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With so many options (now), how do I choose the best treatment for low-risk MDS?

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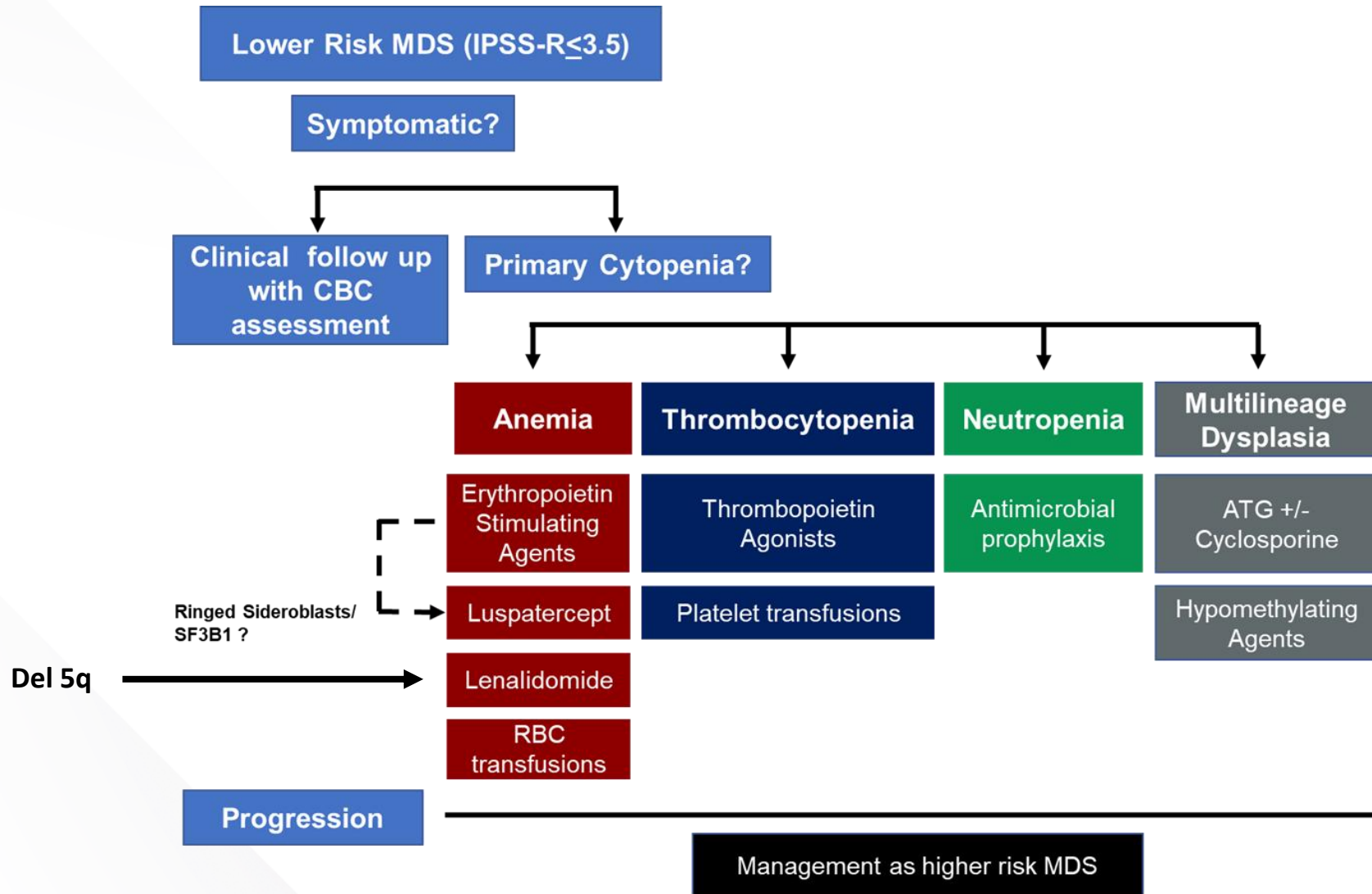
University of Miami Miller School of Medicine

Sylvester Comprehensive Cancer Center

Presentation Roadmap

1. Overall Treatment Algorithm
2. Del 5q Minus MDS- Lenalidomide and general updates
3. Managing Anemia- ESAs and Newer Agents
4. Targeted Therapies
5. Other Treatment options to consider

Therapeutic Algorithm



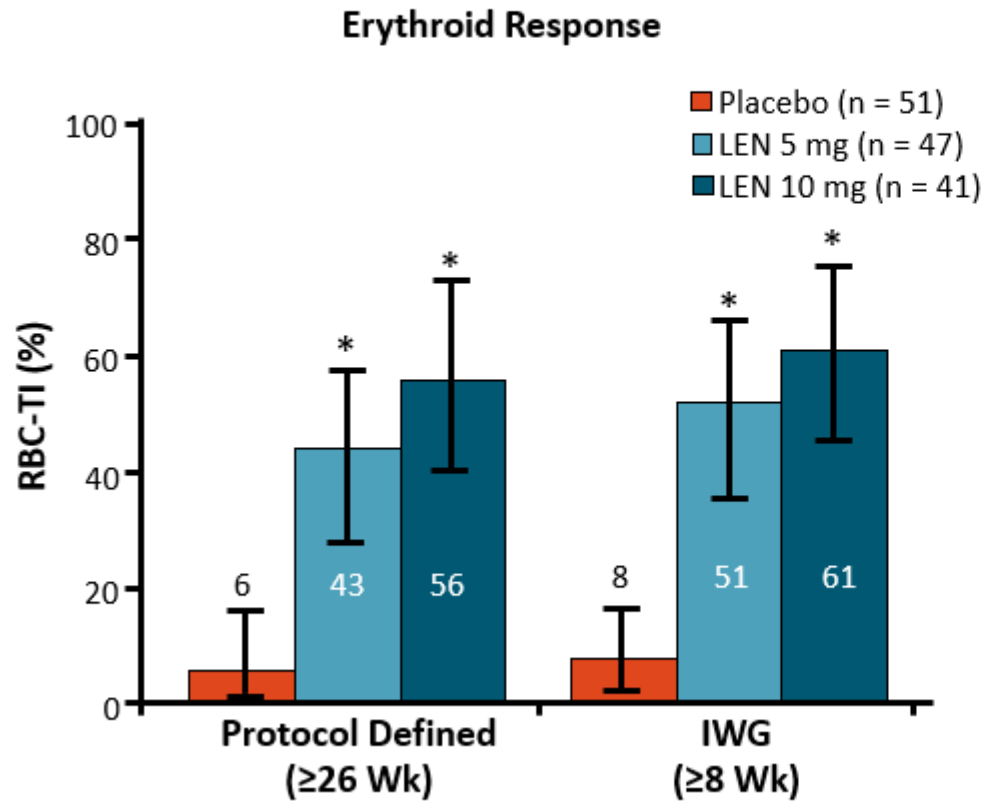
Things to remember:

- Our prognostication has improved since some of these therapies were approved
- We need to integrate new data with old

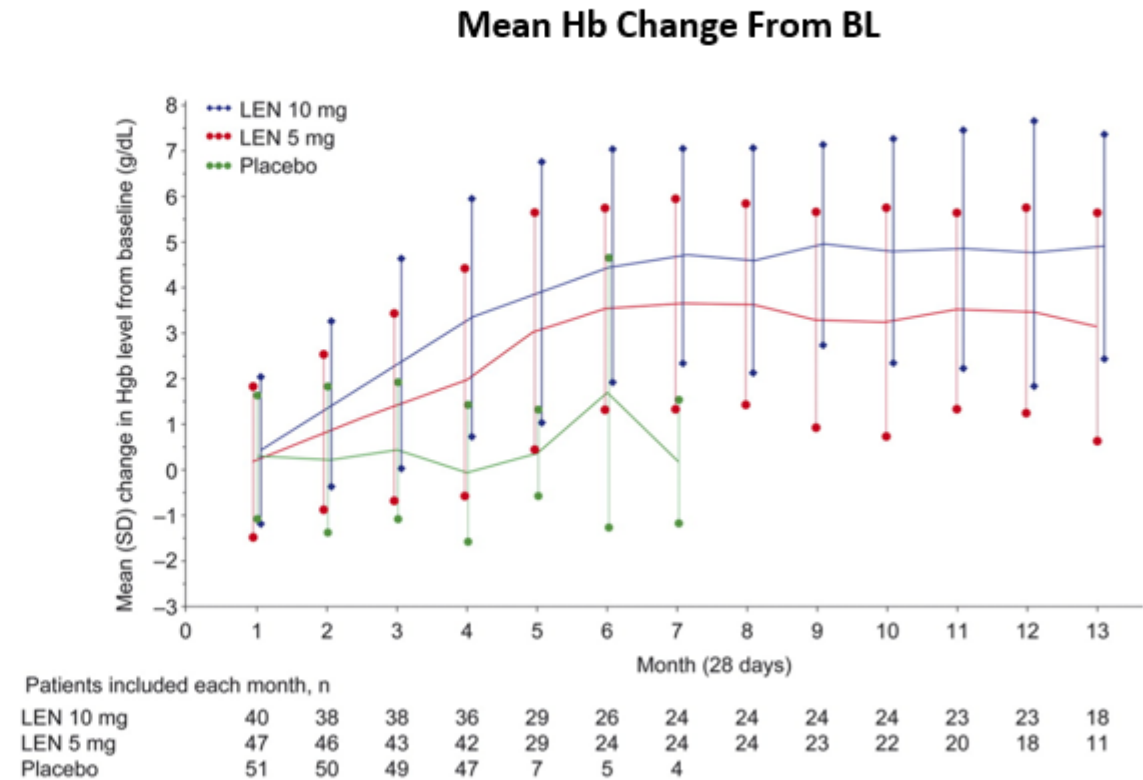
Management of Isolated Del(5q) MDS

MDS-004: LEN vs Placebo in Patients With del(5q) MDS

- Randomized, double-blind phase III trial to assess efficacy and safety of LEN in transfusion-dependent patients with MDS



* $P < .001$ vs placebo.

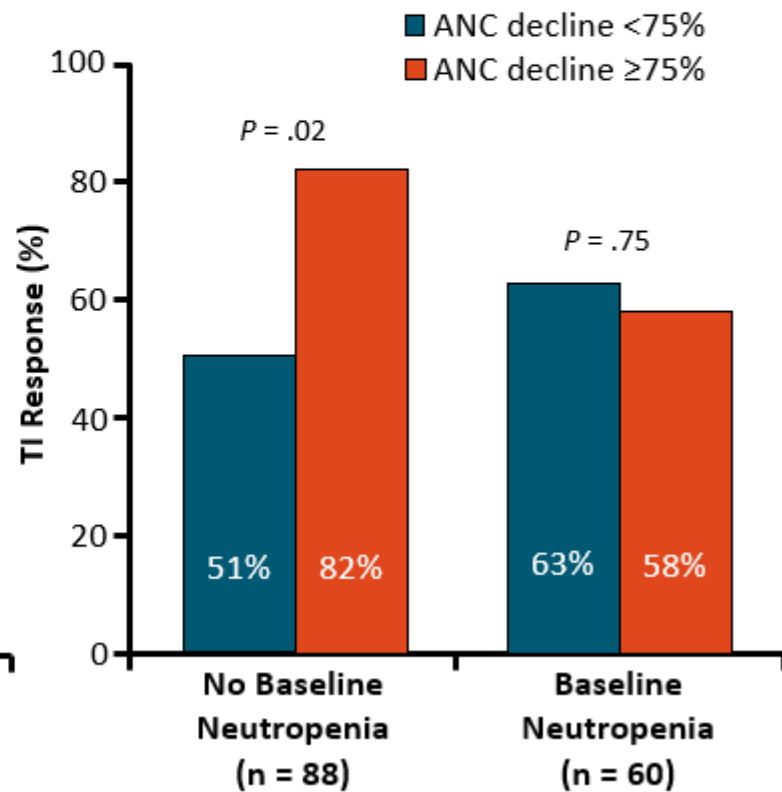
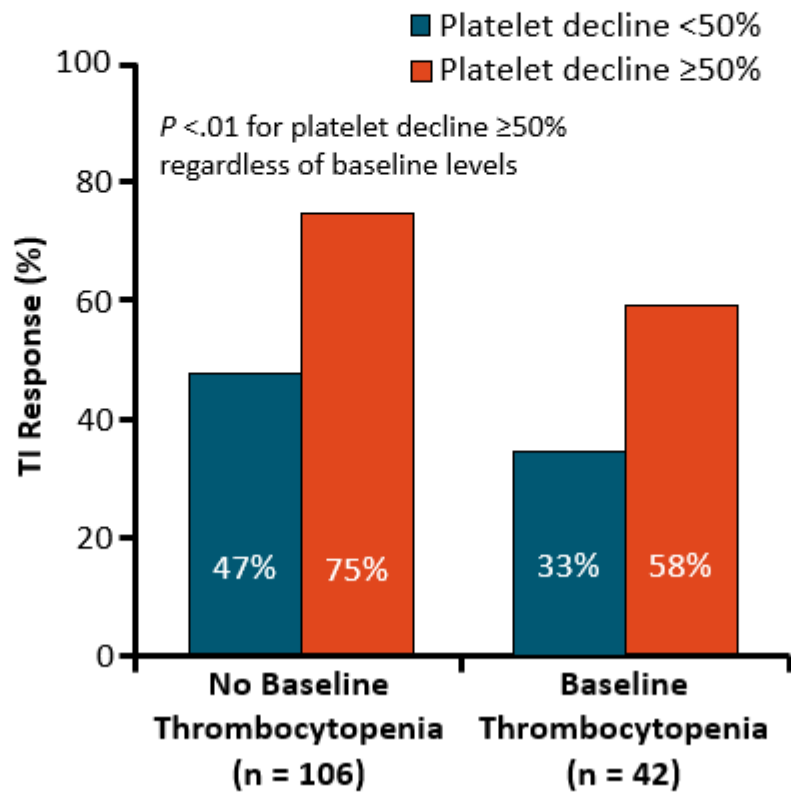


Therapy-Related Cytopenias With Disease-Modifying Therapy

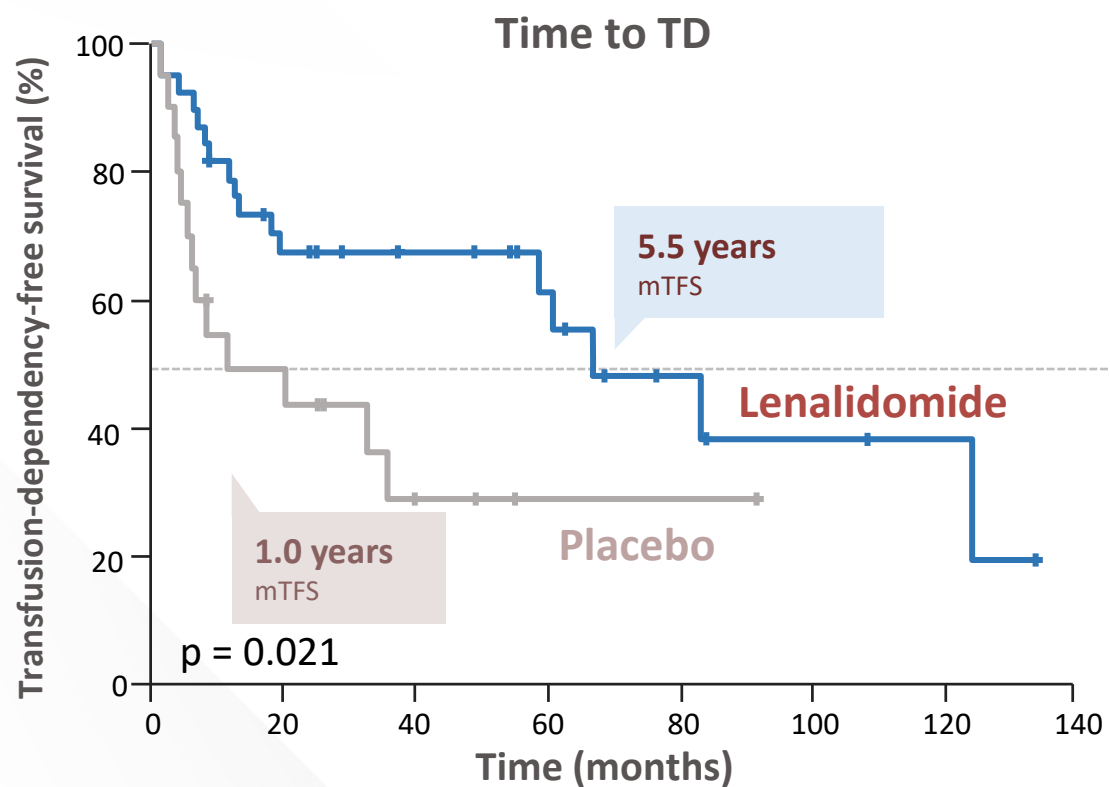
- Acute onset anemia can be seen with initiation of disease-modifying agents, but therapy should be continued

eg, Lenalidomide

**Direct cytotoxic effect
may predict response.**



Early lenalidomide treatment in anemic non-TD MDS-del(5q) SintraRev Phase 3 trial



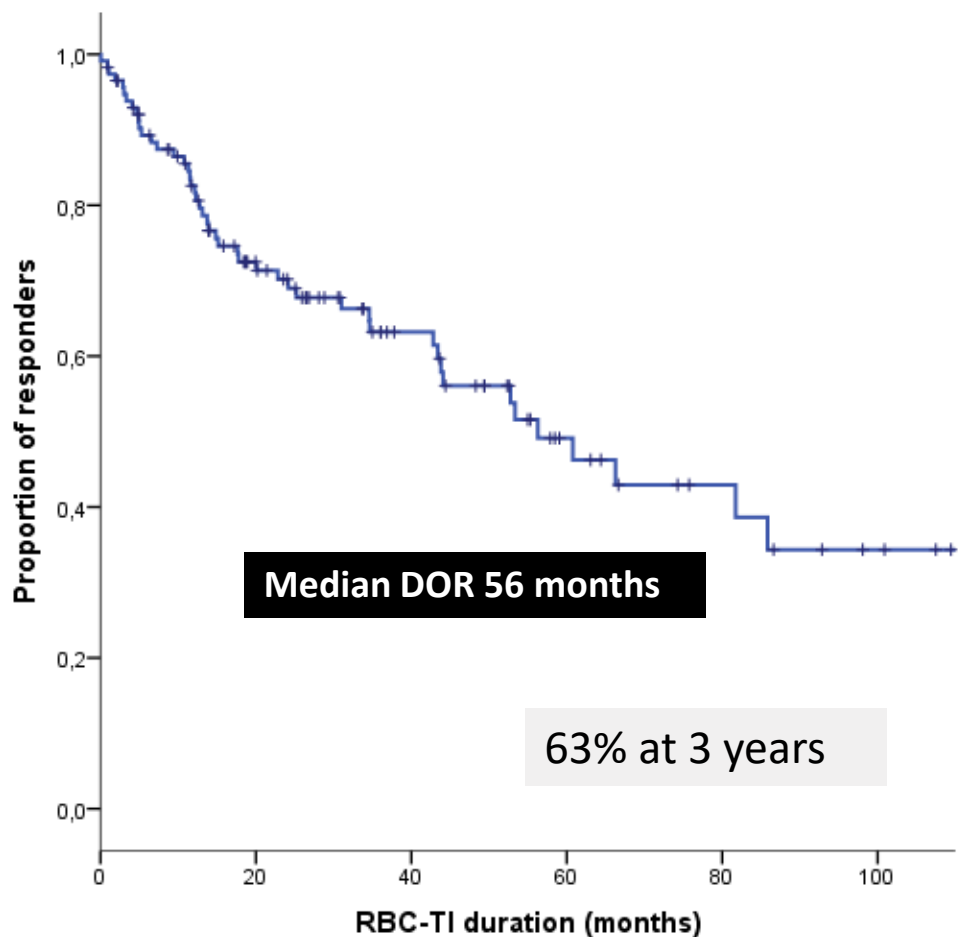
Efficacy outcomes

	Lenalidomide (n = 40)	Placebo (n = 21)
Time to TD, months	66.3	11.6 ^a
HI-E, %	70.0	0 ^b
Cytogenetic response, %	80.0	0 ^b

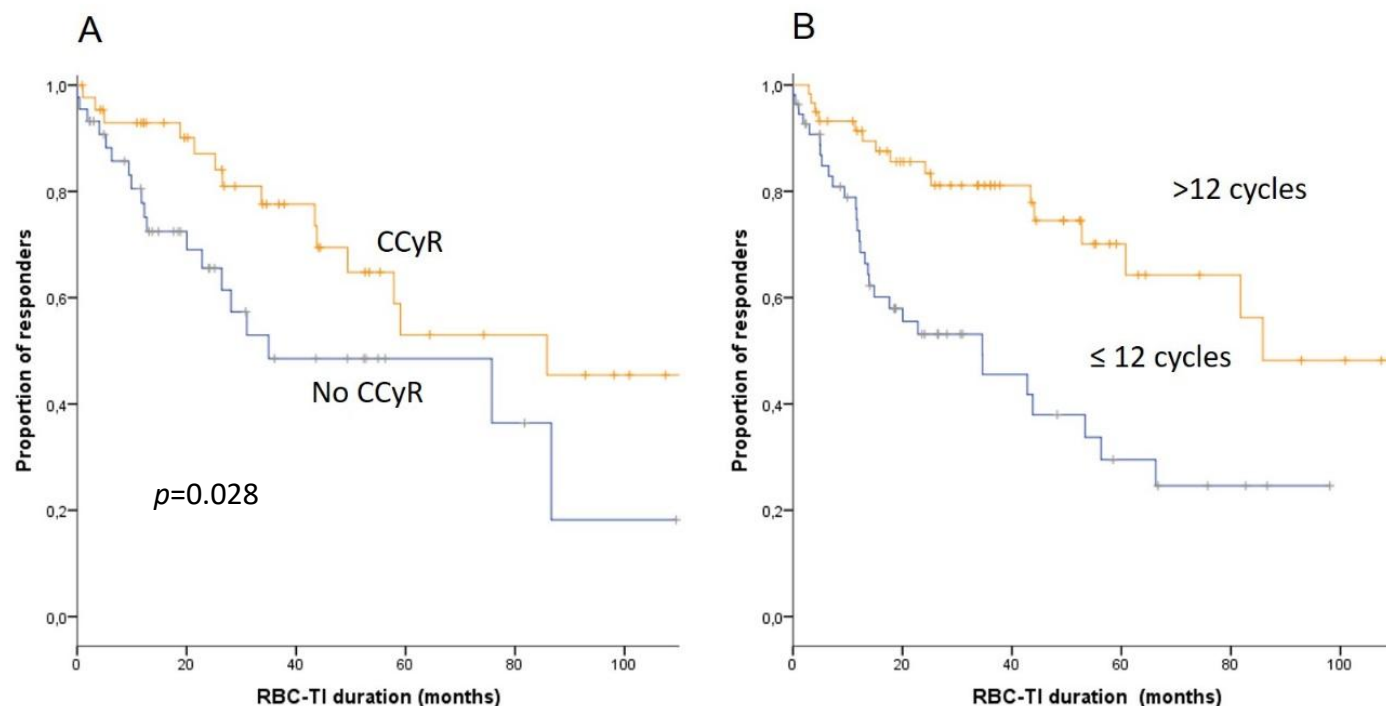
LEN Interruption: RBC transfusion independence can be maintained after LEN discontinuation (del5q) (HARMONY Alliance Study)

- **118 pts** with diagnosis of MDS del(5q)
- IPSS-R very low, low or intermediate at len treatment start for TD
- RBC-TI achieved with lenalidomide
- Stop for toxicity or pts decision

Median DOR 86 vs 35 months



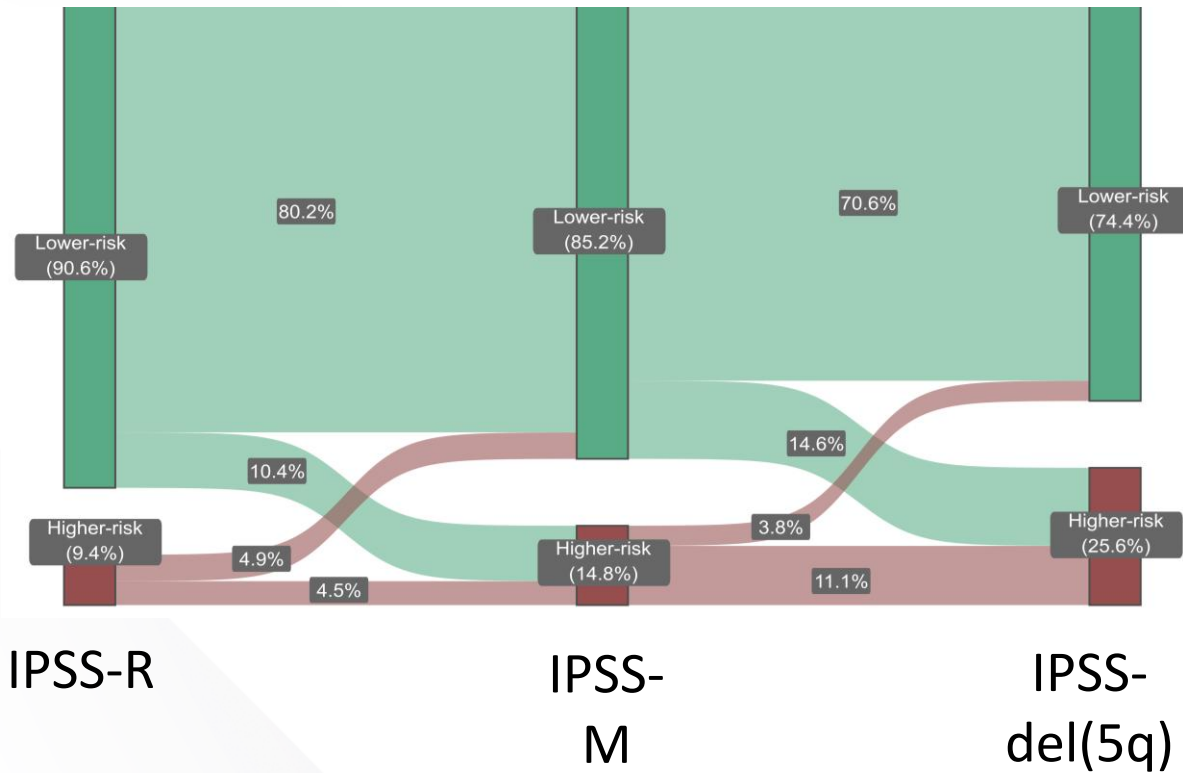
RBC-TI duration after lenalidomide discontinuation according to cytogenetic response (A) and n° of lenalidomide cycles before treatment discontinuation (B)



48 (40%) pts lost TI;
Len rechallenge : 57% second response

MDS-del(5q) : Is it all the same?

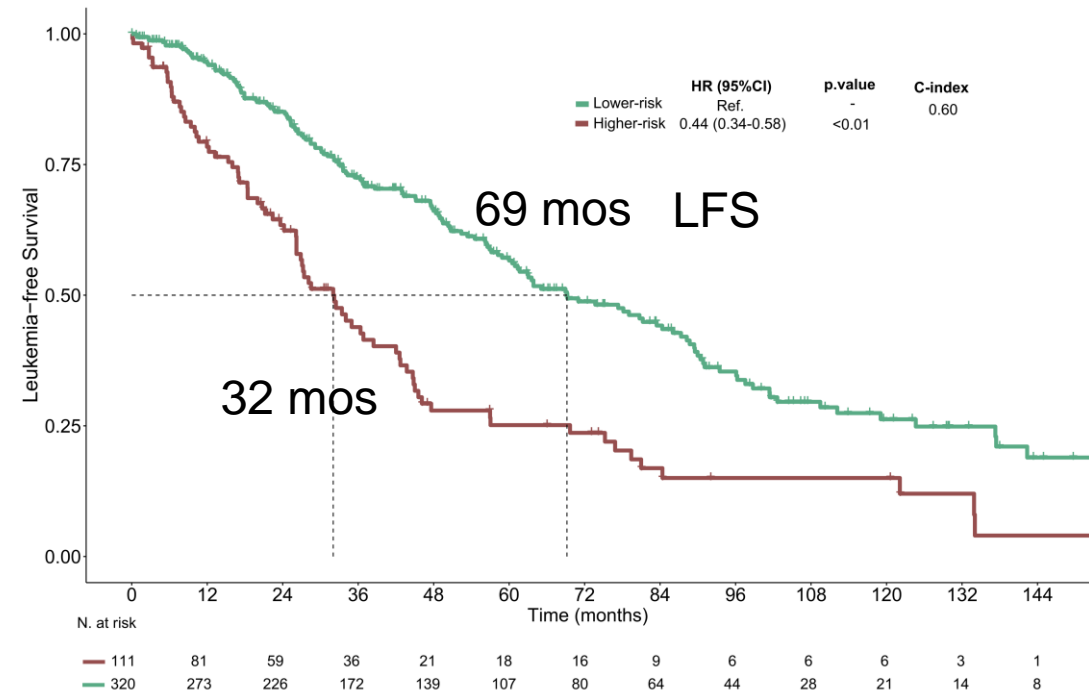
Responses to treatment vary.



*New Risk Score!

Variable	Points
Sex, male	1
Hemoglobin ≤ 10 g/dL	2
Platelet $\leq 100 \times 10^9/L$	2
≥ 2 additional mutations	2
SF3B1 mutations	1
High Risk-TP53 status	1

≤ 3 points standard risk
 >3 points high risk



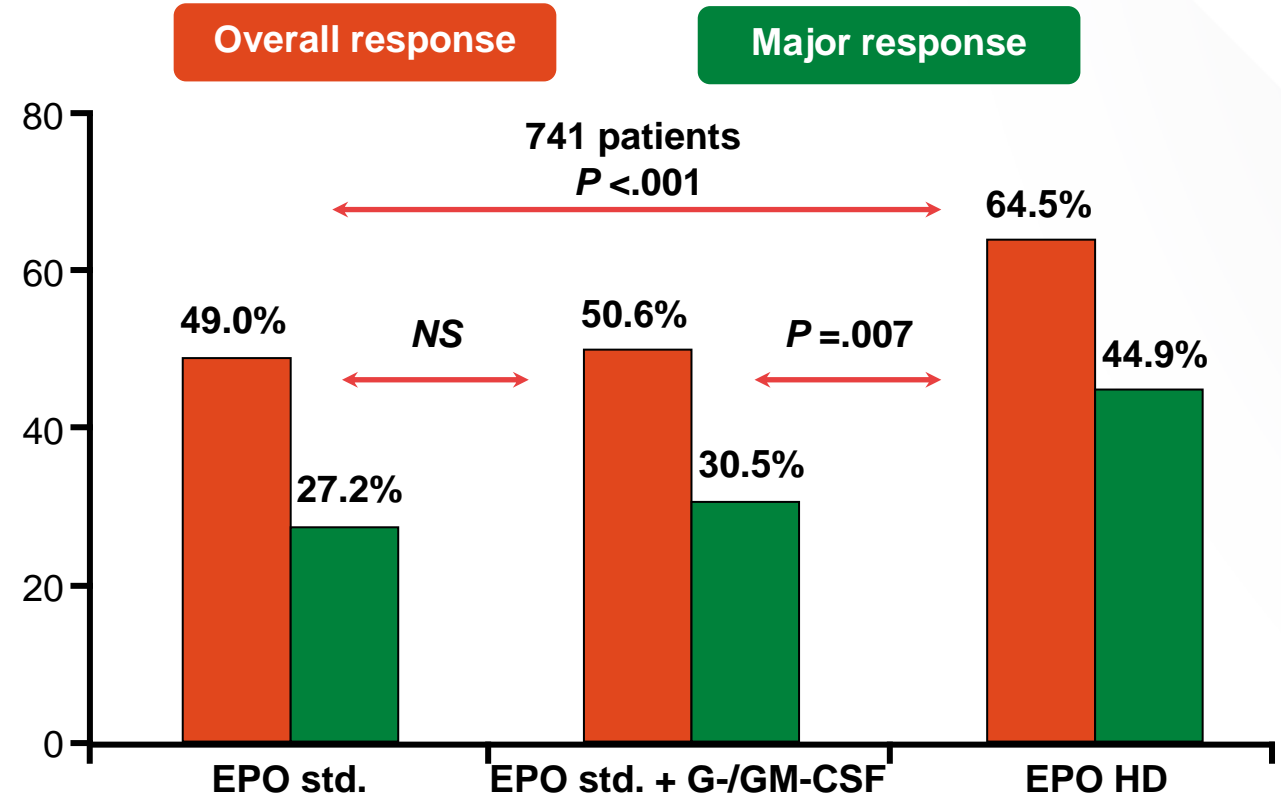
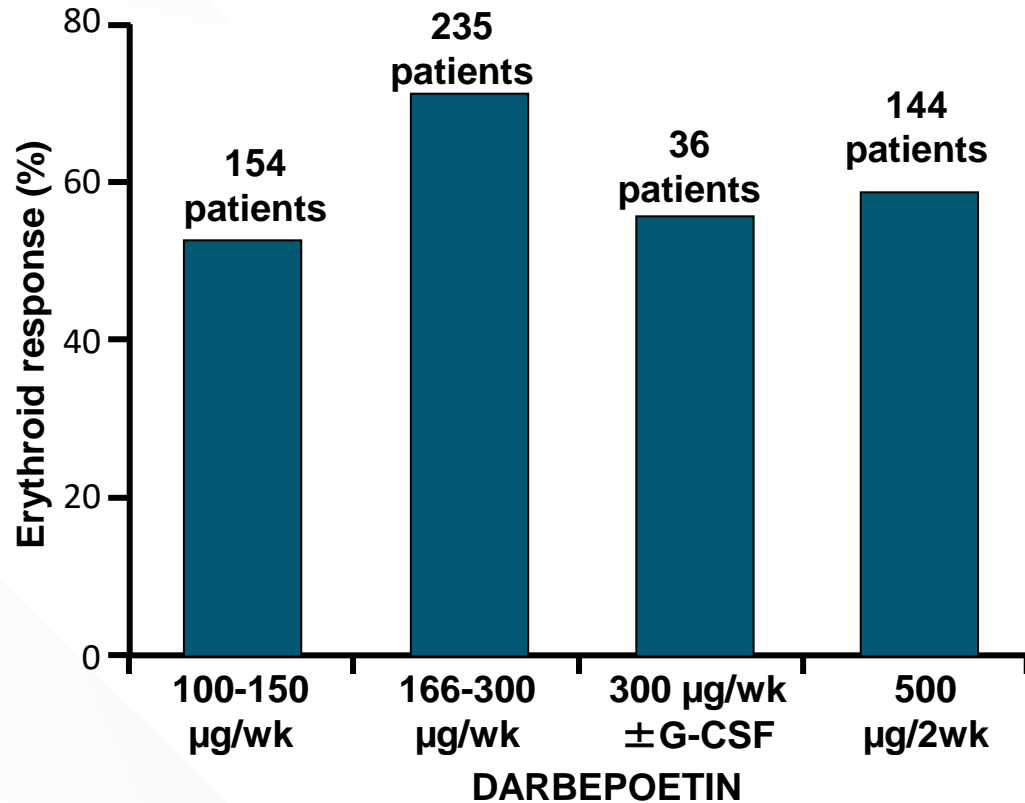
Anemia Management



Managing Anemia: Erythropoietin-Stimulating Agents in MDS

- Focus on the **early phases of erythropoiesis** by blocking apoptosis, encouraging the proliferation of erythroid precursors responsive to erythropoietin, and facilitating the maturation of erythroid cells.
- Clinical trials involving erythropoiesis-stimulating agents (ESAs) in patients with lower-risk myelodysplastic syndromes (MDS) have shown **hematologic improvements and increased transfusion independence in up to 40% of individuals**, with most positive responses observed within three months. The typical duration of response averages between 12 to 15 months.
- Standard ESA treatment for MDS involves higher dosages, specifically EPO at 60,000-80,000 U per week and DAR at 500 µg every two to three weeks.
- The patients who are most likely to gain from ESA treatment are those with **minimal transfusion needs and low serum erythropoietin levels (below 500)**. A lower transfusion requirement is characterized by receiving 3 to 7 units of packed red blood cells (pRBCs) within a 16-week timeframe (Platzbecker et al., 2019).

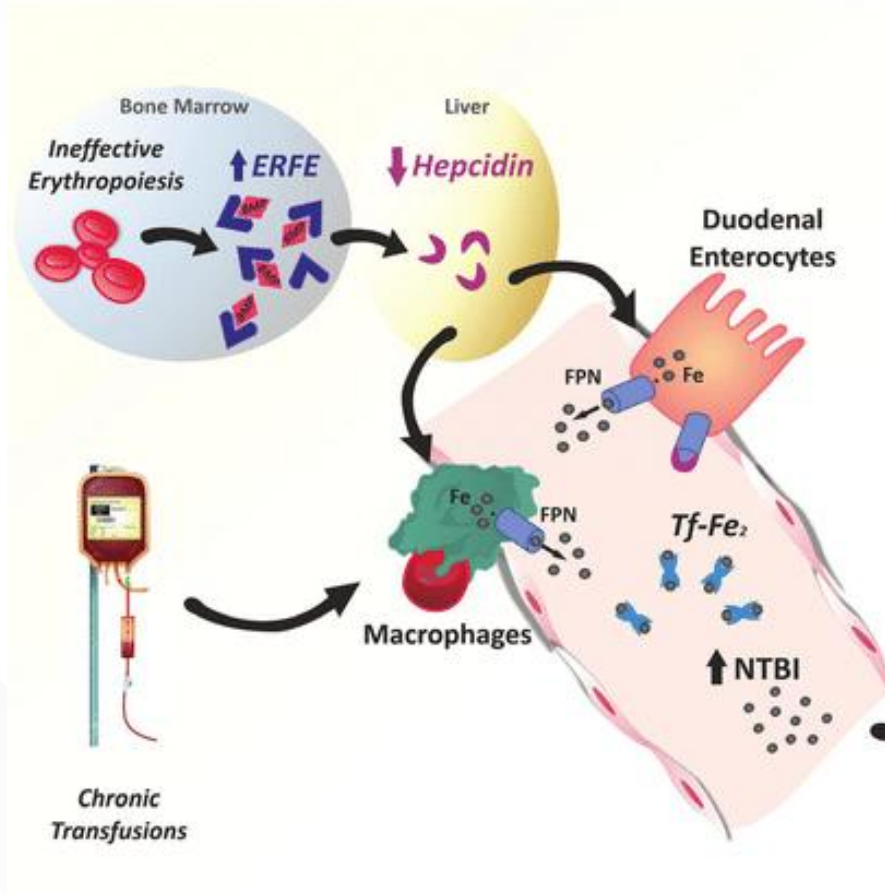
Managing Anemia: Erythropoeisis Stimulating Agents



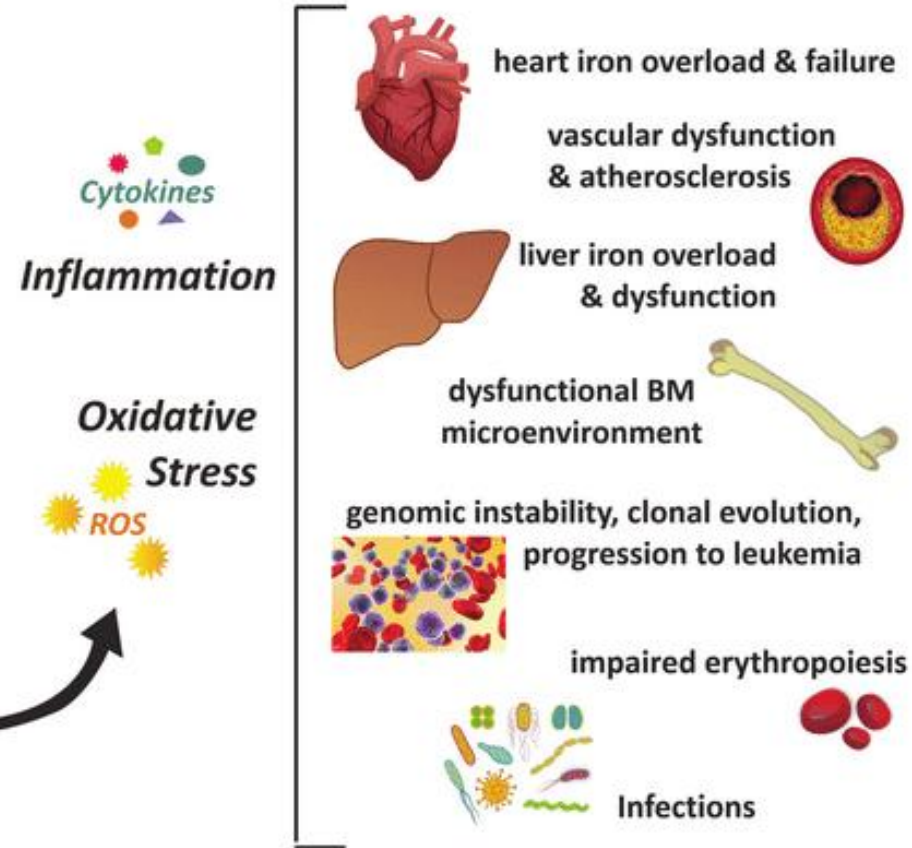
Higher dosing regimens of both epoetin alfa (weekly dose 60-80 K IU) and darbepoetin alfa (weekly dose 150-300 mcg) correlate with higher erythroid response rates

Tackling Anemia: When to Treat?

A Molecular Mechanisms of Iron Overload

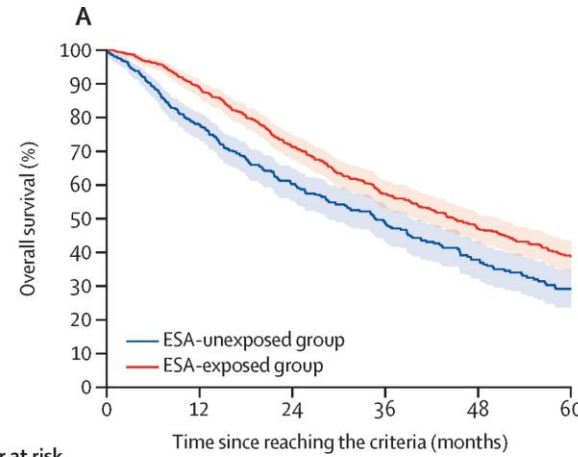


B Consequences of Iron Overload

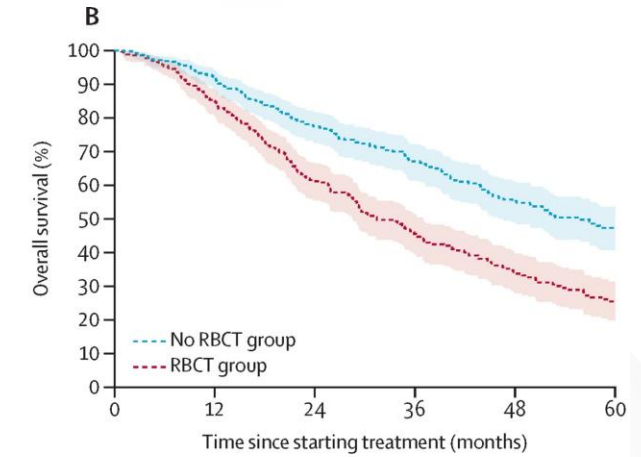


Early ESA initiation

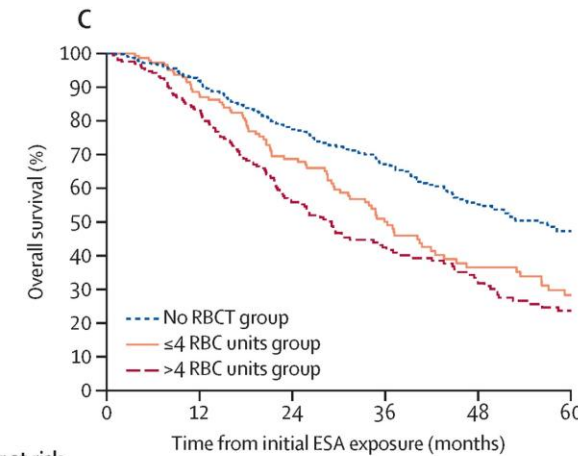
- Multiple studies suggest RBC transfusion need is associated with worsened outcomes
- Retrospective data suggests ESA could mitigate transfusion
- Risk varies by degree of transfusion needs



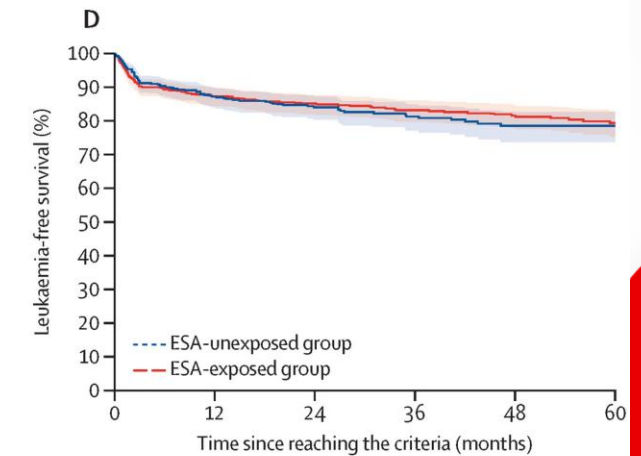
Number at risk (number censored)		0	12	24	36	48	60
ESA-unexposed group	(102)	574	320 (64)	194 (34)	135 (27)	84 (17)	51 (-)
ESA-exposed group	(73)	596	567 (108)	415 (76)	289 (48)	199 (31)	134 (-)



Number at risk (number censored)		0	12	24	36	48	60
No RBCT group	(30)	396	320 (46)	222 (27)	160 (26)	109 (14)	71 (-)
RBCT group	(51)	353	277 (73)	172 (40)	107 (25)	68 (15)	43 (-)



Number at risk (number censored)		0	12	24	36	48	60
No RBCT group	(30)	396	320 (46)	222 (27)	160 (26)	109 (14)	71 (-)
≤4 RBC units group	(17)	146	117 (24)	80 (20)	51 (12)	30 (6)	19 (-)
>4 RBC units group	(34)	207	160 (49)	92 (20)	56 (13)	38 (9)	24 (-)



Number at risk (number censored)		0	12	24	36	48	60
ESA-unexposed group	(66)	574	354 (11)	245 (7)	180 (5)	117 (0)	81 (-)
ESA-exposed group	(79)	596	520 (12)	398 (8)	306 (5)	225 (5)	146 (-)

EPO-PRETAR trial (NCT03223961)

121 patients screened 2018-2022 → 84 fulfill inclusion

Pt Characteristics

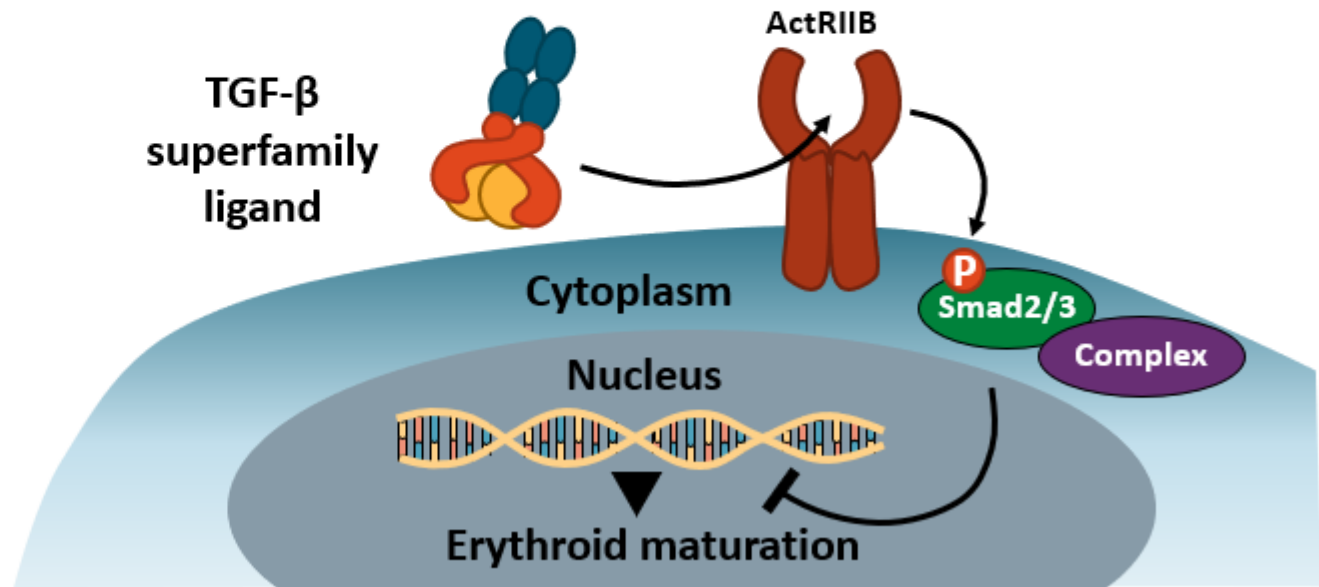
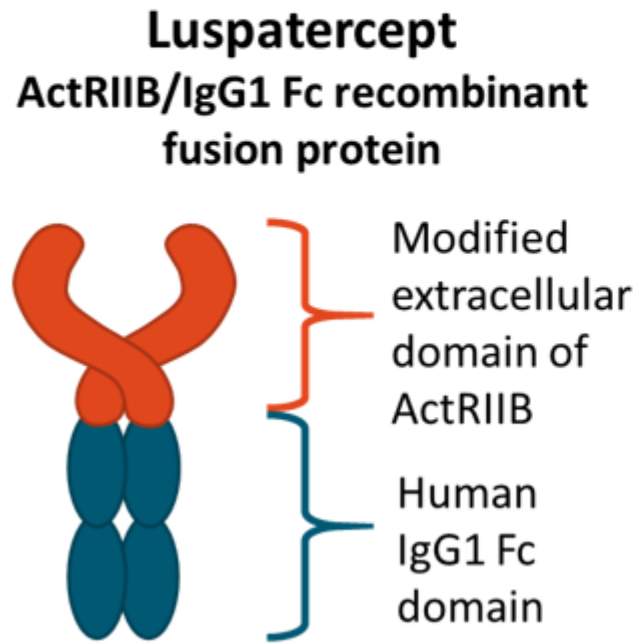
Median age	84 years
Gender	54% males
Cardiovascular comorbidities	75%
Sideroblastic MDS	46%
Non-sideroblastic MDS	54%
Median baseline Hb level	10.2 g/dL
Median sEPO level	37 IU/L

Outcome	Early Onset Arm	Late Onset Arm	p-value
RBC Transfusion Dependence (TD)	14 patients (32%) became RBC TD	18 patients (44%) became RBC TD	0.28
Hematologic Improvement-Erythroid (HI-E)	79.5% achieved HI-E	54% achieved HI-E	0.03
HI-E Duration	30.6 months	12.7 months	0.02
Median Time to RBC TD	36.4 months	36.4 months	0.3
Progression to Higher Risk MDS or AML	13 patients	10 patients	-
AML Transformation	9.5% in both arms	9.5% in both arms	-
Median Progression-Free Survival (PFS)	60.6 months	Not reached	0.4
Median Overall Survival (OS)	49.6 months	55 months	0.3
Quality of Life (QOL) and Cardiovascular Events	No significant differences between the two arms	No significant differences between the two arms	-

Median follow-up	34 months
Early onset arm	40 patients started ESA (3 withdrew consent)
Late onset arm	23 patients (56%) started ESA by the study's closing date

Luspatercept

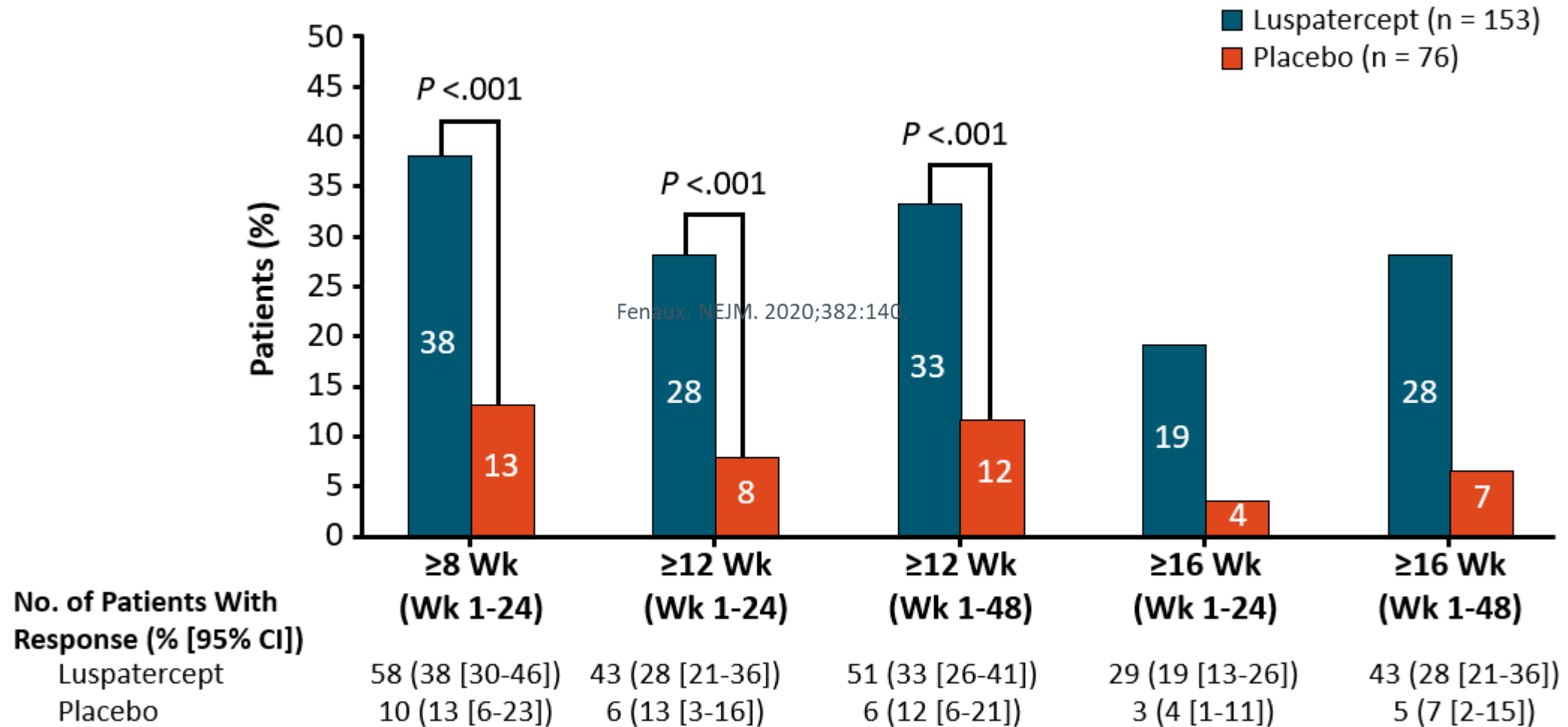
- First-in-class erythroid maturation agent inhibits abnormal SMAD2/3 signaling by neutralizing select TGF- β superfamily ligands and improves late-stage erythropoiesis in MDS models¹
- Phase II study in patients with LR non-del(5q) MDS, luspatercept yielded high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes²



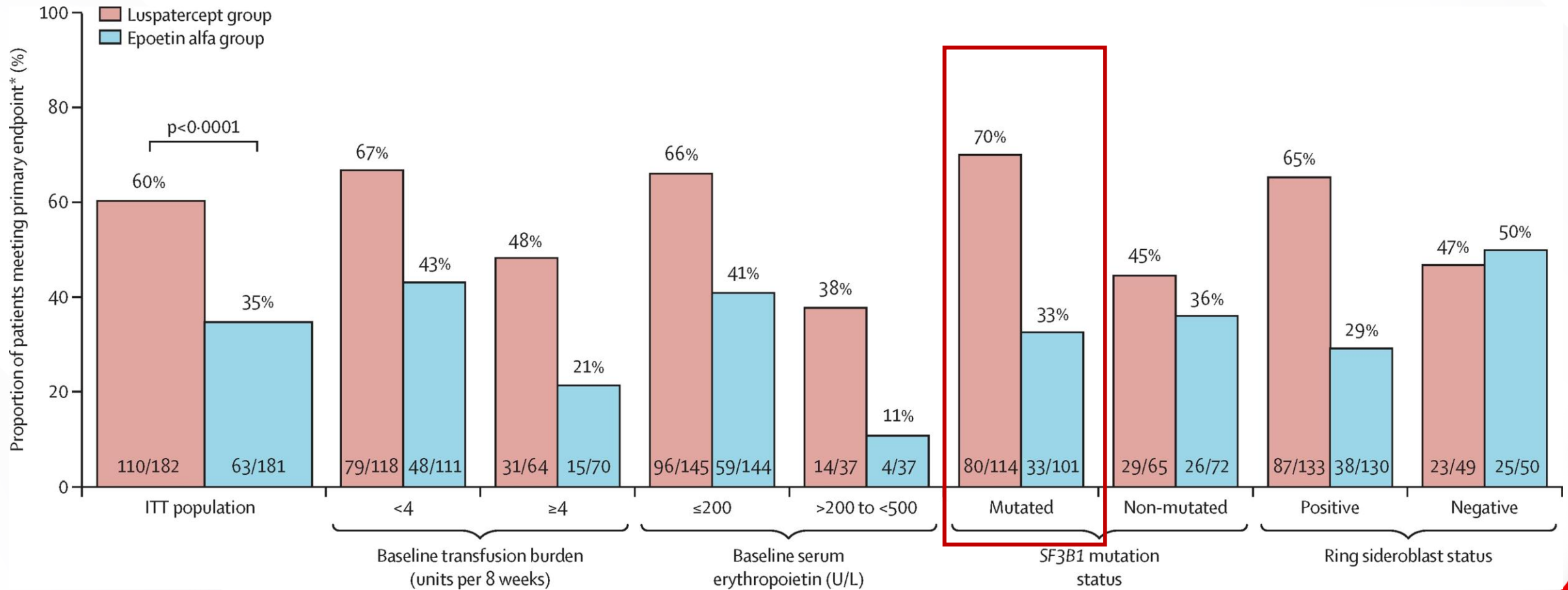
1. Suragani et al. Nat Med. 2014

2. Platzbecker et al. Lancet Oncol. 2017

MEDALIST: Red Cell Transfusion Independence With Luspatercept in MDS-RS



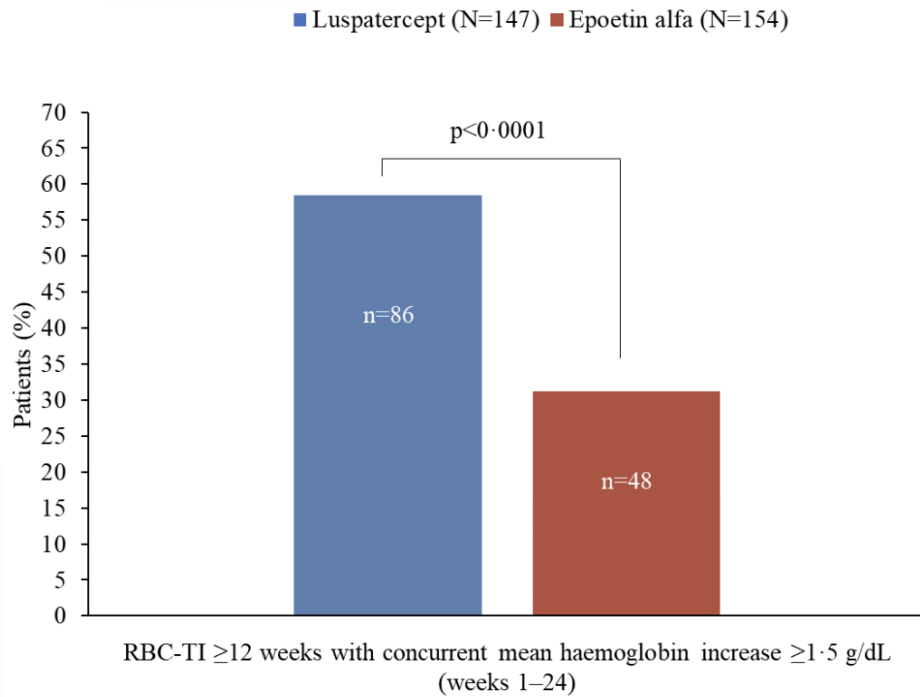
COMMANDS: Luspatercept vs ESA in Front-Line MDS



Luspatercept: Frontline v. Secondline

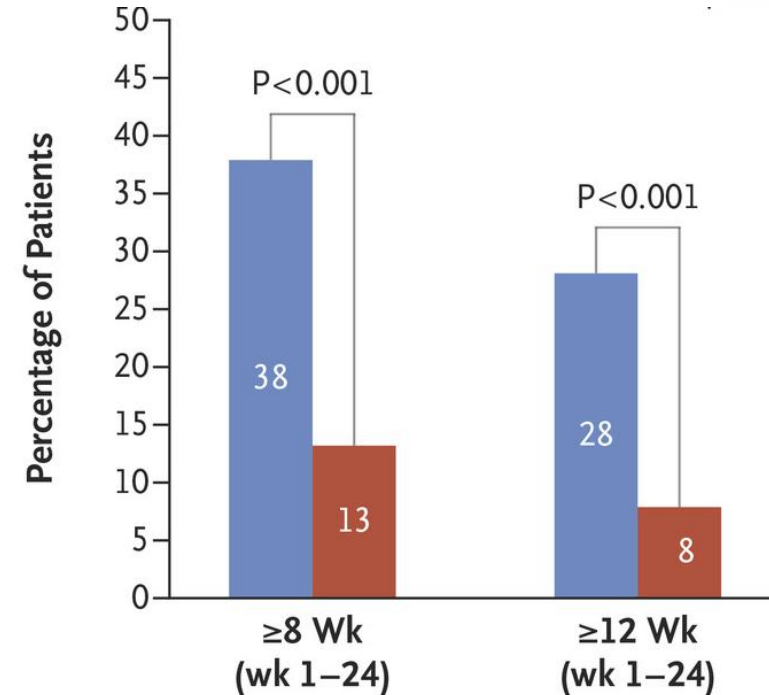
COMMANDS – Front Line, EPO <500

- Epo vs Luspatercept



MEDALIST – Post-ESA or high EPO

- Luspatercept vs Placebo



Sequencing ESA and Luspatercept

Cumulative Expected Benefit According to Sequence of First- and Second-Line Therapies for LR-MDS With Anemia



vs.

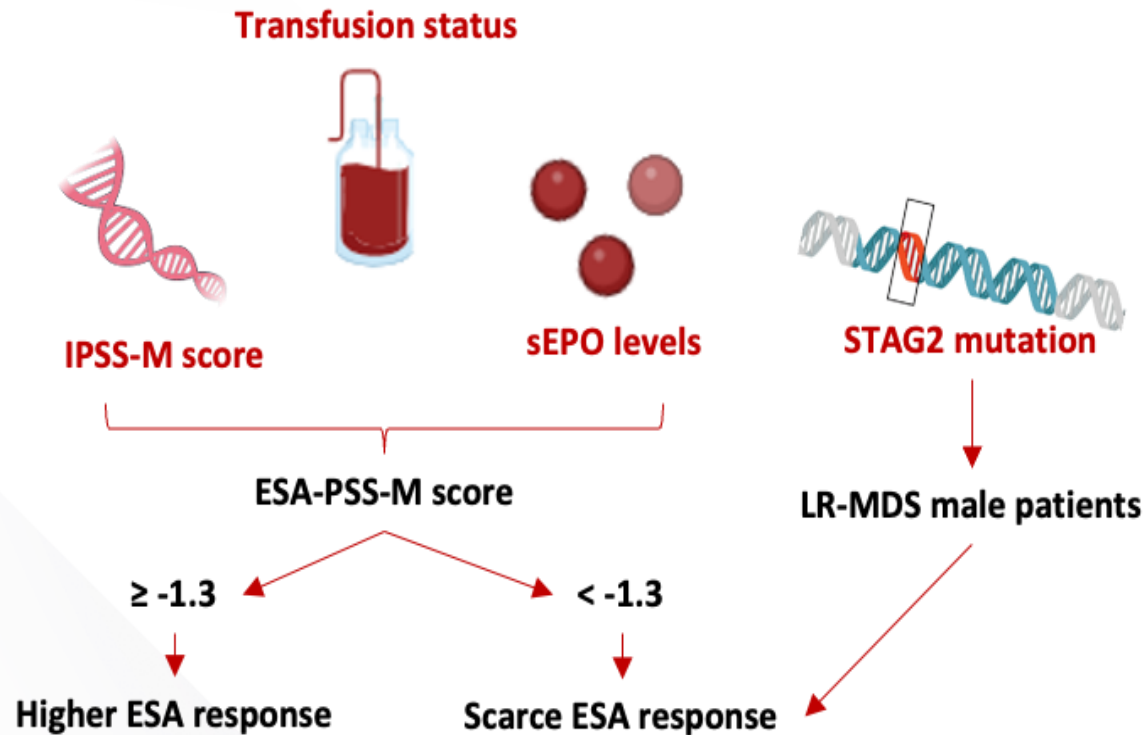


Duration of Response

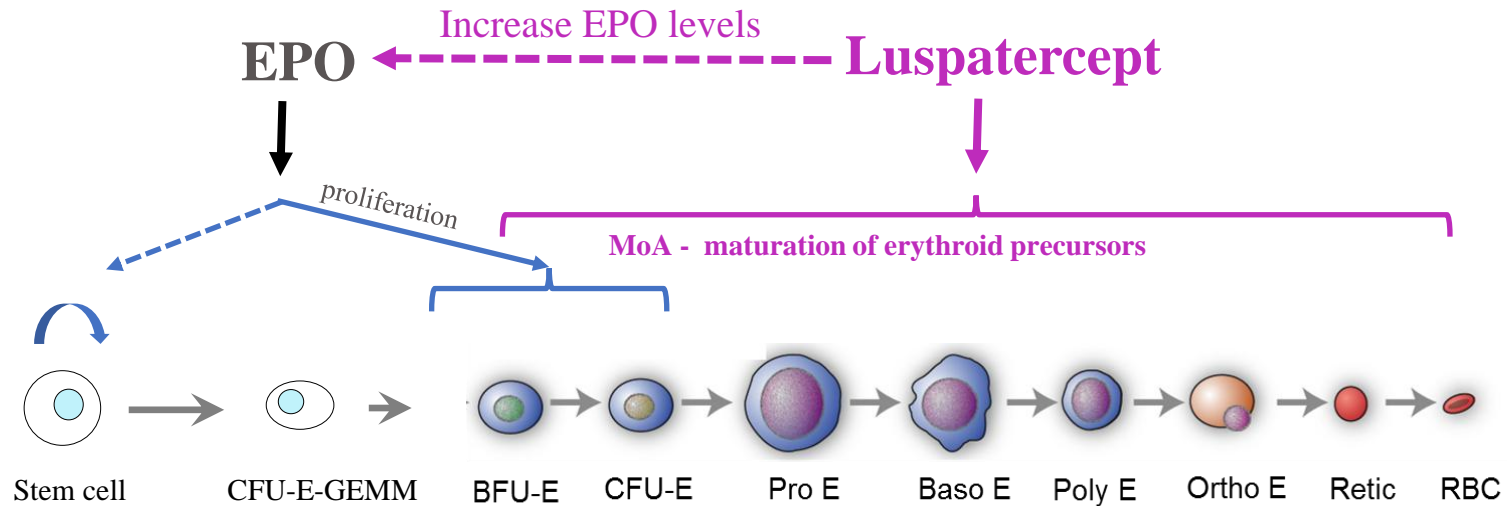


Refining Erythropoiesis-Stimulating Agent (ESA) Use

* Because we love our risk scores- IPSS-M risk and sex-associated somatic mutations improve prediction of response to ESAs in LR-MDS



Stimulating the two stages of erythropoiesis? 1+1= 2... or 4?



NCT05181735
ESA^a + luspatercept
combination^b (N = 28)^{2,3}

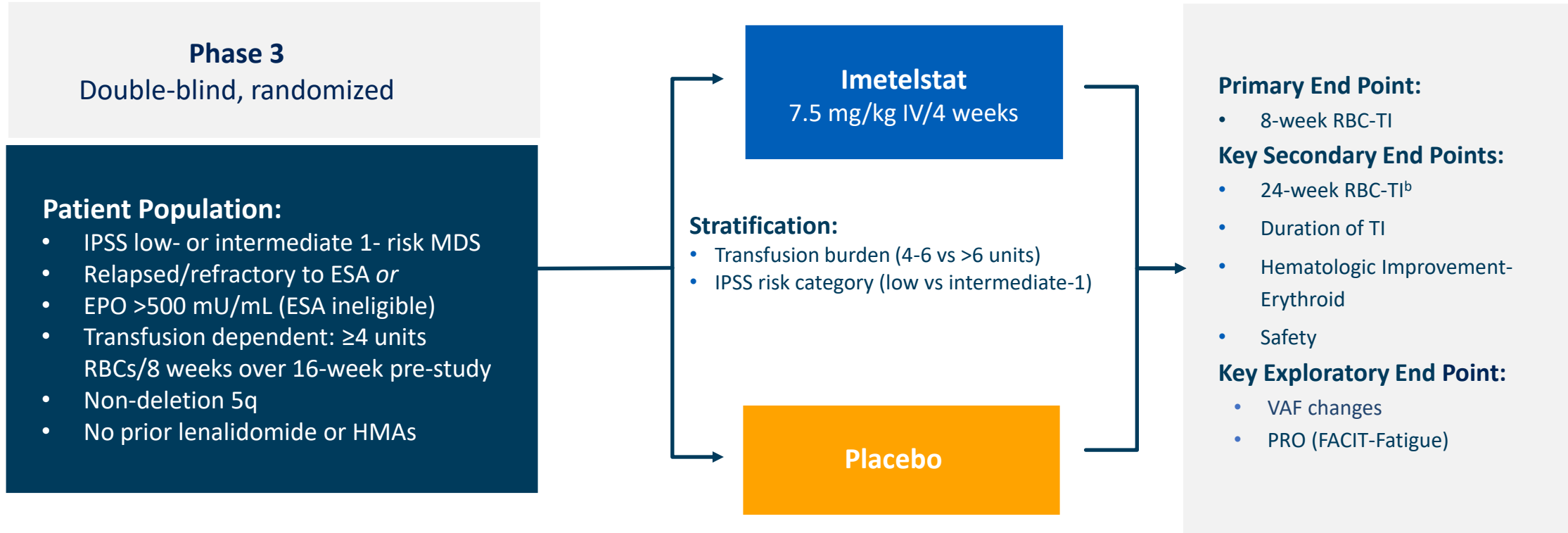
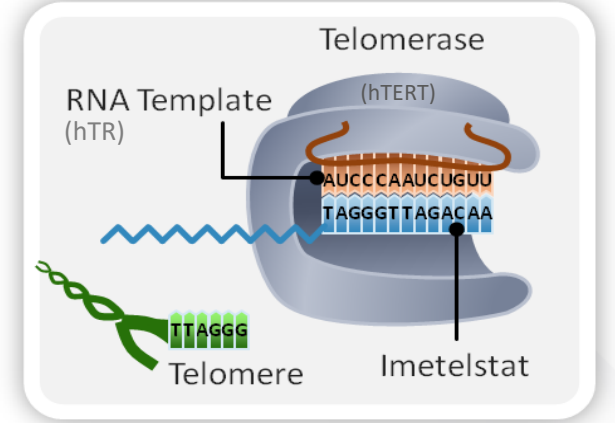
Including patients with:

- Refractory to luspatercept monotherapy
- Loss of response to luspatercept monotherapy
- Treatment-naïve

ORR	All patients (N = 28)	Refractory (n = 18)	Loss of response (n = 7)	Treatment-naïve (n = 3)
Any one of : <ul style="list-style-type: none"> • Hb increase > 1.5g/dL • RBC-TI • > 50% reduction in RBC TB 	36%	17%	71%	67%

Imetelstat for TD LR MDS

- iMerge Phase 3 Trial

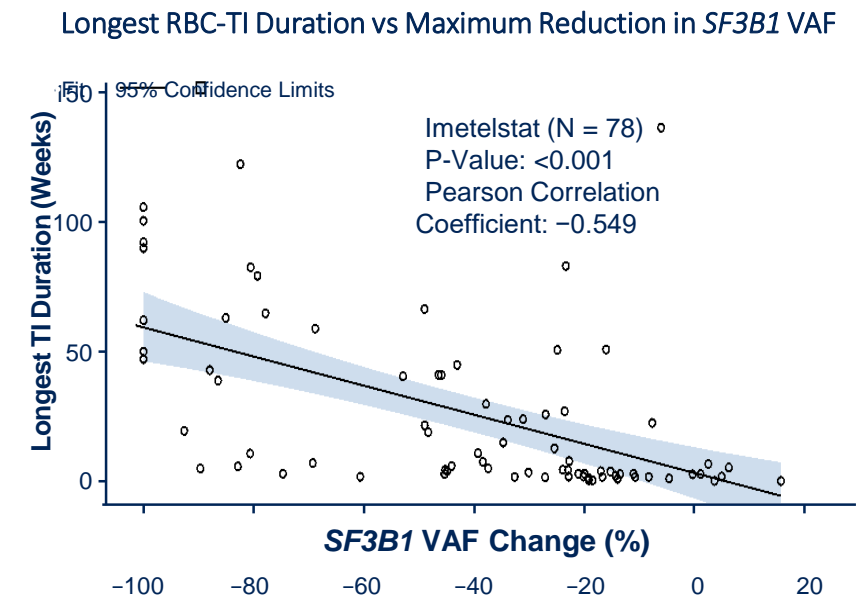
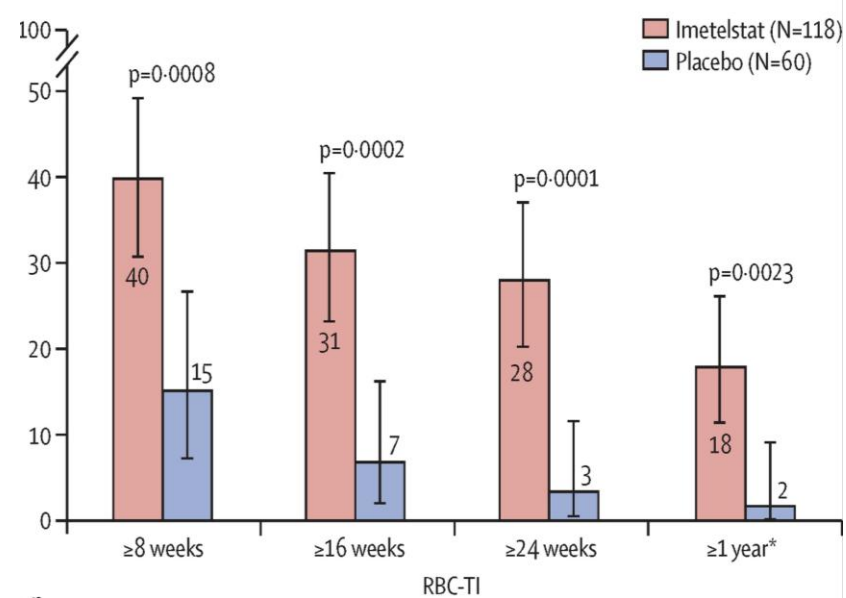
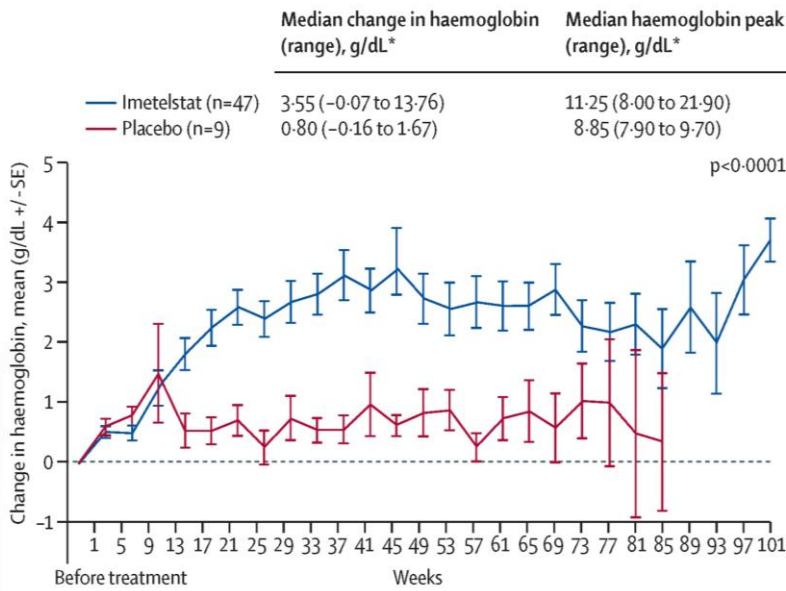


Imetelstat for Anemia

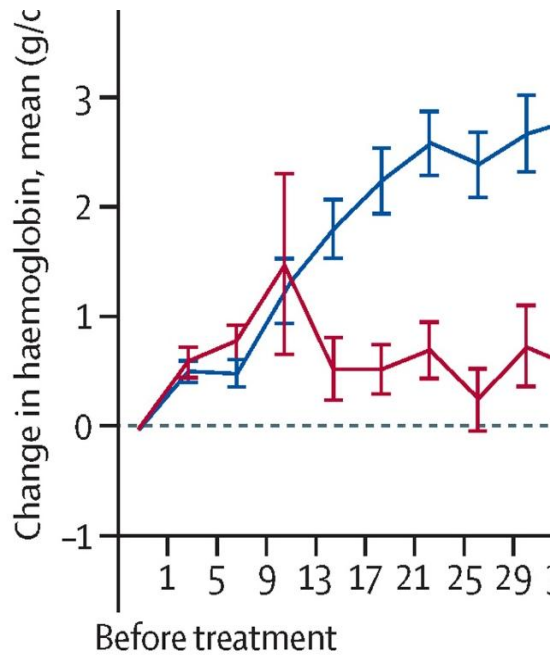
Median Hgb ↑ 3.5 g/dL

Durable TI > 1 year

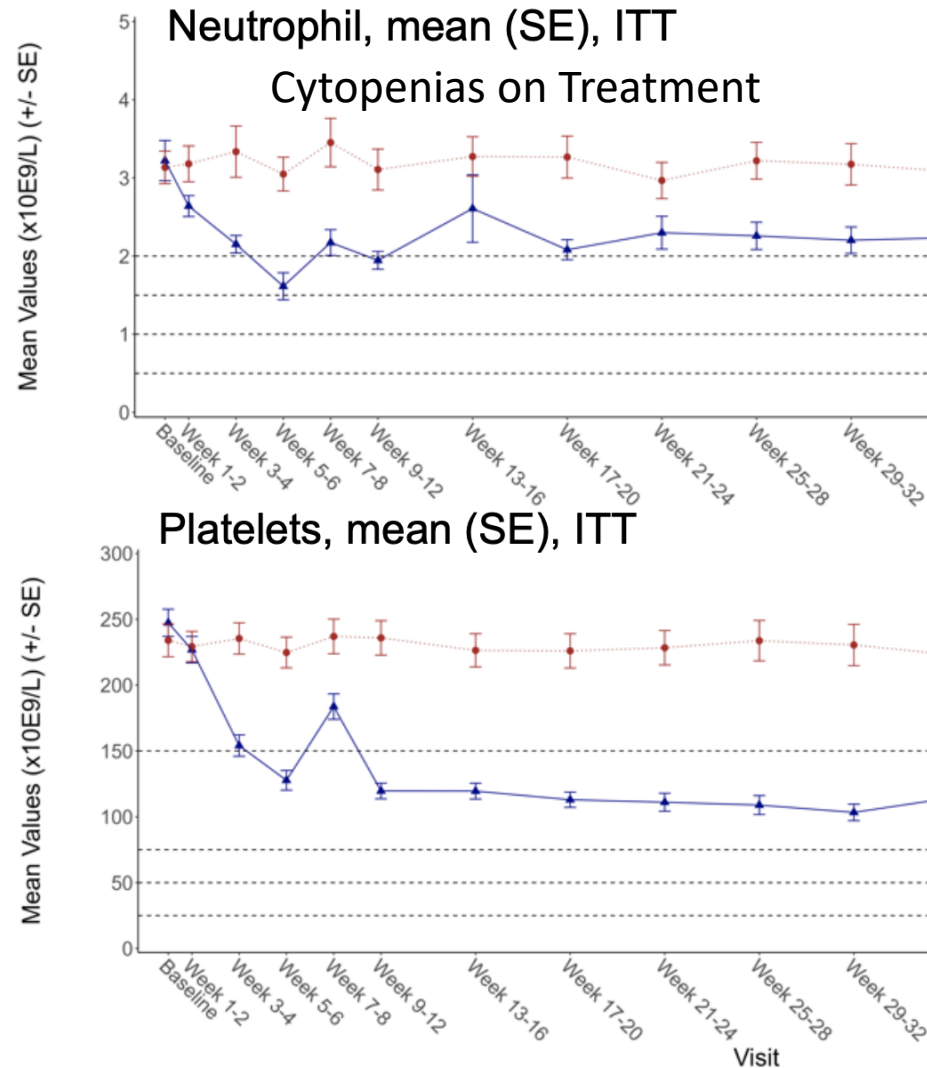
↓ VAF – Disease Modifying?



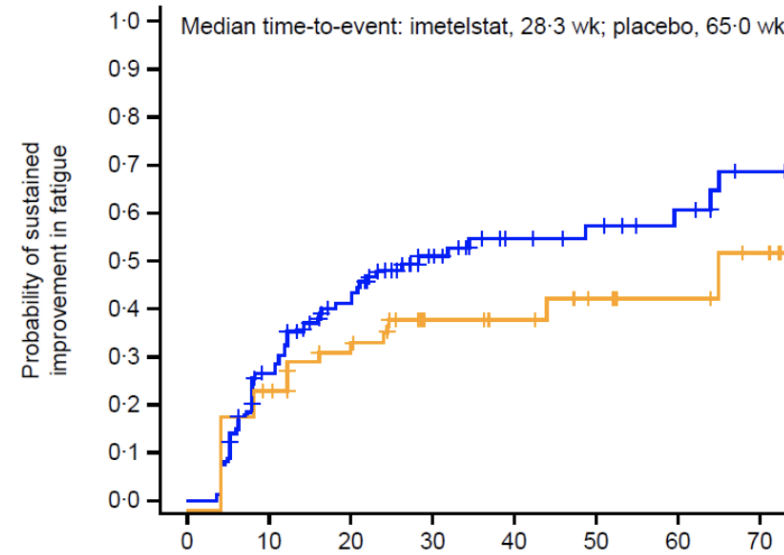
Things to consider when using this Imtelstat



Time to Response



Cytopenias on treatment



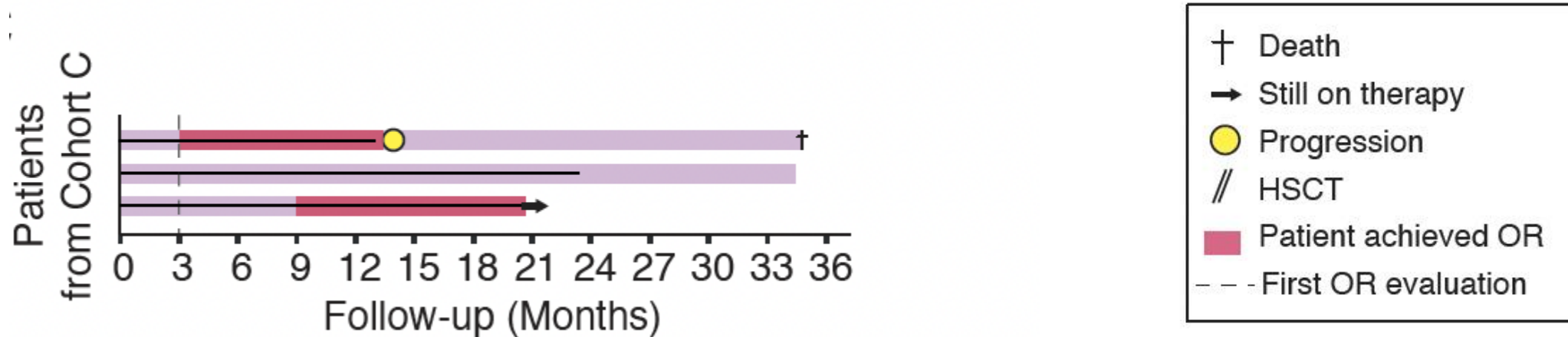
Fatigue improvement takes time

Targeted Therapies: Enasidenib Monotherapy in ESA Refractory LR- MDS (Ideal Phase 2 GFM/ EMSCO Study)

Number of patients	11
Adverse Events (Grade 3 or more)	5 patients experienced grade 3+ adverse events, with 2 related to ENA (thrombocytopenia and increasing bilirubin level), all resolved after temporary drug interruption.
Severe Adverse Events (SAE)	4 severe adverse events reported in 4 patients, none related to ENA.
Differentiation Syndrome	None reported.
Response Rate	6 out of 11 patients (55%) achieved complete response (CR) with transfusion independence.
Median Time to Response	3 cycles.
Transplant	2 patients were bridged to transplant after 4 and 7 cycles.
Survival	At data cut-off, none of the responders had lost response, and only one patient had died (not related to disease or ENA).
Median Follow-Up	29.9 months.
Median Overall Survival (OS)	Not reached.

Targeted Therapies: EPO R/R LR-MDS treated with ivosidenib

Pts were treated with **21-day cycles of IVO - 500 mg PO QD**



- Two of the 3 patients achieved CR, with transfusion independency, one after 3 cycles, one after 9 cycles
- One patient died 2 years after inclusion from progression after 13 cycles (DOR, 10 months)
- Two others are still alive without progression, one still in CR on therapy (20 cycles)
- No toxicity

Other Options to Consider

- Immunosuppressive therapy for Hypoplastic MDS
- Hypomethylating Agents are an option in LR MDS (discuss more in HR MDS setting)
- While not the first line, Consider Allogeneic transplant for appropriate patients

- Thrombocytopenia can be treated with Thrombopoietin agonists in LR MDS
 - (Romiplostim Plt response rate: 36.5%)
 - (Eltrombopag Plt response rate: 47%)
- Routine use of G-CSF not recommended for neutropenia

Data has shown there is hesitance to Use Disease-Modifying Therapy in Older Patients With MDS- Improvement in disease can lead to improved quality of life



Obrigado!

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