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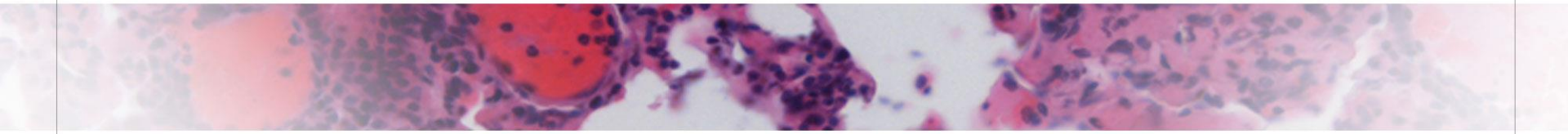

The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

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MEDALIST Trial
Background and Rationale

- Patients with lower-risk (LR)[a] transfusion-dependent MDS have a poorer prognosis, with greater risk of progression to AML and inferior overall survival compared with patients with transfusion-independent MDS
- RBC transfusion-dependent LR, non-del(5q) MDS patients have a transient response to ESAs, with an attendant risk of iron overload and secondary organ complications
- Few treatment options exist for the large number of patients with LR MDS who are either refractory to or become unresponsive to ESAs[1]

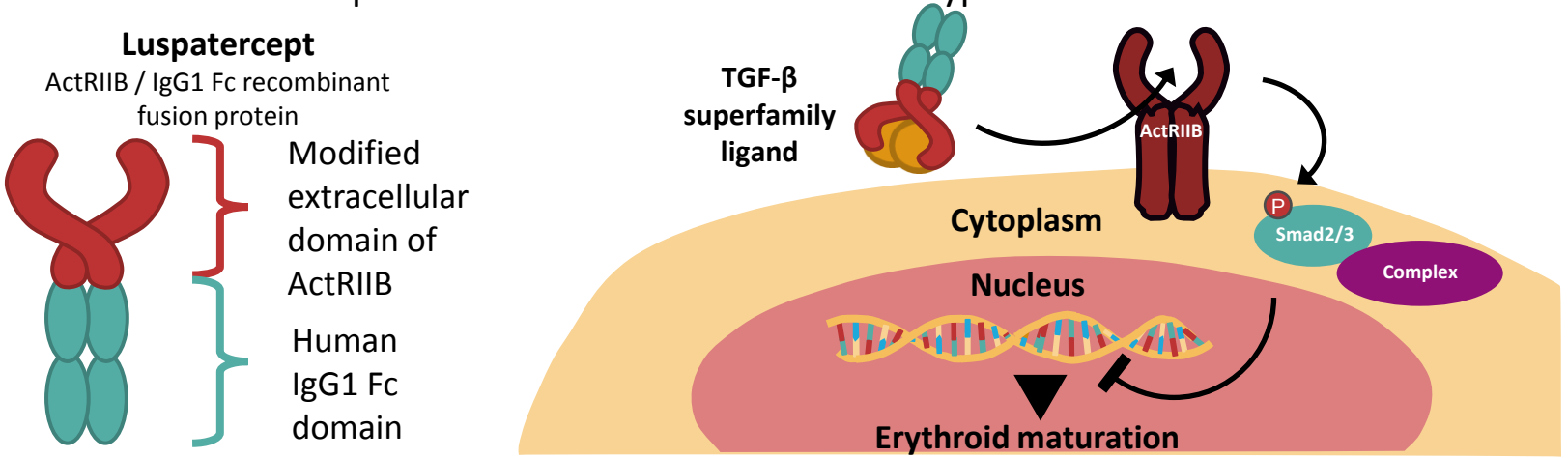
[a] IPSS-R-defined criteria.

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell.

1. Fenaux P, and Adès L. Blood. 2013;121:4280-4286.

MEDALIST Trial
Luspatercept

- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]



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

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

MEDALIST Trial

Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

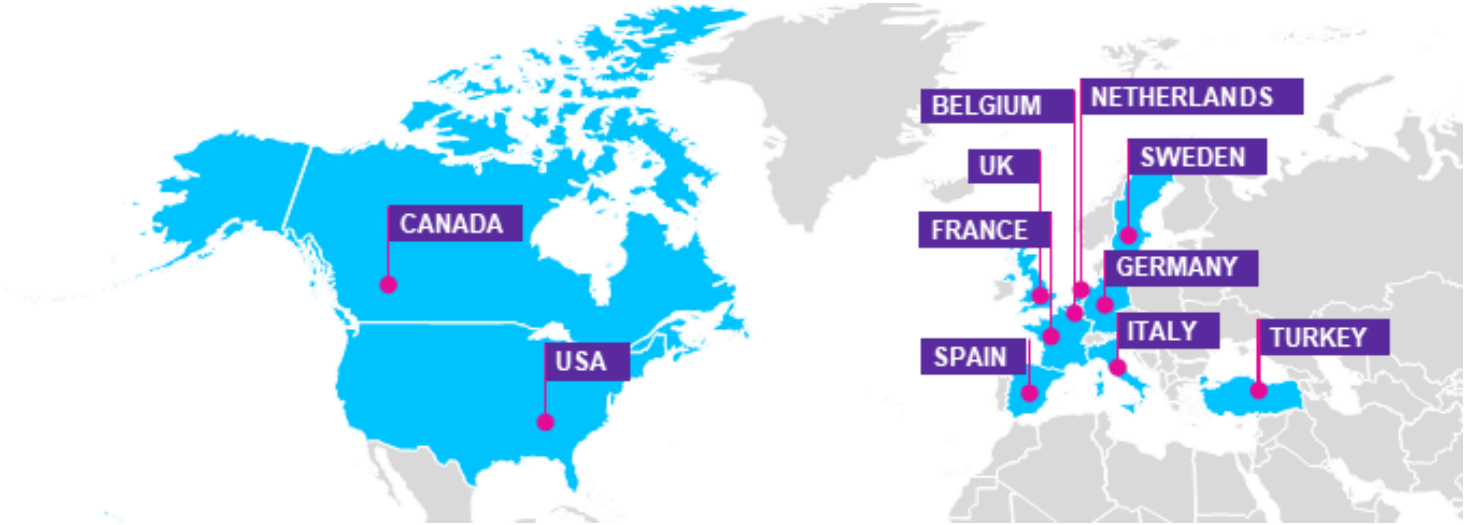
Disease & Response Assessment week 24 & every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

MEDALIST Trial
Study Design (cont.)

- Patients were randomized between March 2016 and June 2017 at 65 sites in Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, Sweden, Turkey, UK, and USA



MEDALIST Trial
Study Endpoints

Primary endpoint:

- Red blood cell transfusion independence ≥ 8 weeks (weeks 1–24)

Key secondary endpoint:

- Red blood cell transfusion independence ≥ 12 weeks (weeks 1–24 and weeks 1–48)

Additional secondary endpoints:

- HI-E (IWG 2006 criteria[1]) for any consecutive 56-day period
  - Reduction in red blood cell transfusion burden ≥ 4 RBC units/8 weeks[a] or
  - Mean Hb increase of ≥ 1.5 g/dL/8 weeks[b]
- Duration of response
- Hb change from baseline

[a] In patients with baseline RBC transfusion burden ≥ 4 units/8 weeks. [b] In patients with baseline RBC transfusion burden < 4 units/8 weeks.
Hb, hemoglobin; HI-E, hematological improvement–erythroid.

1. Cheson BD, et al. Blood. 2006;108:419-425.

MEDALIST Trial

Demographics and Baseline Disease Characteristics

Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Age, median (range), years	**71 (40–95)**	**72 (26–91)**
Male, n (%)	**94 (61.4)**	**50 (65.8)**
Time since original MDS diagnosis, median (range), months	**44.0 (3–421)**	**36.1 (4–193)**
WHO classification		
RCMD-RS, n (%)	**145 (94.8)**	**74 (97.4)**
RBC transfusion burden, median (range), units/8 weeks[a]	5 (1–15)	5 (2–20)
≥ 6 units/8 weeks, n (%)	**66 (43.1)**	**33 (43.4)**
< 6 units/8 weeks, n (%)	87 (56.9)	43 (56.6)
Pre-transfusion Hb, median (range), g/dL	**7.6 (6–10)**	**7.6 (5–9)**
IPSS-R risk category[b]		
Very Low, Low, n (%)	127 (83.0)	63 (82.9)
Intermediate, n (%)	25 (16.3)	13 (17.1)
***SF3B1* mutation, n (%)**	**141 (92.2)**	**65 (85.5)[c]**
Serum EPO		
< 200 U/L, n (%)	88 (57.5)[c]	50 (65.8)
≥ 200 U/L, n (%)	64 (41.8)[c]	26 (34.2)

[a] In the 16 weeks prior to randomization. [b] 1 (0.7%) patient in the luspatercept arm was classified as IPSS-R High-risk. [c] Data were missing for 1 patient.
RCMD-RS, refractory cytopenia with multilineage dysplasia with RS.

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Treatment Exposure

Parameter	Luspatercept (n = 153)	Placebo (n = 76)
Treatment duration, median (range), weeks	**49 (6–114)**	**24 (7–89)**
Completed ≥ 24 weeks of treatment (primary phase), n (%)	128 (83.7)	68 (89.5)
Completed ≥ 48 weeks of treatment, n (%)	78 (51.0)	12 (15.8)
Number of doses received, median (range)	16 (2–37)	8 (3–30)
Maximum dose escalation, n (%)[a]		
1.0 mg/kg	35 (22.9)	5 (6.6)
1.33 mg/kg	28 (18.3)	8 (10.5)
1.75 mg/kg	90 (58.8)	63 (82.9)
Patients remaining on treatment, n (%)	**70 (45.8)**	**6 (7.9)**
Patients discontinued from treatment, n (%)	**83 (54.2)**	**70 (92.1)**
Lack of benefit	51 (33.3)	50 (65.8)
Patient withdrawal	14 (9.2)	10 (13.2)
AE	10 (6.5)	4 (5.3)
Disease progression	3 (2.0)	2 (2.6)
Other	5 (3.3)	4 (5.3)

[a] Dose may be titrated up to a maximum of 1.75 mg/kg.
AE, adverse event.

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Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

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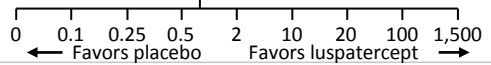
Primary Endpoint: Subgroup Analysis

	Luspatercept, n (%)	Placebo, n (%)	OR (95% CI)	*P* Value
Overall	58/153 (37.9)	10/76 (13.2)	5.06 (2.28–11.3)	< 0.0001
Average baseline RBC transfusion requirement				
≥ 6 units/8 weeks	6/66 (9.1)	1/33 (3.0)	3.20 (0.37–27.7)	0.2699
< 6 units/8 weeks	52/87 (59.8)	9/43 (20.9)	5.61 (2.40–13.1)	< 0.0001
4 to < 6 units/8 weeks	15/41 (36.6)	1/23 (4.3)	12.7 (1.55–104)	0.0046
< 4 units/8 weeks	37/46 (80.4)	8/20 (40.0)	6.17 (1.95–19.5)	0.0013
Baseline serum EPO (U/L)				
< 100	23/51 (45.1)	7/31 (22.6)	2.82 (1.03–7.71)	0.0413
100 to < 200	14/37 (37.8)	2/19 (10.5)	5.17 (1.04–25.9)	0.0338
200–500	17/43 (39.5)	1/15 (6.7)	9.15 (1.10–76.2)	0.0188
Age group				
≤ 64 years	17/29 (58.6)	3/16 (18.8)	6.14 (1.43–26.3)	0.0108
65–74 years	23/72 (31.9)	4/29 (13.8)	2.93 (0.91–9.41)	0.0635
≥ 75 years	18/52 (34.6)	3/31 (9.7)	4.94 (1.32–18.5)	0.0120
Gender				
Male	32/94 (34.0)	4/50 (8.0)	5.94 (1.96–18.0)	0.0006
Female	26/59 (44.1)	6/26 (23.1)	2.63 (0.92–7.48)	0.0673
Time since initial diagnosis at baseline				
≤ 2 years	14/40 (35.0)	3/19 (15.8)	2.87 (0.71–11.6)	0.1312
> 2–5 years	30/62 (48.4)	4/34 (11.8)	7.03 (2.21–22.3)	0.0004
> 5 years	14/51 (27.5)	3/23 (13.0)	2.52 (0.65–9.83)	0.1756
Baseline IPSS-R risk				
Very Low or Low	48/127 (37.8)	9/63 (14.3)	3.65 (1.65–8.05)	0.0009
Intermediate	10/25 (40.0)	1/13 (7.7)	8.00 (0.89–71.6)	0.0398
Baseline platelet count				
< 100 × 10^9/L	2/8 (25.0)	1/6 (16.7)	1.67 (0.11–24.3)	0.7171
100–400 × 10^9/L	42/128 (32.8)	8/61 (13.1)	3.24 (1.41–7.42)	0.0042
> 400 × 10^9/L	14/17 (82.4)	1/9 (11.1)	37.3 (3.31–422)	0.0006



OR, odds ratio.

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Key Secondary Endpoint: Red Blood Cell Transfusion Independence ≥ 12 Weeks

RBC-TI ≥ 12 Weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).

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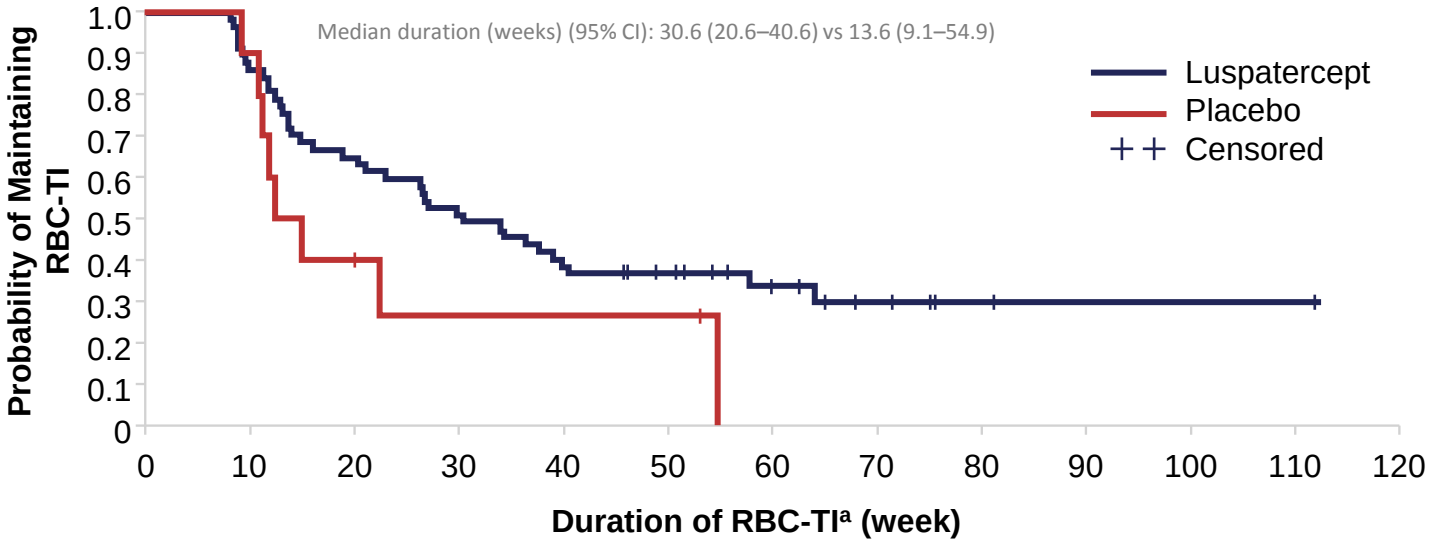
Duration of RBC-TI Response in Primary Endpoint Responders



Number of patients

Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

MEDALIST Trial

Secondary Endpoint: Erythroid Response (HI-E)

	Luspatercept (n = 153)	Placebo (n = 76)
Achieved HI-E[a] (weeks 1–24), n (%)	**81 (52.9)**	**9 (11.8)**
Reduction of ≥ 4 RBC units/8 weeks (baseline transfusion burden ≥ 4 units/8 weeks)	52/107 (48.6)	8/56 (14.3)
Hb increase of ≥ 1.5 g/dL (baseline transfusion burden < 4 units/8 weeks)	29/46 (63.0)	1/20 (5.0)
95% CI	44.72–61.05	5.56–21.29
P value[b]	< 0.0001	
Achieved HI-E[a] (weeks 1–48), n (%)	**90 (58.8)**	**13 (17.1)**
Reduction of ≥ 4 RBC units/8 weeks (baseline RBC transfusion burden ≥ 4 units/8 weeks)	58/107 (54.2)	12/56 (21.4)
Hb increase of ≥ 1.5 g/dL (baseline RBC transfusion burden < 4 units/8 weeks)	32/46 (69.6)	1/20 (5.0)
95% CI	50.59–66.71	9.43–27.47
P value[b]	< 0.0001	

[a] Defined as the proportion of patients meeting the HI-E criteria per IWG 2006 criteria (Cheson et al. 2006) sustained over a consecutive 56-day period during the indicated treatment period.
[b] Luspatercept compared with placebo, Cochran–Mantel–Haenszel test.

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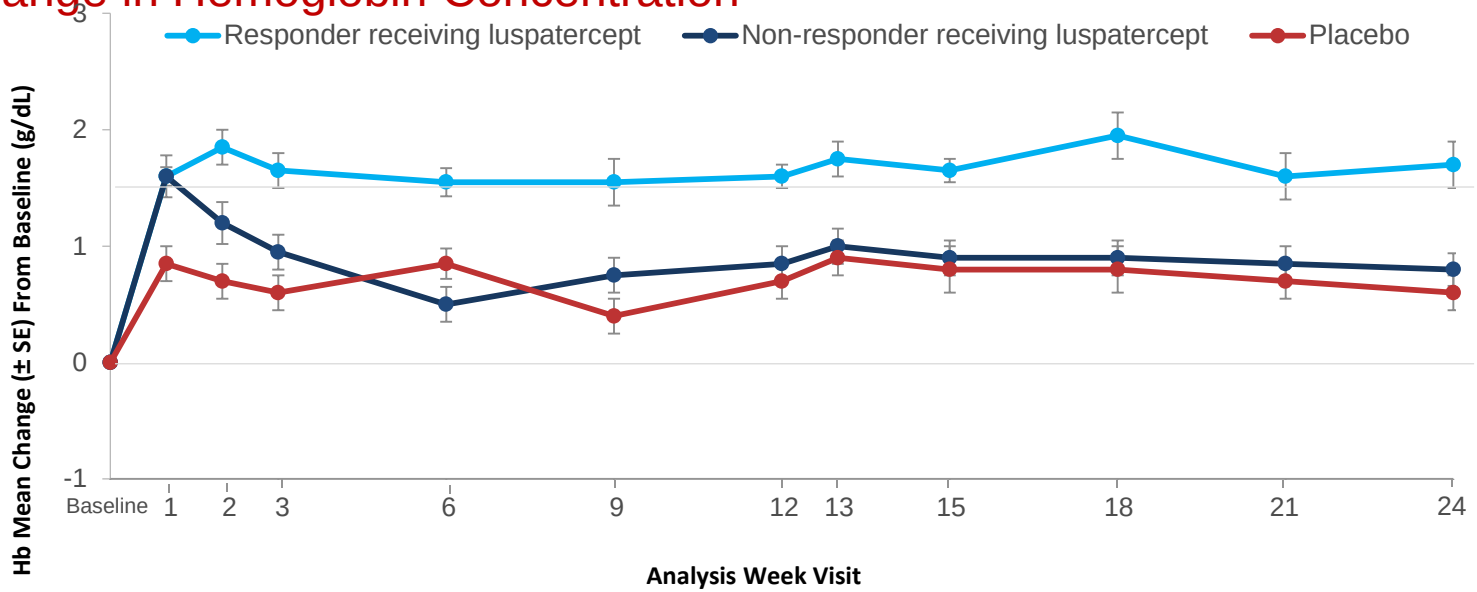
Change in Hemoglobin Concentration



- Median peak hemoglobin increase in luspatercept responders: 2.55 g/dL (1–4.1 g/dL)

Number of patients												
Responder[a]	153	24	36	55	53	52	50	42	47	50	42	45
Non-responder		33	51	61	52	60	53	34	45	56	48	35
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

[a] LS mean difference (95% CI) for luspatercept responders versus placebo: 1.08 (0.84, 1.31), $P < 0.0001$.

Only patients with RBC-TI ≥ 8 weeks during weeks 1–24 are included. Hb measurement was excluded within 14 days after a RBC transfusion unless within 3 days prior to another RBC transfusion. Mean and SE were not calculated if the number of patients was < 8 in the luspatercept non-responder group or < 4 in the placebo group. SE, standard error.

MEDALIST Trial
Safety Summary

	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE, n (%)	**150 (98.0)**	**70 (92.1)**
Patients with ≥ 1 serious TEAE	48 (31.4)	23 (30.3)
Patients with ≥ 1 Grade 3 or 4 TEAE	65 (42.5)	34 (44.7)
Patients with TEAEs leading to death[a]	5 (3.3)	4 (5.3)
Patients with ≥ 1 TEAE causing discontinuation, n (%)	**13 (8.5)**	**6 (7.9)**

- TEAEs were balanced between the arms[b]
- Progression to AML occurred in 4 patients (3/153 [2.0%] in the luspatercept arm; 1/76 [1.3%] in the placebo arm)

[a] In luspatercept arm: sepsis (n = 2), multiple organ dysfunction syndrome, renal failure, and hemorrhagic shock; in placebo arm: sepsis, urosepsis, general physical health deterioration, and respiratory failure. [b] The most common grade 3 or 4 TEAEs reported in luspatercept-treated patients were anemia (6.5% of patients), fall (4.6%), and fatigue (4.6%).
TEAE, treatment-emergent adverse event.

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TEAEs ≥ 10% Incidence in Either Arm

n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	41 (26.8)	10 (13.2)
Diarrhea	34 (22.2)	7 (9.2)
Asthenia	31 (20.3)	9 (11.8)
Nausea	31 (20.3)	6 (7.9)
Dizziness	30 (19.6)	4 (5.3)
Back pain	29 (19.0)	5 (6.6)
Cough	27 (17.6)	10 (13.2)
Edema peripheral	25 (16.3)	13 (17.1)
Headache	24 (15.7)	5 (6.6)
Dyspnea	23 (15.0)	5 (6.6)
Bronchitis	17 (11.1)	1 (1.3)
Constipation	17 (11.1)	7 (9.2)
Urinary tract infection	17 (11.1)	4 (5.3)
Fall	15 (9.8)	9 (11.8)

TEAEs ≥ 10% incidence in either arm by preferred term

MEDALIST Trial
Conclusions

- In lower-risk, RS-positive MDS, treatment with luspatercept resulted in a significantly higher percentage of patients who achieved RBC-TI, major RBC transfusion reduction, or hemoglobin increase, compared with placebo
- Erythroid responses were durable, with approximately 40% of patients achieving RBC-TI sustained at 12 months of treatment
- Luspatercept was generally well tolerated in this patient population
- Luspatercept is a potential new therapy for the treatment of patients with lower-risk, RS-positive MDS with RBC transfusion-dependent anemia

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