2025 DEBATES AND DIDACTICS in Hematology and Oncology

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Contemporary Management of Low-Risk MDS

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Disclosures

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Learning Objectives

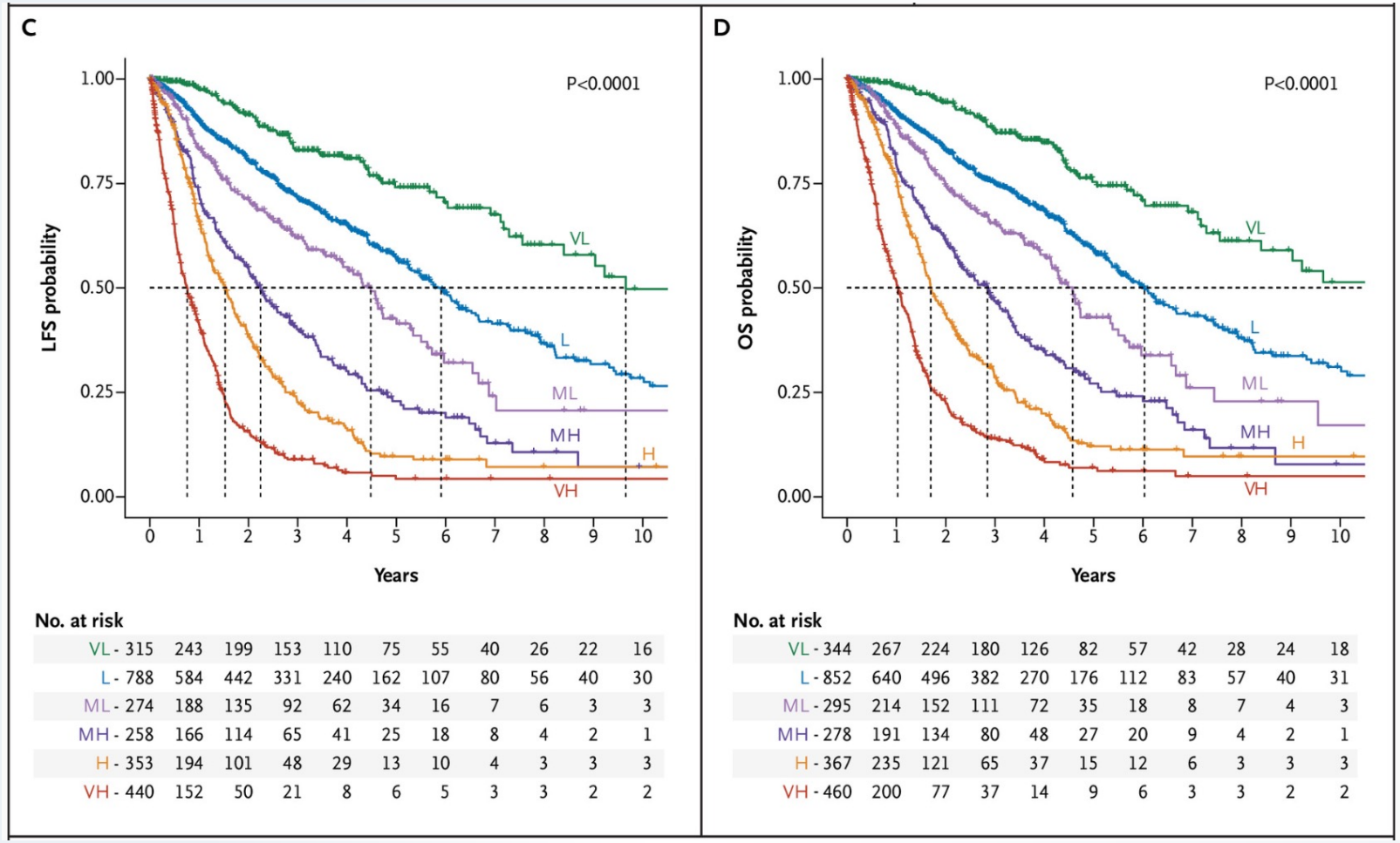
- Review updates regarding risk stratification in MDS
- Summarize recent pivotal studies investigating novel anemia-directed therapies
- Highlight ongoing trials and future treatment approaches

Case

- A 65-year-old gentleman with a history of hypertension, hyperlipidemia, presents for evaluation of symptomatic anemia in the setting of recently diagnosed MDS
- CBC: WBC 3.8, ANC 2.0, Hgb 8.3, Platelet count 155
- Bone marrow biopsy: hypercellular marrow with multilineage dysplasia, 2% blasts
- Chromosome analysis: 46,XY[20]
- NGS: DNMT3A, TET2, SRSF2 mutations
- Erythropoietin level 156

- Which treatment do you recommend?

Risk Stratification: International Prognostic Scoring System-Molecular estimation of LFS and OS across risk categories



Bernard E, Tuechler H, Greenberg PL, et al. *NEJM Evid*. 2022;1(7)

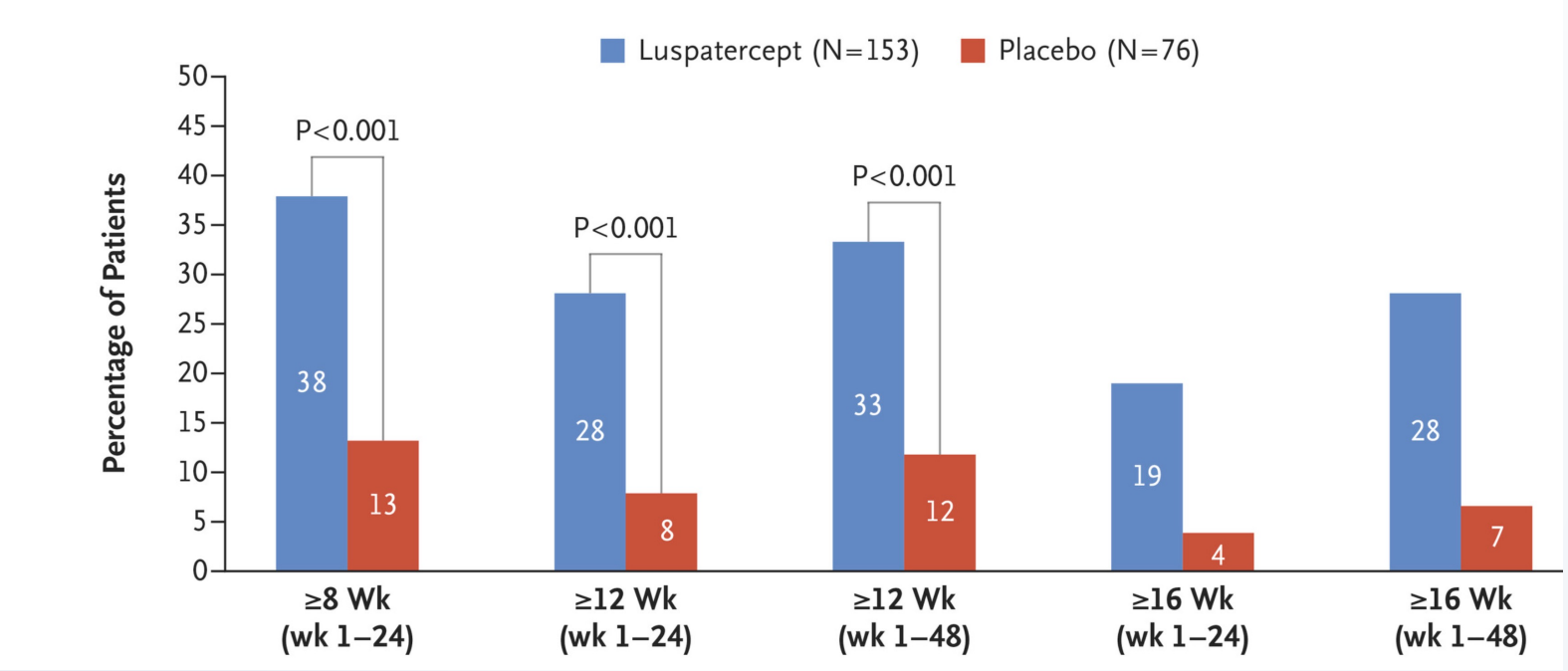
Refining Risk Stratification in sub-groups: IPSS-del(5q)

- 682 patients included; median follow-up 69 months
- 23% AML evolution at 60 months
- Variables included in risk score: male sex, hemoglobin ≤ 10, Platelet count ≤ 100, ≥ 2 additional mutations, SF3B1 mutation, high risk TP53 mutation status
- 25.6% deemed higher-risk, compared to 9.4% by IPSS-R and 14.8% by IPSS-M
- Leukemia-free survival difference
  - IPSS-del(5q) high-risk 32.0 months
  - IPSS-del(5q) standard-risk 70.0 months ($p<0.01$)

Montoro MJ, Palomo L, Haferlach C, et al. Blood. 2024;144(suppl 1):666.

Luspatercept in lower-risk MDS: MEDALIST trial

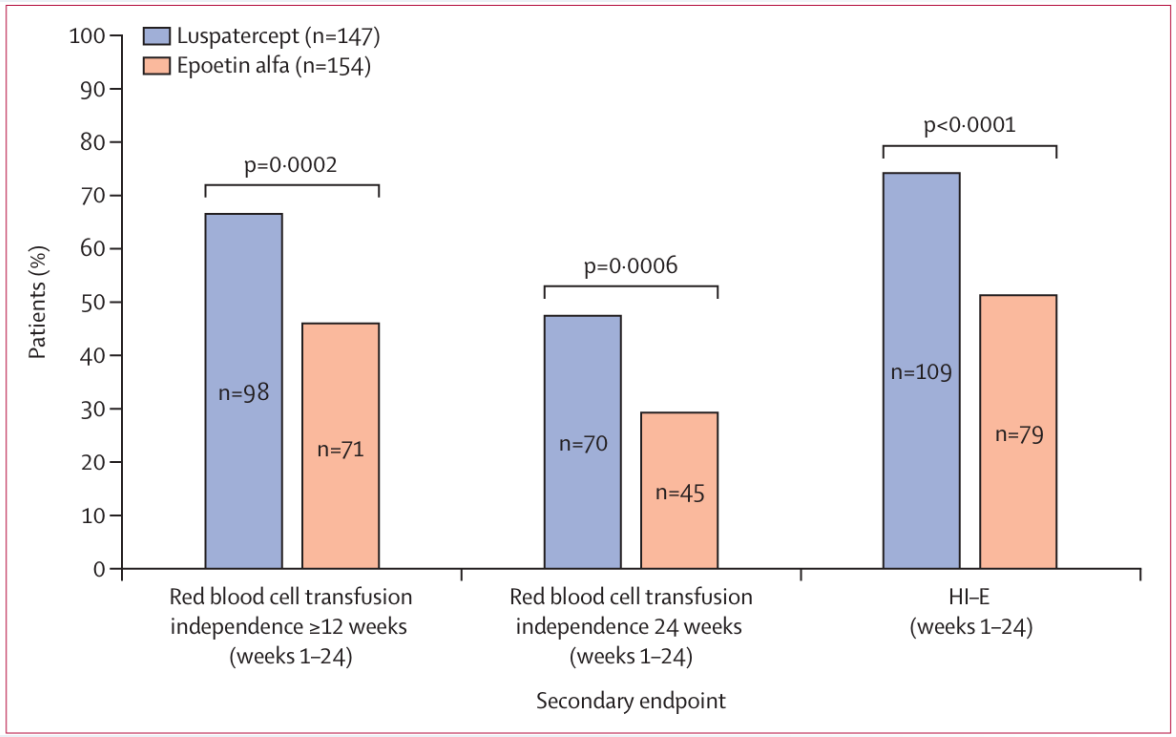
- Luspatercept: recombinant fusion protein that binds transforming growth factor β superfamily ligands to reduce SMAD2 and SMAD3 signaling
- Included patients with lower-risk MDS with ring sideroblasts receiving red blood cell transfusions and refractory or unlikely to respond to ESA



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

Efficacy and Safety of Luspatercept versus Epoetin alfa in COMMANDS trial

- Lower-risk MDS, ESA-naïve and required red blood cell transfusions
- 73% had ring sideroblasts; 61% had SF3B1 mutations, 80% with EPO ≤200

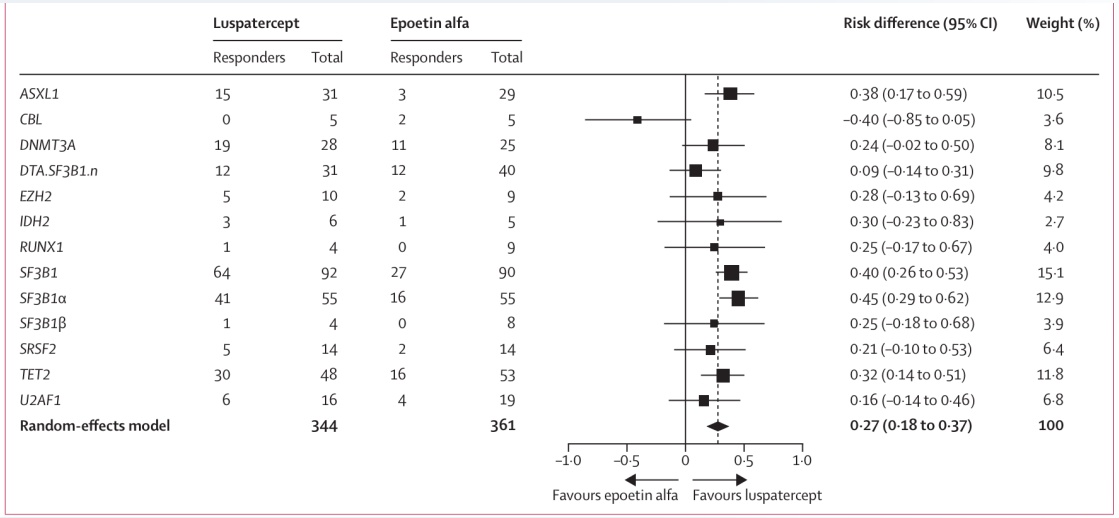


	Luspatercept (n=178)		Epoetin alfa (n=176)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
General disorder or administration site conditions				
Fatigue	26 (15%)	1 (1%)	12 (7%)	1 (1%)
Peripheral oedema	23 (13%)	0	12 (7%)	0
Asthenia	22 (12%)	0	25 (14%)	1 (1%)
Infections and infestations				
COVID-19	19 (11%)	6 (3%)	17 (10%)	2 (1%)
Gastrointestinal disorders				
Diarrhoea	26 (15%)	2 (1%)	20 (11%)	1 (1%)
Nausea	21 (12%)	0	13 (7%)	0
Respiratory, thoracic, or mediastinal disorders				
Dyspnoea	21 (12%)	7 (4%)	13 (7%)	2 (1%)
Vascular disorders				
Hypertension	23 (13%)	15 (8%)	12 (7%)	8 (5%)
Blood and lymphatic system disorders				
Anaemia	17 (10%)	13 (7%)	17 (10%)	12 (7%)

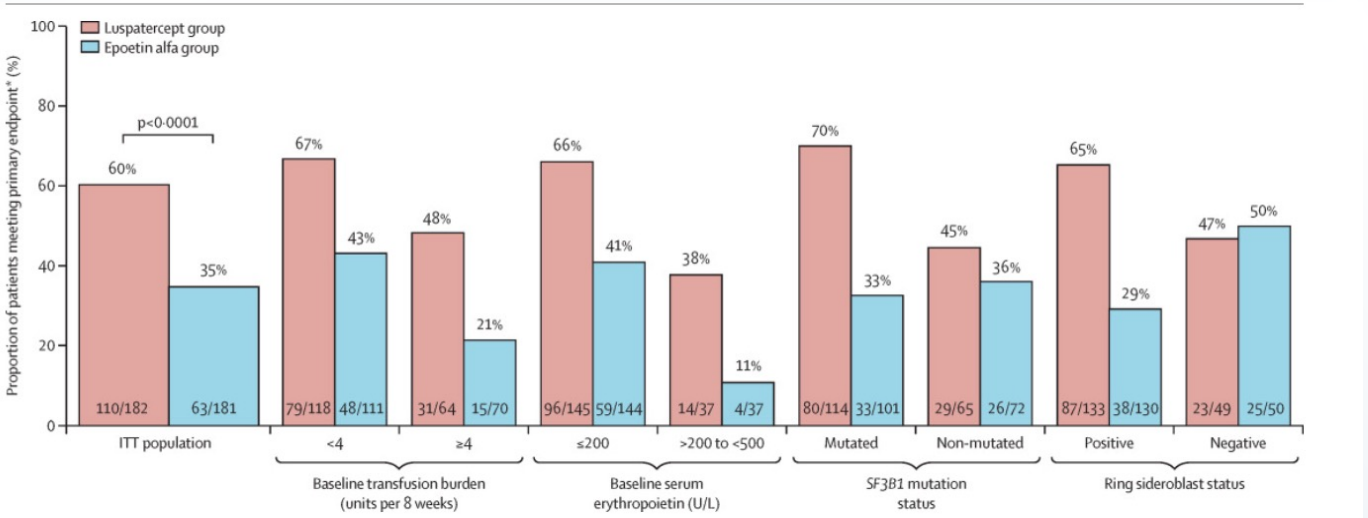
Platzbecker U, Della Porta MG, Santini V, et al. *Lancet*. 2023;402(10399):373-385.

Efficacy and Safety of Luspatercept versus Epoetin alfa in COMMANDS trial

- 84.6% of patients required dose-escalation in the luspatercept arm
- Median duration of response was 126.6 weeks in the luspatercept arm



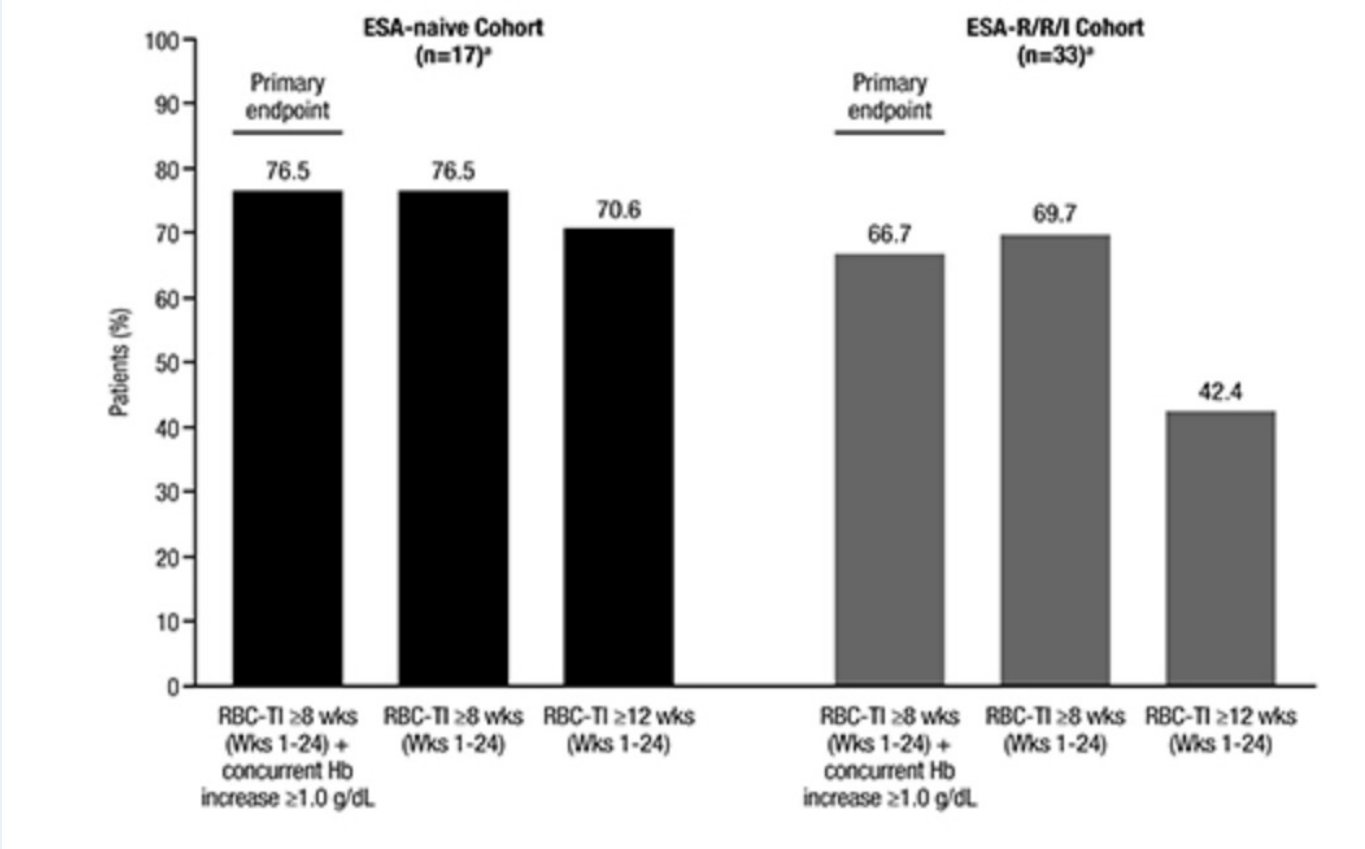
	Luspatercept		Epoetin alfa		Risk difference (95% CI)	Weight (%)
	Responders	Total	Responders	Total		
ASXL1	15	31	3	29	0·38 (0·17 to 0·59)	10·5
CBL	0	5	2	5	−0·40 (−0·85 to 0·05)	3·6
DNMT3A	19	28	11	25	0·24 (−0·02 to 0·50)	8·1
DTA.SF3B1.n	12	31	12	40	0·09 (−0·14 to 0·31)	9·8
EZH2	5	10	2	9	0·28 (−0·13 to 0·69)	4·2
IDH2	3	6	1	5	0·30 (−0·23 to 0·83)	2·7
RUNX1	1	4	0	9	0·25 (−0·17 to 0·67)	4·0
SF3B1	64	92	27	90	0·40 (0·26 to 0·53)	15·1
SF3B1α	41	55	16	55	0·45 (0·29 to 0·62)	12·9
SF3B1β	1	4	0	8	0·25 (−0·18 to 0·68)	3·9
SRSF2	5	14	2	14	0·21 (−0·10 to 0·53)	6·4
TET2	30	48	16	53	0·32 (0·14 to 0·51)	11·8
U2AF1	6	16	4	19	0·16 (−0·14 to 0·46)	6·8
Random-effects model		**344**		**361**	**0·27 (0·18 to 0·37)**	**100**



Della Porta MG, Garcia-Manero G, Santini V, et al. *Lancet Haematol*. 2024;11(9):e646-e658
Garcia-Manero, et al. ASCO 2025.

Optimization of Luspatercept Dosing: MAXILUS study

- Lower-risk MDS, required red blood cell transfusions
- Two cohorts; ESA-naïve and ESA-R/R/I; starting dose 1.75mg/kg



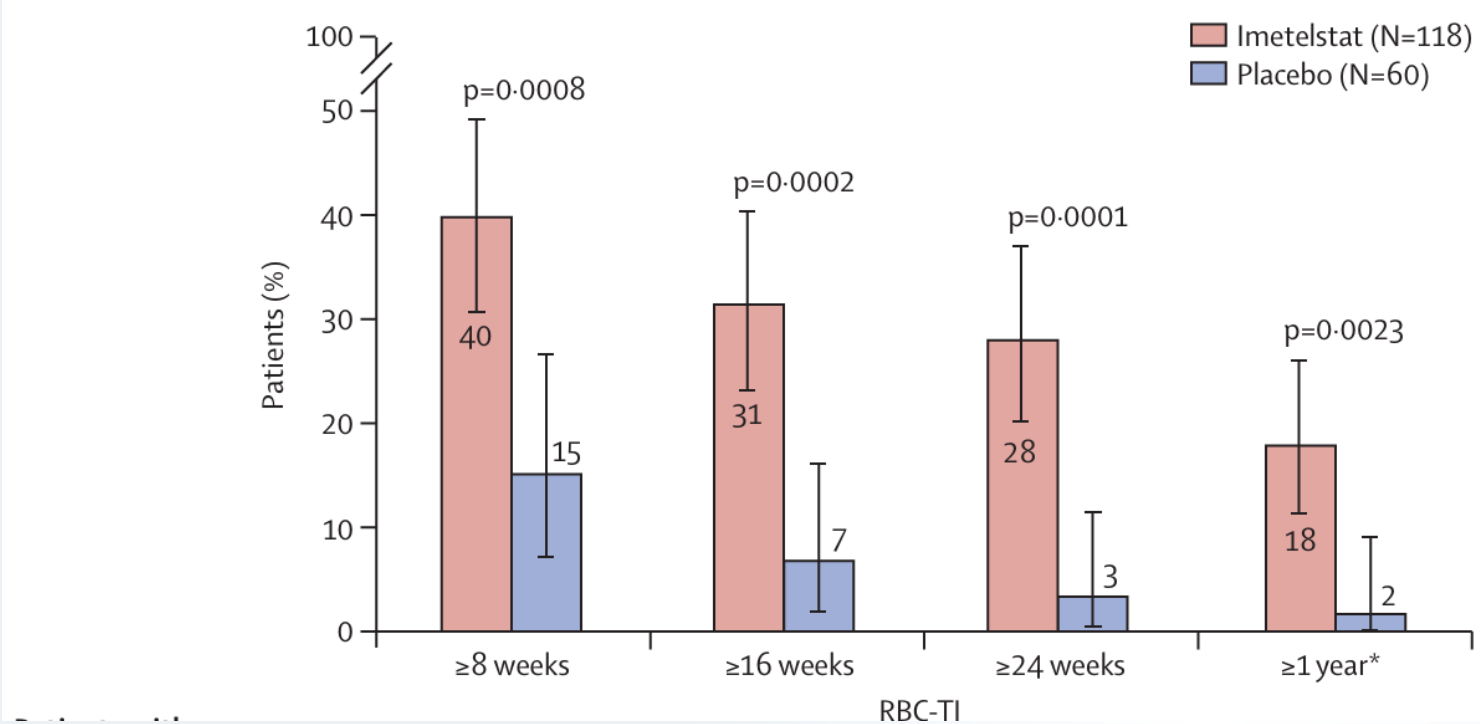
Della Porta, et al. *EHA 2025 Abstract PF634*.

Selection of upfront therapy for anemia in lower-risk MDS

- Anemia present in ~90% of lower-risk MDS cases and can significantly impact quality of life and lead to worsening cardiopulmonary and/or neurocognitive decline
- Considerations
  - Goals of care
  - Timing of treatment initiation
    - ELEMENT-MDS Trial (NCT05949684)
  - Molecular profile, bone marrow biopsy and aspiration results
  - Clinical factors (high transfusion burden, serum erythropoietin level, etc.)
  - Treatment-emergent toxicities

Imetelstat: IMerge trial

- Imetelstat: first-in-class telomerase inhibitor
- Non-del(5q) lower-risk MDS, ESA-R/R/I, 62% ring sideroblasts, median EPO 361



	Imetelstat (N=118)		Placebo (N=59)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Haematological				
Thrombocytopenia	89 (75%)	73 (62%)	6 (10%)	5 (8%)
Neutropenia	87 (74%)	80 (68%)	4 (7%)	2 (3%)
Anaemia	24 (20%)	23 (19%)	6 (10%)	4 (7%)
Leukopenia	12 (10%)	9 (8%)	1 (2%)	0
General disorders and administration site conditions				
Asthenia	22 (19%)	0	8 (14%)	0
Oedema peripheral	13 (11%)	0	8 (14%)	0
Pyrexia	9 (8%)	2 (2%)	7 (12%)	0
COVID-19	22 (19%)†	3 (3%)‡	8 (14%)†	3 (5%)‡
Gastrointestinal disorders				
Diarrhoea	14 (12%)	1 (1%)	7 (12%)	1 (2%)
Constipation	9 (8%)	0	7 (12%)	0
Headache	15 (13%)	1 (1%)	3 (5%)	0
Alanine aminotransferase increased	14 (12%)	3 (3%)	4 (7%)	2 (3%)
Hyperbilirubinaemia	11 (9%)	1 (1%)	6 (10%)	1 (2%)

Platzbecker U, Santini V, Fenaux P, et al. Lancet. 2024 Jan 20;403(10423):248.

Lenalidomide in lower-risk non-del(5q) MDS

- Transfusion-dependent, refractory to or ineligible for ESA
- Lenalidomide 10mg daily

Response	Lenalidomide, No. (%)	Placebo, No. (%)
No. of patients	160	79
RBC-TI ≥ 8 weeks	43 (26.9)*	2 (2.5)
Median duration of RBC-TI ≥ 8 weeks, weeks (95% CI)†	30.9 (20.7 to 59.1)	NE‡
Median time to RBC-TI ≥ 8 weeks, weeks (range)†	10.1 (0.3 to 23.6)	0.3 (0.3 to 0.3)
RBC-TI ≥ 24 weeks	28 (17.5)*	0
Erythroid response (IWG 2006)§		
≥ 4 pRBC units transfusion reduction	57 (36.5)	15 (19.5)
≥ 1.5 g/dL hemoglobin increase	31 (19.4)	2 (2.5)

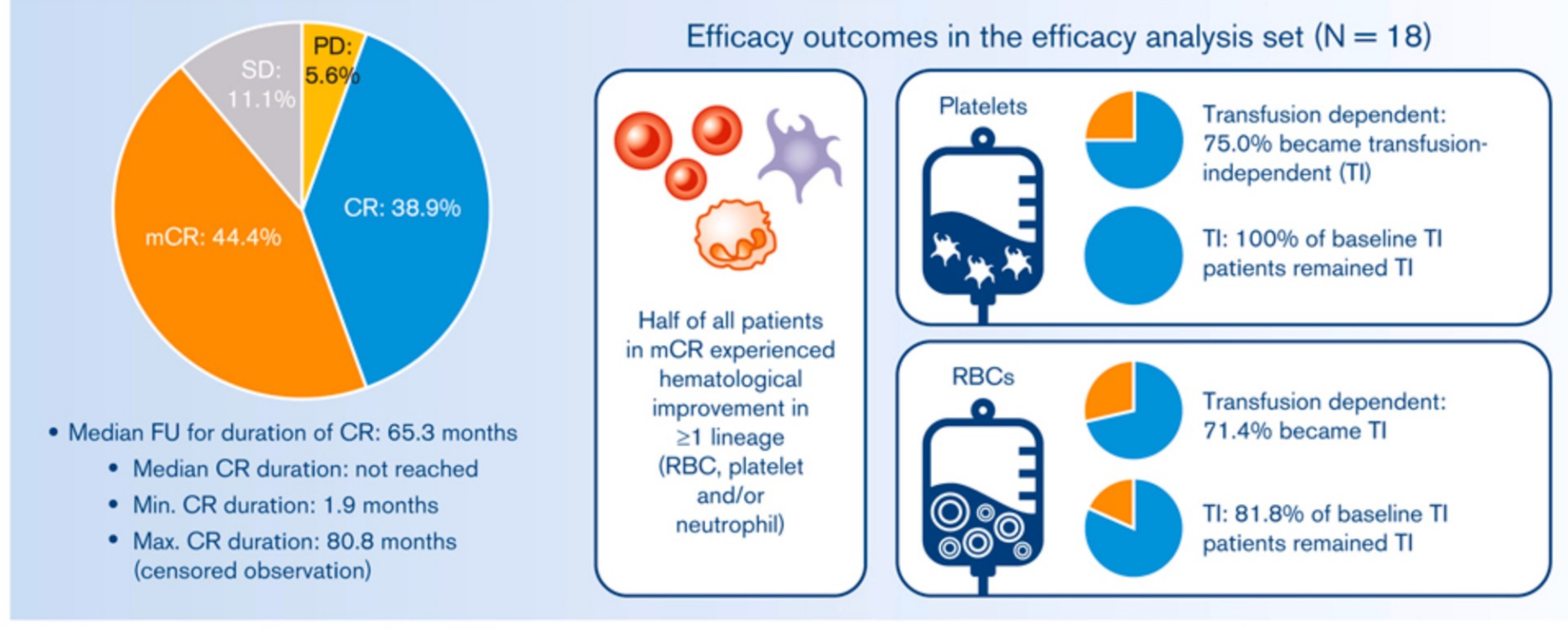
Table 4. Treatment-Emergent Adverse Events

Adverse Event	Any Grade, No.(%)		G
	Lenalidomide	Placebo	Lenalidomid
No. of patients	160	79	160
Hematologic			
Neutropenia	103 (64.4)	10 (12.7)	99 (61.9)
Thrombocytopenia	63 (39.4)	6 (7.6)	57 (35.6)
Infection	83 (51.9)	34 (43.1)	23 (14.4)
Bleeding	33 (20.6)	8 (10.1)	3 (1.9)
Nonhematologic			
Venous thromboembolism	5 (3.1)	0	3 (1.9)
Arterial thromboembolism	4 (2.5)	2 (2.5)	2 (1.3)
Hepatic disorder	23 (14.4)	4 (5.1)	8 (5.0)
Renal failure	6 (3.8)	0	2 (1.3)
Peripheral neuropathy	4 (2.5)	1 (1.3)	0
Cardiac failure	8 (5.0)	4 (5.1)	3 (1.9)
Cardiac arrhythmia	18 (11.3)	7 (8.9)	2 (1.3)
Ischemic heart disease	3 (1.9)	3 (3.8)	3 (1.9)
Interstitial lung disease	4 (2.5)	0	0
Cutaneous reactions	16 (10.0)	1 (1.3)	2 (1.3)
Angioedema	7 (4.4)	1 (1.3)	1 (0.6)
Diarrhea	68 (42.5)	18 (22.8)	4 (2.5)
Constipation	36 (22.5)	10 (12.7)	0

Santini V, Almeida A, Giagounidis A, et al. J Clin Oncol. 2016;34(25):2988-2996.

Ivosidenib in IDH1-mutated MDS

- R/R following standard-of-care therapies



DiNardo CD, Roboz GJ, Watts JM, et al. Blood Adv. 2024;8(15):4209-4220.

Additional treatment considerations

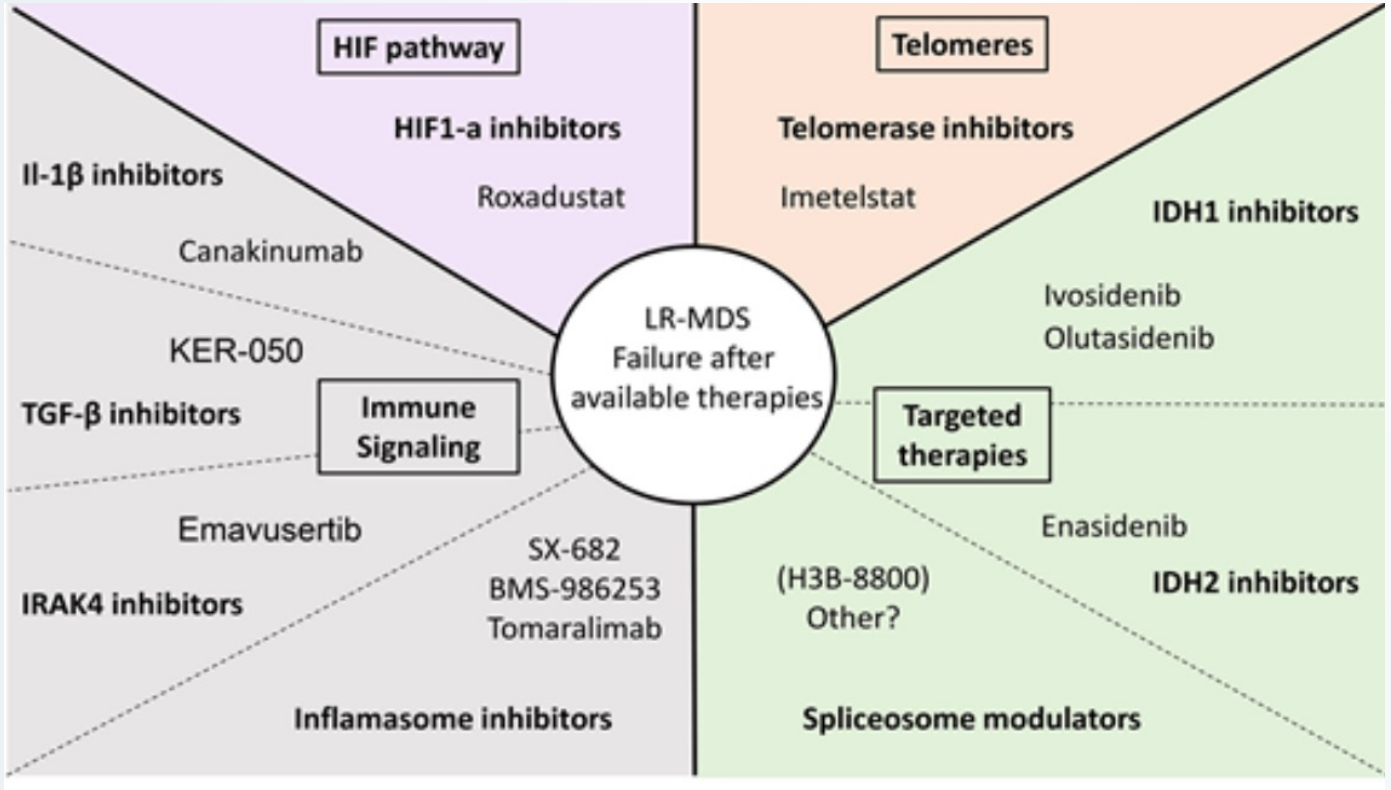
- Clinical trials
- Hypomethylating agents
  - Novel approaches consisting of "low-dose" schemas
- Allogeneic stem cell transplantation

Supportive care considerations in lower-risk MDS

- Transfusions as necessary
- Iron chelation if indicated
- Reduction of bleeding events
- Reduction of infectious complications
- Optimizing bone health
- Multidisciplinary plan of care

Emerging therapies for lower-risk MDS

- Lower-risk MDS is a heterogeneous disease
- Advancements in our understanding of the pathophysiology of the disease have facilitated development of novel treatment approaches



Sebert. *Hematology Am Soc Hematol Educ Program* (2023) 2023 (1): 59–64.

Enrolling studies at Emory University

- NCT05490446: A Phase 2a/2b, Open-label, Proof of Concept (Phase 2a) and Open-label (Phase 2b), Multicenter, Efficacy, and Safety Study of AG-946 in Participants With Anemia Due to Lower-Risk Myelodysplastic Syndromes
- NCT04245397: A Phase 1, Open-Label, Dose-Escalation with Expansion Study of SX-682 Alone and in Combination with Oral or Intravenous Decitabine in Subjects with Myelodysplastic Syndrome

Enrolling studies at Emory University

- NCT04798339: A Phase 1b/2 Study Evaluating the Safety and Efficacy of Canakinumab With Darbepoetin Alfa in Patients With Lower-Risk Myelodysplastic Syndromes (MDS) Who Have Failed Erythropoietin Stimulating Agents (ESA)
- NCT05143996: A Phase 1, Open-label, Preliminary Pharmacokinetics (PK) and Safety Study of CLN-049 (An Fms-like Tyrosine Kinase 3 [FLT3] x Cluster of Differentiation 3 [CD3] Bispecific T Cell Engager) in Patients With Relapsed/Refractory Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Conclusions

- Refinement of risk stratification systems has led to improved prognostication and has facilitated a personalized approach to the treatment of lower-risk MDS.
- Recently approved therapies have substantially improved the care of many patients with lower-risk MDS. Optimizing treatment sequencing and/or combination approaches, while monitoring for side effects, remains essential.
- The development of additional effective therapies is paramount; clinical trials are available in the frontline and relapsed/refractory settings.