA; These factors play an additional role in the formation of the intermolecular helix between the 5' end of U2 and the 3' end of U6 snRNAs
- Splicing Factor 3 Binding Partner 1 -SF3B1 (155kDa) is one of seven SF3 spliceosome associated proteins that are incorporated into the spliceosome during the assembly of pre-splicing complex and become part of the U2 snRNP

- Most mutations in *SF3B1* are heterozygous substitutions and tend to cluster in exons 12–16 of the gene (chromosome 2q33.1)
- The *SF3B1* **K700E** mutation usually accounts for 50% of the variants, with additional codons such as 666, 662, 622, and 625 acting as hot spot sites

Patnaik MM, Tefferi A. *Am J Hematol* 2015;90(6):549-559.

Those typically are heterozygotic mutations. The hotspot K700 mutation is usually the most common observed. SF3B1 mutation is the only mutation associated with a favorable outcome in patients with MDS.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Proposed Diagnostic Criteria for the MDS with Mutated *SF3B1* in 2020

- Cytopenia defined by standard hematologic values
- Somatic SF3B1 mutation
- Isolated erythroid or multilineage dysplasia*
- Bone marrow blasts <5% and peripheral blood blasts <1%
- WHO criteria for MDS with isolated del(5q), MDS/MPN-RS-T or other MDS/MPNs, and primary myelofibrosis or other MPNs are not met
- Normal karyotype or any cytogenetic abnormality other than del(5q); monosomy 7; inv(3) or abnormal 3q26, complex (≥3)
- Any additional somatically mutated gene other than *RUNX1* and/or *EZH2*[†]

*RS are not required for the diagnosis
[†]Additional *JAK2V617F*, *CALR*, or *MPL* mutations strongly support the diagnosis of MDS/MPN-RS-T
Malcovati L, et al. *Blood*. 2020;136(2):157-170.

Now, there is a proposal from the MDS International Working Group just published recently by Dr. Malcovati in *Blood* suggesting that patients with MDS mutant SF3B1 could be considered as a single identity or a unique identity where patients have less than 5% ring sideroblasts; they don't have complex karyotype chromosome 5, 7, or 3 abnormality; no presence of RUNX1 or EZH1 mutation; and those should be considered as a separate group. The presence of multilineage or single lineage dysplasia does not affect the outcome. It's only the presence of more than 5% blasts. The complex karyotype or those mentioned cytogenetic or somatic abnormalities is what impact the outcome among those patients.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Constitutive Activation of TGF-β Signaling Suppresses Hematopoiesis in MDS

- TGFβ Type I receptor kinase phosphorylates Smad2 and 3 forming transcriptional complexes, whereas the inhibitory Smad7 extinguishes TGFβ-R1 activity
- miR-21 upregulation significantly reduces Smad7 in MDS BM progenitors
- R1 kinase is constitutively activated in MDS with sustained Smad2 phosphorylation
- Suppression of R1 kinase improves MDS progenitor CFC *in vitro*

Phospho-Smad2 IHC

Schmierer B, et al. *Nat Rev Molec Cell Biol.* 2007;8(12):970-982.

Zhou L, et al. *Blood.* 2008;112:3434-3443.;
Tushar D, et. al. *Blood.* 2013;121:2875-2881.

The reason we discussed all of this that finally after a decade in MDS, we have the first drug approved, particularly for patients with MDS with ring sideroblasts. This is worked by Amit Verma several years ago looking at TGF-beta pathway demonstrating that this pathway is overactivated in MDS patients contributing to myelosuppression.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Excess Smad2/3 Signaling Suppresses Late-Stage RBC Maturation in MDS

Bone marrow microenvironment

TGF-β ligands (eg, GDF15, GDF11, BMP6, activin A) <u>negatively</u> regulate late erythropoiesis

Luspatercept releases maturation block

500 cells   8–64 cells

SCF
IL-3
EPO

EPO

EPO-responsive   EPO-dependent

BFU-E   CFU-E   Pro-E   Baso E   Poly E   Ortho E   Reticulocyte   RBC

Sustained Hb increase

Rapid Hb increase

- Mobilizes cells from precursor pools into blood
- Effect relies on continuous formation of late-stage precursors from earlier progenitors

Zhou L, et al. *Blood*. 2008;112:3434-3443.

And treatments or monoclonal antibodies, namely luspatercept, were developed to target this pathway. Luspatercept, which was recently approved by the FDA for treatment of MDS ring sideroblasts lower-risk MDS who are transfusion dependent, is a TGF-beta ligand fusion trap protein neutralizing antibody, so it binds the TGF-beta ligands in the serum before they bind the receptor, namely GDF-11. Those ligands tend to be important in regulation of erythropoiesis, the terminal steps of erythroid maturation, so they work as negative regulators of terminal erythroid maturation contrary to erythropoietin that works on early stages of erythroid differentiation or promotion. So luspatercept by inhibiting GDF-11 will release the block on the erythroid maturation and thus we use now the term erythroid maturating agents, and luspatercept is the first in that class to be approved.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

PACE-MDS Study HI with Luspatercept
0.75-1.75 mg/KG (n=51)

	IWG-HI	TI
All patients	32/51 (63%)	16/42 (38%)
Transfusion burden		
Low	11/17 (65%)	6/8 (75%)
High	21/34 (62%)	10/34 (29%)
Ring sideroblasts		
Positive	29/42 (69%)	14/33 (32%)
Negative	3/7 (43%)	2/7 (29%)
Unknown	0/2	0/2
SF3B1mutation		
Positive	24/31(77%)	11/25 (44%)
Negative	6/15 (40%)	5/13 (39%)
Unknown	2/5 (40%)	0/4
Any splicing mutation		
Positive	27/37 (73%)	15/30 (50%)
Negative	5/14 (36%)	1/12 (8%)

Platzbecker U, et al. *Lancet Oncol.* 2017;18(10):1338-1347.

Originally, it was tested by our colleagues in Germany in a study called the PACE study, where they observed higher responses among patients with ring sideroblasts, SF3B1 mutation, or splicing mutations.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

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

Pierre Fenaux, Uwe Platzbecker, Ghulam J. Mufti, Guillermo Garcia-Manero, Rena Buckstein, Valeria Santini, María Díez-Campelo, Carlo Finelli, Mario Cazzola, Osman Ilhan, Mikkael A. Sekeres, José F. Falantes, Beatriz Arrizabalaga, Flavia Salvi, Valentina Giai, Paresh Vyas, David Bowen, Dominik Selleslag, Amy E. DeZern, Joseph G. Jurcic, Ulrich Germing, Katharina S. Götze, Bruno Quesnel, Odile Beyne-Rauzy, Thomas Cluzeau, Maria Teresa Voso, Dominiek Mazure, Edo Vellenga, Peter L. Greenberg, Eva Hellström-Lindberg, Amer M. Zeidan, Abderrahmane Laadem, Aziz Benzohra, Jennie Zhang, Anita Rampersad, Peter G. Linde, Matthew L. Sherman, Rami S. Komrokji, Alan F. List

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

And that led to a randomized phase 3 clinical trial looking at luspatercept in patients with lower-risk MDS, ring sideroblasts who are transfusion dependent.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MEDALIST Trial
Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO): ≥15% RS or ≥5% with *SF3B1* mutation
- <5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO >200 U/L
- Average RBC transfusion burden ≥2 units/8 weeks
- No prior treatment with disease-modifying agents (eg, iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

Disease & Response Assessment week 24 & every 6 months Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥3 years post final dose for AML progression, subsequent MDS treatment and overall survival

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

Randomized in 2:1 fashion between luspatercept given at a subQ injection as 1 mg/kg starting dose every three weeks compared to placebo with a primary endpoint of red blood cell transfusion independency more than eight weeks during the first 24 weeks, but also looking at 48 weeks and during the whole duration of study.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Demographic and Disease Characteristics of the Patients at Baseline

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
Median age (range) — yr	71 (40–95)	72 (26–91)	71 (26–95)
Male sex — no. (%)	94 (61)	50 (66)	144 (63)
Median time since original diagnosis of MDS (range) — mo	44.0 (3–421)	36.1 (4–193)	41.8 (3–421)
WHO classification of MDS — no. (%)†			
MDS with refractory anemia with ring sideroblasts	7 (5)	2 (3)	9 (4)
MDS with refractory cytopenia with multilineage dysplasia‡	145 (95)	74 (97)	219 (96)
IPSS-R risk category — no. (%)§			
Very low	18 (12)	6 (8)	24 (10)
Low	109 (71)	57 (75)	166 (72)
Intermediate	25 (16)	13 (17)	38 (17)
Median serum erythropoietin level (range) — U/liter¶	156.9 (12–2454)	130.8 (29–2760)	153.2 (12–2760)
Serum erythropoietin level category — no. (%)			
<100 U/liter	51 (33)	31 (41)	82 (36)
100 to <200 U/liter	37 (24)	19 (25)	56 (24)
200 to 500 U/liter	43 (28)	15 (20)	58 (25)
>500 U/liter	21 (14)	11 (14)	32 (14)
Missing data	1 (1)	0	1 (<1)
Mutated SF3B1 — no./total no. (%)‖	138/148 (93)	64/74 (86)	202/222 (91)
Median red-cell transfusion burden (range) — no. of units/8 wk over period of 16 wk**	5 (1–15)	5 (2–20)	5 (1–20)
Red-cell transfusion-burden category — no. (%)			
≥6 units/8 wk	66 (43)	33 (43)	99 (43)
4 to <6 units/8 wk	41 (27)	23 (30)	64 (28)
<4 units/8 wk	46 (30)	20 (26)	66 (29)
Median pretransfusion hemoglobin level (range) — g/dl††	7.6 (6–10)	7.6 (5–9)	7.6 (5–10)
Received ESA previously — no. (%)	148 (97)	70 (92)	218 (95)
Disease refractory to ESA — no./total no. (%)	144/148 (97)	69/70 (99)	213/218 (98)
Discontinued previous ESA-containing regimen owing to an adverse event — no./total no. (%)	4/148 (3)	1/70 (1)	5/218 (2)
Previous iron chelation therapy — no. (%)	71 (46)	40 (53)	111 (48)
Median platelet count (range) — 10⁻⁹/liter	235.0 (59–892)	222.5 (60–689)	234.0 (59–892)

* Percentages may not total 100 because of rounding. ESA denotes erythropoiesis-stimulating agent, IPSS-R Revised International Prognostic Scoring System, MDS myelodysplastic syndrome, and WHO World Health Organization.
† One patient in the luspatercept group had locally diagnosed MDS with ring sideroblasts with multilineage dysplasia.
‡ All the patients were classified as having refractory cytopenia with multilineage dysplasia with ring sideroblasts because they were required to have ring sideroblasts according to the inclusion criteria.
§ MDS in one patient (1%) in the luspatercept group was classified as IPSS-R high-risk. This case was a protocol violation, and the patient entered the trial in error.
¶ The baseline erythropoietin level was defined as the highest erythropoietin value within 35 days before the first dose.
‖ The analysis included only patients with available baseline gene mutation data.
** The analysis included data only within the 16 weeks before randomization.
†† The pretransfusion hemoglobin level was defined as the last value measured on or before the date and time of the first dose.

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

The baseline characteristics were similar between patients that got luspatercept and placebo. As expected, most of those patients had ring sideroblasts, majority of them harbored the SF3B1 mutation, and almost half of those patients were heavily transfusion dependent receiving more than six units of red blood cell transfusion.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Independence from Red Cell Transfusion

Fenaux P, et al. *N Engl J Med.* 2020;382(2):140-151.
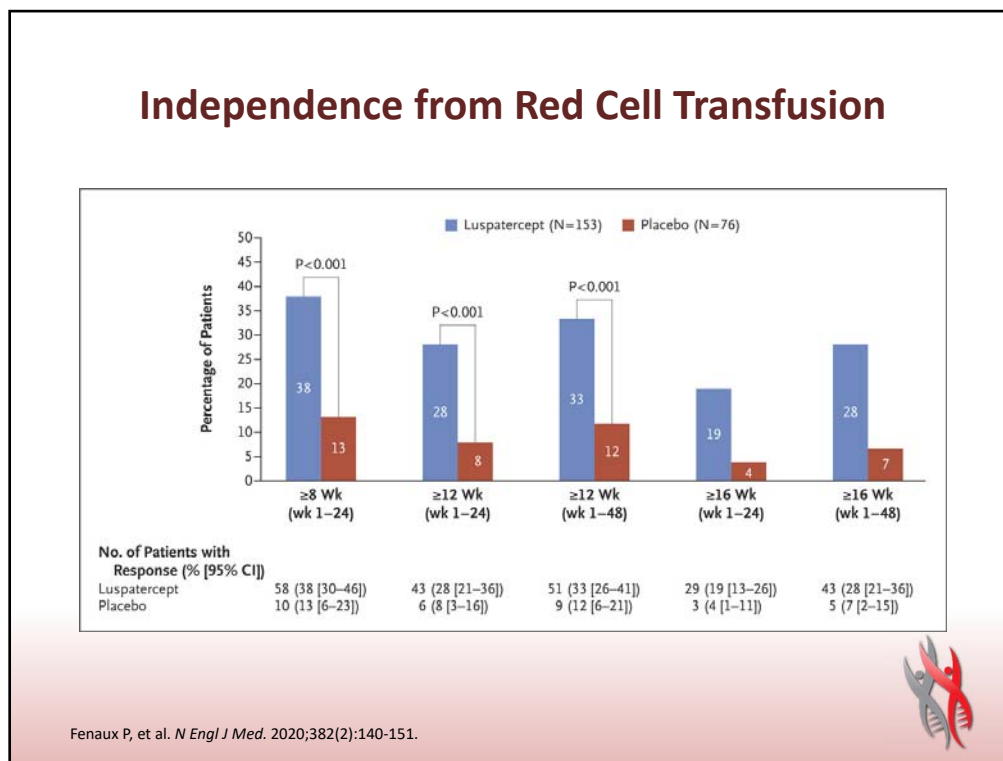
And the study met the primary endpoint at 24 weeks, as well as later on there was higher rate of red blood cell transfusion independency observed with luspatercept compared to placebo. If you look at during the first 24 weeks, it was 38% with luspatercept compared to 13% with placebo, which was the primary endpoint of the study. But if you look at those patients that achieved durable, more than 16 weeks red blood cell transfusion dependency during the 48 weeks on study, 28% was observed with luspatercept compared to 7% with placebo.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MEDALIST Trial
Primary Endpoint: Subgroup Analysis

		Luspatercept, n (%)	Placebo, n (%)	OR (95% CI)	P Value
Overall		58/153 (37.9)	10/76 (13.2)	5.06 (2.28–11.3)	< 0.0001
Average baseline RBC transfusion requirement					
≥ 6 units/8 weeks		6/66 (9.1)	1/33 (3.0)	3.20 (0.37–27.7)	0.2699
< 6 units/8 weeks		52/87 (59.8)	9/43 (20.9)	5.61 (2.40–13.1)	< 0.0001
4 to < 6 units/8 weeks		15/41 (36.6)	1/23 (4.3)	12.7 (1.55–104)	0.0046
< 4 units/8 weeks		37/46 (80.4)	8/20 (40.0)	6.17 (1.95–19.5)	0.0013
Baseline serum EPO (U/L)					
< 100		23/51 (45.1)	7/31 (22.6)	2.82 (1.03–7.71)	0.0413
100 to < 200		14/37 (37.8)	2/19 (10.5)	5.17 (1.04–25.9)	0.0338
200–500		17/43 (39.5)	1/15 (6.7)	9.15 (1.10–76.2)	0.0188
Age group					
≤ 64 years		17/29 (58.6)	3/16 (18.8)	6.14 (1.43–26.3)	0.0108
65–74 years		23/72 (31.9)	4/29 (13.8)	2.93 (0.91–9.41)	0.0635
≥ 75 years		18/52 (34.6)	3/31 (9.7)	4.94 (1.32–18.5)	0.0120
Gender					
Male		32/94 (34.0)	4/50 (8.0)	5.94 (1.96–18.0)	0.0006
Female		26/59 (44.1)	6/26 (23.1)	2.63 (0.92–7.48)	0.0673
Time since initial diagnosis at baseline					
≤ 2 years		14/40 (35.0)	3/19 (15.8)	2.87 (0.71–11.6)	0.1312
> 2–5 years		30/62 (48.4)	4/34 (11.8)	7.03 (2.21–22.3)	0.0004
> 5 years		14/51 (27.5)	3/23 (13.0)	2.52 (0.65–9.83)	0.1756
Baseline IPSS-R risk					
Very Low or Low		48/127 (37.8)	9/63 (14.3)	3.65 (1.65–8.05)	0.0009
Intermediate		10/25 (40.0)	1/13 (7.7)	8.00 (0.89–71.6)	0.0398
Baseline platelet count					
< 100 × 10^9/L		2/8 (25.0)	1/6 (16.7)	1.67 (0.11–24.3)	0.7171
100–400 × 10^9/L		42/128 (32.8)	8/61 (13.1)	3.24 (1.41–7.42)	0.0042
> 400 × 10^9/L		14/17 (82.4)	1/9 (11.1)	37.3 (3.31–422)	0.0006

0   0.1   0.25   0.5   2   10   20   100   1,500
← Favors placebo   Favors luspatercept →

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

And that benefit was observed among all subsets of patients, maybe less in terms of red blood cell transfusion independency in patients that were heavily transfusion dependent or those patients that had thrombocytopenia.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)

Y-axis: Probability of Maintaining RBC-TI (0 to 1.0)
X-axis: Duration of RBC-TI^a (week) (0 to 120)

Legend:
— Luspatercept
— Placebo
— Censored ++

Number of patients

Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

^a During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.
Fenaux P, et al. *N Engl J Med.* 2020;382(2):140-151.

If you look at the responses, those were durable, around 40% of patients on luspatercept maintained red blood cell transfusion independency at one year mark.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Erythroid Response and Increase in Mean Hb Levels

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

* Analysis was based on the proportion of patients meeting the modified criteria for erythroid response (also called hematologic improvement–erythroid) according to International Working Group 2006 criteria[14] sustained over a consecutive 56-day period during the indicated treatment period: for patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks, a transfusion reduction of at least 4 red-cell units per 8 weeks; and for patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks, a mean increase of hemoglobin of at least 1.5 g per deciliter.
† Analysis was based on the number of patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks.
‡ Analysis was based on the number of patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks.
§ Analysis was based on the proportion of patients with an increase from baseline of at least 1 g per deciliter (>14 days after the last red-cell transfusion or within 3 days before the next red-cell transfusion) that was sustained over any consecutive 56-day period in the absence of red-cell transfusions.

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

And if you look at the clinical benefit using the International Working Group hematological improvement criteria, so if you look at those patients that were heavily transfusion dependent with more than six units of blood, although there were less complete red blood cell transfusion independency, however, there was meaningful red blood cell transfusion reduction among that group. And if you look at the patients, particularly that were not heavily red blood cell transfusion dependent with less than four units of blood every eight weeks, we observed an objective increase on the hemoglobin of more than 0.5 g in almost 70% of those patients on luspatercept compared to placebo. So for me suggesting that early intervention using this for patients that are not highly red blood cell transfusion dependent will probably maximize the benefit for our patients.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

MEDALIST Trial: Safety Summary

	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥1 TEAE, n (%)	**150 (98.0)**	**70 (92.1)**
Patients with ≥1 serious TEAE	48 (31.4)	23 (30.3)
Patients with ≥1 Grade 3 or 4 TEAE	65 (42.5)	34 (44.7)
Patients with TEAEs leading to death[a]	5 (3.3)	4 (5.3)
Patients with ≥1 TEAE causing discontinuation, n (%)	**13 (8.5)**	**6 (7.9)**

- TEAEs were balanced between the arms[b]
- Progression to AML occurred in 4 patients (3/153 [2.0%] in the luspatercept arm; 1/76 [1.3%] in the placebo arm)

[a] In luspatercept arm: sepsis (n = 2), multiple organ dysfunction syndrome, renal failure, and hemorrhagic shock; in placebo arm: sepsis, urosepsis, general physical health deterioration, and respiratory failure. [b] The most common grade 3 or 4 TEAEs reported in luspatercept-treated patients were anemia (6.5% of patients), fall (4.6%), and fatigue (4.6%). TEAE, treatment-emergent adverse event.

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

The treatment in general was well tolerated, rarely adverse events led to discontinuation. No safety signals of increased risk of AML was observed on study.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Adverse Events Occurring in at Least 10% of Patients

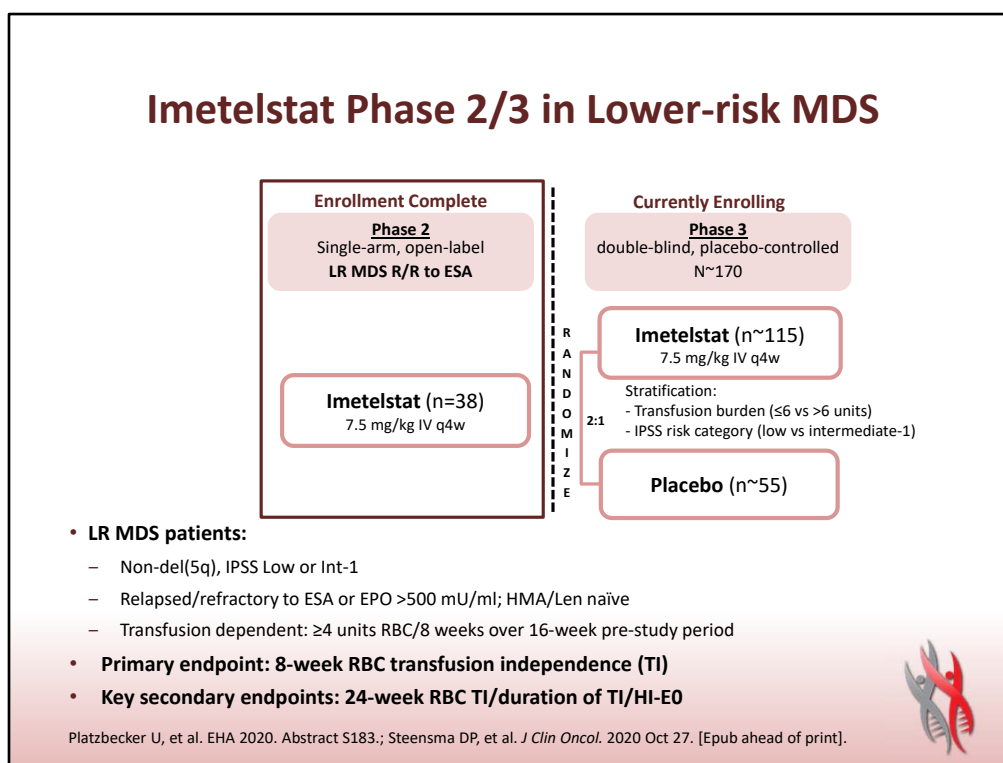**Table 3. Adverse Events Occurring in at Least 10% of Patients.***

Event	Luspatercept (N = 153)		Placebo (N = 76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
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)
Gastrointestinal 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)

* Adverse events during the trial were not adjusted for treatment exposure.
† At least one serious adverse event occurred: nausea (in one patient receiving luspatercept), back pain (in three receiving luspatercept), dyspnea (in one receiving luspatercept), bronchitis (in one receiving luspatercept), and urinary tract infection (in one receiving placebo).

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

The most common observed side effects are typically fatigue, peripheral edema, GI toxicity, musculoskeletal aches, and bone pain. Fatigue is typically observed through the first few rounds, namely cycle one to two and three, and then subsequently decreases as the treatment leads to hematological improvement.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Imetelstat Phase 2/3 in Lower-risk MDS

Enrollment Complete

Phase 2
Single-arm, open-label
LR MDS R/R to ESA

Imetelstat (n=38)
7.5 mg/kg IV q4w

Currently Enrolling

Phase 3
double-blind, placebo-controlled
N~170

RANDOMIZE 2:1

Imetelstat (n~115)
7.5 mg/kg IV q4w

Stratification:
- Transfusion burden (≤6 vs >6 units)
- IPSS risk category (low vs intermediate-1)

Placebo (n~55)

- **LR MDS patients:**
  - Non-del(5q), IPSS Low or Int-1
  - Relapsed/refractory to ESA or EPO >500 mU/ml; HMA/Len naïve
  - Transfusion dependent: ≥4 units RBC/8 weeks over 16-week pre-study period
- **Primary endpoint: 8-week RBC transfusion independence (TI)**
- **Key secondary endpoints: 24-week RBC TI/duration of TI/HI-E0**

Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].

Now, how about other promising agents in lower-risk MDS? This is data on imetelstat, a telomerase inhibitor that had been tested in essential thrombocythemia and myelofibrosis. And it finished a phase two study now published in *Journal of Clinical Oncology* (JCO) recently and started the phase 3 enrollment. This was a study looking at lower-risk MDS patients that were either in relapsed/refractory to ESA or had low chance of response. LEN and HMA naïve and the primary endpoint was transfusion independency.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Baseline Patient Characteristics

Parameters	N = 38
Age, years, median (range)	71.5 (46 – 83)
Male, n (%)	25 (66)
ECOG PS 0-1, n (%)	34 (89)

IPSS risk, n (%)
    Low
    Intermediate-1
	
	24 (63)
	14 (37)

RBC transfusion burden, units/8 weeks, median (range)	**8 (4 – 14)**
4-5 units / 8 weeks at baseline, n (%)	6 (16)
≥6 units / 8 weeks at baseline, n (%)	**32 (84)**

WHO 2001 category, n (%)
    RARS or RCMD-RS
    RA, RCMD or RAEB-1
	
	27 (71)
	11 (29)

Prior ESA use, n (%)	34 (89)
sEPO >500 mU/mL, n (%)	**12 (32)** (from 37 patients with baseline sEPO levels)

Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].

In this study with 38 patients, there was again a bias or enrichment of patients with ring sideroblasts included in this study.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Meaningful and Durable Transfusion Independence (TI) with Imetelstat Treatment

Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	**11 (29)**

[a] Kaplan Meier method; [b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; [c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
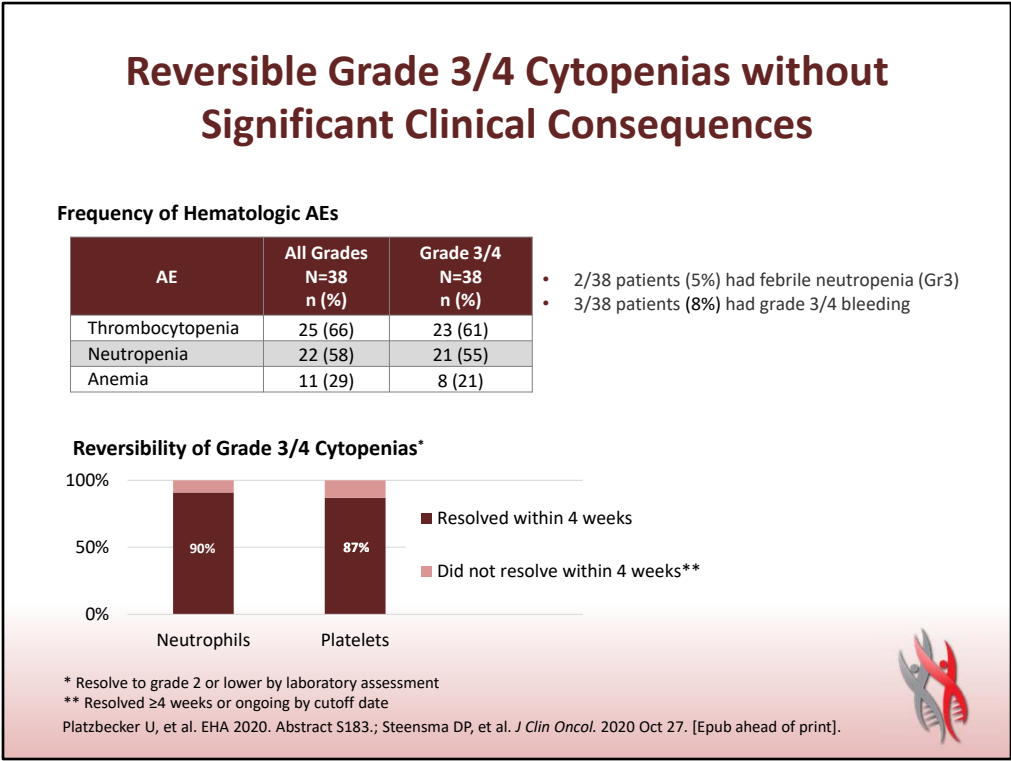CI, confidence interval; Hb, hemoglobin
*Longest TI > 2.7 years

Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].
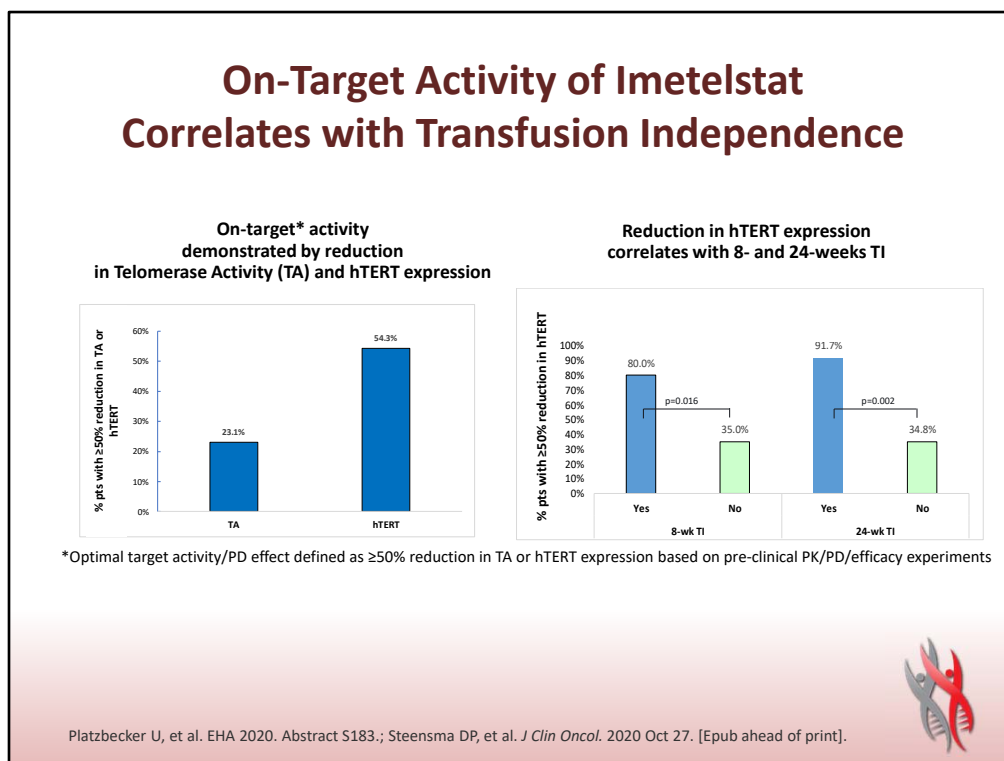
But early promising signal was observed with around 42% of the patients achieving transfusion independency for more than eight weeks. And if you look at one year transfusion independency, around one-third of the patients maintained durable responses with the longest transfusion independency maintained at 2.7 years.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Reversible Grade 3/4 Cytopenias without Significant Clinical Consequences

Frequency of Hematologic AEs

AE	All Grades N=38 n (%)	Grade 3/4 N=38 n (%)
Thrombocytopenia	25 (66)	23 (61)
Neutropenia	22 (58)	21 (55)
Anemia	11 (29)	8 (21)

- 2/38 patients (5%) had febrile neutropenia (Gr3)
- 3/38 patients (8%) had grade 3/4 bleeding

Reversibility of Grade 3/4 Cytopenias*

- Neutrophils: 90%
- Platelets: 87%

■ Resolved within 4 weeks
■ Did not resolve within 4 weeks**

* Resolve to grade 2 or lower by laboratory assessment
** Resolved ≥4 weeks or ongoing by cutoff date
Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].

Treatment in general was well tolerated. Thrombocytopenia and neutropenia, as expected and known from prior studies, was observed in those patients. However, typically subsided and counts recovered back by the time of the subsequent cycle. It's important to note that this is an IV treatment given at a schedule of every four-week cycle.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

On-Target Activity of Imetelstat Correlates with Transfusion Independence

On-target* activity demonstrated by reduction in Telomerase Activity (TA) and hTERT expression

Reduction in hTERT expression correlates with 8- and 24-weeks TI

*Optimal target activity/PD effect defined as ≥50% reduction in TA or hTERT expression based on pre-clinical PK/PD/efficacy experiments

Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].

Also, there's some nice growth of work showing correlation between reduction and hTERT expression, and the transfusion independency observed.

Potential Disease-Modifying Activity with Imetelstat Treatment: Reduction of Malignant Clones Associated with Treatment Response

11 patients had SF3B1 mutations detected at baseline and had paired post-treatment mutation data available:

A. 10/11 had reduction (ranging 10-93%) in SF3B1 variant allele frequency (VAF)

B. The greater reduction of SF3B1 VAF, the longer TI duration patients maintained

C. Significant correlation between greater reduction of SF3B1 VAF and shorter onset time to achieve the longest TI interval (Pearson correlation coefficient r=0.646, P=0.032)

A. Reduction of SF3B1 VAF with Imetelstat treatment
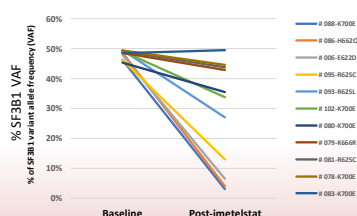
B. Reduction of SF3B1 VAF vs the longest TI duration
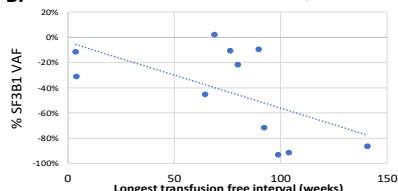
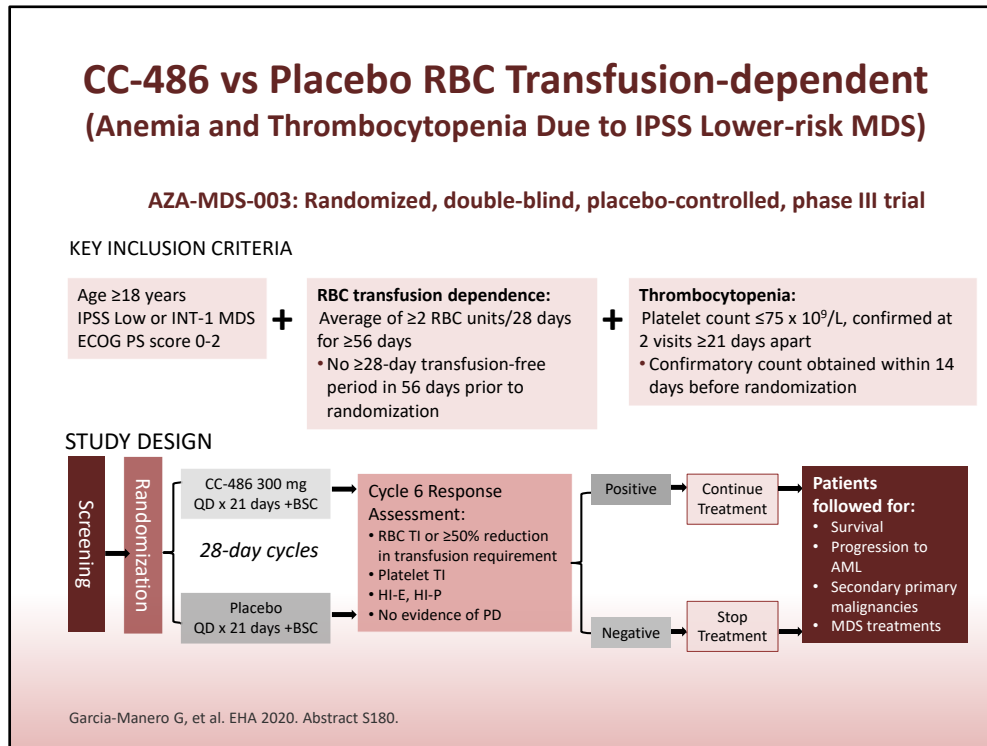**C. Reduction of SF3B1 VAF vs time to the longest TI**

Patient ID	The longest TI interval (weeks)	Time to the longest TI interval start (weeks)	% SF3B1 VAF reduction
200088*	98.9	6.6	-93.3%
200086*	104	4.3	-91.8%
200006	140.9	9.9	-86.4%
200095	92.4	5.4	-71.9%
200093*	64.6	40.7	-45.5%
200102*	4	32.9	-31.2%
200080	79.9	44.1	-21.9%
200079	3.6	20.7	-11.6%
200081*	76.3	12.1	-10.9%
200078*	89.7	23.1	-9.8%
200083*	68.9	37.1	2.0%

*Remain on treatment as of 4 Feb 2020

Platzbecker U, et al. EHA 2020. Abstract S183.; Steensma DP, et al. *J Clin Oncol.* 2020 Oct 27. [Epub ahead of print].

And more interestingly, a very early exploration of potentially disease altering features with the treatment in a small subset of patients, 11 patients, that had SF3B1 mutation, 10 out of those, they observed a reduction in the allele burden, suggesting that this treatment may have a disease-modifying activity. So, we are excited about the phase three ongoing study that hopefully will confirm those early promising results observed in this phase 2 study.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

CC-486 vs Placebo RBC Transfusion-dependent
(Anemia and Thrombocytopenia Due to IPSS Lower-risk MDS)

AZA-MDS-003: Randomized, double-blind, placebo-controlled, phase III trial

KEY INCLUSION CRITERIA

Age ≥18 years
IPSS Low or INT-1 MDS
ECOG PS score 0-2

+

RBC transfusion dependence:
Average of ≥2 RBC units/28 days for ≥56 days
• No ≥28-day transfusion-free period in 56 days prior to randomization

+

Thrombocytopenia:
Platelet count ≤75 x 10^9/L, confirmed at 2 visits ≥21 days apart
• Confirmatory count obtained within 14 days before randomization

STUDY DESIGN

Screening → Randomization

CC-486 300 mg QD x 21 days +BSC

28-day cycles

Placebo QD x 21 days +BSC

→ Cycle 6 Response Assessment:
• RBC TI or ≥50% reduction in transfusion requirement
• Platelet TI
• HI-E, HI-P
• No evidence of PD

Positive → Continue Treatment

Negative → Stop Treatment

Patients followed for:
• Survival
• Progression to AML
• Secondary primary malignancies
• MDS treatments

Garcia-Manero G, et al. EHA 2020. Abstract S180.

The other compounds to discuss obviously are oral hypomethylating agents. Oral decitabine is now approved by the FDA for patients with intermediate- and higher-risk MDS, which is equivalent to using decitabine IV in that population, and it's been looked at in lower-risk MDS patients. Oral azacitidine got approved recently also by FDA for maintenance in AML patients after induction and consolidation for those patients not proceeding to transplant. Dr. Garcia-Manero and his colleagues presented this data at the EHA meeting, the European Hematology meeting, exploring using oral azacitidine in lower-risk MDS patients. The patients that were selected had higher-risk features with concomitant thrombocytopenia, had to be red blood cell transfusion dependent, and the schedule of oral azacitidine was 300 mg for three weeks while the approved schedule for oral azacitidine in AML maintenance studies, for example, for two weeks, so it's a different schedule. And it's important to note that oral azacitidine is different from subcutaneous or IV azacitidine, so they are not interchangeable because of different pharmacokinetics of the two compounds.

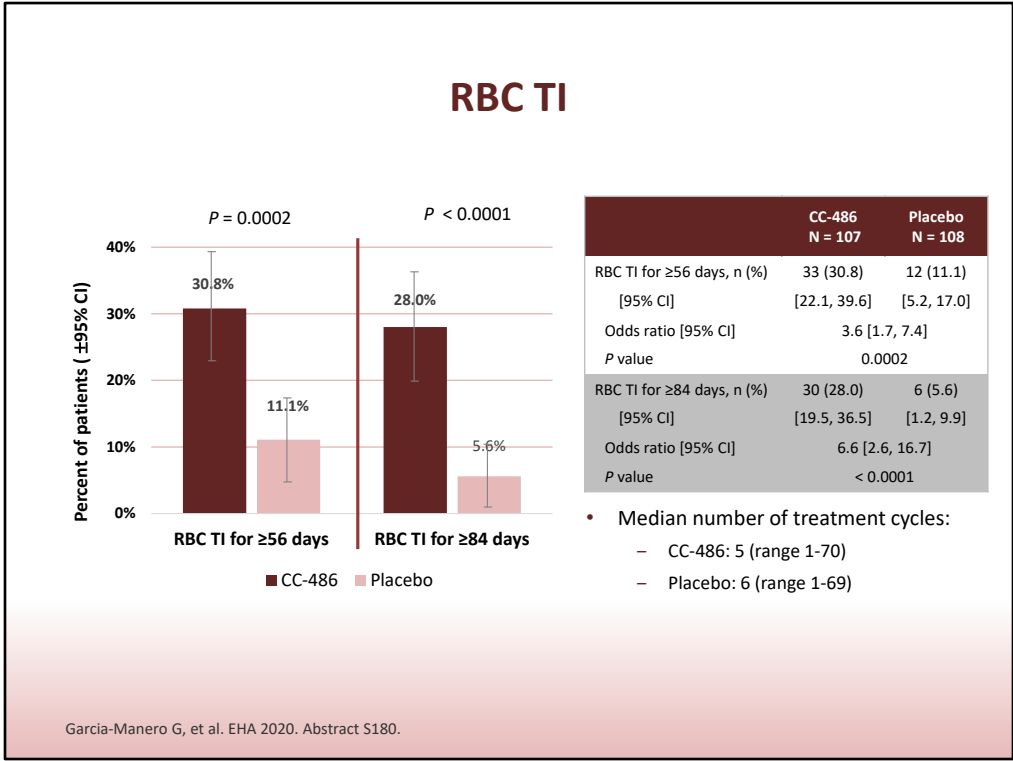# Treatment Protocols for Patients with Symptomatic Low-risk MDS

Baseline Characteristics

	CC-486 N = 107	Placebo N = 109		CC-486 N = 107	Placebo N = 109
	n (%) / median (range)			n (%) / median (range)	
Age (years)	74 (30-89)	73 (44-88)	IPSS cytogenetic risk		
Male sex	79 (74)	79 (72)	Good	87 (81)	90 (83)
ECOG PS 0-1	91 (85)	94 (86)	Intermediate	17 (16)	14 (13)
Time since diagnosis (months)	18.9 (0.9-153)	16.1 (0.4-381)	IPSS-R risk		
			Very Low/Low	24 (22)	21 (19)
WHO MDS classification			Intermediate	51 (48)	48 (44)
RCMD	80 (75)	73 (67)	High/Very High	28 (26)	33 (30)
RAEB-1	17 (16)	29 (27)	RBC units transfused/28 days	3.3 (1.3-10)	3.3 (1.3-9.5)
			>4 units/28 days	36 (34)	34 (31)
IPSS risk			Bone marrow blasts, %	3 (0-9)	3.5 (0-9)
Low	0	0	Hemoglobin, g/dL	8.3 (5.4-11)	8.1 (5.7-10)
Intermediate-1	106 (99)	109 (100)	Platelets, 10^9/L	24 (5-66)	25 (5-73)
Prior lenalidomide	5 (5)	5 (5)	ANC, 10^9/L	1.4 (0.1-25)	1.3 (0.1-20)

Garcia-Manero G, et al. EHA 2020. Abstract S180.

In this study again, lower-risk MDS patients, but with higher-risk features, were included.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

The study showed a meaningful transfusion independency in around 30% of the patients.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

Safety

Adverse events (all grades) reported in ≥30% of patients in either arm	CC-486 N = 107	Placebo N = 109
	n (%)	
Nausea	81 (76)	25 (23)
Diarrhea	73 (68)	25 (23)
Vomiting	67 (63)	10 (9)
Neutropenia	54 (50)	16 (15)
Constipation	51 (48)	24 (22)
Pyrexia	36 (34)	18 (17)

Grade 3-4 adverse events reported in ≥10% of patients in either arm	CC-486 N = 107	Placebo N = 109
	n (%)	
≥1 grade 3-4 AE	96 (90)	80 (73)
Neutropenia	50 (47)	13 (12)
Thrombocytopenia	31 (29)	17 (16)
Febrile neutropenia	30 (28)	11 (10)
Anemia	20 (19)	18 (17)
Pneumonia	13 (12)	10 (9)

- Treatment interruption due to AEs: CC-486 62%, placebo 37%
- Dose reduction due to AEs: CC-486 29%, placebo 4%
- Treatment discontinuation due to AEs: CC-486 30%, placebo 28%
- Treatment-related AEs more common with CC-486, occurred mostly during early treatment cycles

Garcia-Manero G, et al. EHA 2020. Abstract S180.

However, there was excessive febrile neutropenia and early mortality on the oral azacitidine arm. I think what we learned from this study is that dosing is not going to be the optimal dosing for patients with lower-risk MDS, and we still have further to work on finding the optimal dosing of hypomethylating agent to be used in lower-risk MDS patients.

Treatment Protocols for Patients with Symptomatic Low-risk MDS

National Comprehensive Cancer Network. Myelodysplastic syndromes. Version 1.2021. September 11, 2020.
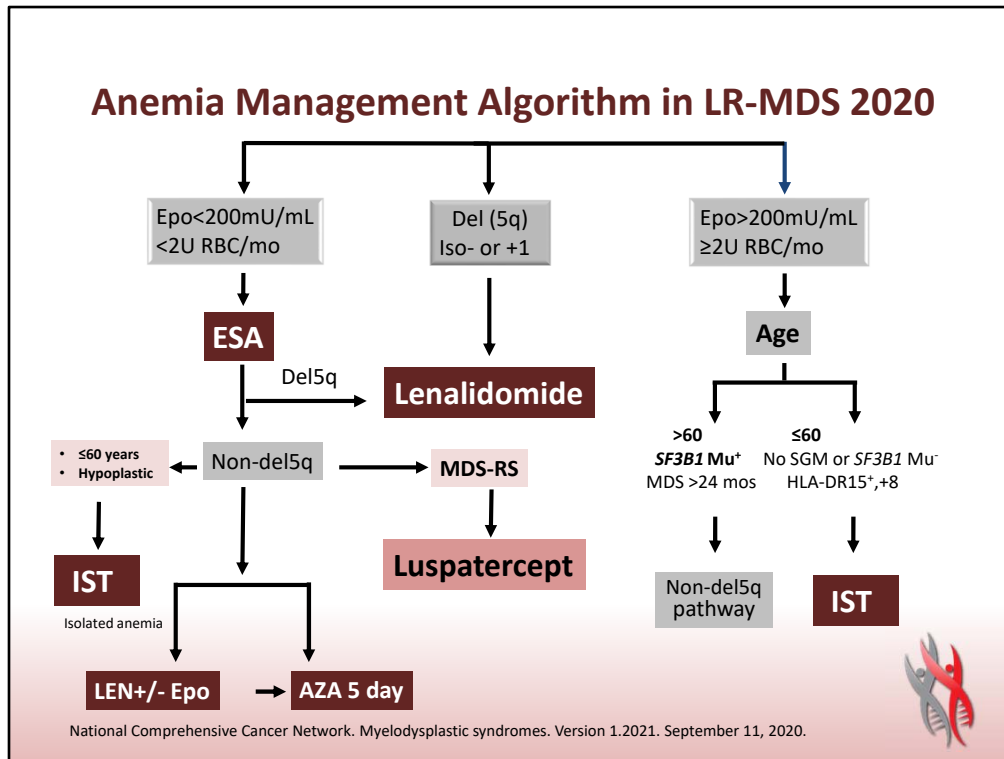
So, I will end just putting all this in context of what we do today or how we manage lower-risk MDS patients. As I said, the first question we ask, do the patients need treatment if they are lower risk? If patients have mild anemia asymptomatic, then they don't need treatment. There is typically no magic threshold to start treatment for anemia. Most clinicians, when hemoglobin is nine or below would start treatment to prevent transfusion dependency. We rarely will be treating for thrombocytopenia or neutropenia, but as I said their presence sometimes could dictate the choice of treatment. If patients are anemic, not heavily transfusion dependent with low endogenous serum EPO level, we start with erythroid-stimulating agents. If they are responding, we continue, at time of failure whether it's primary or secondary. If patients have deletion 5q, then the standard of care for those patients is lenalidomide. Nowadays, if patients have ring sideroblasts, the standard of care after ESA failure is luspatercept. In selected patients, if they are young and have early disease, no SF3B1, immunosuppressive therapy with ATG cyclosporine could be an option, particularly for patients with bi- or trilineage cytopenias. In other patients, if we're just treating anemia, non-del 5q, non-ring sideroblasts, there is a subset of patients with isolated anemia that we can use lenalidomide erythropoietin. And finally, hypomethylating agents currently at five days azacitidine but hopefully moving to three days regimens as well as to oral hypomethylating agents down the road are still part of the treatment options for our patients with lower-risk MDS.

Thank you for listening, and hope you enjoyed this brief overview of how I manage lower-risk MDS patients.