FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

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Patogenesi e conseguenze cliniche dell'anemia nelle MDS

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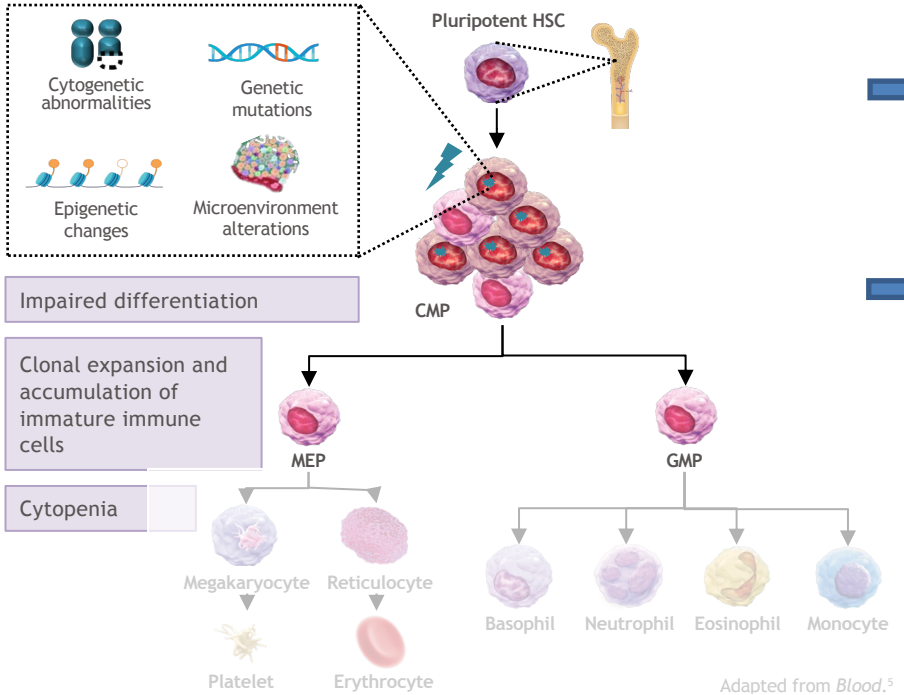
Disclosures of Elena Crisà

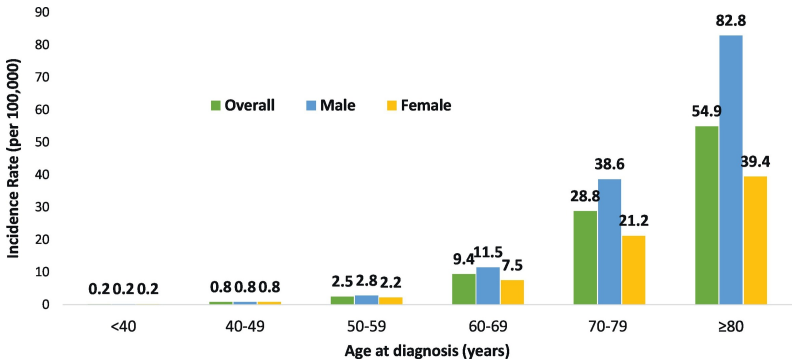
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS					x		
Glaxo						x	

Myelodysplastic Neoplasm



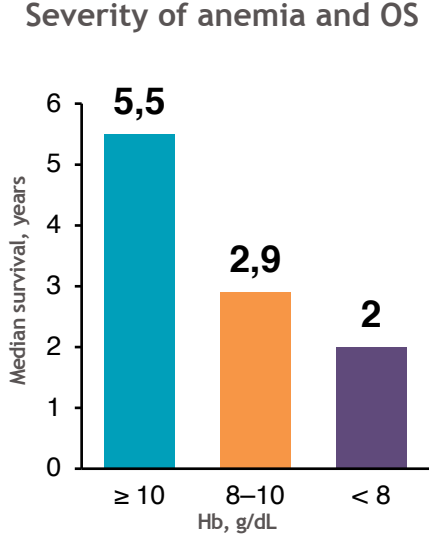
- Anemia
- Trombocytopenia
- Leukopenia

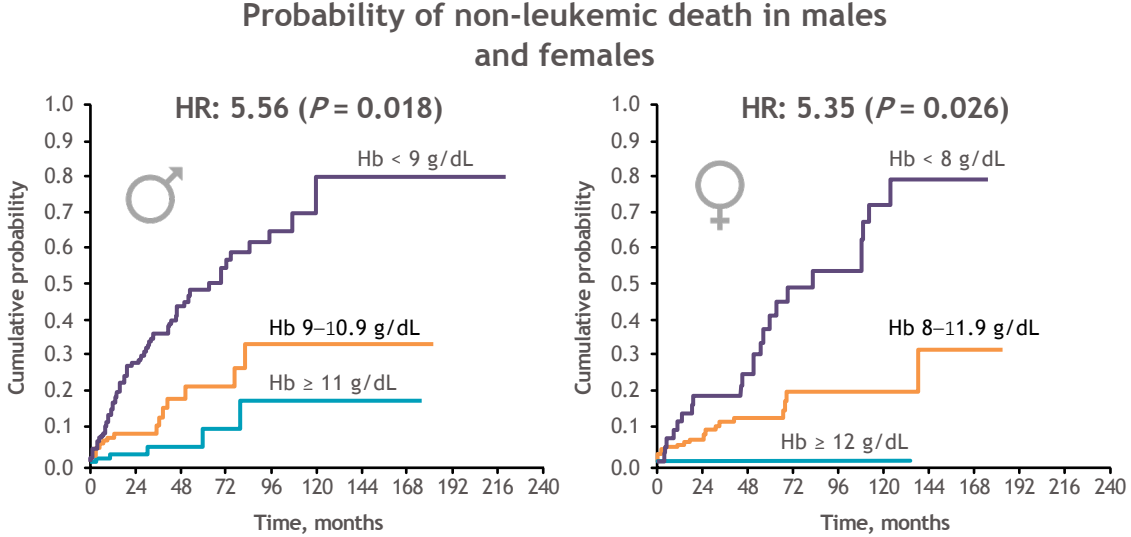
Increase in immature cells: blasts



Zeidan AM et, al Blood reviews 2019, Hellström-Lindberg E, et al. Haematologica. Adès L, et al. Lancet. 5. Shastri A, et al. Blood. 2017;129:1586–1594

Anemia occurs in up to 90% of patients with MDS resulting in significantly increased risk of mortality





1. Zeidan AM, et al. Blood Rev. 2019;34:1–15; Malcovati L, et al. Haematologica. 2011;96:1433–1440; Greenberg PL, et al. Blood. 2012;120:2454–2465 Filet et al Transfusion 2016;.

Mechanisms of Cytopenias in Early MDS

Increased apoptosis→ ineffective hematopoiesis→ cytopenia

- age-related defects in HSC: altered survival, dormancy and regenerative capacity
- age-related inflammatory microenvironment triggers the genetic insult

Mechanisms of Cytopenias in late MDS

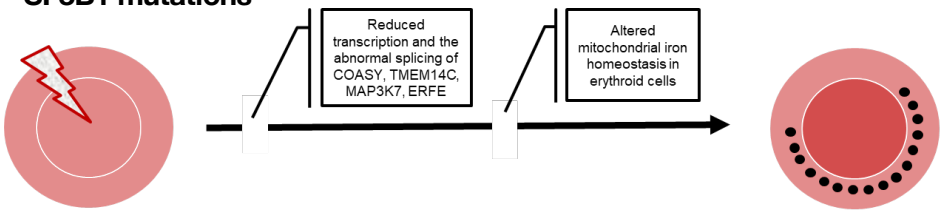
Impaired differentiation of mutant HSC →

- accumulation of progenitors
- acquisition of mutations that further drive the development of the disease.

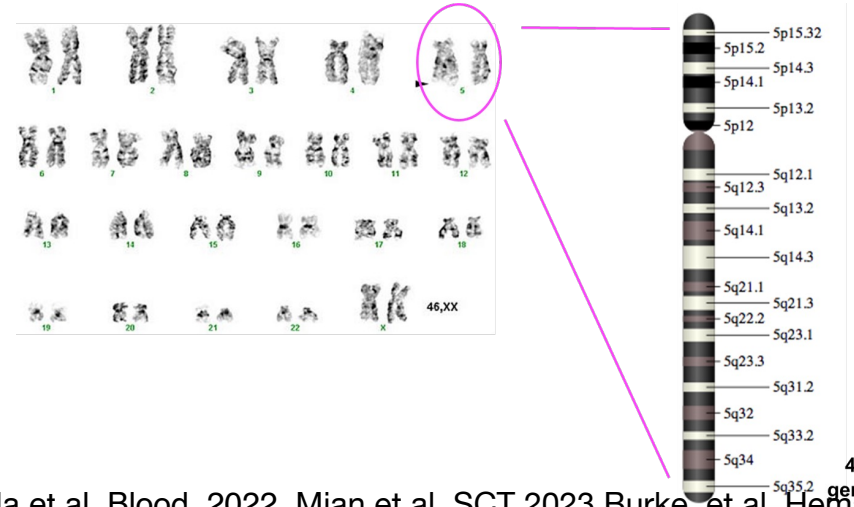
→ leukemia transformation

Anemia in MDS is due to ineffective erythropoiesis

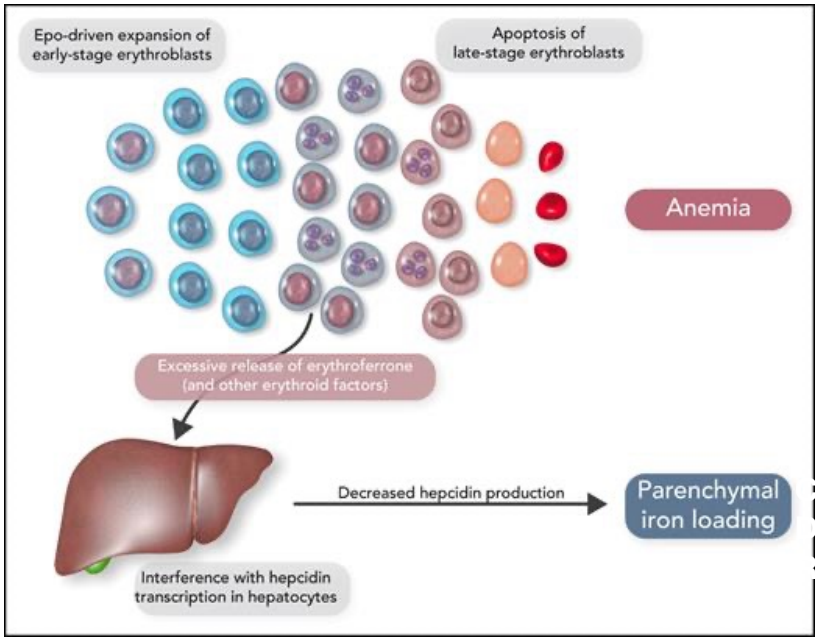
SF3B1 mutations



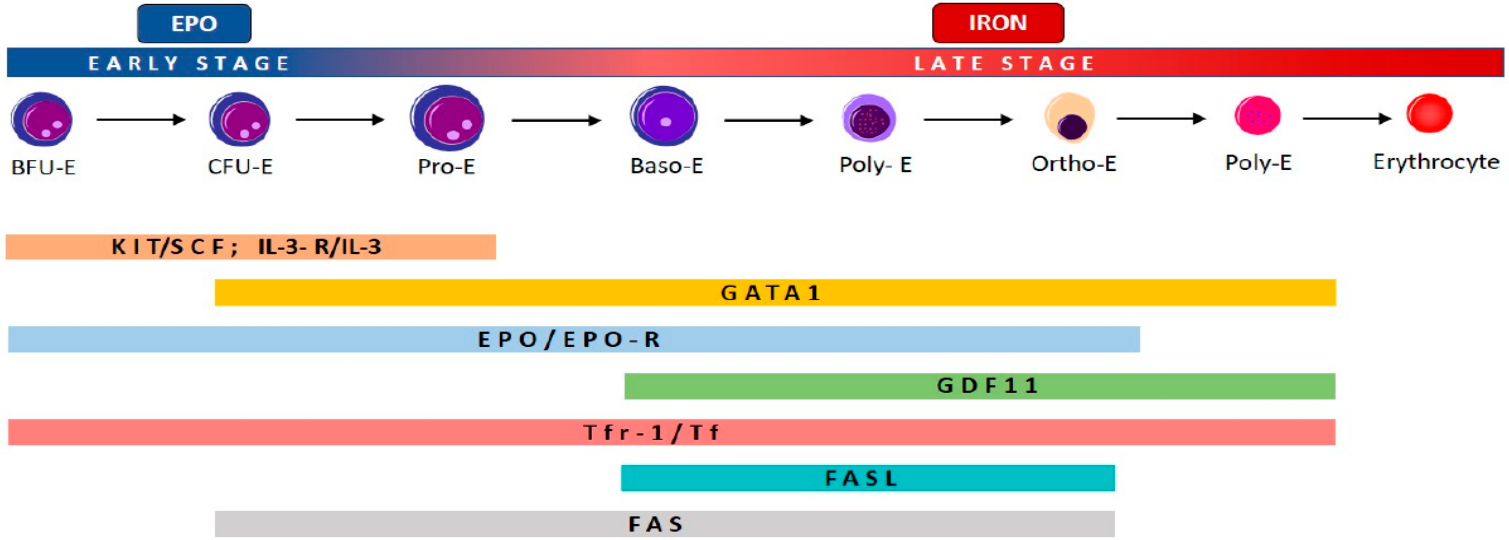
Erythroid cell with ring sideroblast



44 genes



Cazzola et al, Blood, 2022, Mian et al, SCT 2023,Burke, et al, Hemasphere, 2025, Boultwood et al. 2002. Blood

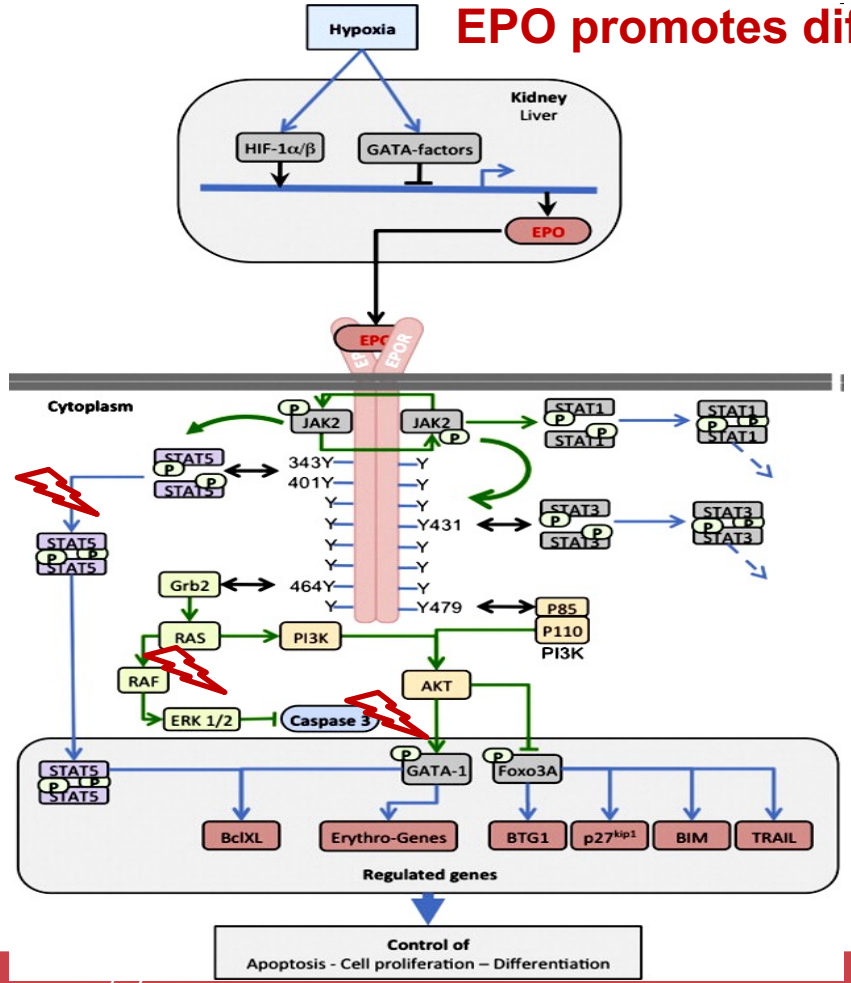


The main pathways involved in anemia in MDS are those regulated by

- Transforming growth factor (TGF)-β, which negatively regulates erythrocyte differentiation and maturation
- Erythropoietin (EPO), which acts on the early-stage erythropoiesis.

Gupta R et al, Hematol Oncol Clin North Am 2018; Oikonomidou PR et al, Blood Rew 2018; Bewersdorf JP et al, Leukemia 2019; Hata A et al, Cold Spring Harb Perpect Biol 2018

EPO promotes differentiation and decrease apoptosis of erythroblasts

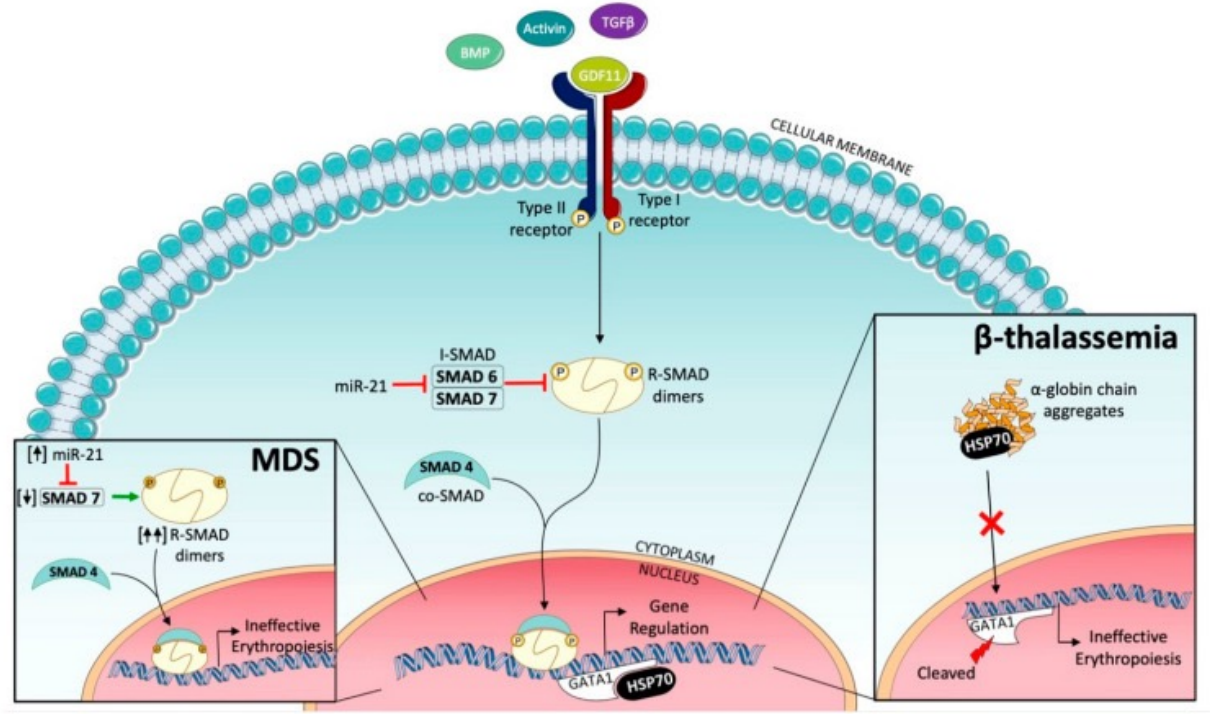


- **Described signaling pathways: JAK2/STAT5 (STAT3), PI3K/AKT, Grb2/RAS/RAF/MEK/ERK1/2.**

In MDS there is an alteration of EPO signaling pathway and an increase of pro apopthotic mechanism (FAS/CD 95)

S. Chateauvieux et al. Biochem Pharmacol 2011 Hoefslooot LH Blood 1997;Baxkx B Leukemia 1996

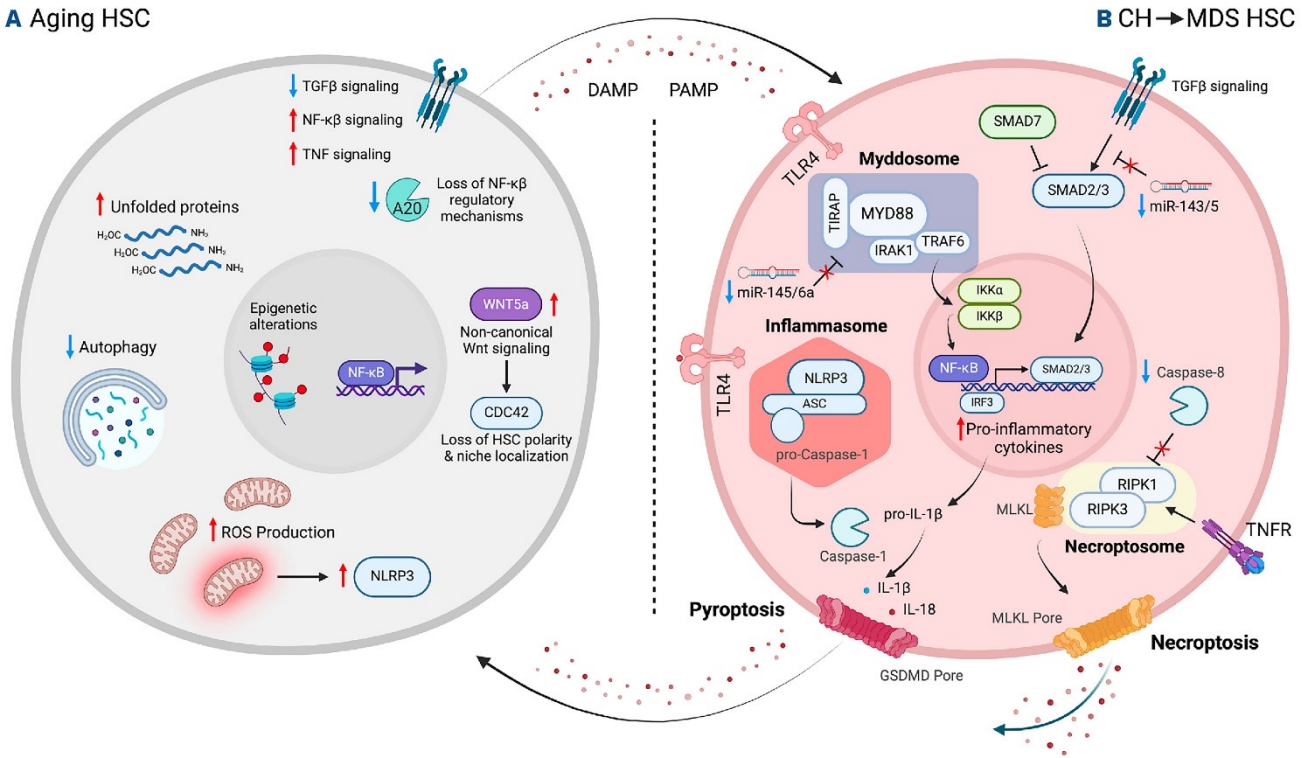
TGF-β superfamily signaling is altered in MDS



- MDS patients display an overactivation of SMAD2/3 signaling due to the altered expression of mir-21 and SMAD7

➔ luspatercept
➔ elritercept

Parisi S, et al. Int J Mol Sci. 2021

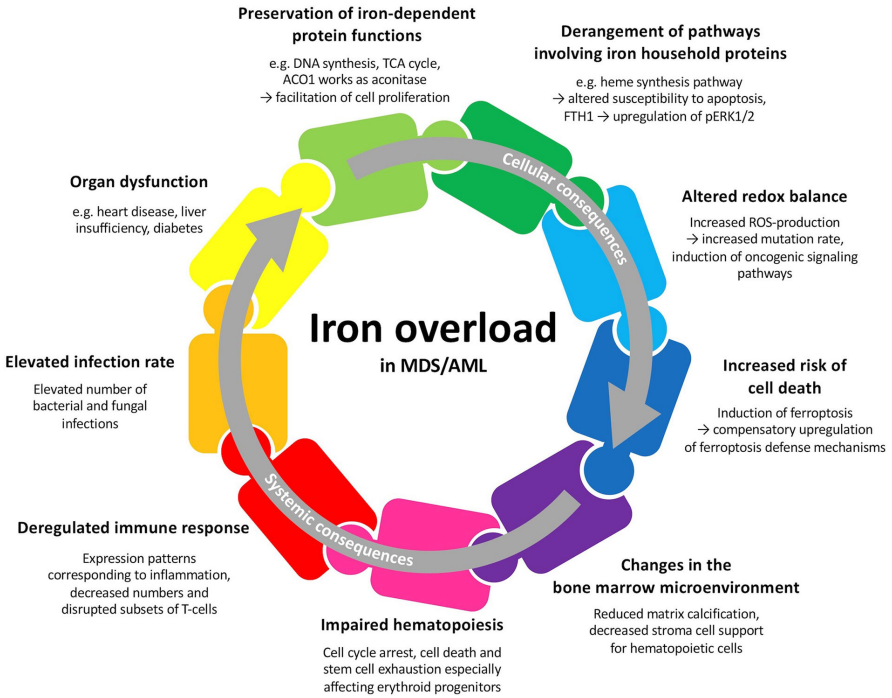


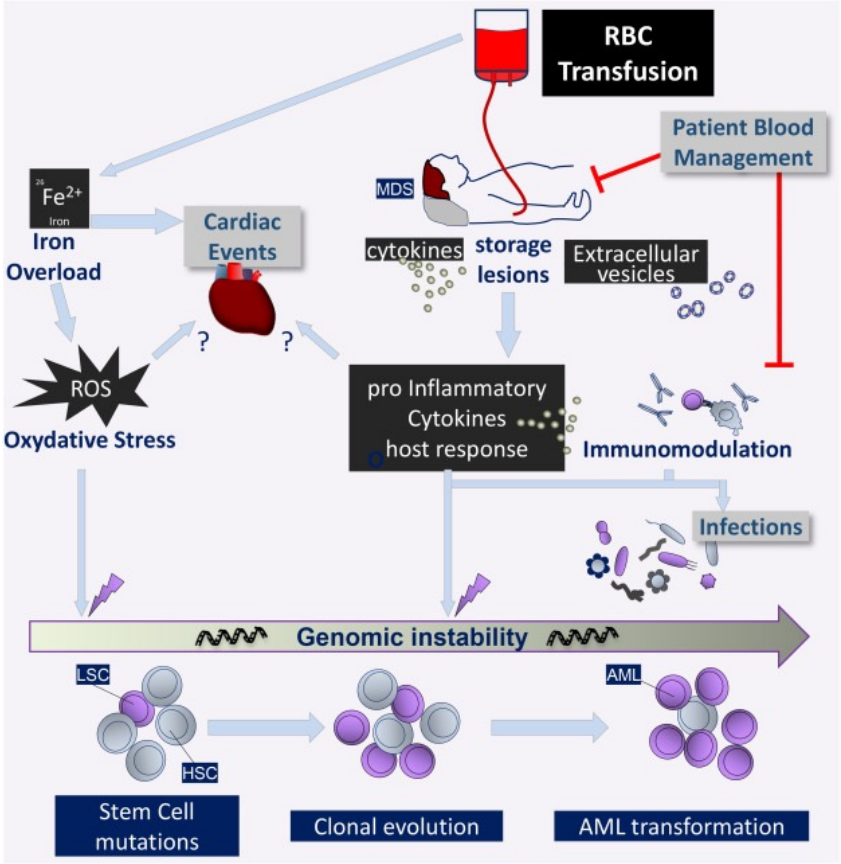
- **increased TGF-β signaling via SMAD** due to loss of the miR-143/5 negative regulators
- **Increase in programmed inflammatory cell death mechanisms** -> pro-inflammatory positive feedback cycle further triggering inflammatory pathways in neighboring HSC
- **dysregulated innate immune signaling** via TLR receptor triggering **of NF-κB**

DAMP: damage-associated molecular pathogens; PAMP: pathogen-associated molecular pathogens

Adapted from Villaume MT and Savona MR Haematologica 202

Impact of anemia and RBC transfusions on MDS patients

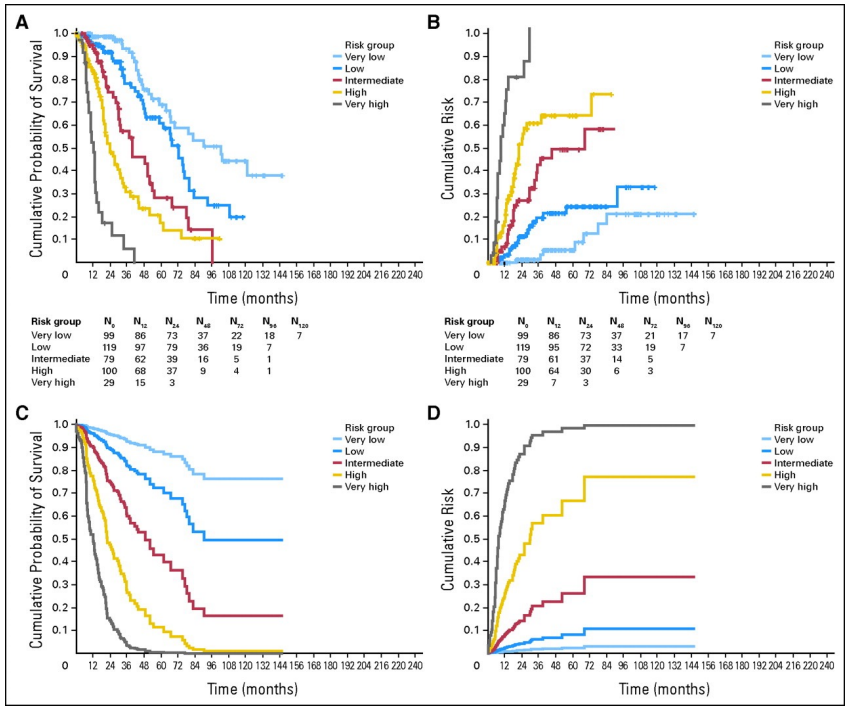




Kaphan E et al Blood reviews 2019

Impact of transfusion dependency in MDS

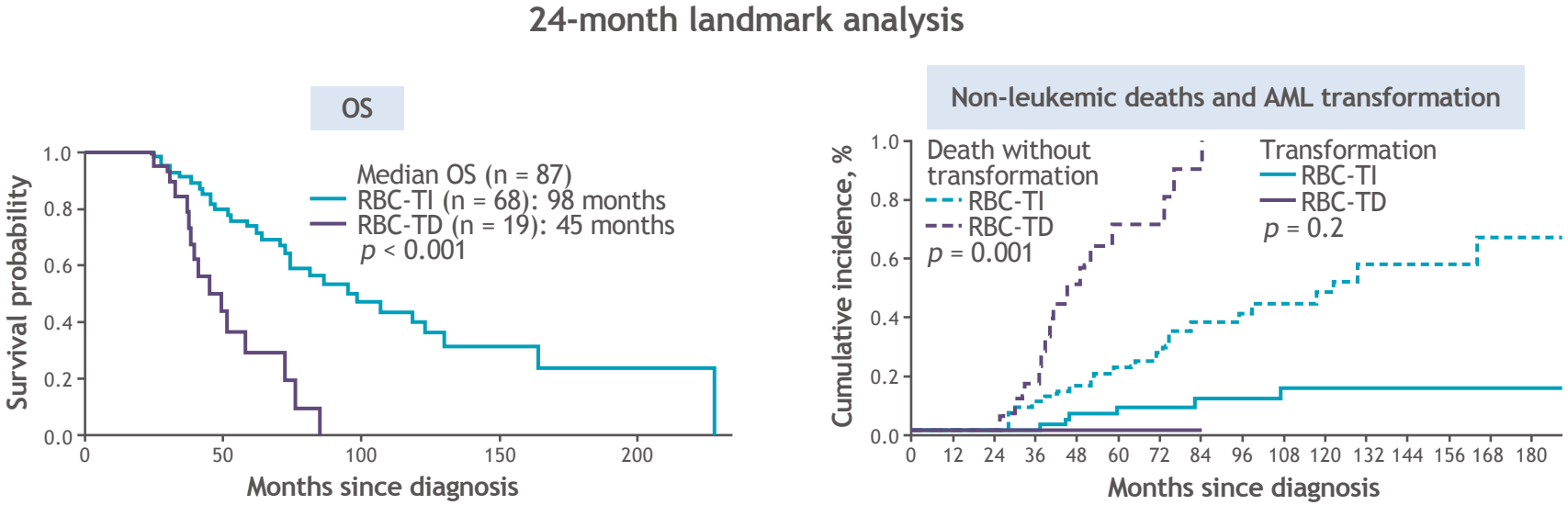
RBC-transfusion dependency (RBC-TD) is an independent prognostic factor for poor overall survival (OS) in the WHO classification-based prognostic scoring system (WPSS) for MDS patients



Malcovati et al JCO 2007

Impact of transfusion dependency in MDS

» Patients with LR-MDS and RBC-TD have significantly worse OS, more non-leukemic deaths, compared with patients who are RBC-TI



AML, acute myeloid leukemia; LR-MDS, low-risk myelodysplastic syndrome; MDS, myelodysplastic syndrome; OS, overall survival; RBC-TD, red blood cell transfusion dependence; RBC-TI, red blood cell transfusion independence; TD, transfusion dependence; TI, transfusion independence.

Hiwase DK, et al. Am J Hematol. 2017;92:508-514.

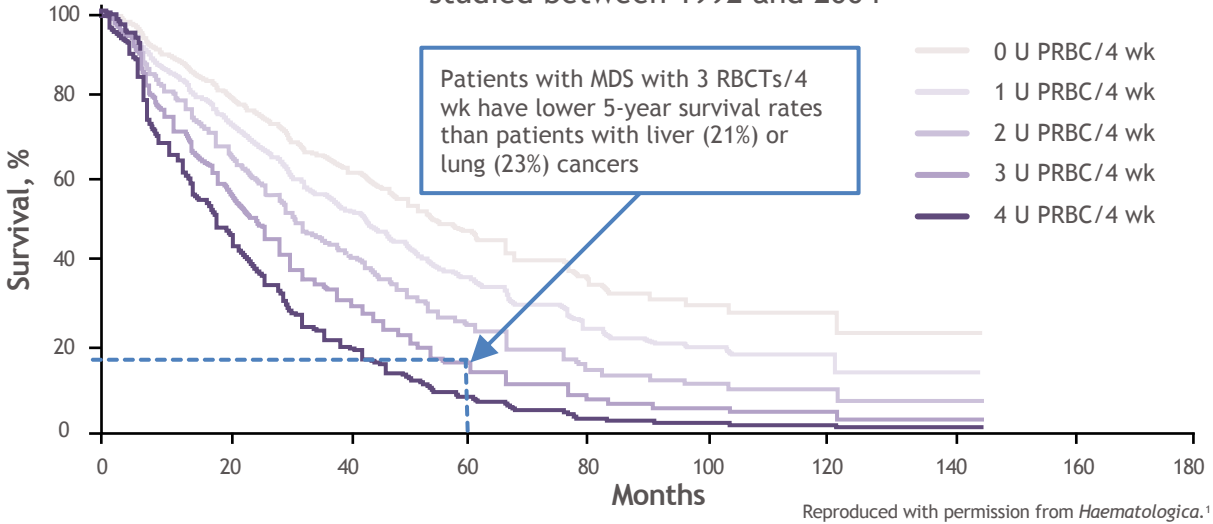
Severity of transfusion requirements can be associated with OS in patients with MDS[1]

TD is associated with worse prognosis compared to TI

56%
Decreased risk of death

Patients with MDS who are TI have a 56% decreased risk of death compared with those who are TD [HR, 0.44; 95% CI, 0.34-0.55]

Based on a retrospective cohort of 426 Italian patients with MDS studied between 1992 and 2004[1]

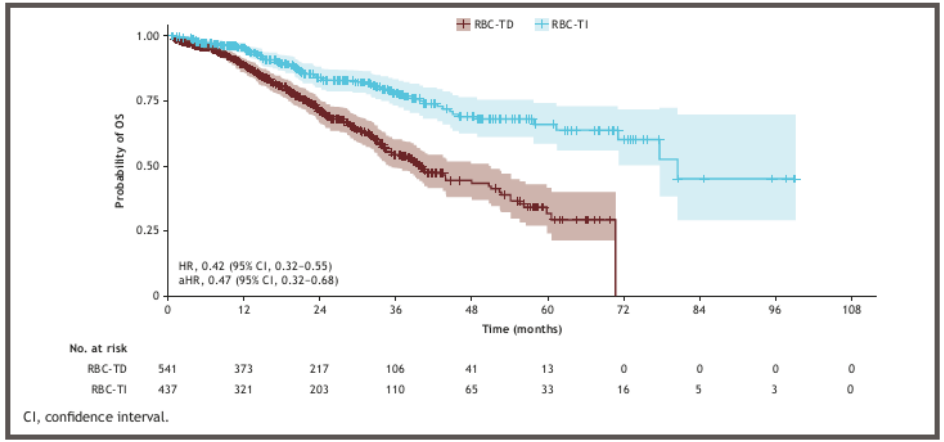


Reproduced with permission from *Haematologica*.[1]

1. Malcovati L, et al. Haematologica. 2006;91:1588–1590; 2. Braga Lemos M, et al. Eur J Haematol. 2021;107:3–23; 3. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. 5-year relative survival rates, 2012–2018, all stages by sex, all races, all ages. Available at: https://seer.cancer.gov/statistics-network/explorer/application.html. Accessed March 31, 2023.

Improving anemia and TI impact OS in lower-risk MDS

Figure 1. Kaplan-Meier curve for OS



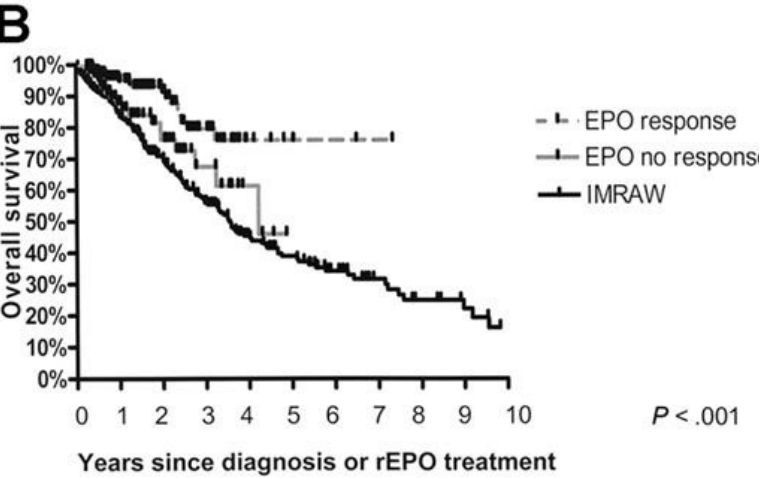
Unadjusted results indicated that patients who achieved ≥ 12 weeks of RBC-TI in the first 24 weeks had > 2 times greater OS (hazard ratio [HR], 0.42; 95% CI, 0.32-0.55)

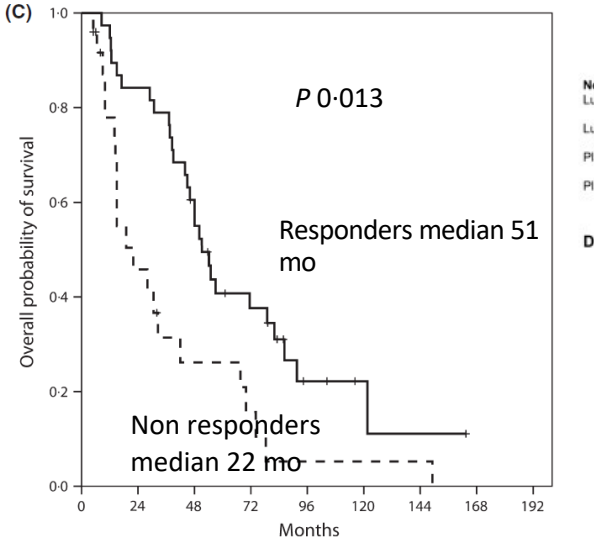
Among patients who became RBC-TI, those who had a mean Hb increase of ≥ 1.5 g/dL had approximately 2 times greater survival than those who did not (aHR, 0.53; 95% CI, 0.29-0.98), highlighting the benefi t gained from increased Hb levels

Individual patient data (IPD) meta-analyses were performed using 6 clinical trials among patients with TD LR-MDS:—Three luspatercept trials (COMMANDS [NCT03682536], MEDALIST [NCT02631070], and PACE [NCT01749514 and NCT02268383]) —Three lenalidomide trials (5013-MDS-0036 [NCT00065156], 5013-MDS-0047[NCT00179621], and 5013-MDS-0058 [NCT01029262])

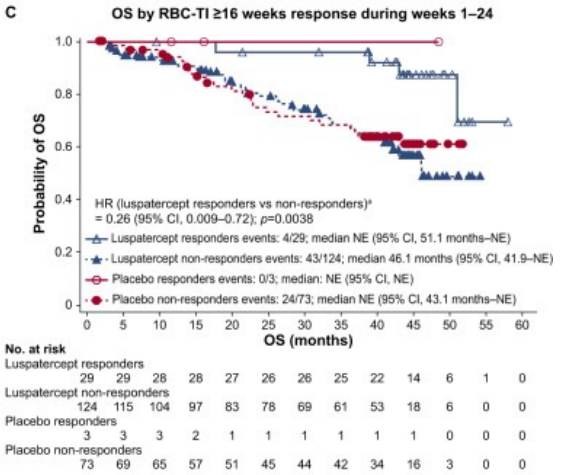
Malcovati L et al. Poster presentation at the 29th EHA Annual Congress; June 13-16, 2024; Madrid, Spain. Poster P782.

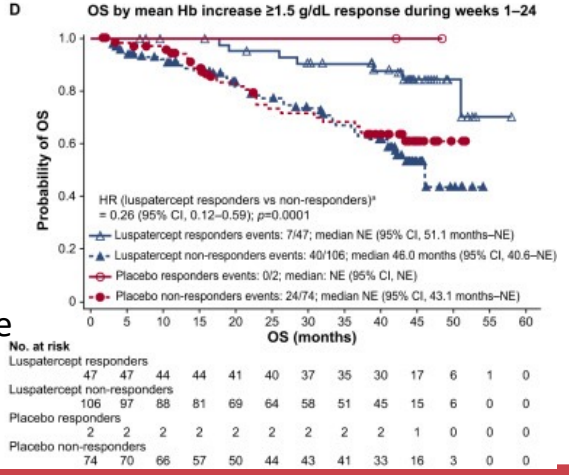
Improving anemia and TI impact OS in lower-risk MDS regardless treatment





OS according to erythroid response





Platzbecker et al , Leukemia 2023;Park S et al Blood 2008;Crisà BJH 2012

Goals of treatment for patients with MDS:

Priorities in low-risk MDS	Priorities in high-risk MDS
1 Improvement of cytopenia(s) Less transfusions Less iron overload	1 Delay disease progression Improve survival Cure
2 Tolerability of a given treatment Quality of life	2 Reduction of disease burden Improvement of cytopenia(s) Less transfusions
3 Delay disease progression Improve survival	3 Tolerability of a given treatment
4 Cure	4 Quality of life

» AML, acute myeloid leukemia; LR-MDS, lower-risk myelodysplastic syndromes; OS, overall survival; RBC, red blood cell.

1. Cogle CR, et al. Leuk Res. 2017;60:123–128; 2. Garcia-Manero G. Am J Hematol. 2015;90:831–841; 3. Germing U, et al. HemaSphere. 2019;3:e314.

Several studies have shown that health-related quality of life of patients with MDS is significantly worse compared with the general population

Physical problems

- **41%** of patients with MDs reported moderate or severe **mobility issues**[1]
- Suffering from MDS causes a substantial and persistent functional decrement in a variety of areas, partially due to fatigue[3.2]

QUALITY OF LIFE

Emotional problems

- **37.9%** of patients with MDS reported moderate or severe issues with **anxiety/depression**
- Patients have often viewed the **emetional impact of MDS as being more problematic** than the physical consequences[4]

Role functioning

- **36.1%** of patients with MDS repoted moderate or severe problems with **usual activities** (eg, work, housework, or leisure activities)[1.4]

Social functioning

- **34%** of patients receiving transfusions felf their blood transfusions were **burdening** their family[3]

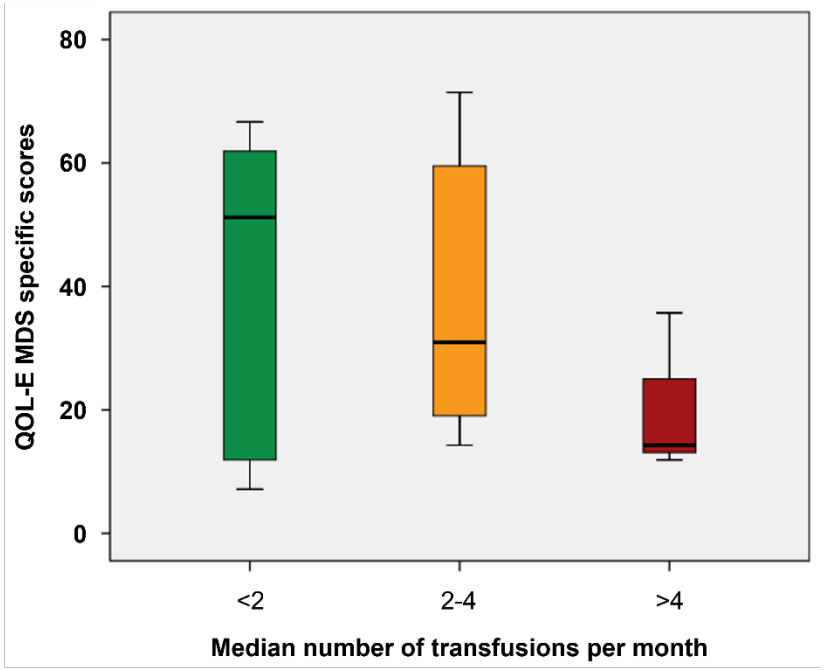
» Stauder R, et al. Leukemia. 2018; Ria R, et al. Clin Interv Aging. 2009; Oliva EN, et al. Blood Rev. 2021; Soper J, et al. Patient Relat Outcome Meas. 2022 Sekeres MA, et al. Oncologist. 2011

AIPASIM survey involving 259 patients and 105 caregivers

- **67% of patients received transfusions**. The increasing frequency of transfusions (26% <2 times per month; 61% 2-4 times per months, 13% >4 times per month) was associated with worse HM-PRO and QOL-E scores.
- Only **2%** received transfusions at home; however, **40% percent would prefer being transfused at home** (30% of those treated in the center of care and 50% of those treated in another center)

	Preferred place for transfusions Median scores		
	home	**hospital**	**P value**
HM-PRO scores			
physical behavior	64	42	0.001
Emotional behavior	54	40	0.002
Part A score	54	30	0.004
QOL-E			
functional	11	33	0.002
fatigue	31	36	0.020
treatment-outcome index	20	28	0.012

increasing frequency of transfusions was associated with worse HM-Pro (PB, SB and part A scores) and QOL-E scores (Soc , Fat, MDSS and Gen scores)



Box plot of QOL-E MDS specific scores according to transfusion frequency.

- For 70% (49/70) of TD-patients treatment impacted negatively on everyday life as compared to 49% (46/94) of TI-patients, *p*=0.011
- TD patients had significantly worse scores across all domains of QOL-E and HM -Pro

Crisà et al, Cancers 2025

CONCLUSION

- **Anemia is the prevalent cytopenia in MDS**
- **Anemia and transfusion dependence impact on OS and quality of life**
- **Anemia in MDS is still unmet clinical need as current available treatments (**rEPO, luspatercept, lenalidomide, iron chelation) **are limited**
- **Treatment of anemia should start early to avoid transfusions /reduce transfusion burden**
- **Possible future perspectives:** therapeutic intervention aimed at restoring hematopoietic homeostasis in the aging population and potentially even preventing MDS (inhibitors of inflammatory mediators, new targetable immune checkpoints..).

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