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Zeidan AM et al. ASH 2025 [Abstract 789]

Luspatercept reduces cardiac stress and improves cardiac function in a TET2-deficient mouse model with features of heart failure with preserved ejection fraction: evidence from phase 3 COMMANDS trial and preclinical studies

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Background and objective

- Luspatercept is an inhibitor of activin receptor–Smad2/3 signaling and is approved as first-line treatment of anemia in adult patients with LR-MDS based on the COMMANDS trial (NCT03682536)[1]
- Common MDS-related somatic mutations (eg, *SF3B1*, *TET2*, *DNMT3A*, *ASXL1*) lead to dysregulated immune signaling, which may drive both hematologic malignancies and cardiovascular complications[1,2]
  - Patients with MDS also exhibit elevated NT-proBNP levels, a biomarker of cardiovascular morbidity and mortality[3]
- Recently, a higher prevalence of *TET2* and *SF3B1* mutations was reported in patients with HFpEF[4]
- In preclinical models, loss of TET2 has been shown to drive HFpEF pathogenesis and enhance pro-inflammatory cytokine production[5]
- Currently, no treatments are available to address CVD risk in patients with MDS

Objective: to investigate the cardioprotective effects of luspatercept in patients with LR-MDS and in a TET2-deficient HFpEF-like mouse model

CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; NT-proBNP, N-terminal pro-brain natriuretic peptide; TET2, ten-eleven translocation methyl-cytosine dioxygenase 2.

1. Platzbecker U et al. *Lancet*. 2023;402:373–385. 2. Villaume MT, Savona MR. *Haematologica*. 2025;110:283–299. 3. Alonso-Fernandez-Gatta M et al. *Br J Haematol*. 2021;195:536–541. 4. Pandey A et al. *Circulation*. 2025;151:1622–1625. 5. Cochran JD et al. *Circulation*. 2023;148:1165–1178.

COMMANDS: study design

COMMANDS (NCT03682536) is a global, phase 3, open-label, randomized controlled trial for the treatment of anemia due to IPSS-R very low–, low-, or intermediate-risk MDS[1]

Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low-, or intermediate-risk MDS (with or without RS) by WHO 2016 classification, with < 5% BM blasts[a]
- Required RBC transfusions (2–6 pRBC U/8 weeks, minimum of 8 weeks prior to randomization)
- ESA-naive
- Endogenous sEPO < 500 U/L

R 1:1

Luspatercept
1.0 mg/kg SC Q3W
titration up to 1.75 mg/kg
(n = 182)

Epoetin alfa[b]
450 IU/kg SC QW
titration up to 1050 IU/kg
(n = 181)

Response assessments at Day 169 and then every 24 weeks thereafter

End of treatment

- Due to lack of clinical benefit[c] or disease progression per IWG 2006 criteria

Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, and survival for 5 years from first dose

Primary endpoint

- RBC-TI for ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (Weeks 1-24)

Select secondary endpoints

- RBC-TI for ≥ 12 weeks (Weeks 1-24)
- Duration of RBC-TI ≥ 12 weeks (Weeks 1-EOT)
- OS
- Progression to AML
- Safety

Study assessments

Serum and bone marrow samples were analyzed at baseline and Week 24 using proteomics in COMMANDS trial patient samples

Genomic analysis

Next-generation sequencing[d] of 82 myeloid-specific genes was performed on baseline BMMCs

Statistical analysis

Prognostic factors were evaluated for survival outcomes using multivariable Cox regression

AML, acute myeloid leukemia; BMMC, bone marrow mononuclear cell; BM, bone marrow; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HR-MDS, higher-risk myelodysplastic syndromes; IPSS-R, International Prognostic Scoring System-Revised; IU, international units; IWG, International Working Group; OS, overall survival; pRBC, packed red blood cell; Q3W, once per 3 weeks; QW, once per week; R, randomized; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; SC, subcutaneous; sEPO, serum erythropoietin; U, units; WHO, World Health Organization.

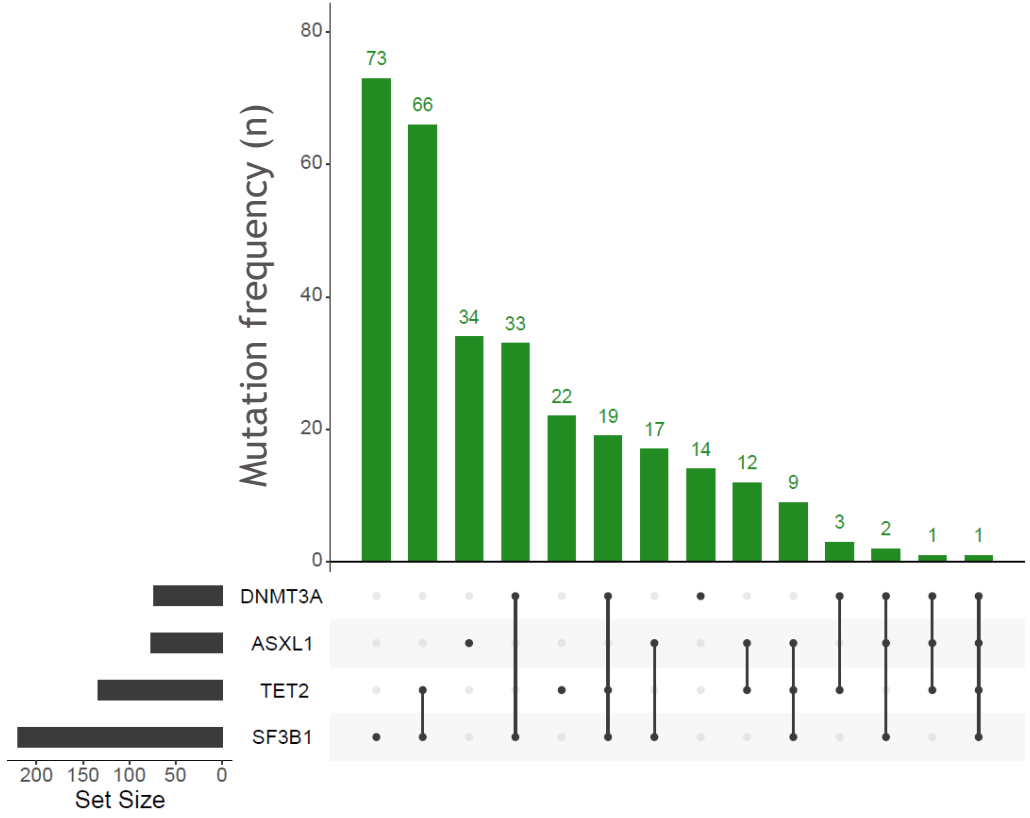
[a]Patients with del(5q) were excluded. [b]Two patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose. [c]Clinical benefit was defined as transfusion reduction of ≥ 2 pRBC U/8 weeks versus baseline.

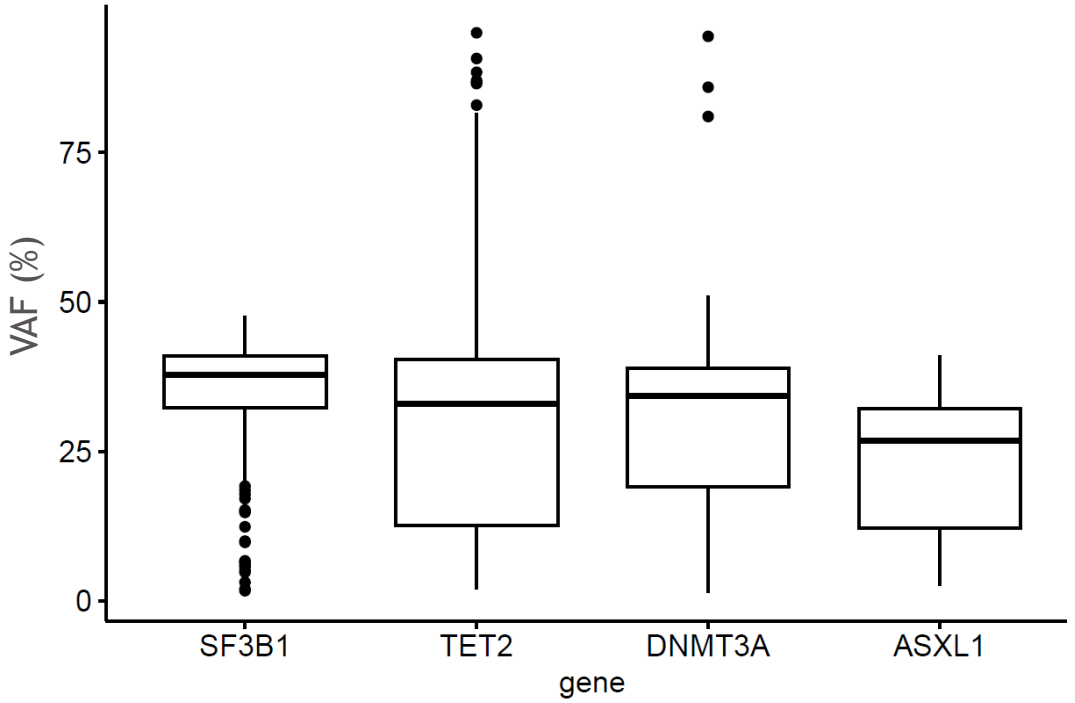
[d]n = 350; ≥ 2400 × exon coverage; 3% sensitivity; NovaSeq 6000 (Illumina®).

1. Platzbecker U et al. *Lancet*. 2023;402:373-385.

COMMANDS: prevalence of the most frequent MDS-related mutations

- At BL, 87% (306/350) of the profiled population had ≥ 1 of the most frequent MDS-related mutations (eg, *SF3B1*, *TET2*, *DNMT3A*, *ASXL1*), with a median VAF ranging from 3% to 50%





BL, baseline; VAF, variant allele frequency.

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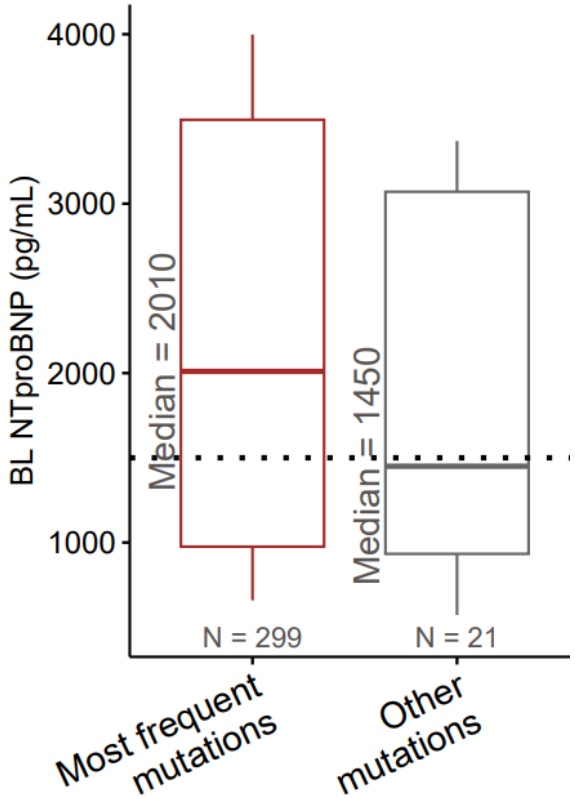
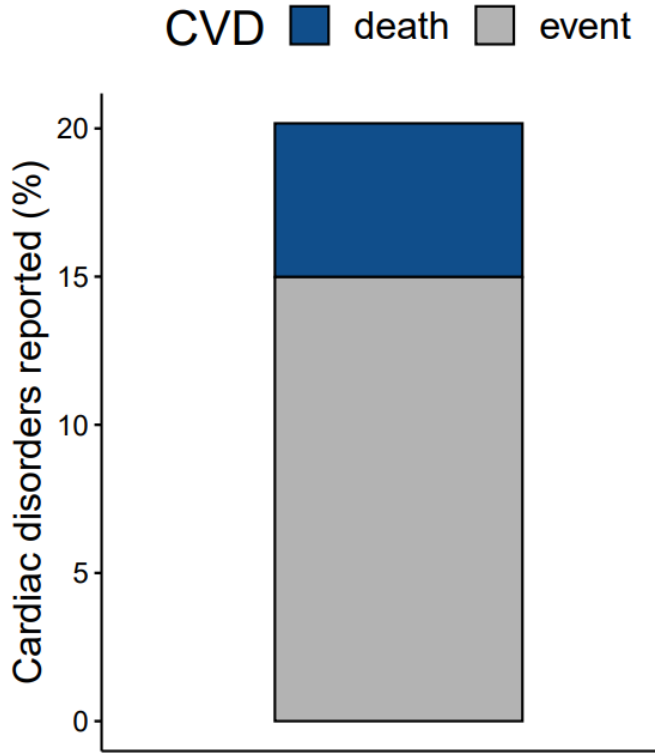
COMMANDS: NT-proBNP levels and incidence of cardiac disorders in patients with common MDS-related mutations

- High NT-proBNP levels were observed in patients harboring common MDS-related mutations (eg, *SF3B1*, *TET2*, *DNMT3A*, *ASXL1*)
- Cardiac disorders reported as AEs or cause of death (~20%) were predominantly associated with somatic mutations in *TET2*, *SF3B1*, *DNMT3A*, *and ASXL1* (~**89% of total cardiac AEs**)





AE, adverse event.

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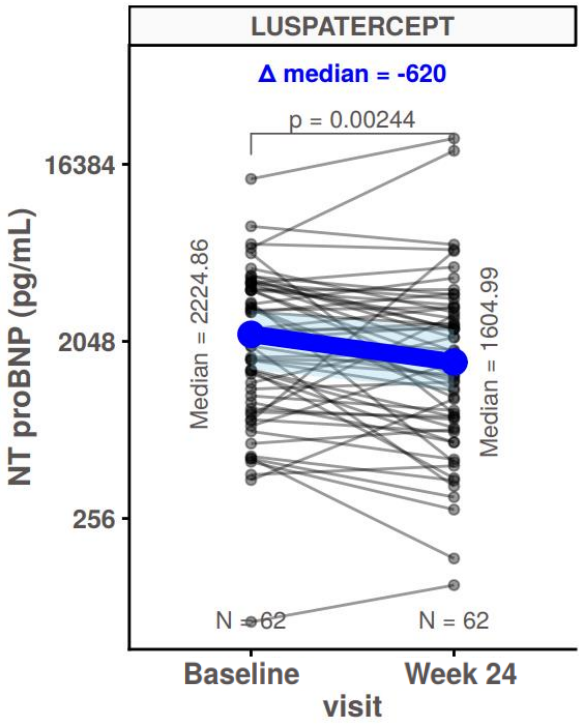
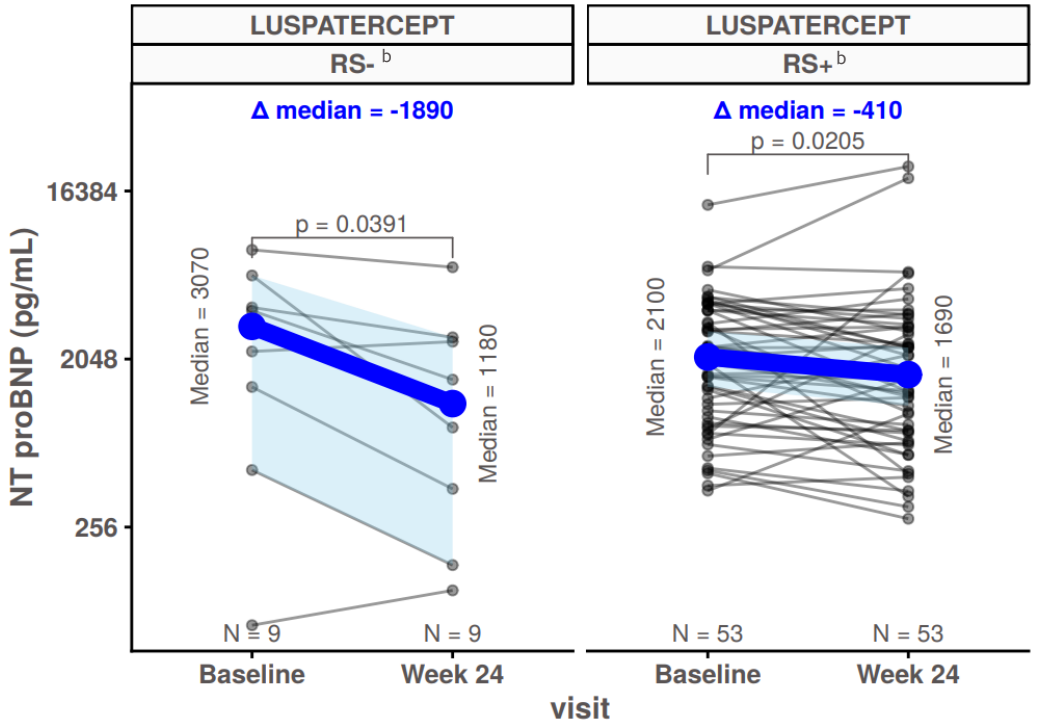
COMMANDS: change in NT-proBNP levels in patients who achieved the primary endpoint following luspatercept

- Luspatercept treatment significantly lowered NT-proBNP levels in responders[a] (**overall ~28% reduction from BL at Week 24;** *P* = 0.002; **paired analysis**)
  - **~61% reduction in NT-proBNP levels from BL at Week 24** was observed in patients with LR-MDS and RS− status (n = 9[b]; *P* = 0.03), a subgroup of MDS that is associated with poor prognosis[1]
  - **~20% reduction in NT-proBNP levels from BL at Week 24** was observed in patients with LR-MDS and RS+ status (n = 53[b]; *P* = 0.02)





[a]Includes all patients who achieved the primary endpoint of RBC-TI ≥ 12 weeks, with a concurrent mean Hb increase of ≥ 1.5 g/dL (Weeks 1–24).
[b]Data are among responders (all patients who achieved the primary endpoint of RBC-TI ≥ 12 weeks, with a concurrent mean Hb increase of ≥ 1.5 g/dL [Weeks 1–24]) who had NT-proBNP measurements available at BL and at Week 24.
1. Jain AG et al. *Haematologica*. 2024;109:2157-2164.

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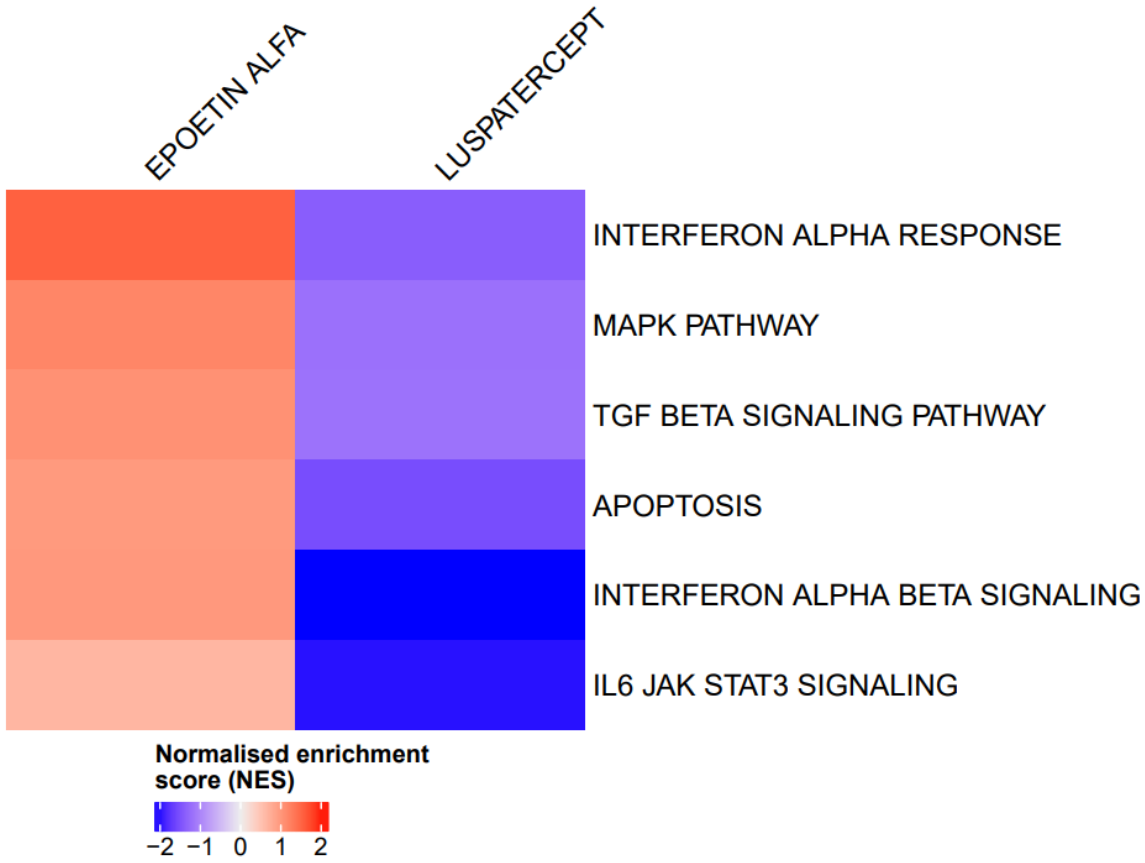
COMMANDS: paired comparison of inflammatory pathways at BL versus Week 24 in patients who achieved the primary endpoint

- In responders,[a] proteomic analysis revealed downregulation of inflammatory pathways with luspatercept compared with epoetin alfa



IL, interleukin; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor.
[a]Includes all patients who achieved the primary endpoint of RBC-TI ≥ 12 weeks, with a concurrent mean Hb increase of ≥ 1.5 g/dL (Weeks 1–24).

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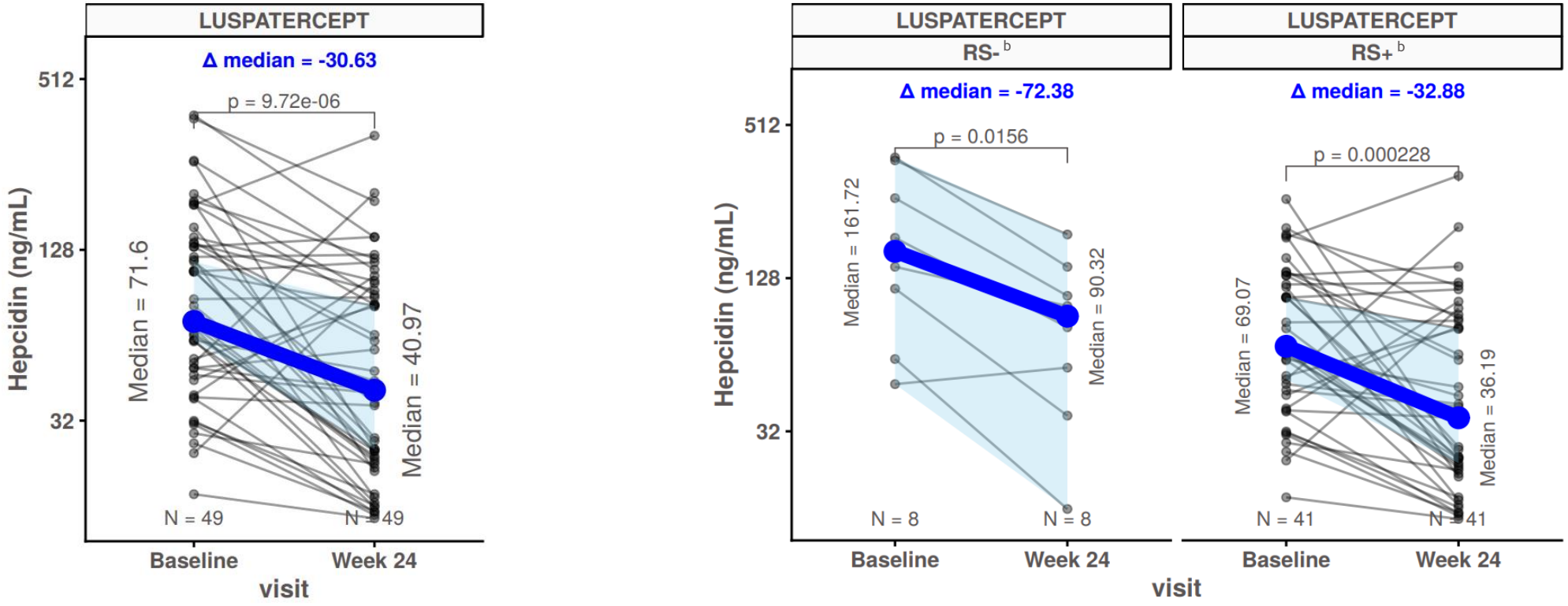
COMMANDS: modulation of hepcidin levels in patients who achieved the primary endpoint following luspatercept

- Hepcidin levels are associated with iron homeostasis and are also linked to inflammation and CVD[1]
- Luspatercept treatment significantly lowered hepcidin levels in responders[a] from the COMMANDS trial (**overall ~43% reduction from BL at Week 24;** *P* = 9.72e-06; **paired analysis**)



[a]Includes all patients who achieved the primary endpoint of RBC-TI ≥ 12 weeks, with a concurrent mean Hb increase of ≥ 1.5 g/dL (Weeks 1–24).
[b]Data are among responders (all patients who achieved the primary endpoint of RBC-TI ≥ 12 weeks, with a concurrent mean Hb increase of ≥ 1.5 g/dL [Weeks 1–24]) who had hepcidin measurements available at BL and at Week 24.

1. Anand IS, Gupta P. *Circulation*. 2018;138:80-98.

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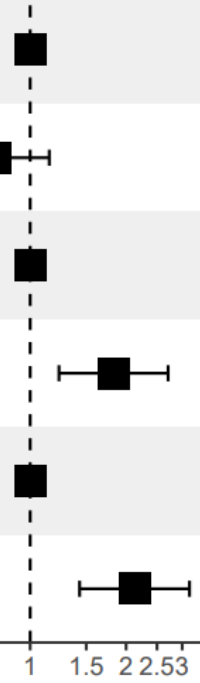
COMMANDS: multivariable analysis of prognostic factors in patients with the most frequent MDS-related mutations

- In a multivariable Cox regression analysis of prognostic factors, elevated NT-proBNP and hepcidin levels carried a higher risk of mortality in patients with the most frequent MDS-related somatic mutations
- Treatment with luspatercept was associated with a reduced risk of mortality compared with epoetin alfa; however, this difference was not statistically significant (*P* = 0.208)

Variable		n	Hazard ratio	*P*
ARM	EPOETIN ALFA	137	Reference	
	LUSPATERCEPT	138	0.78 (0.53, 1.15)	0.208
BL_NTproBNP	Low	136	Reference	
	High	139	1.83 (1.23, 2.71)	0.003
BL_Hepcidin	Low	148	Reference	
	High	127	2.13 (1.43, 3.16)	< 0.001



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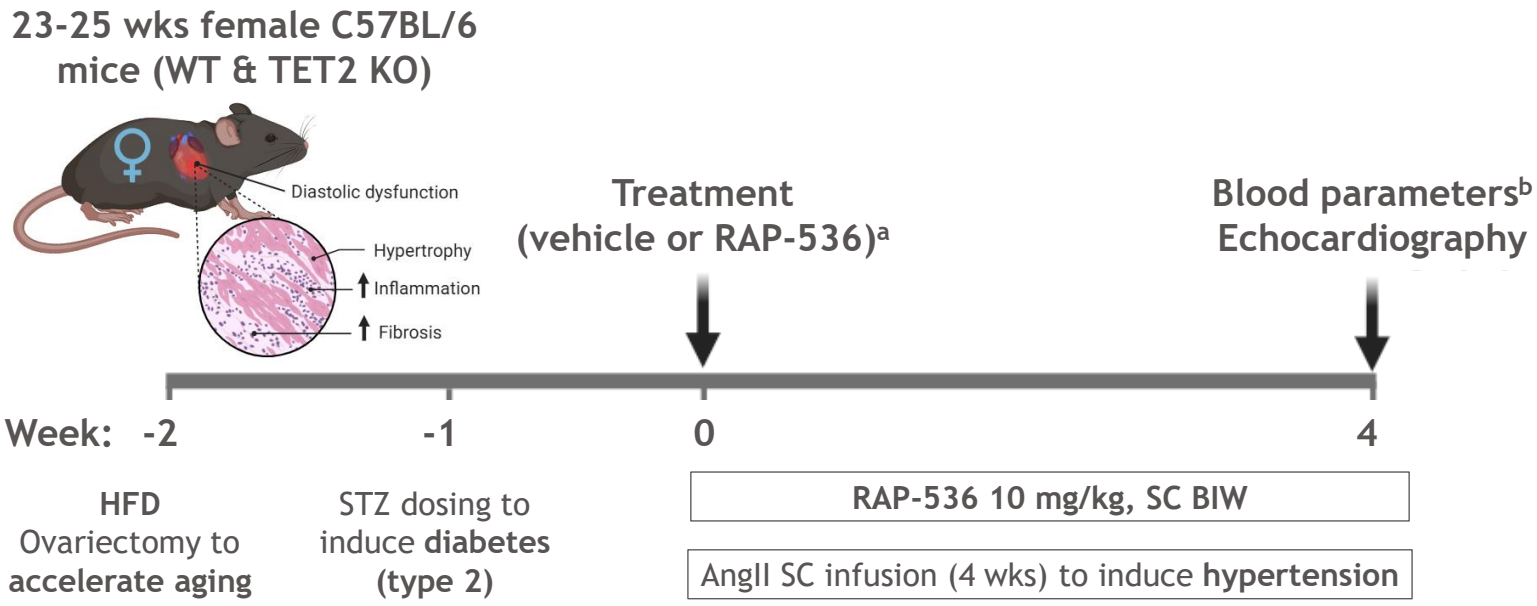
Preclinical HFpEF-like mouse model

- **Anemia** is common in patients with HF (30%–50%)[1] and is an independent risk factor for HFpEF
- The most frequent **underlying cause of anemia** is inflammation and chronic disease[1]
- **Anemia** is associated with **poor** clinical **outcomes**[1,2]
- Hb < 13.9 g/dL in female mice is considered anemia[3] (in the TET2 KO HFpEF-like model, Hb = 13.54 g/dL)

- Murine analog of luspatercept (RAP-536) was used in an experimental HFpEF-like model in WT and TET2 KO C57BL/6 mice
- Blood parameters were measured following 4 weeks of treatment with RAP-536
- Echocardiographic assessment was performed for cardiac hypertrophy and function

HFpEF-like model: HFD, hypertension, aging, diabetes[4]



AngII, angiotensin II; BIW, biweekly (twice per week); HF, heart failure; HFD, high-fat diet; KO, knockout; SC, subcutaneous; STZ, streptozocin; wk, week; WT, wild-type.
[a]RAP-536 is a murine analog of luspatercept. [b]Blood parameters included B-type natriuretic peptide levels, complete blood count, and Hb levels.
1. Anand IS, Gupta P. *Circulation*. 2018;138:80-98. 2. Groenveld HF et al. *J Am Coll Cardiol*. 2008;52:818-827. 3. Turner PV et al. *J Am Assoc Lab Anim Sci*. 2011;50:680-685. 4. Created in BioRender. Hasan, M. (2025) https://BioRender.com/3fy2ymt.

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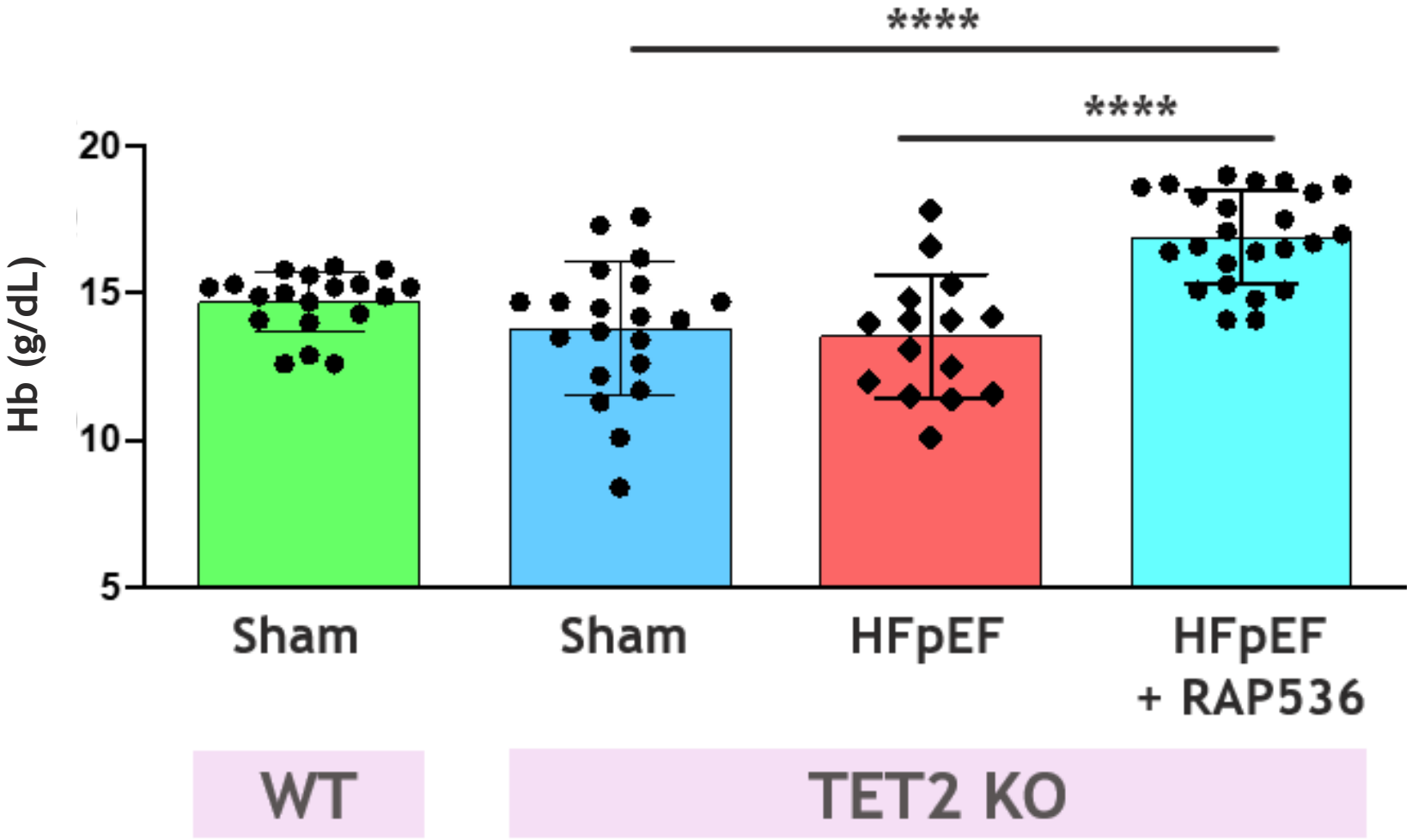
HFpEF-like model: evaluation of the murine analog of luspatercept (RAP-536) on TET2 KO-induced anemia

- The murine analog of luspatercept (RAP-536) alleviates TET2 KO-associated anemia in the HFpEF-like model



**** $P < 0.0001$.

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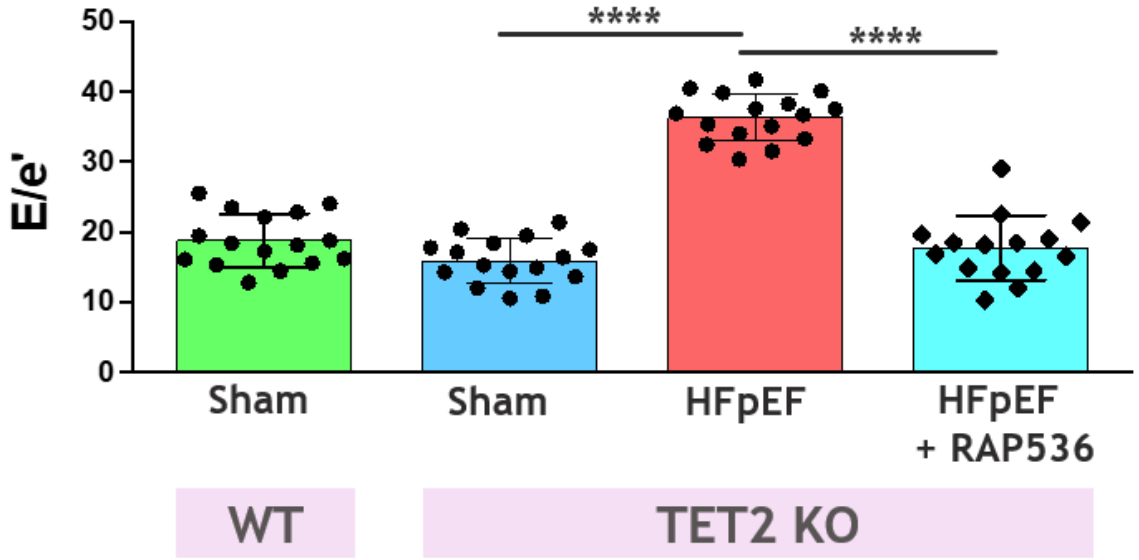
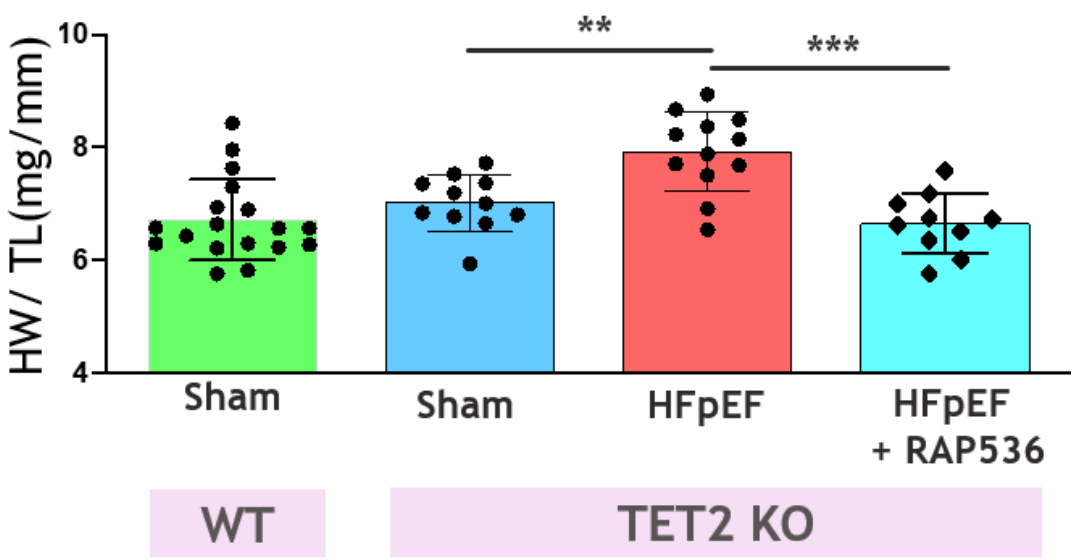
HFpEF-like model: effect of RAP-536 on diastolic dysfunction and cardiac hypertrophy

- The murine analog of luspatercept (RAP-536) ameliorates diastolic dysfunction and cardiac hypertrophy in the HFpEF-like model

E/e': measure of diastolic dysfunction[a]



HW/TL[b]: measure of cardiac hypertrophy



E/e', echocardiography measure; HW, heart weight; TL, tibia length.
**P = 0.003; ***P = 0.0004; ****P < 0.0001.
[a]Estimate of left ventricular filling pressure; increase in E/e' is suggestive of diastolic dysfunction or HFpEF. [b]HW was normalized to TL.

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Summary

- In the COMMANDS trial, patients with frequent MDS-related somatic mutations (eg, *SF3B1*, *TET2*, *DNMT3A*, *ASXL1*) exhibited markedly elevated NT-proBNP levels
- Luspatercept treatment reduced inflammatory signaling and decreased levels of NT-proBNP (a cardiac stress marker) and hepcidin (an iron homeostasis marker) in the COMMANDS trial
  - Robust reduction in NT-proBNP levels was observed in RS− patients, a subgroup of LR-MDS associated with poor prognosis
- Multivariable Cox regression analyses in patients with frequent MDS-related mutations in the COMMANDS trial showed that high NT-proBNP and hepcidin levels are independent risk factors for mortality
  - Treatment with luspatercept reduced the risk of mortality associated with elevated levels of NT-proBNP and hepcidin compared with epoetin alfa
- The murine analog of luspatercept (RAP-536) improved anemia and cardiac function in a TET2-deficient mouse model that exhibited HFpEF features

These results demonstrate the potential cardioprotective effects of luspatercept in patients with anemia and HFpEF with common MDS-related somatic mutations

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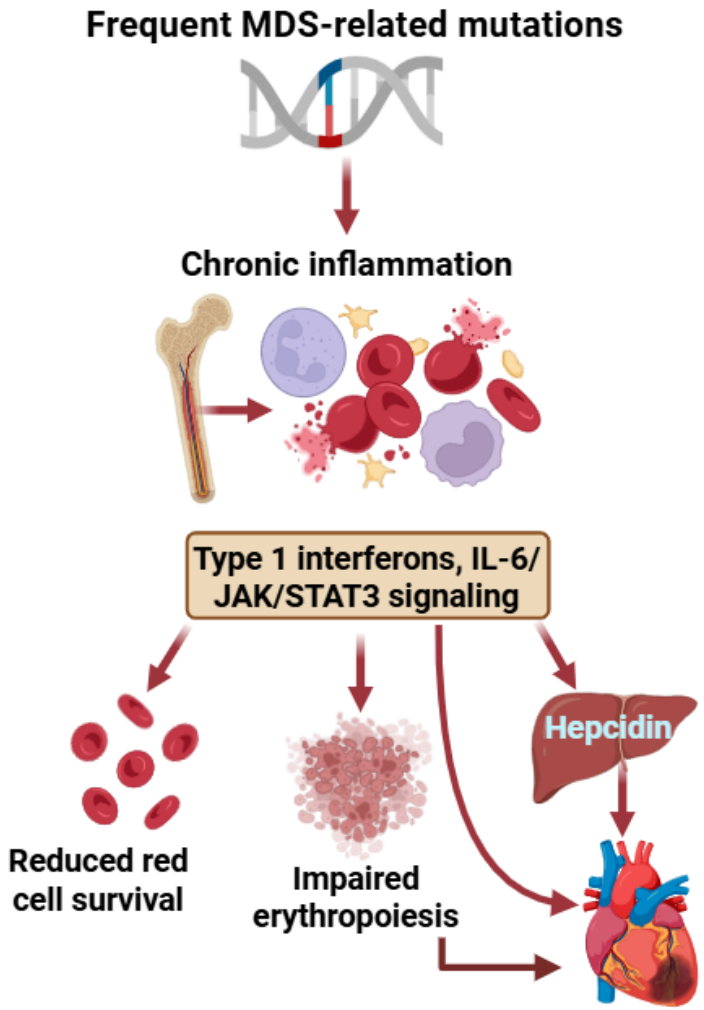
Potential cardioprotective mechanism of luspatercept



Potential mechanism of luspatercept

- ↑ Hb (Improves anemia)
- ↑ Erythropoiesis
- ↓ Inflammatory pathways
- ↓ Hepcidin
- ↓ NT-proBNP

Murine analogue of luspatercept (RAP-536): Beneficial impact on cardiac remodeling

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