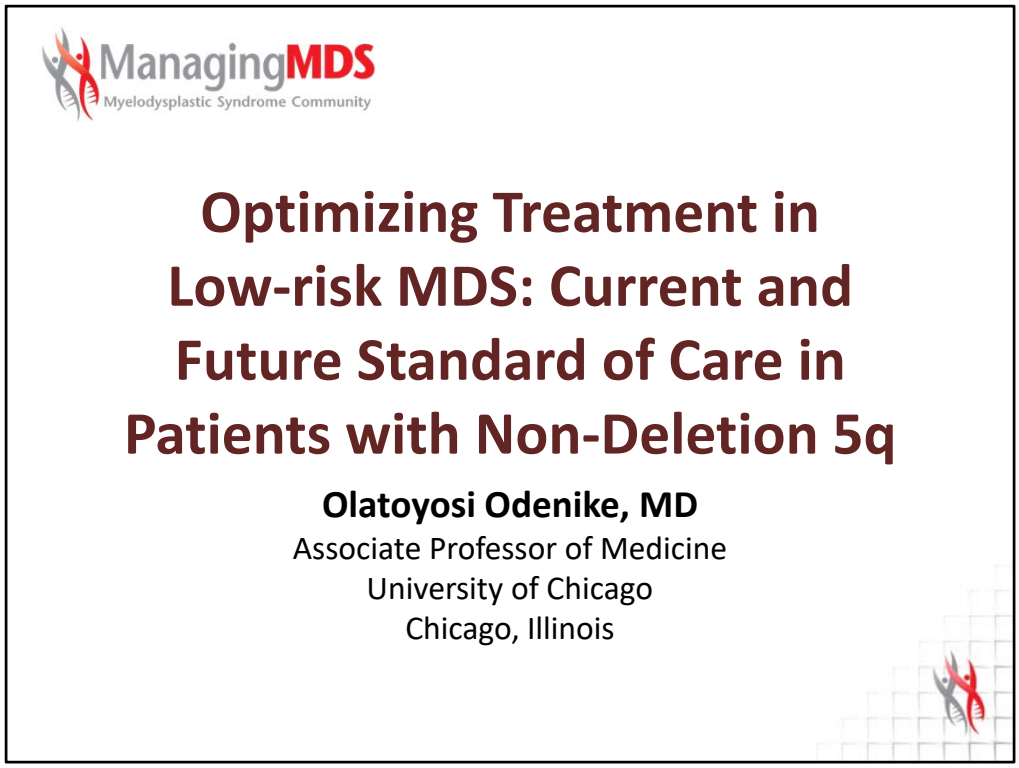
Optimizing Treatment in Low-risk MDS: Current and Future Standard of Care in Patients with Non-Deletion 5q



Welcome to *Managing MDS*, I am Dr. Toyosi Odenike. Today I will review optimizing treatment in lower-risk MDS, including the current and future standard of care in patients with non-deletion 5q. In this presentation, I will summarize the treatment goals and practice challenges associated with lower-risk MDS patients with non-del(5q), outline the treatment approach and current standard of care in low-risk MDS with non-del(5q), and describe recent advances and future directions in this patient population.

Disclosures

- Research Support: Abbvie, Agios, Astex, Celgene, CTI/Baxalta, NS-Pharma, Janssen, Incyte
- Consultant: Abbvie, CTI/Baxalta, Dava Oncology, Jazz Pharmaceuticals, Pfizer
- Committee Member: ABIM

These are my disclosures.

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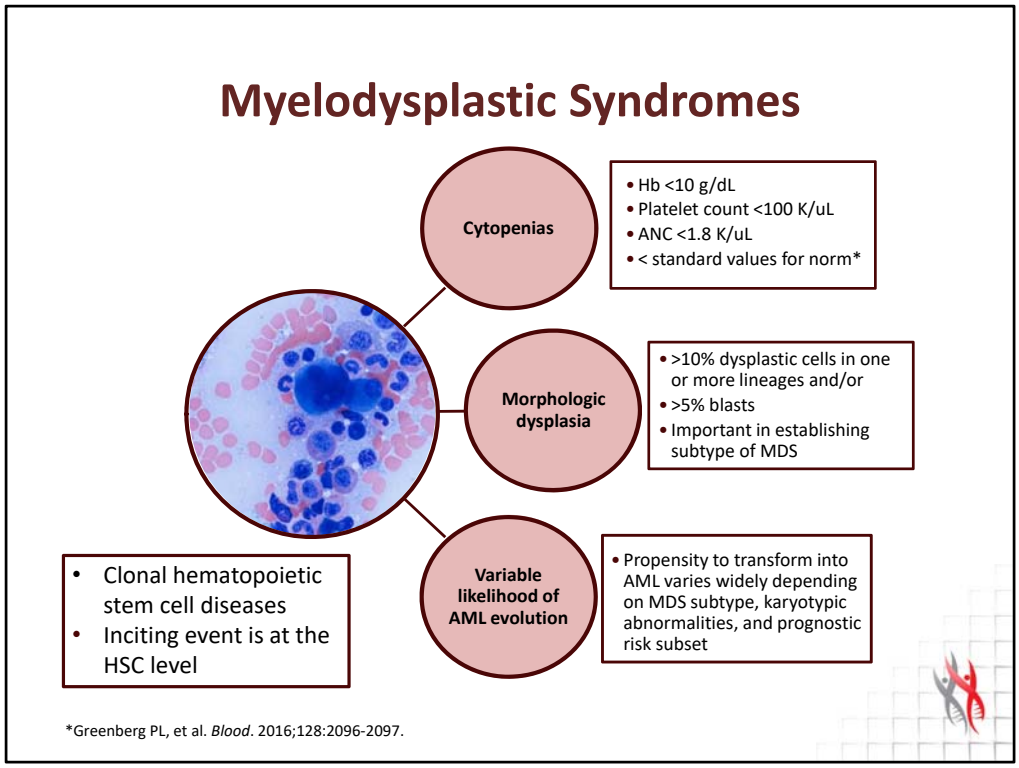

To put this talk in context, I'd like to provide a brief overview of myelodysplastic syndromes including our approach to risk stratification. Myelodysplastic syndromes are clonal hematopoietic stem cell diseases characterized by cytopenias, morphologic dysplasia, and a variable likelihood of AML evolution. The propensity to transform into acute myeloid leukemia varies widely depending on the MDS subtype, karyotypic abnormalities, and prognostic risk subset. We believe that the inciting event that propels these groups of diseases is at the level of the hematopoietic stem cell.

Evolving Classification of MDS

2016 Revision to the WHO Classification of MDS
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS) • MDS-RS and single lineage dysplasia • MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition

Arber DA, et al. *Blood*. 2016;127:2391-2405.

The classification of MDS has evolved over time. The most recent iteration is the 2016 revision to the WHO classification of MDS which subcharacterizes MDS into the various morphologic subtypes shown. One exception is MDS with isolated deletion 5q, which refers to patients with MDS who have deletion 5q as a sole abnormality, or have just one additional karyotypic abnormality. These will not be the focus of today's presentation.

Why Risk Stratify?

- Clinically and molecularly heterogeneous disease
- Outcomes vary substantially
  - Even within same morphologic subtypes
- Risk stratification facilitates tailoring of therapeutic interventions

So why do we risk stratify patients with MDS? We do this because these disorders are clinically and molecularly heterogeneous, and outcomes vary widely even within the same morphologic subtypes. Risk stratification facilitates tailoring of therapeutic interventions and also helps in assignment of patients to clinical trials.

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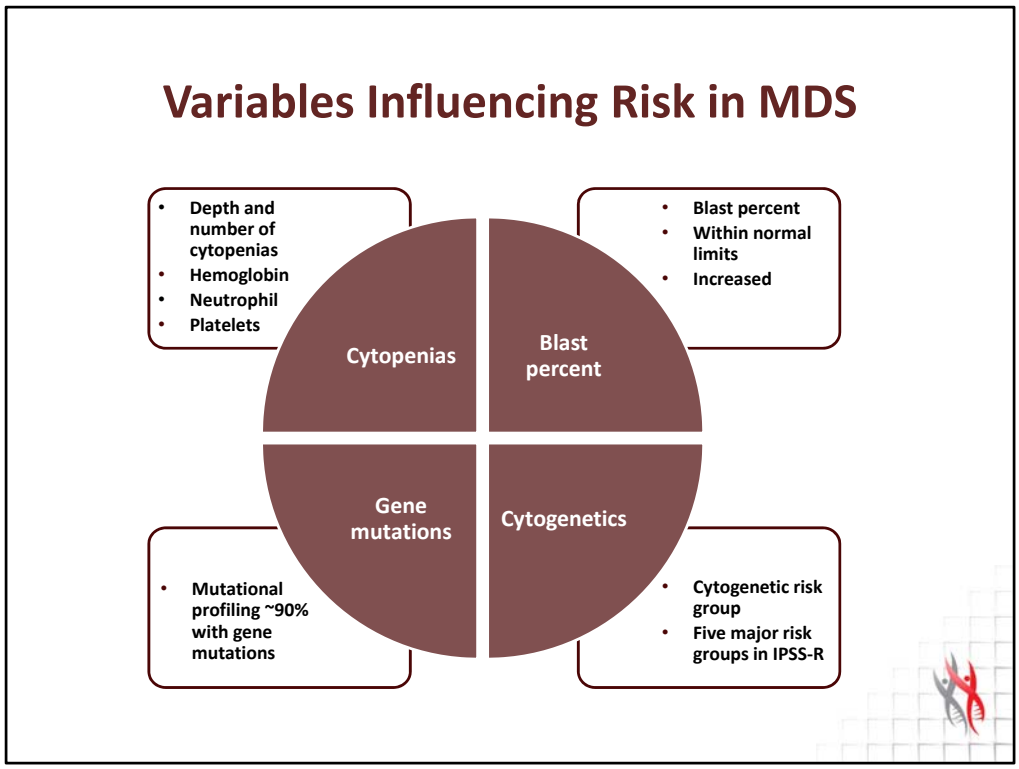

What are the variables influencing risk in MDS? These include the depth and number of cytopenias, the blast percentage as assessed by the morphologic review of the bone marrow, and bone marrow metaphase cytogenetics (this is crucial in the assessment of any patient with a presumed diagnosis of MDS). In this era, we are increasingly applying mutational profiling. Although only approximately half of patients with MDS will have a cytogenetic abnormality, approximately 90% will have gene mutations which we are now starting to understand have both prognostic significance and perhaps will ultimately have therapeutic implications.

IPSS-R: Prognostic Variables and Score Values

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

BM=bone marrow; ANC=absolute neutrophil count
Greenberg P, et al. *Blood.* 2012;120(12):2454-2465.

The most contemporary prognostic scoring system today is the IPSS-R which incorporates the prognostic variables shown, and the respective score values assigned are shown on the slide. In this regard, cytogenetics, bone marrow blast percent, and the depth of cytopenias are the variables that go into factoring the individual risk score.

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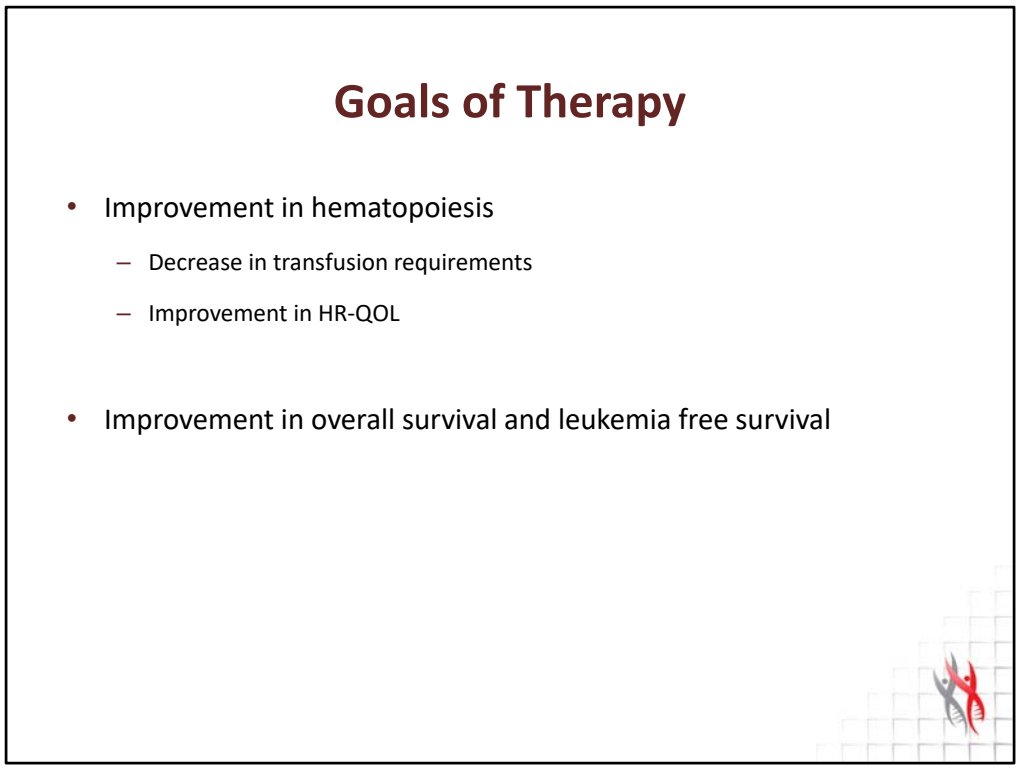
Stratification Based on IPSS/IPSS-R

	Score	Risk Group	Median Survival in Years	
IPSS (N=816)	0	Low	5.7	Score=0 to 1.0: Lower-risk MDS
	0.5-1.0	Intermediate-1	3.5	
	1.5-2.0	Intermediate-2	1.2	
	≥2.5	High	0.4	

	Points	Risk Score	Median Survival in Years	
IPSS-R (N=7,012)	≤1.5	Very Low	8.8	*Score=<3.5: Lower-risk MDS
	>1.5-3	Low	5.3	
	>3-4.5	Intermediate	3.0	
	>4.5-6	High	1.6	
	>6	Very High	0.8	

Adapted from: Greenberg P, et al. *Blood.* 1997;89(6):2079-2088.; Schanz J, et al. *Blood.* 2012;30:820.; *Pfeilstocker M, et al. *Blood.* 2016;128:902-910.

Previously we employed the IPSS which stratifies patients into the risk groups shown. I bring up the IPSS in this context because several of the clinical trials and approaches that I will present in the context of this talk still employ the IPSS. The IPSS-R is more discriminant and has been widely validated. For the purposes of my talk, lower-risk MDS is referred to as either low or intermediate-1 by the IPSS, or very low and low risk by the IPSS-R. A few patients with intermediate risk in the IPSS-R may also be included, so generally patients with an IPSS-R score of less than 3-1/2 will be considered to have lower-risk MDS.



What are the goals of therapy in MDS? These include improvement in hematopoiesis since cytopenias and complications related to cytopenias are a hallmark of this disease. We would also hope that therapies could lead to improvement in overall survival and leukemia-free survival. That obviously is an ongoing challenge in this disease.

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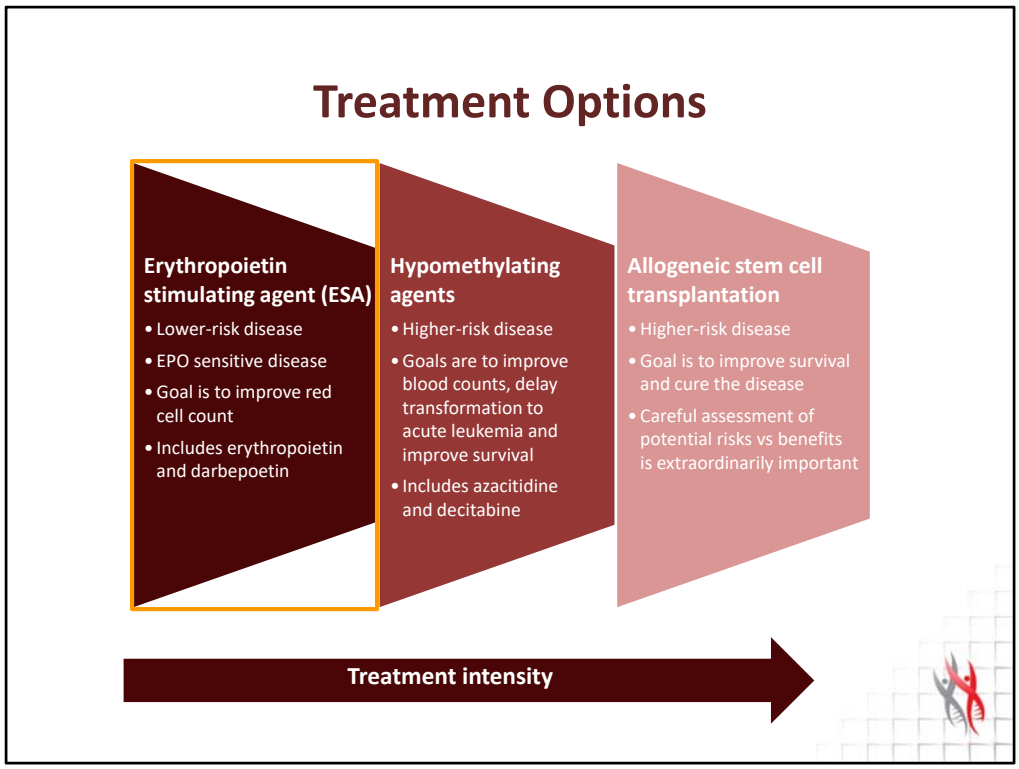

What are the treatment options? Well, they range from erythropoietin-stimulating agents for lower-risk disease, to hypomethylating agents for higher-risk disease, to allogeneic stem cell transplantation also for higher-risk disease. Of course, the treatment intensity increases from one end of the spectrum to the other; and a careful balance of risk versus potential benefits is important in terms of individualizing therapies in this disease. In lower-risk disease, a cornerstone of treatment is the use of erythropoietin-stimulating agents where the goal is to improve red blood cell counts.

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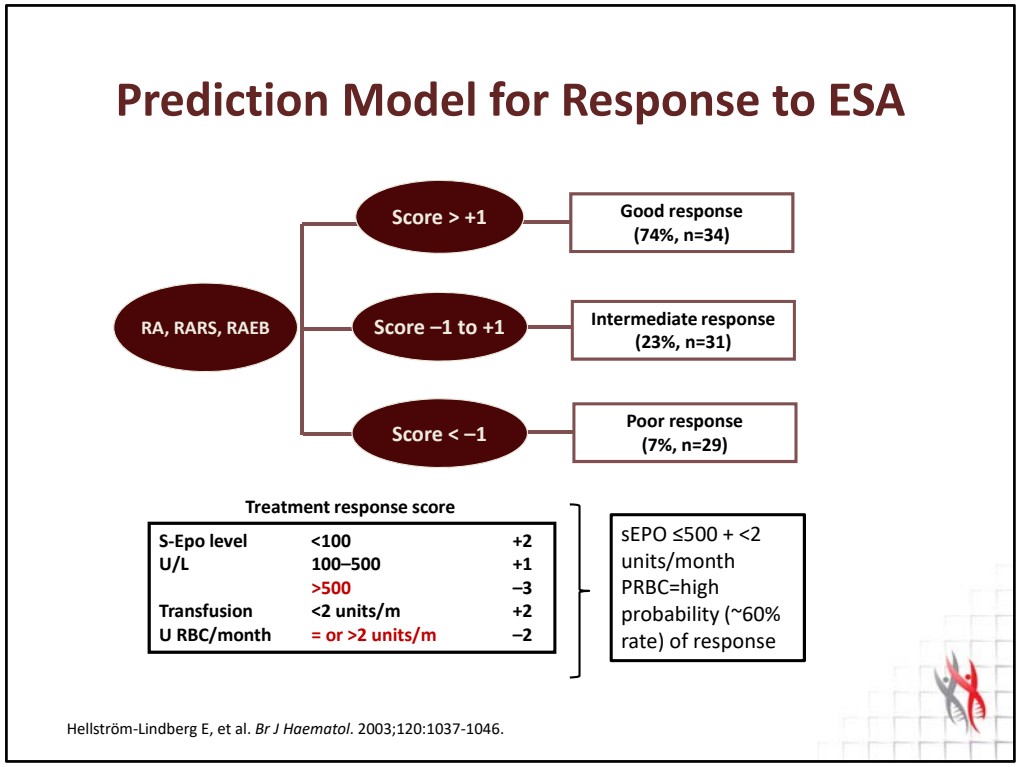

As we think about the individual patient with lower-risk disease whose predominant problem is anemia, one important question as we consider or recommend the use of ESAs is to try to figure out what the likelihood of response of that individual would be to an erythropoietin-stimulating agent. In this regard, we know that an endogenous erythropoietin level of over 500, or higher transfusion burden of more than two units per month, would be associated with a very low likelihood (less than 10%) of response. Therefore, the ideal candidate for ESA therapy in lower-risk disease would be one who has a low endogenous erythropoietin level and who also has a relatively low transfusion burden at baseline. Those patients will have response rates approaching 60% or above.

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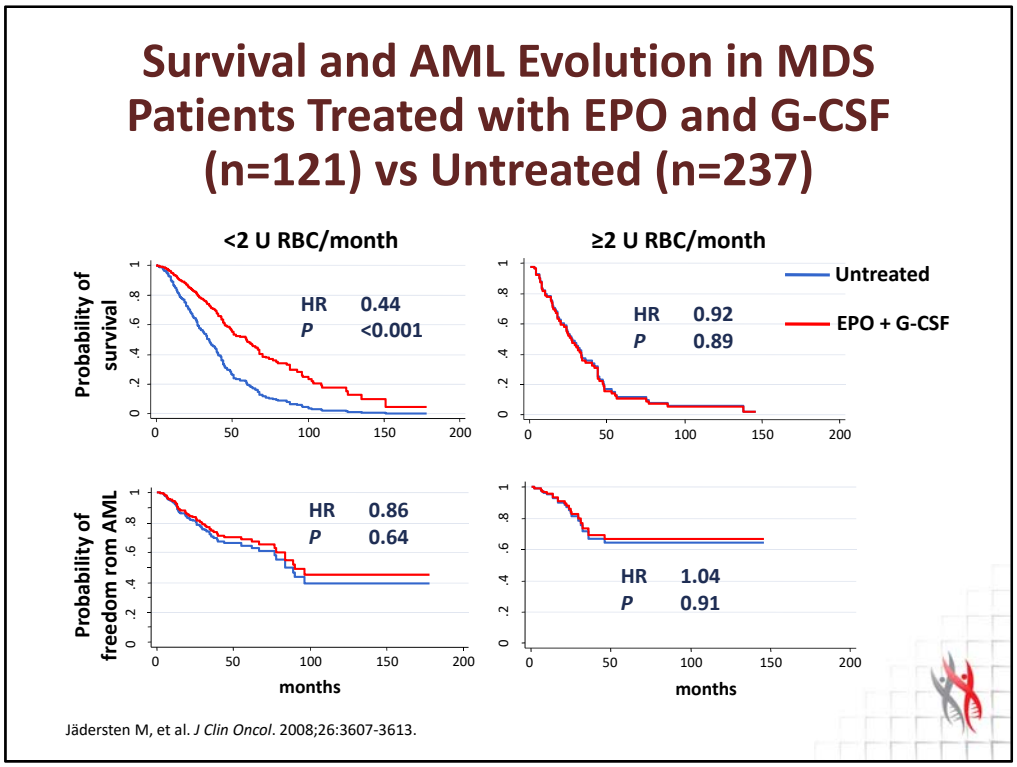

One potential concern with the use of growth factors, including both erythropoietin and G-CSF in patients with MDS who are cytopenic is the potential for acceleration to acute myeloid leukemia. As you may know, erythropoietin-stimulating agents for a long time had carried a black box warning in patients who have various malignancies. While we know that in MDS, if you have a low transfusion burden, erythropoietin-stimulating agents are actually associated with an improvement in survival – or a trend towards an improvement in survival – when compared with untreated matched controls; and that there is no evidence whether in lower transfusion burden at baseline or in those with a higher transfusion burden at baseline that these agents either impair survival or accelerate transformation to acute leukemia. Therefore, we know there is no reason to be particularly concerned about that.

What are the treatment options in ESA-refractory or resistant lower-risk MDS? Since approximately half or more patients with lower-risk disease will end up being either ineligible for ESAs because of high baseline EPO level; or they get exposed to ESAs but after a 12-week trial are found to be refractory or resistant, what are the options in this patient population?

Lenalidomide in Lower-risk MDS

- Immunomodulatory agent with pleiotropic effects
- Significant activity in MDS with del(5q)[1,2]
  - Red cell transfusion independence rate of 67%
  - Sensitivity linked to haploinsufficiency of CSKN1 in commonly deleted region of 5q[3]
- FDA-approved for use in MDS associated with del(5q)
- Activity in non-del(5q) is modest[4]

[1]List A, et al. *N Engl J Med*. 2005;352(6):549-557. [2]Fenaux P, et al. *Blood*. 2011;118(14):3765-3776.
[3]Kronke J, et al. *Nature*. 2015;523(7559):183-188. [4]Raza A, et al. *Blood*. 2008;111(1):86-93.

Lenalidomide has been widely investigated in lower-risk MDS. This is an immunomodulator agent, a thalidomide analog with pleotropic effects, and has significant activity in MDS with del(5q) where it is FDA-approved for that indication. The activity in non-del(5q) MDS, on the other hand, is relatively modest; and this was seen early on in single-arm phase 2 trials.

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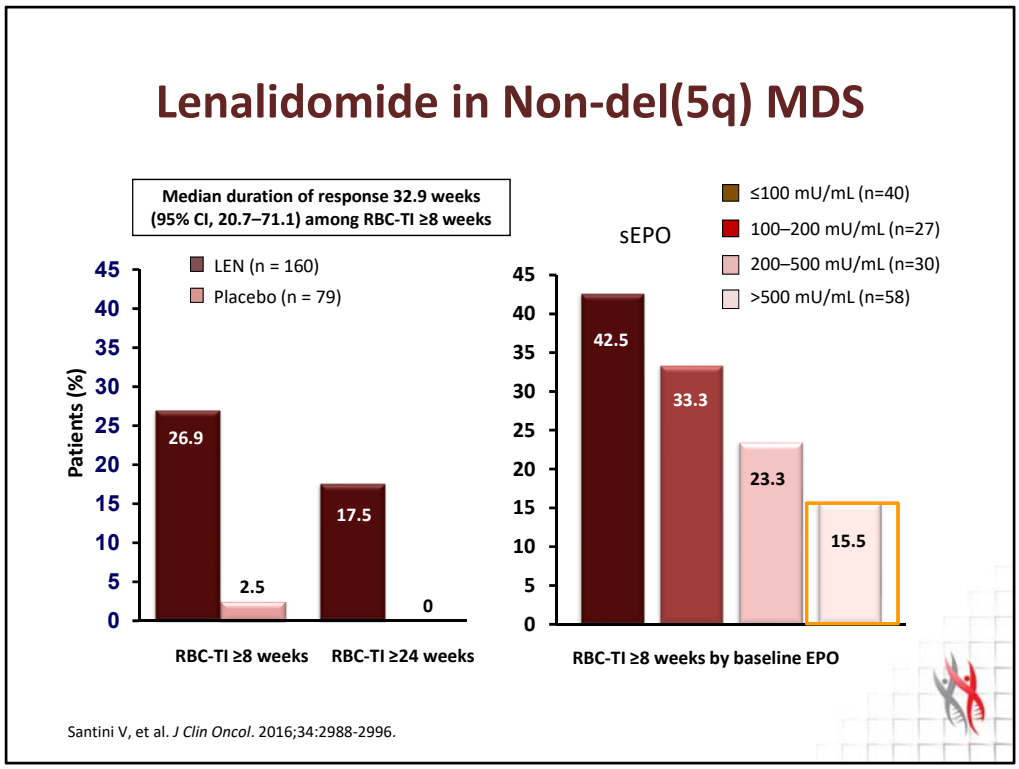

The need for other approaches in patients who are ESA-refractory or resistant has fueled further investigation of lenalidomide in this patient population. It is now being investigated in the phase 3 setting in transfusion-dependent lower-risk patients with non-del(5q) MDS. In this setting, you can see that compared with placebo, the use of lenalidomide was associated with an approximately 27% transfusion-independent rate. Of note, patients who had a baseline erythropoietin level of over 500 were the least likely to respond, emphasizing that this patient population continues to be an area of ongoing unmet need in terms of strategies to try to improve hematopoiesis in this class of patients.

Lenalidomide + EPO in Transfusion Dependent ESA Refractory Non-del(5q) Lower-risk MDS

Variable	Lenalidomide + EPO (n=66)	Lenalidomide (n=66)	*P*-value
HI-E	39.4%	23.1%	*P* = .044
RBC-TI	24.2%	13.8%	*P* = .13
Median duration of response	15.1	18.1	*P* = .47

HI-E=hematologic improvement in erythroid lineage; RBC-TI=red blood cell transfusion independent

North American Intergroup study-E2905 (accrual complete): Randomized phase III trial comparing the frequency of major erythroid response to treatment with lenalidomide alone and in combination with epoetin alfa in subjects with low- or intermediate-risk MDS and symptomatic anemia

Toma A, et al. *Leukemia.* 2016;30:897-905.

Another approach that has been evaluated is the addition of erythropoietin to lenalidomide in transfusion-dependent ESA-refractory non-del(5q) lower-risk MDS. In this regard, the addition of erythropoietin was associated with a modest improvement in erythroid response as shown; but there was no evidence of a significant improvement in either transfusion independence or in the median duration of response. Currently there is a North American Intergroup study evaluating the same approach and focused on patients who are ESA-refractory or who are considered ineligible for ESAs and who have symptomatic anemia.

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Low-dose Hypomethylating Agents in LR-MDS

Response	DAC (N=70) n (%)	AZA (N=39) n (%)	*P*
CR	26 (37)	14 (36)	0.90
mCR	6 (9)	2 (5)	
HI	17 (24)	3 (8)	

Median number of cycles: 9 (range: 1-41)

Decitabine 20 mg/m^2 IV D1-3 every 4 weeks, ORR (CR+HI)=54%
Azacitidine 75 mg/m^2 SC D1-3 every 4 weeks, ORR (CR+HI)=44%

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

What about low-dose hypomethylating agents in lower-risk MDS? That has been recently looked at and was just published, evaluating lower-dose intensity of decitabine and azacitidine. Decitabine is generally given for five days and azacitidine for seven days, when we are using standard doses and schedules. This is often focused on higher-risk MDS; but in this study, the focus was on patients with lower-risk MDS. You can see that these agents are associated with an overall response rate roughly in the 50% range, so this is an approach that is useful to consider in those who are ESA-refractory or ineligible for ESA therapy.

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Immunosuppressive Therapy in MDS

Variable	ATG +CSA (n=45)	BSC (n=43)	*P*-value
Hematologic response CR+PR (%)	29	9	0.016
Median duration of response (months)	16.4	NA	
2-year survival (%)	49	63	0.83
2-year transformation-free survival (%)	46	55	0.73

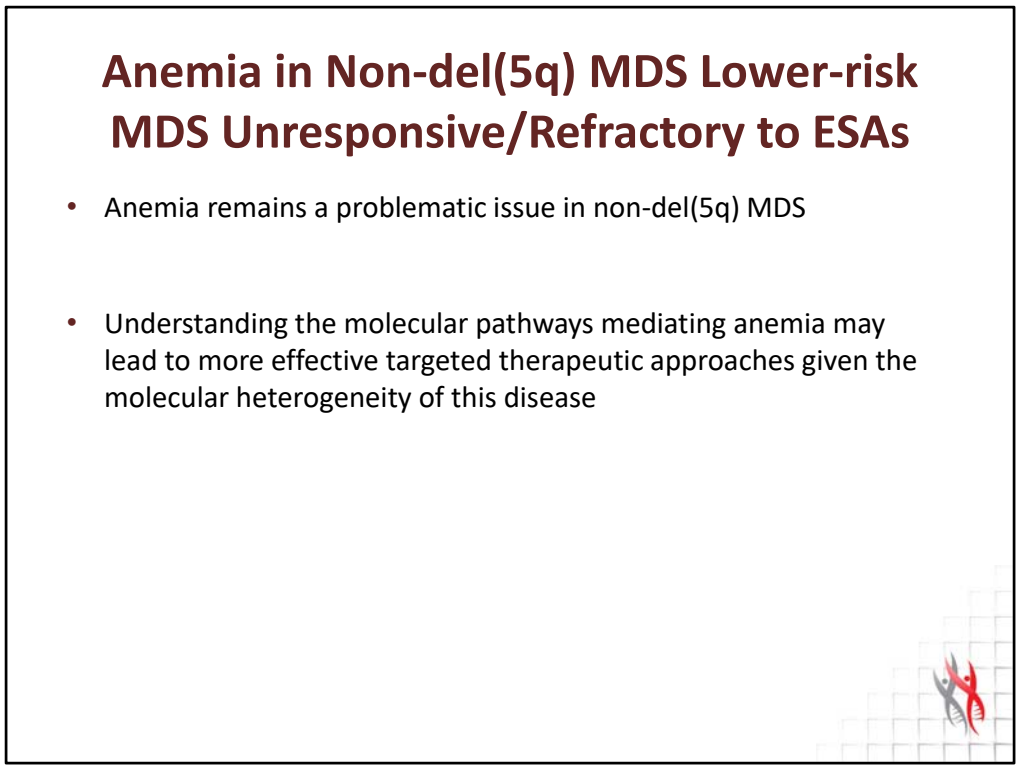
Hypocellular marrow was strongest predictor of outcome, response rate=50% in that subgroup of patients

Passweg JR, et al. *J Clin Oncol*. 2011;29:303-309.

Immunosuppressive therapy has been investigated widely in MDS but generally in small, uncontrolled studies. This study, however, randomized patients to ATG and cyclosporine versus best supportive care. The majority of the patients with MDS enrolled had lower-risk disease. As you can see, the use of ATG and cyclosporine was associated with a hematologic response rate of about 29% and this was significant. Unfortunately, there was no impact on overall survival or transformation-free survival. It is an ongoing question of who is the ideal candidate for immunosuppressive therapy in MDS, and what are the best predictors of that. In this study, hypocellular marrow was the strongest predictor of outcome and the response rate in that context was about 50% in that subgroup of patients; so this is a worthwhile approach to consider in patients with hypocellular MDS, particularly the ESA-ineligible or ESA-refractory.

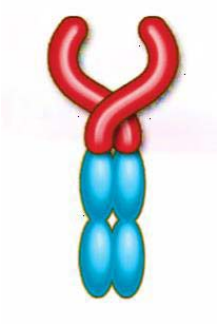
Novel Agents for the Treatment of Anemia in Lower-risk MDS

So far, you can see that the issue of finding good approaches for ESA-refractory or ESA-ineligible patients with lower-risk MDS remains an ongoing problem.



It is possible that understanding the molecular pathways mediating anemia in this patient population may lead to more effective targeted therapeutic approaches.

Luspatercept (ACE-536)



- Modified activin receptor type IIB (ActRIIB) fusion protein
  - Binds TGF beta ligands and modulates TGF beta signaling pathway
- TGFB signaling is linked to ineffective erythropoiesis in MDS
- Early phase clinical trials demonstrate potential for anemia improvement in MDS
- Larger clinical trials in lower-risk MDS would be worthwhile

Attie KM, et al. *Am J Hematol*. 2014;89:766-770.; Suragani RN, et al. *Nat Med.* 2014;20:408-414.

Along those lines, there is now an interesting group of agents which are the activin receptor type IIB fusion proteins. These bind TGF-β ligands and modulate TGF-β signaling (TGF-β signaling has been linked to ineffective erythropoiesis in MDS). The murine analog of luspatercept has been shown to be effective in murine models of the disease, and there are now early-phase trials that are demonstrating the potential for anemia improvement in MDS which is fueling the development of larger clinical trials in this patient population.

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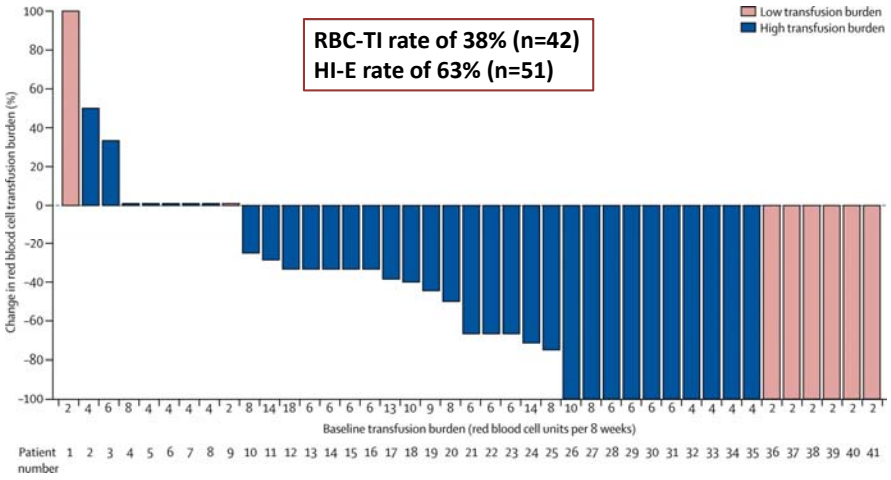
Luspatercept in LR-MDS (PACE-MDS): Change in Red Cell Transfusion Burden



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

The PACE-MDS trial is an ongoing early-phase trial in lower-risk MDS, which so far has shown a transfusion-independent rate of about 38% in this patient population, and a hematologic improvement in the erythroid lineage of 63%. As you can see from this waterfall plot, this agent was effective both in low transfusion burden and high transfusion burden lower-risk MDS.

HI-E Response Rates to Luspatercept by Baseline EPO Level/RS Status

Patients Treated at Doses ≥0.75 mg/kg

Response Rates	IWG-HI-E, n/N (%) (N=99)	RBC-TI, n/N (%) (N=67)
All patients	52/99 (53)	29/67 (43)
ESA-naïve	28/53 (53)	17/31 (55)
Prior ESA	24/46 (52)	12/36 (33)
RS Status		
RS+	40/62 (65)	22/42 (52)
Non-RS	12/35 (34)	7/23 (30)
Unknown	0/2 (0)	0/2 (0)
Baseline EPO <200 U/L		
RS+	25/39 (64)	16/24 (67)
Non-RS	7/13 (54)	3/7 (43)
Baseline EPO 200-500 U/L		
RS+	10/14 (71)	4/9 (44)
Non-RS	4/8 (50)	3/5 (60)

RS=ring sideroblasts

Platzbecker U, et al. *Lancet Oncol.* 2017;18:1338-1347.; Platzbecker U, et al., ASH poster 2982.

In addition, both ESA-naïve patients as well as those who had had prior ESA exposure had an equal likelihood of responding. Individuals who had ring sideroblast morphology appeared to have heightened sensitivity to therapy with luspatercept, although you can see that even those who did not have ring sideroblast morphology also had a decent likelihood of response.

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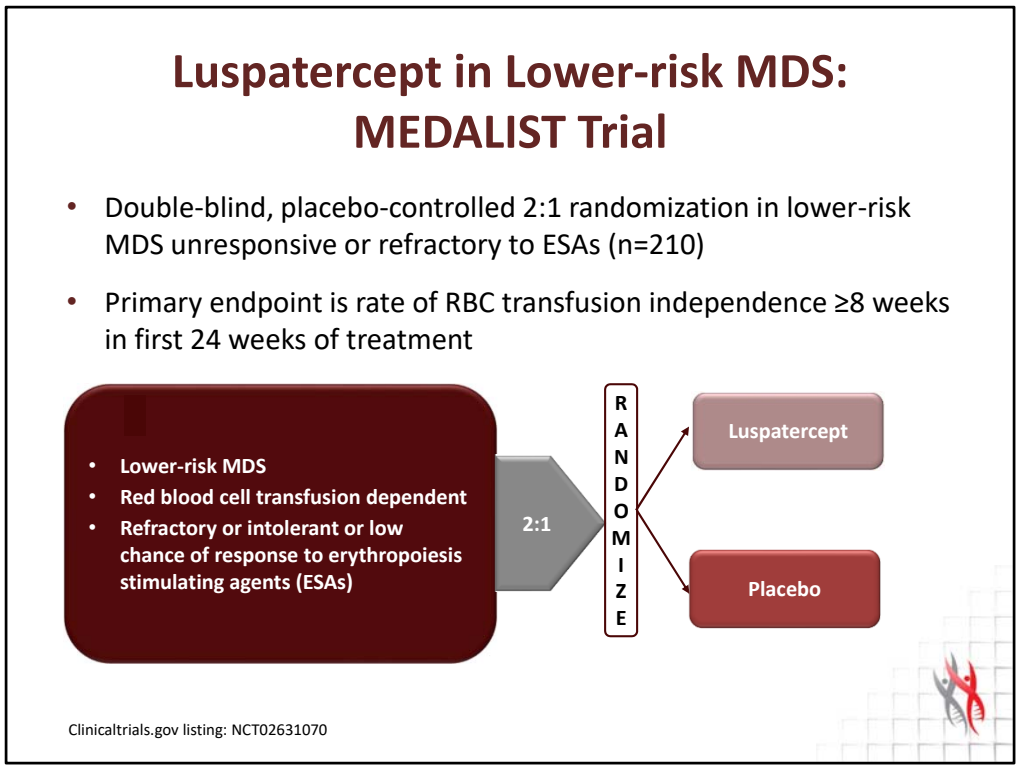


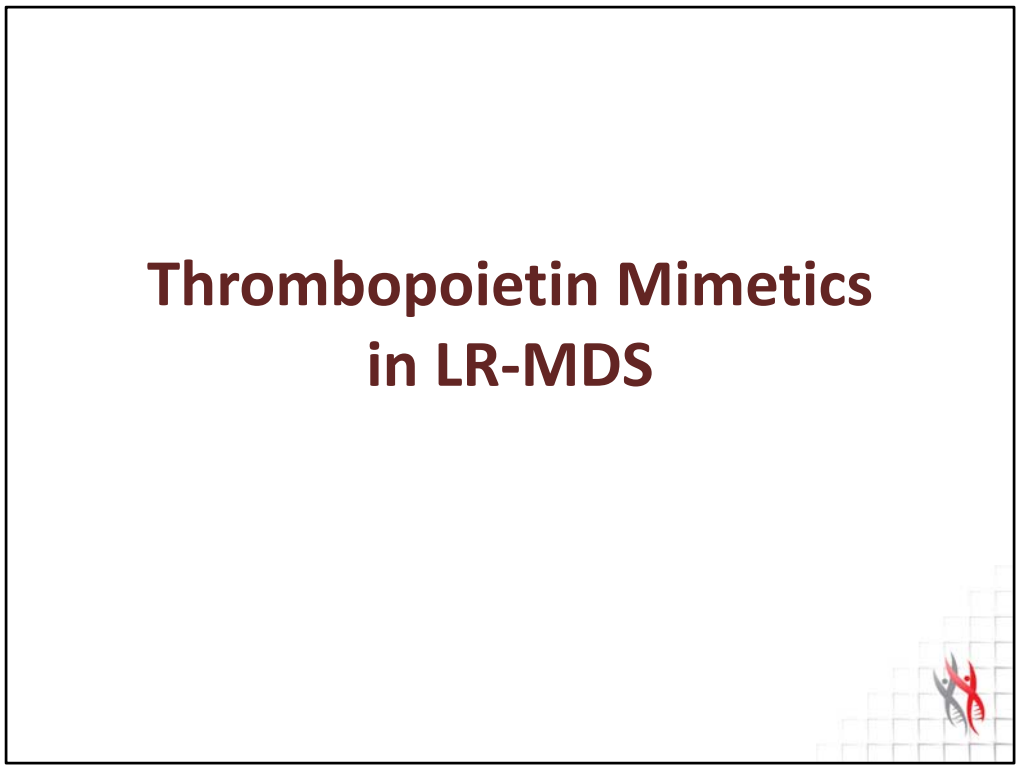
This has led to the development of a double-blind placebo-controlled randomization in lower-risk MDS unresponsive or refractory to ESAs where the primary endpoint is the rate of transfusion independence, and we eagerly await the results of this trial.

Sotatercept (ACE-011)

- Novel activin receptor type IIA fusion protein
  - Ligand trap that neutralizes negative regulators of late stage erythropoiesis
- Open-label phase II trial in LR-MDS, transfusion dependent and resistant/refractory to ESAs
  - 36 of 74 (49%) achieved HI-E

Komrokji R, et al. *Lancet Haematol.* 2018;5:e63-e72.

Sotatercept is a similar agent that neutralizes negative regulators of late-stage erythropoiesis. Recent results of the early-phase, open-label phase 2 trial in lower-risk MDS, transfusion-dependent and resistant or refractory to ESAs, were just published. Approximately half of patients achieved hematologic improvement in erythroid series, underscoring the potential promise of this class of agents; and we look forward to perhaps a day soon when these will be more widely available.

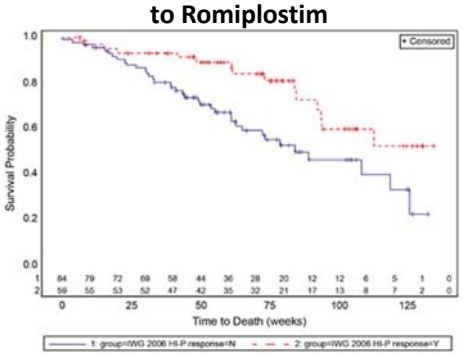


What about patients who have thrombocytopenia in lower-risk MDS where the predominant cytopenia is the low platelet count? In these patients, thrombopoietin mimetics should be considered.

Romiplostim in MDS

- In a dose ranging study (n=44):
  - Durable platelet response in 19 (46%), treatment-related SAE rate of 11%
- In a randomized study of romiplostim vs placebo:
  - 61 of 167 (36.5%) patients on romiplostim achieved HI-P versus 3 of 83 patients (3.6%) in placebo arm
  - Number of bleeding events was marginally lower with romiplostim (RR=0.922; 95% CI, 0.86-0.94)
  - No difference in survival or AML trans-formation rate between both arms early on and at 5 years of follow up

Survival According to Response to Romiplostim



Kantarjian H, et al. *J Clin Oncol*. 2010;28:437-444.; Giagounidis A, et al. *Cancer*. 2014;120:1838-1846.; Platzbecker U, et al. *Leukemia*. 2014;28:2418-2421.

Along those lines, romiplostim has been investigated in MDS in a randomized study where the agent was compared to placebo. About a third of patients achieved an improvement in their platelet counts, but the gain in terms of the number of bleeding events was only marginally lower with romiplostim when compared with placebo; and there was no difference in survival or AML transformation rates between both arms. That had been an initial concern with romiplostim, but the randomized data do not support the view that these agents actually worsen survival or accelerate transformation to AML. For those who respond, a survival advantage accrued to those patients.

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Eltrombopag vs Placebo for LR-MDS and Platelet Count <30 x 10^9/L

Variable	Eltrombopag N=59	Placebo N=31	*P* value
Response rate N (%)	28 (47%)	1 (3%)	0.0017
Bleeding events	8 (14%)	13 (42%)	0.0025
Mean platelet count increase	53.2 x 10^9/L	NS	
Grade 3/4 Adverse events, N (%)	27 (46%) Nausea, transaminitis most common	5 (16%) Marrow fibrosis most common	*P*=.0053 Stopping rule not reached
Disease progression or AML evolution, N (%)	7 (12%)	5 (16%)	*P*=.81

Platelet response defined as: a) if baseline platelet >20 x 10^9/L: absence of bleeding and increase by ≥30 x 10^9/L; b) if baseline platelet <20 x 10^9/L: platelets >20 x 10^9/L and increase by ≥100%, not due to platelet transfusions.

Oliva E, et al. *Lancet Hematol.* 2017;4:e127-136.

Eltrombopag has also been compared to placebo in lower-risk MDS with significant thrombocytopenia, and you can see that the response rates are over 40% in this relatively small trial. There seemed to be a trend towards less bleeding events on the eltrombopag. The agent was also relatively well-tolerated, and there was no evidence of acceleration of disease progression or AML evolution with eltrombopag when compared with placebo.

Key Points

- Improvement in blood counts is a major goal of therapy in lower-risk MDS
- Anemia is the predominant cytopenia in this subgroup and ESAs are the cornerstone of therapy
  - Baseline endogenous EPO level and transfusion burden are major predictors of response to ESA
- Therapeutic options for non-del(5q) LR-MDS resistant/refractory to ESAs include hypomethylating agents, immunosuppressive therapy
- Experimental approaches include
  - Lenalidomide +/- ESA, activin receptor II fusion proteins in anemic patients
  - TPO mimetics in predominantly thrombocytopenic patients

To conclude, I would like to leave you with these key takeaway points. Improvement in blood counts is a major goal of therapy in lower-risk MDS. Anemia is the predominant cytopenia in this subgroup, and ESAs are the cornerstone of therapy. Baseline endogenous EPO level and transfusion burden are major predictors of response to ESA. Therapeutic options for non-del 5q lower-risk MDS resistant or refractory to ESAs include hypomethylating agents and immunosuppressive therapy. Experimental approaches include lenalidomide-based approaches; as well as these novel, very interesting molecules, the activin receptor II fusion proteins in anemic patients. In those who are predominantly thrombocytopenic, thrombopoietin mimetics can be considered. Thank you for viewing this activity.