Efficacy and safety of luspatercept treatment in patients with myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis: a retrospective analysis from the MEDALIST study

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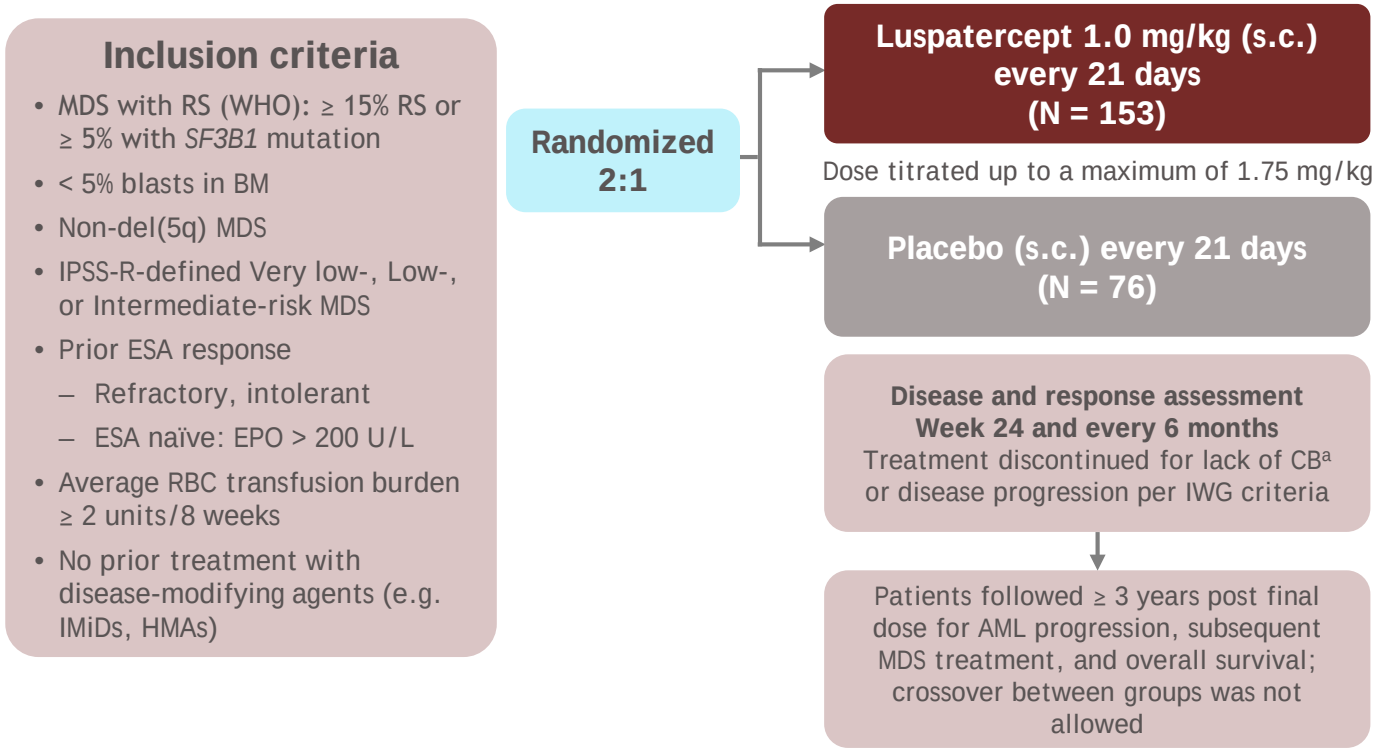
Background

- MDS/MPN-RS-T represents a unique myeloid disorder characterized by both myelodysplastic and myeloproliferative features[1]
- Anemia represents the main therapeutic challenge for patients with MDS/MPN-RS-T, with up to 50% of patients becoming transfusion dependent[2]
- This analysis assesses the efficacy and safety of luspatercept in patients with MDS/MPN-RS-T enrolled in the MEDALIST study (NCT02631070)
  - Primary endpoint: achievement of RBC-TI ≥ 8 weeks during Weeks 1–24

Figure 1. Study design of the phase 3 MEDALIST trial



Primary analysis data cutoff May 8, 2018; current data cutoff July 1, 2019

[a]CB: achievement of RBC-TI ≥ 8 weeks and/or mHI-E response during Weeks 1–24. mHI-E response was assessed per IWG 2006 criteria[3] (i.e. ≥ 4 units/8 weeks reduction in RBC transfusion in patients with ≥ 4 units/8 weeks baseline RBC transfusion burden; Hb increase by ≥ 1.5 g/dL).

AML, acute myeloid leukemia; BM, bone marrow; CB, clinical benefit; EPO, erythropoietin; ESA, erythroid-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; IMiD, immunomodulatory drug; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; MDS/MPN-RS-T, myelodysplastic syndromes/myeloproliferative neoplasm with RS and thrombocytosis; mHI-E, modified hematologic improvement-erythroid; RBC, red blood cell; RBC-TI, RBC transfusion independence; RS, ring sideroblasts; s.c., subcutaneous; WHO, World Health Organization.

1. Patnaik MM, et al. *Am J Hematol* 2019;94:475-488. 2. Broseus J, et al. *Haematologica* 2012;97:1036-1041. 3. Cheson BD, et al. *Blood* 2006;108:419-425.

Results

Table 1. Baseline characteristics of patients with MDS/MPN-RS-T in the MEDALIST trial

Characteristic	Luspatercept (N = 14)	Placebo (N = 9)	Total (N = 23)
Age, median (range), years	69.5 (56.0–83.0)	66.0 (26.0–81.0)	69.0 (26.0–83.0)
Time since original diagnosis of MDS, median (range), months	49.9 (10.0–108.0)	44.1 (9.2–152.1)	47.3 (9.2–152.1)
RBC transfusion burden category over period of 16 weeks, n (%)			
< 4 units/8 weeks	6 (42.9)	4 (44.4)	10 (43.5)
4 to < 6 units/8 weeks	6 (42.9)	3 (33.3)	9 (39.1)
≥ 6 units/8 weeks	2 (14.3)	2 (22.2)	4 (17.4)
Pretransfusion Hb level, median (range), g/dL[a]	7.5 (7.0–8.6)	8.1 (7.6–9.0)	7.7 (7.0–9.0)
Serum EPO level, median (range), U/L[b]	71.9 (29.2–368.8)	54.0 (38.2–138.1)	59.9 (29.2–368.8)
Received ESA previously, n (%)	13 (92.9)	8 (88.9)	21 (91.3)
Reasons for ESA discontinuation, n (%)			
Refractory	12 (85.7)	8 (88.9)	20 (87.0)
Intolerant	1 (7.1)	0	1 (4.3)
Missing	1 (7.1)	1 (11.1)	2 (8.7)
Previous iron chelation therapy, n (%)	3 (21.4)	3 (33.3)	6 (26.1)
Platelet count, median (range), $\times 10^9$/L	462.5 (360.0–892.0)	447.0 (327.0–689.0)	447.0 (327.0–892.0)
Leukocyte count, median (range), $\times 10^9$/L	4.8 (2.5–12.4)	7.5 (3.2–12.9)	5.1 (2.5–12.9)
Mutated *SF3B1*, n (%)	13 (92.9)	8 (88.9)	21 (91.3)

[a]Baseline value is defined as the last value measured on or before the date and time of the first dose; [b]Baseline EPO level is defined as the highest EPO value within 35 days before the first dose.
SF3B1, splicing factor 3B subunit 1.

Results (cont.)

Figure 2. Rates of CB, mHI-E, and RBC-TI ≥ 8 weeks in patients with MDS/MPN-RS-T during Weeks 1-24

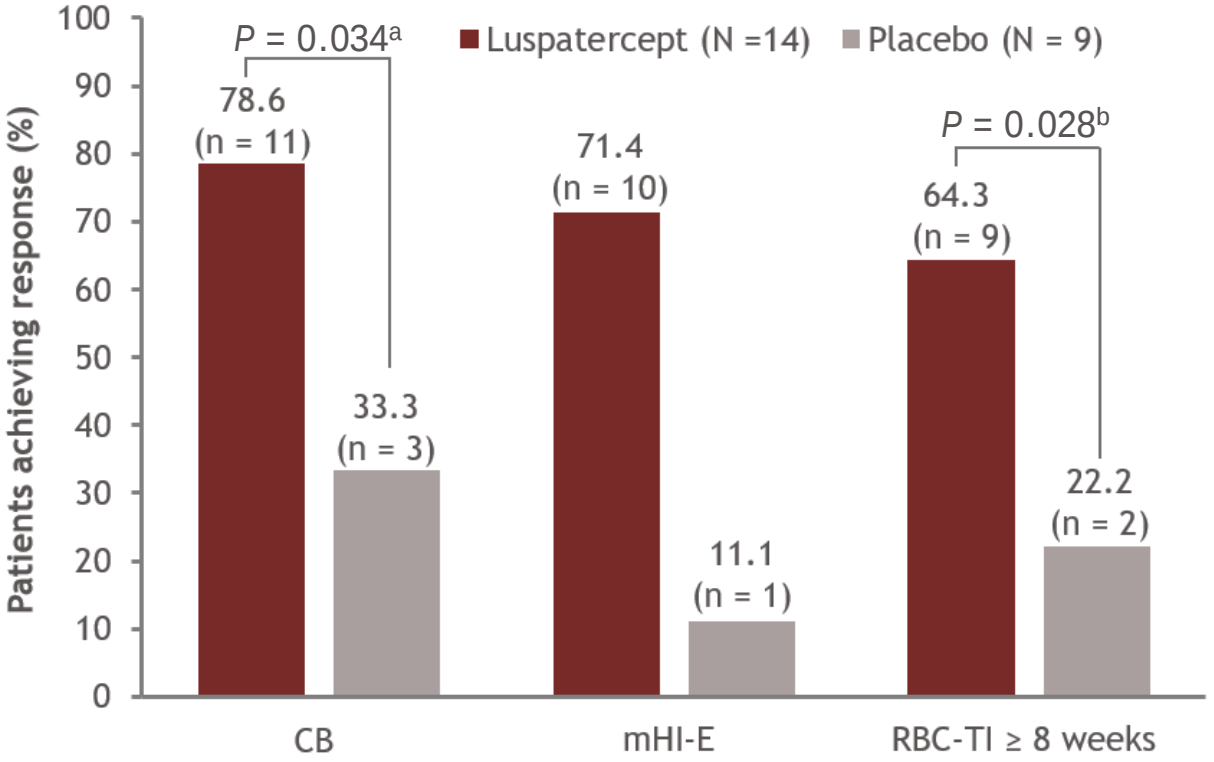
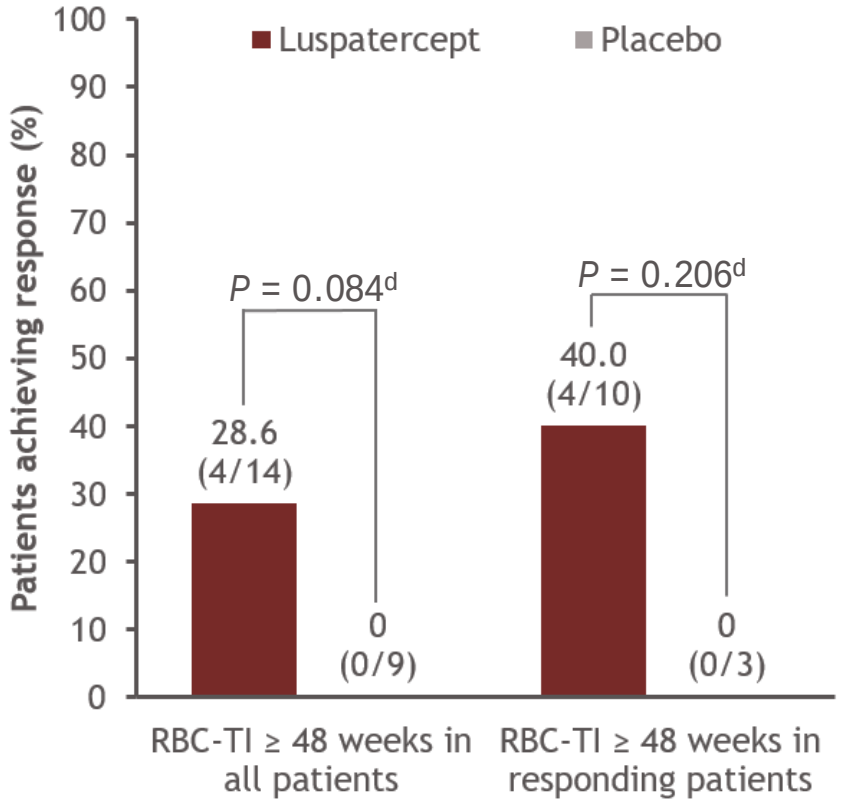


Figure 3. Rates of RBC-TI ≥ 48 weeks at any time during treatment in responding patients[c] with MDS/MPN-RS-T



[a]Unstratified CMH test; OR 7.3; 95% CI 1.11–48.26. [b]CMH test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBC per 8 weeks), and baseline IPSS-R score (Very low- or Low- vs Intermediate-risk); OR 11.3; 95% CI 1.19–106.12. [c]Patients who achieved RBC-TI ≥ 8 weeks at any time on treatment. [d]Unstratified CMH test. OR not determined.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel test; OR, odds ratio,

Results (cont.)

Table 2. Response by baseline transfusion burden during Weeks 1-24

	mHI-E		RBC-TI ≥ 8 weeks	
	Luspatercept (N = 14)	Placebo (N = 9)	Luspatercept (N = 14)	Placebo (N = 9)
Low transfusion burden[a], n/N	4/6	0/4	5/6	2/4
High transfusion burden[b], n/N	6/8	1/5	4/8	0/5

Table 3. Platelet, WBC and neutrophil counts at baseline and post 24 weeks of treatment

	Luspatercept (N = 12)		Placebo (N = 6)		
	Baseline	Week 25	Baseline	Week 25	*P* value[c]
Platelet count, mean, $\times 10^9$/L	514.6	539.3	528.8	458.5	0.276
WBC count, mean, $\times 10^9$/L	5.3	7.8	7.3	6.2	0.0119
ANC, mean, $\times 10^9$/L	3.4	5.1	5.1	4.1	0.0668

Table 4. The incidence of TEAEs of any grade occurring in ≥ 1 patient

TEAE, n (%)	Luspatercept (N = 14)	Placebo (N = 9)
Dizziness	7 (50.0)	0
Nausea	6 (42.9)	2 (22.2)
Diarrhea	6 (42.9)	1 (11.1)
Dyspnea	3 (21.4)	0
Hypertension	3 (21.4)	0
Fatigue	1 (7.1)	1 (11.1)
Arthralgia	1 (7.1)	0

[a]Defined as baseline transfusion burden < 4 units/8 weeks. [b]Defined as baseline transfusion burden ≥ 4 units/8 weeks. [c]Estimates are based on an ANCOVA model with treatment (luspatercept vs. placebo) as main fact, and baseline of values as a covariate.
ANC, absolute neutrophil count; ANCOVA, analysis of covariance; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Summary

- Luspatercept demonstrated clinical efficacy in patients with MDS/MPN-RS-T, with a generally well-tolerated safety profile
- The proportion of patients with MDS/MPN-RS-T receiving luspatercept who achieved RBC-TI ≥ 8 weeks during Weeks 1-24 compared to placebo (64% vs 22%, respectively), was comparable to the entire MEDALIST trial population (38% luspatercept vs 13% placebo)
- After the treatment period, only patients with MDS/MPN-RS-T who received luspatercept experienced a significant increase in WBC count, with also non-significant increases in platelet and neutrophil counts
- These data support the clinical benefits of luspatercept in this patient population with otherwise limited treatment options

Acknowledgments

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