FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

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Trattamento dell'anemia nei pazienti a basso rischio: algoritmo terapeutico e nuovi farmaci

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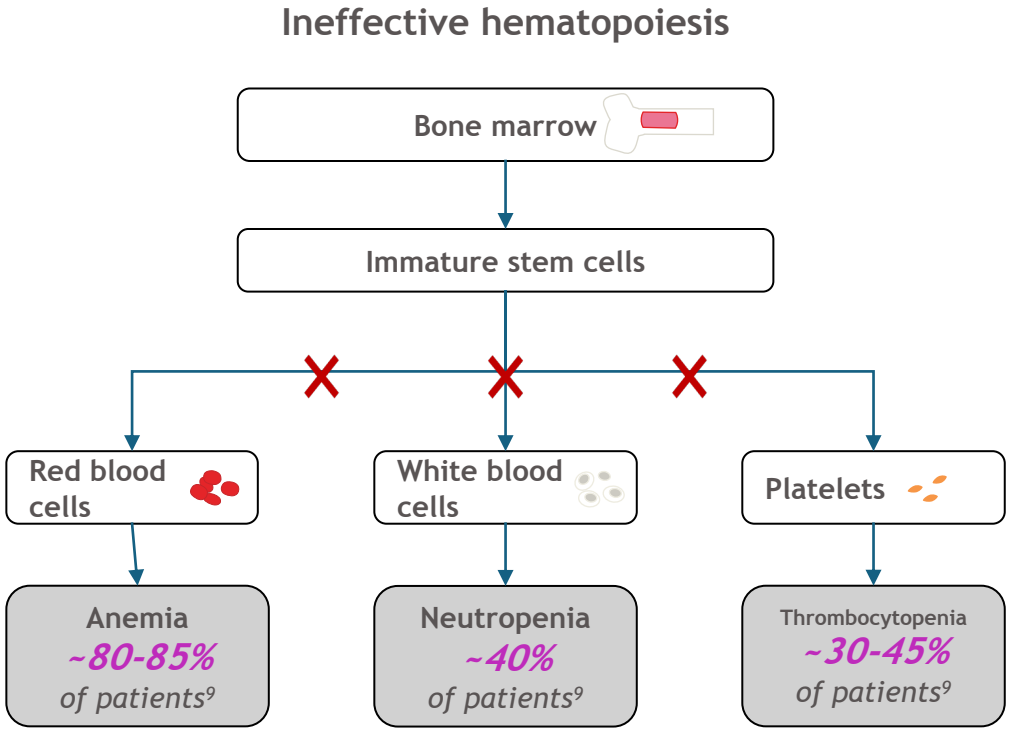
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NA							

MDS is a rare, hematologic neoplasm characterized by ineffective hematopoiesis, resulting in transfusion-dependent anemia

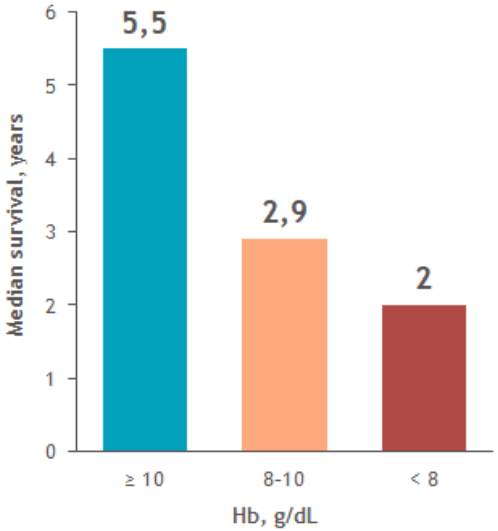
- MDS are a group of **rare hematologic cancers**
- MDS occur primarily in older patients with a **median age at diagnosis of ≥ 70-years old**
- The disease is characterized by **ineffective hematopoiesis, manifesting in progressive cytopenia**
- **Anemia is the most common cytopenia**, occurring in around 80-85% of MDS patients.



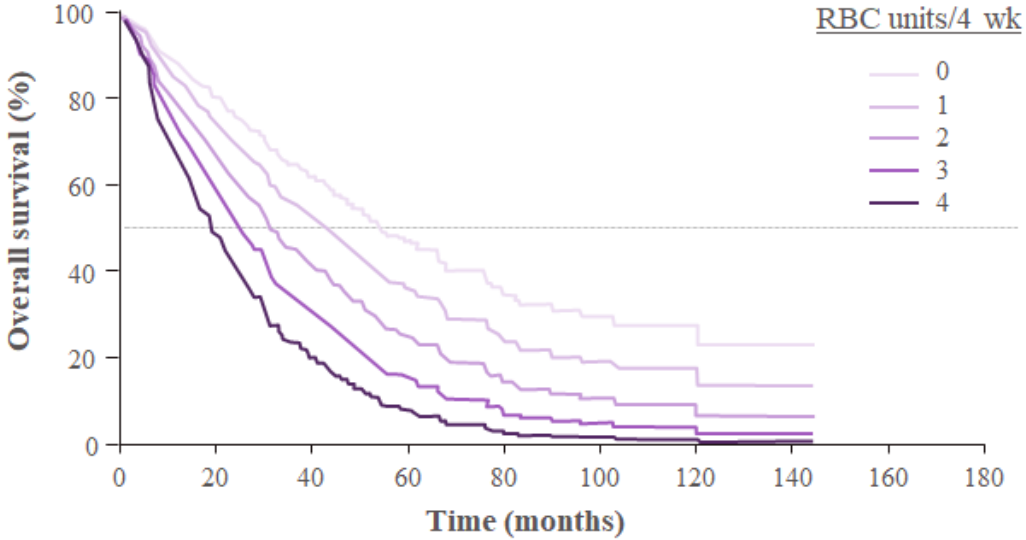
Ades et al. Lancet. 2014; 383:2239-52

Anemia results in significantly increased risk of mortality in low-risk MDS

Severity of anemia and OS (n 7,012)



OS in MDS with transfusion-dependent anemia (n 426)

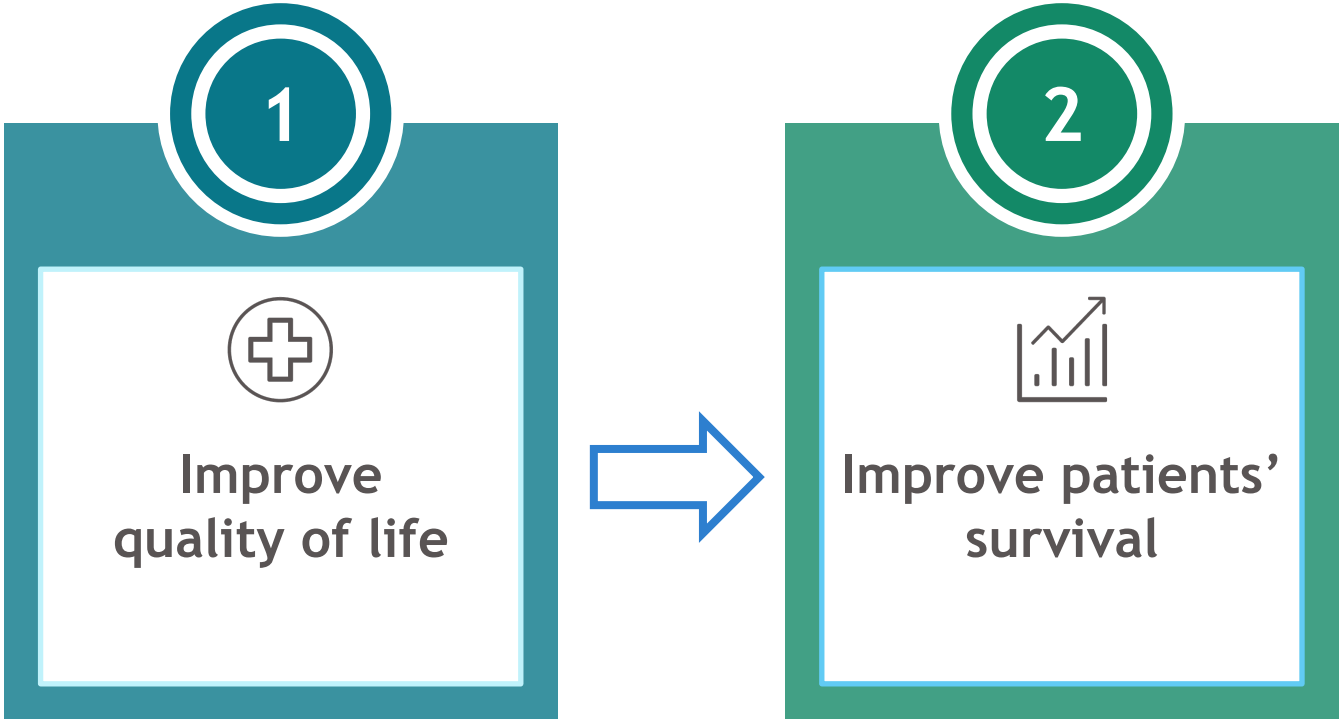


The detrimental effect of anemia in low-risk MDS is associated to

- Increased risk of cardiovascular morbidity and mortality
- Transfusional iron overload
- Increased risk of leukemic evolution

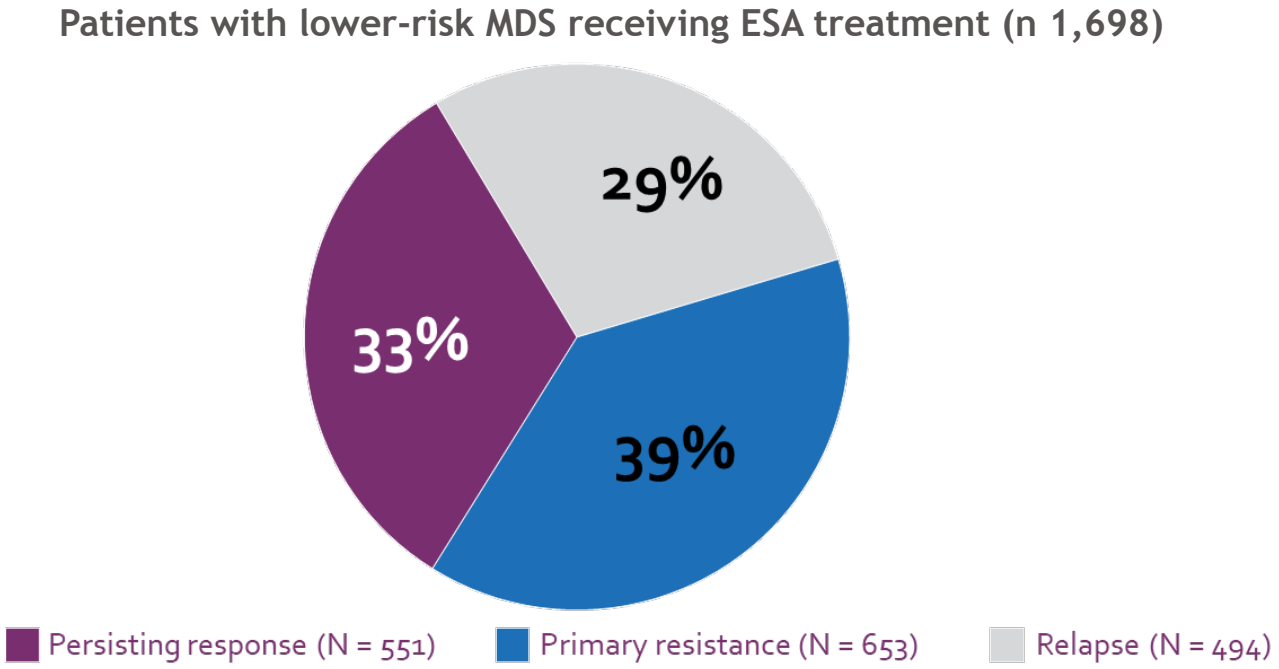
Zeidan AM, et al. Blood Rev. 2019;34:1–15
Malcovati L, et al. Haematologica. 2011;96:1433–1440
Greenberg PL, et al. Blood. 2012;120:2454–2465

Goals of treatment for patients with low-risk-MDS



Garcia-Manero G. Am J Hematol. 2015;90:831-841; Germing U, et al. HemaSphere. 2019;3:e314

Two-thirds of patients with low-risk MDS are R/R to ESAs, the majority of whom then receive RBCTs only



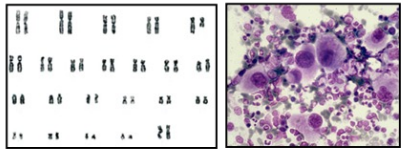
Park S, et al. J Clin Oncol. 2017; 35:1591-1597.

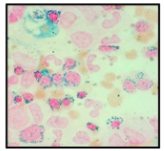
Personalized treatment of anemia in low-risk MDS

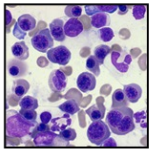
GENOMIC BACKGROUND

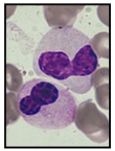
- MDS with isolated 5q- *[Group 6]*
- MDS with isolated 5q- with co-existing mutations and/or TP53 mutations *[Group 1]*
- MDS with TP53 mutations and/or complex karyotype *[Group 2]*
- MDS with isolated SF3B1 mutations (or associated with mutations of clonal hematopoiesis and/or JAK/STAT pathways genes) *[Group 6]*
- MDS with SF3B1 with co-existing mutations *[Group 1]*
- MDS with SRSF2 and concomitant TET2 mutations *[Group 3]*
- MDS with SRSF2 mutations with co-existing mutations *[Group 5]*
- MDS with U2AF1 mutations associated with deletion of chromosome 20q, isolated del(7q) or chromosome 7 monosomy *[Group 4]*
- MDS with AML-like mutations *[Group 7]*
- MDS without specific genomic profiles *[Group 0]*

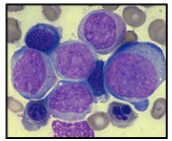
PHENOTYPE











MECHANISM OF INEFFECTIVE ERYTHROPOIESIS

MDS del(5q)
ANEMIA DUE TO RIBOSOMAL DISFUNCTION

ANEMIA DUE TO SPLICING-GENE ABNORMALITES (SF3B1, OTHER)

Bersanelli M et al. JCO 2021; 11:1223-1233

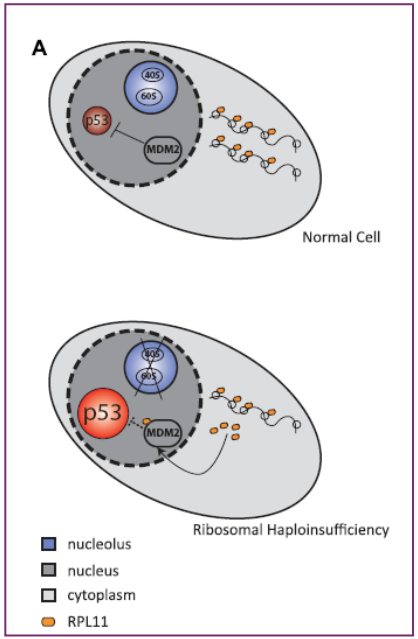
Ineffective erythropoiesis due to ribosomal dysfunction

Ribosomopathies: human disorders of ribosome dysfunction

Disease	Gene Defect	Clinical Features	Cancer Risk	Diagnosis
Diamond Blackfan anemia	RPS19, RPS24, RPS17, RPL35A, RPL5, RPL11, RPS7, RPL36, RPS15, RPS27A	Macrocytic anemia Short stature Craniofacial defects Thumb abnormalities	?osteosarcoma ?MDS	RPS19/RPS24 Sequencing Elevated ADA Elevated Hgb F levels
5q-syndrome	RPS14	Macrocytic anemia Hypolobulated micromegakaryocytes	10% progression to AML	Bone marrow aspiration/biopsy with karyotype
Shwachman-Diamond syndrome	SBDS	Neutropenia/infections Pancreatic insufficiency Short stature	MDS and AML	SBDS gene testing
X-linked dyskeratosis congenita	DKC1	Cytopenias Skin hyperpigmentation Nail dystrophy Oral leukoplakia	AML Head+neck tumors	Telomere length analysis
Cartilage hair hypoplasia	RMRP	Hypoplastic anemia Short limbed dwarfism Hypoplastic hair	Non-Hodgkin lymphoma Basal cell carcinoma	RMRP sequencing
Treacher Collins syndrome	TCOF1	Craniofacial abnormalities	None reported	Physical exam (imaging if needed)

Marrow failure

A p53-dependent mechanism underlies anemia in a mouse model of 5q- syndrome



Narla A et al, Blood. 2010;115(16):3196-3205

Treatment of ineffective erythropoiesis due to ribosomal dysfunction

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, M.D., Robert Knight, M.D., for the Myelodysplastic Syndrome-003 Study Investigators

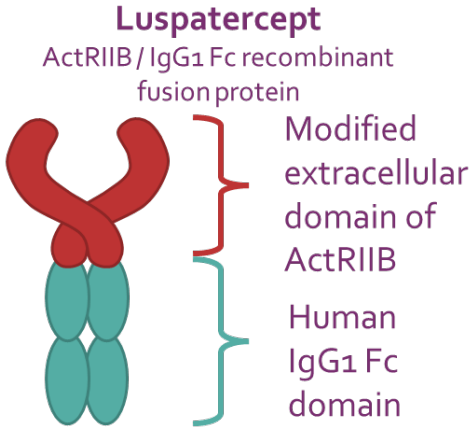
Eligibility: IPSS Low/Int-1 del(5)(q31), Transfusion dependent

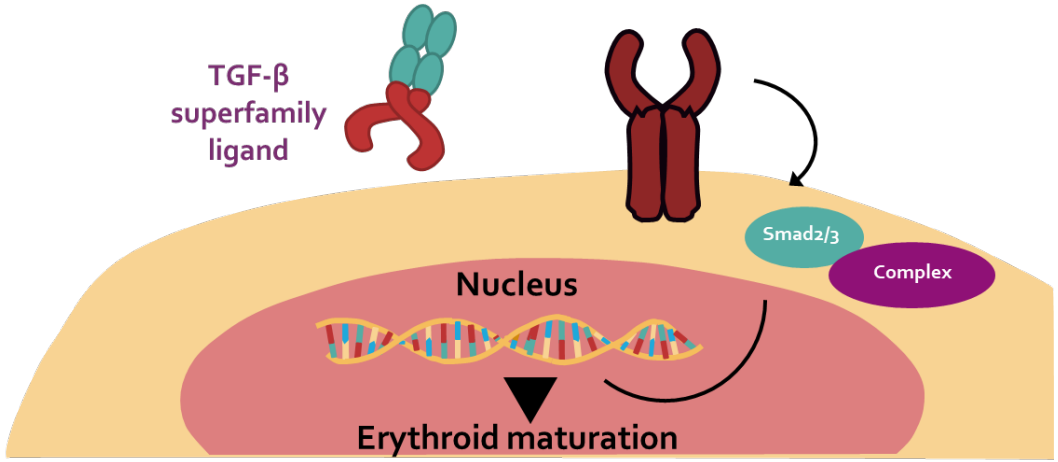
Erythroid response	99/148 (67%)
Median baseline Hb	7.8 g/dL
Median Hb at response	13.4 g/dL
Complete cytogenetic remission	**38/85 (45%)**

List A et al. N Engl J Med 2006;355:1456-65

Anemia due to splicing gene mutations

- Luspatercept is an erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models
- In a phase 2 study in low-risk MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes

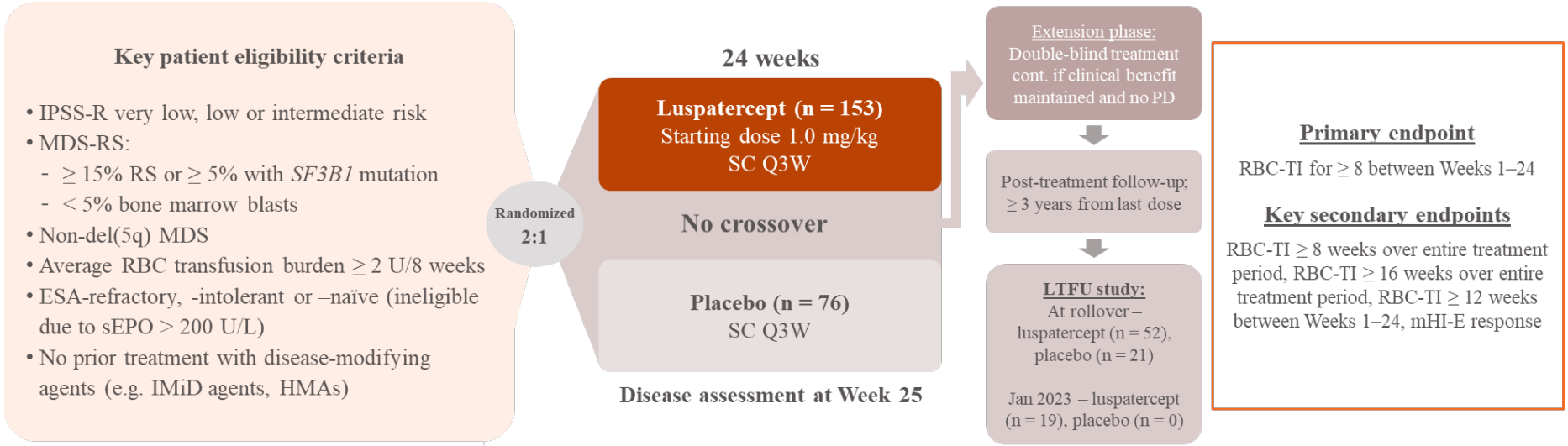




ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-ß, transforming growth factor beta.

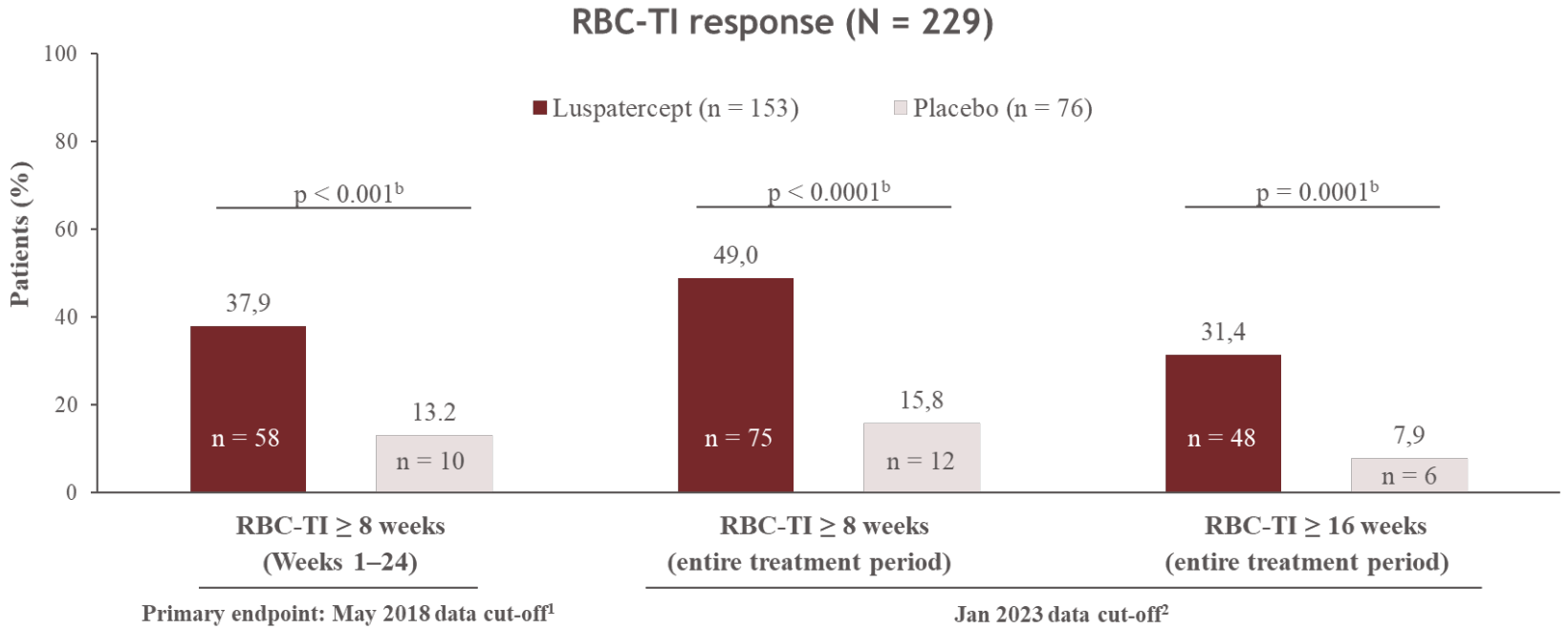
Suragani RN, et al. Nat Med. 2014;20:408-414; Platzbecker U, et. A. Lancet Oncol. 2017; 18:1338.

Luspatercept vs. placebo in lower-risk MDS R/R to ESAs MEDALIST Phase 3 trial



Fenaux P, et al. N Engl J Med 2020;382:140-151.

MEDALIST Phase 3 trial: response rate and duration



- As of Jan 2023, the median duration of treatment was 50.9 weeks for luspatercept and 24.0 weeks for placebo

Fenaux P, et al. N Engl J Med 2020;382:140-151.

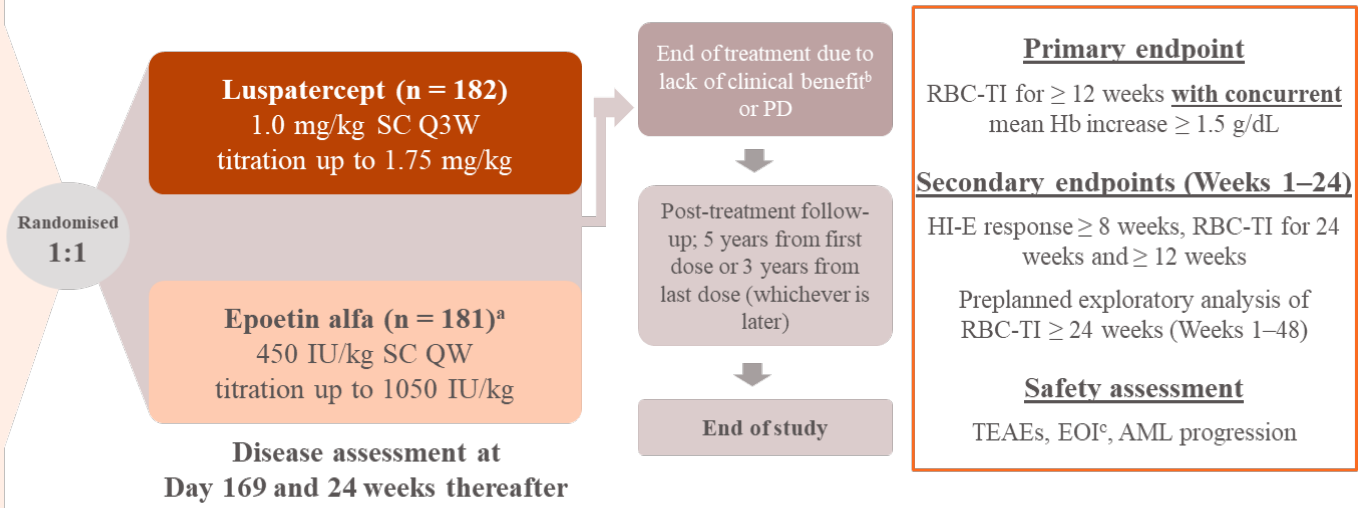
Luspatercept vs. epoetin alfa in in ESA-naïve lower-risk MDS COMMANDS Phase 3 trial

Key patient eligibility criteria

- IPSS-R very low-, low- or intermediate-risk MDS (with or without RS), with < 5% blasts in bone marrow
- Required RBC transfusions (2–6 units/8 weeks for a minimum of 8 weeks immediately prior to randomisation)
- Endogenous sEPO < 500 U/L
- ESA-naïve
- Patients with del(5q) were excluded

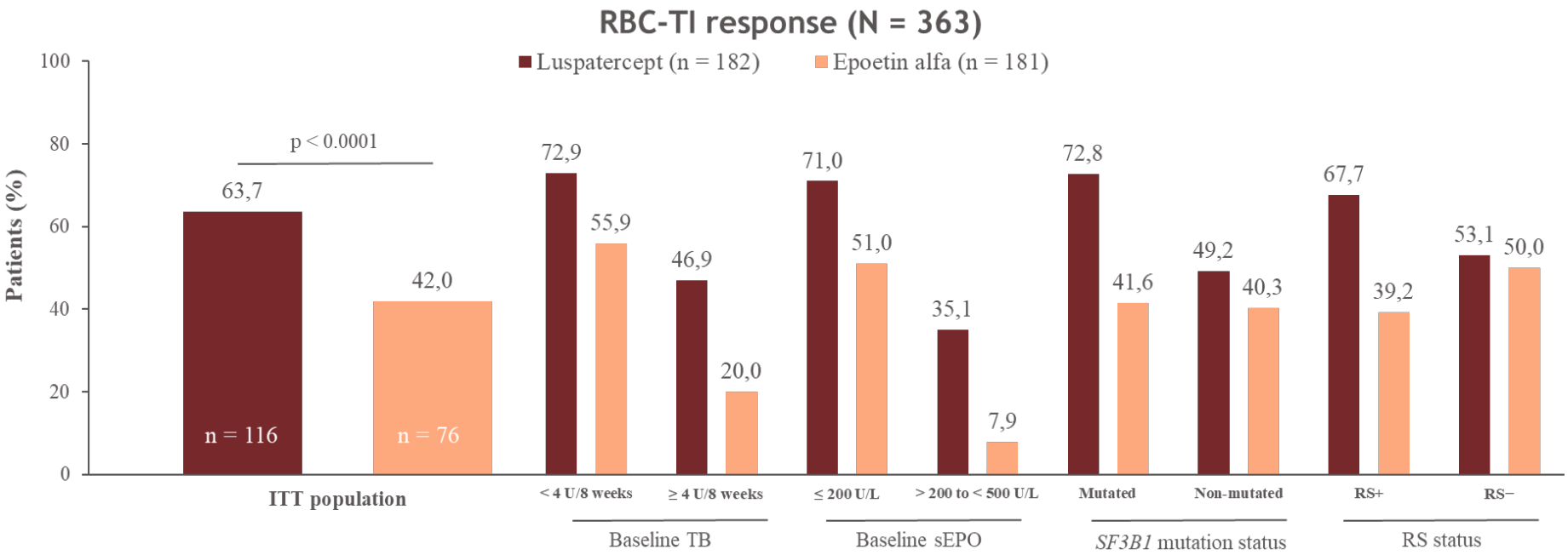
Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status



Platzbecker U, Della Porta MG et al. Lancet 2023;402:373-385.
Della Porta MG et al. Lancet Haematol 2024;11:e646-e658

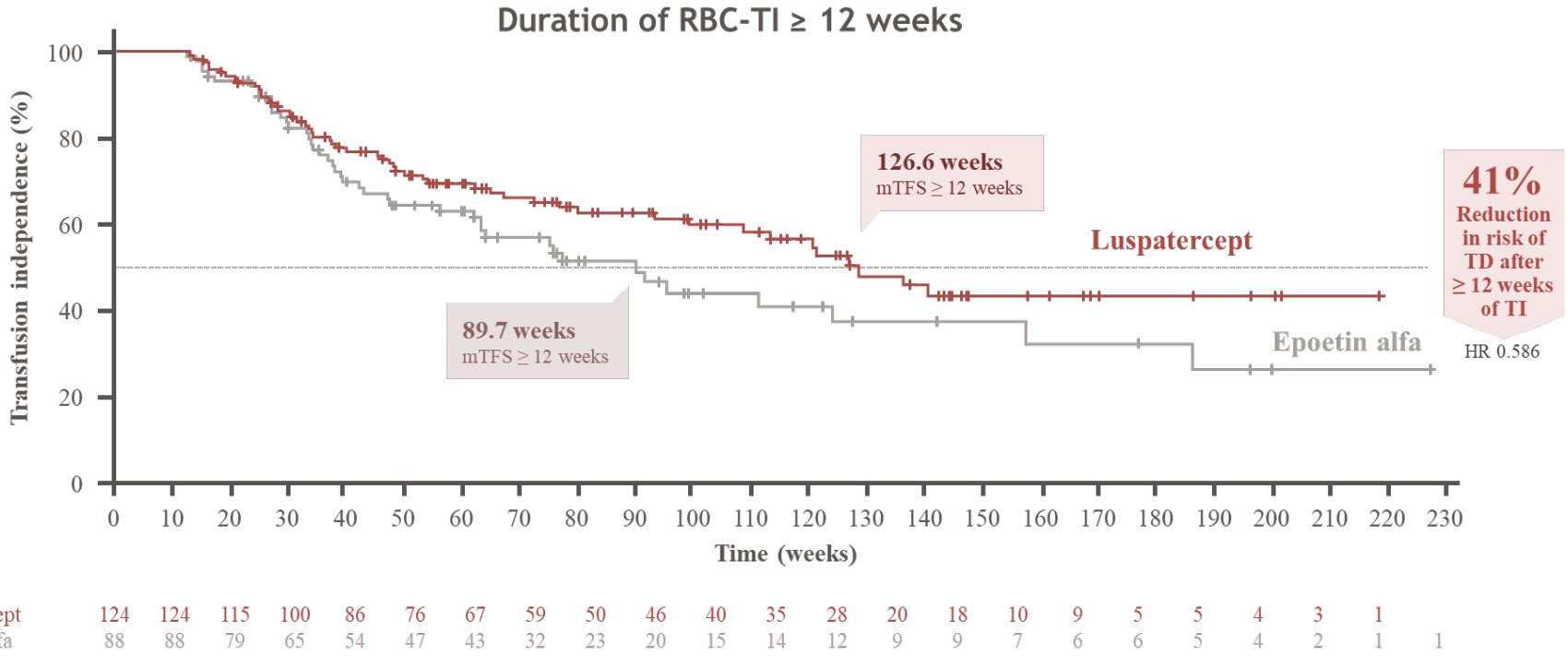
COMMANDS Phase 3 trial: response rate and duration



- Response rates of RBC-TI for ≥ 24 weeks (Weeks 1-48) were greater with luspatercept vs. epoetin alfa regardless of baseline TB, sEPO category, or *SF3B1* mutation status

Platzbecker U, Della Porta MG et al. Lancet 2023;402:373-385.
Della Porta MG et al. Lancet Haematol 2024;11:e646-e658

COMMANDS Phase 3 trial: response rate and duration



Platzbecker U, Della Porta MG et al. Lancet 2023;402:373-385.
Della Porta MG et al. Lancet Haematol 2024;11:e646-e658

Imetelstat overview

Background

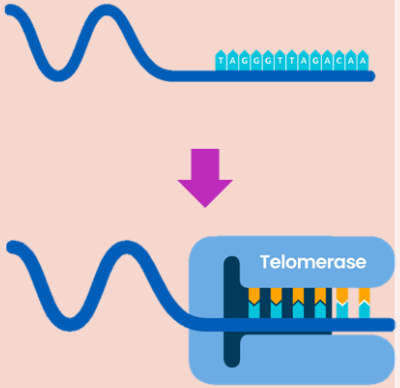
Route of administration
7.1 mg/kg IV every 4 weeks (2-hour infusion)

Modality
Investigational first-in-class telomerase inhibitor

Key trials in MDS
IMerge (Phase 2/3) - NCT02598661

Target patient population
Patients with transfusion-dependent anemia due to LR-MDS, who are R/R to, or ineligible for ESAs

Mechanism of action



- Telomerase activity is elevated in the bone marrow of patients with MDS
- Imetelstat is an NPS oligonucleotide which is complementary to the RNA template of telomerase
- Imetelstat binds to telomerase with high affinity
- Once bound, imetelstat prevents telomerase binding to telomers
- This results in the apoptosis of malignant stem and progenitor cells in the bone marrow

Regulatory status

Approved in US for adults with LR-MDS with TD anemia requiring ≥ 4 or more RBC units over 8 weeks who have not responded to or have lost response to or are ineligible for ESAs

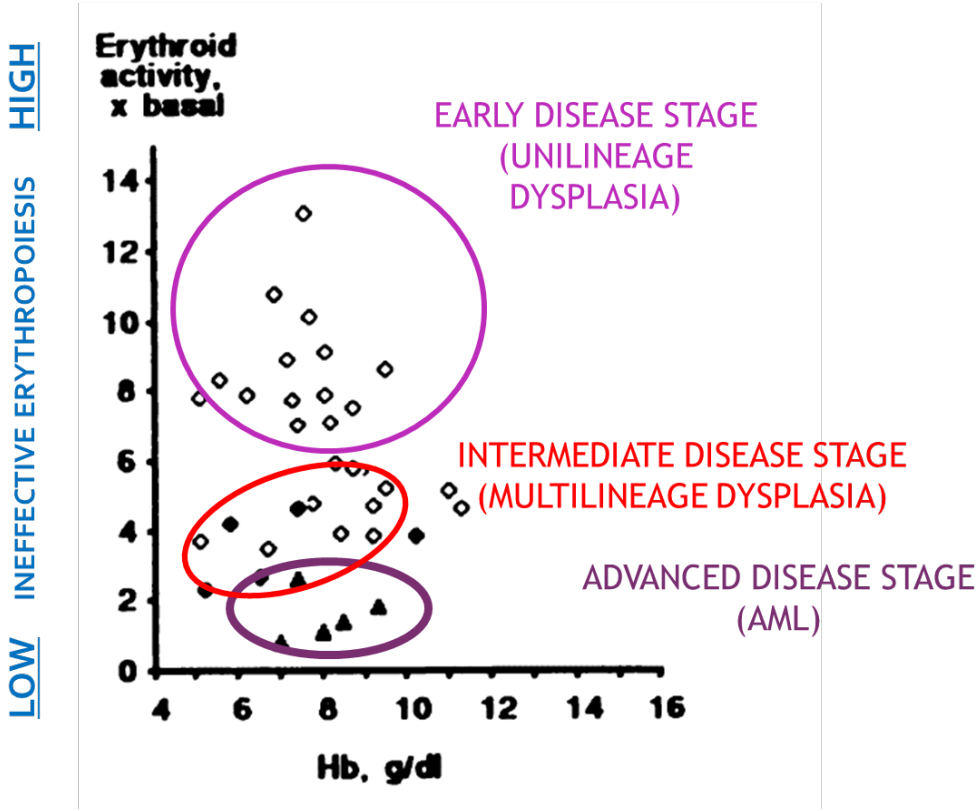
Platzbecker U et al, Lancet. 2024;403:249-260

Imetelstat in patients with lower-risk MDS who have relapsed or are refractory to ESAs (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial

- 178 patients were enrolled
- In the imetelstat group, 47 (40% [95% CI 30·9–49·3]) patients had an RBC-TI of at least 8 weeks versus 9 (15% [7·1–26·6]) in the placebo group (rate difference 25% [9·9 to 36·9]; p=0·0008).
- Overall, 107 (91%) of 118 patients receiving imetelstat and 28 (47%) of 59 patients receiving placebo had grade 3–4 treatment-emergent adverse events.
- The most common treatment-emergent grade 3–4 adverse events in patients taking imetelstat were neutropenia (80 [68%] vs 2 [3%]) and thrombocytopenia (73 [62%] vs 5 [8%]).

Platzbecker U et al, Lancet. 2024;403:249-260

Contribution of ineffective erythropoiesis to anemia during the natural history of MDS-RS



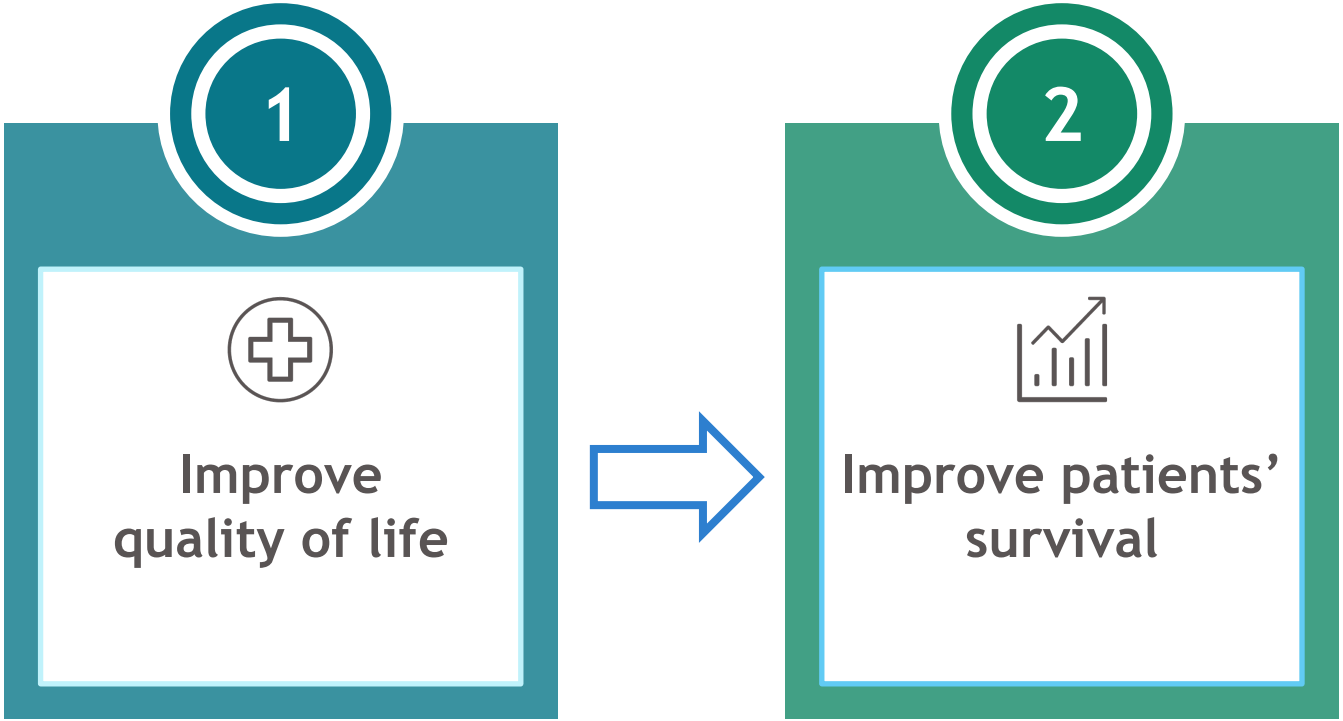
Cazzola M et al. Blood. 1988: 108:337-45

Outcome of early treatment of anemia in MDS

- Low-risk patients with mild anemia treated with ESA had a significantly better response rate /duration than those treated after the onset of transfusions.
- Response rate and duration of response with luspatercept are higher in ESA naïve low-risk MDS than in patients R/R to ESAs
- An early approach with low doses of lenalidomide in MDS with del5q delays the time to transfusion dependency and improves the rate and quality of the responses

Garelius H, J Intern Med . 2017;281:284-299; Della Porta M et al, Lancet Haematol. 2024:24:S2352-3026; Platzbecker et al. Lancet. 2023;402:373-385; Diez-Campelo M et al, Lancet Haematol. 2024;11e659-e670.

Goals of treatment for patients with low-risk-MDS

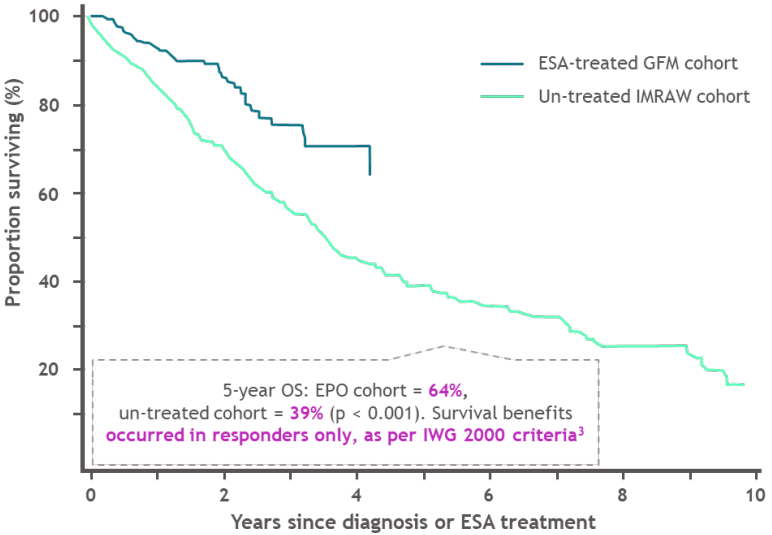


Garcia-Manero G. Am J Hematol. 2015;90:831-841; Germing U, et al. HemaSphere. 2019;3:e314

Achieving sustained and durable erythroid response has been shown to improve survival in low-risk MDS

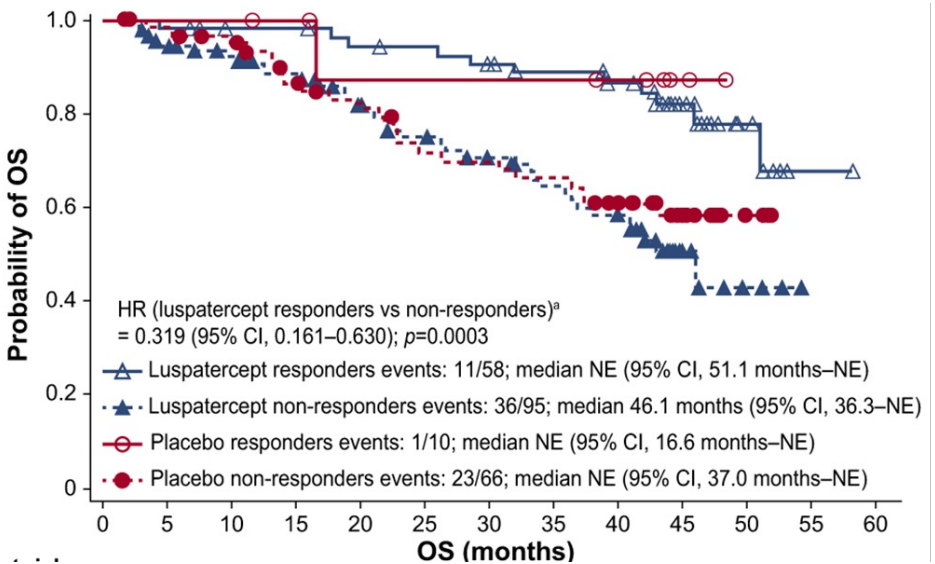
Effect of ESA treatment on OS in LR-MDS

Low and int-1 IPSS patients, Hb <10 g/dL (n = 284, GFM; n = 225, IMRAW); No patients received HMAs or lenalidomide; ESA-treated defined as at least 12 weeks of treatment with epoetin or darbepoetin between 1998-2006



Effect of Luspatercept treatment on OS in LR-MDS

(long-term analysis of MEDALIST trial)



Park S et al. Blood. 2008; 111:574-582; Platzbecker et al. Leukemia. 2023;37:2314-2318

Low-Risk MDS - Summary

- Anemia is the pathological hallmark of the disease in MDS and is now recognized as the most relevant prognostic factor for patients with low-risk disease
- Different molecular mechanisms are associated with ineffective erythropoiesis in MDS primarily involving ribosomal dysfunction and RNA splicing gene mutations, thereby supporting the development of personalized treatment strategies
- Innovative treatments are now available that offer higher response rates and longer response durations compared to ESAs.
- The contribution of ineffective erythropoiesis to anemia in MDS is maximized in early disease stages; early treatment of anemia is associated to better response rate /duration
- Sustained and durable erythroid responses have been shown to improve survival in patients with low-risk MDS, making survival improvement an essential treatment goal alongside enhancing quality of life