Assessment of Longer-Term Efficacy and Safety in the Phase 3, Randomized, Double-Blind, Placebo-Controlled MEDALIST Trial of Luspatercept to Treat Anemia in IPSS-R Very Low-, Low-, or Int-Risk RBC Transfusion-Dependent MDS with Ring Sideroblasts

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INTRODUCTION

- Chronic anemia is the most common cytopenia in LR-MDS and is associated with a number of complications, including fatigue, falls, and decreased quality of life[1,2]
- Treatments for anemia include ESAs and RBC transfusions; however, RBC transfusion dependence is associated with reduced survival[3] and responses to ESAs are limited[2]
- Treatment options are lacking for patients with transfusion-dependent LR-MDS[a] for whom ESA treatment is ineffective or is not an option[2,4]

[a] IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS.

ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System; LR; lower-risk; MDS, myelodysplastic syndromes; RBC, red blood cell.

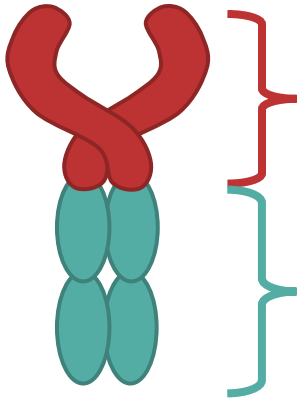
1. Stauder R, et al. Blood. 2018;131:505-514.
2. Fenaux P, Adès L. Blood. 2013;121:4280-4286.
3. Hiwase DK, et al. Blood. 2013;122:abstract 1518.
4. Adès L, et al. Lancet. 2014;383:2239-2252.

INTRODUCTION (cont.)

- Luspatercept is a first-in-class erythroid maturation agent that binds several TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[1]
- Luspatercept is approved by the US FDA for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions[2]
- In the primary results of the MEDALIST trial[3] luspatercept met the following endpoints with statistical significance versus placebo:
  - Primary endpoint: RBC-TI ≥ 8 weeks (Weeks 1–24)
  - Key secondary endpoint: RBC-TI ≥ 12 weeks (Weeks 1–24, Weeks 1–48)
- Presented here is an updated analysis of longer-term clinical benefit and safety data from the MEDALIST trial

Luspatercept

ActRIIB / IgG1 Fc recombinant fusion protein



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, RBC transfusion independence; RS, ring sideroblasts; US FDA, United States Food and Drug Administration.

1. Suragani RN, et al. Nat Med. 2014;20:408-414.
2. Reblozyl [package insert]. Summit, NJ, USA: Celgene Corporation; 2019.
3. MEDALIST authors. Blood. 2018;132:abstract 1.

STUDY DESIGN

Inclusion Criteria

- MDS with RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- Non-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 U/8 weeks
- No prior treatment with disease-modifying agents (e.g. IMiD agents, HMAs)

Randomized 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 3 weeks
(n = 76)

Disease and response assessment
Week 24 and every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria

Patients followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment, and overall survival; crossover between groups was not allowed

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

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

EVALUATION OF EFFICACY AND SAFETY WITH LONGER-TERM FOLLOW-UP

NEW DATA CUTOFF: JULY 1, 2019[a]

Efficacy

Achievement of RBC-TI ≥ 8 weeks over the entire treatment period and number of individual response periods

Cumulative duration of RBC-TI ≥ 8 weeks in all responders

- Defined as the sum of all durations of RBC-TI ≥ 8 weeks for all patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase

Clinical benefit

- Defined as achieving RBC-TI ≥ 8 weeks and / or mHI-E[b]

Total duration of clinical benefit

- Defined as the time from achieving clinical benefit to end of treatment

[a] Primary analysis data cutoff date May 8, 2018.[1] [b] According to IWG 2006 criteria.[2]

IWG, International Working Group; mHI-E, modified hematologic improvement–erythroid.

1. MEDALIST authors. Blood. 2018;132:abstract 1.
2. Cheson BD, et al. Blood. 2006;108:419-425.

BASELINE PATIENT CHARACTERISTICS

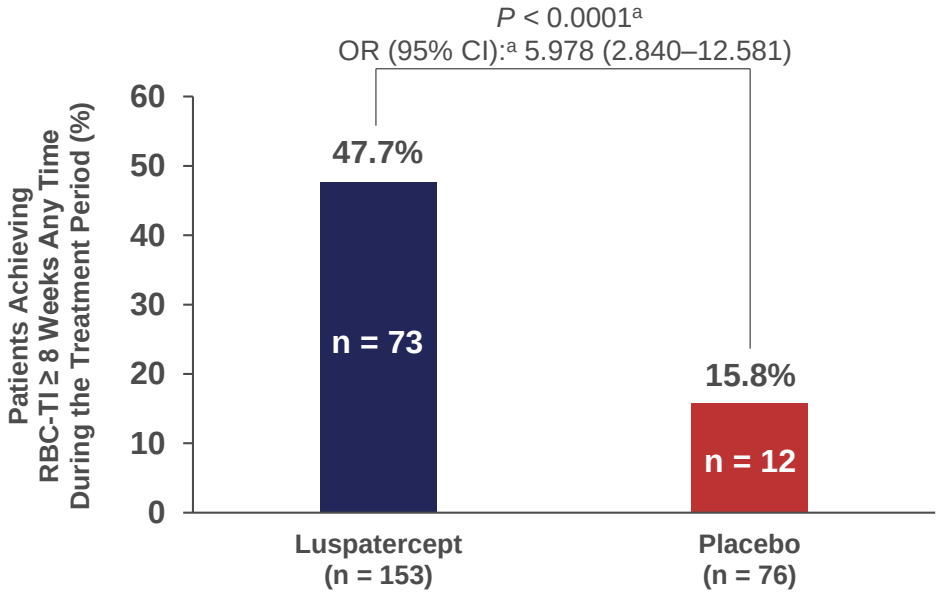
Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Age, median (range), years	71 (40–95)	72 (26–91)
Male, n (%)	94 (61.4)	50 (65.8)
RBC transfusion burden, median (range), U/8 weeks[a]	5 (1–15)	5 (2–20)
≥ 6 U/8 weeks, n (%)	66 (43.1)	33 (43.4)
≥ 4 to < 6 U/8 weeks, n (%)	41 (26.8)	23 (30.3)
< 4 U/8 weeks, n (%)	46 (30.1)	20 (26.3)
IPSS-R, n (%)[b]		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
***SF3B1* mutation, n (%)**[c]	138 (93.2)[c]	64 (86.5)[c]
Serum EPO, n (%)[d]		
< 200 U/L	88 (57.5)	50 (65.8)
≥ 200 U/L	64 (41.8)	26 (34.2)
Baseline hemoglobin, median (range), g/dL[e]	7.6 (6–10)	7.6 (5–9)
Serum ferritin, mean (SD), µg/L	1,348.0 (971.24)	1,503.8 (1,242.94)

[a] In the 16 weeks prior to randomization. [b] 1 patient in the luspatercept arm was classified as IPSS-R High-risk. [c] Of patients with available baseline gene mutation data: n = 148 in the luspatercept arm; and n = 74 in the placebo arm; no patients with *SF3B1* mutation had RS < 15%.[d] Data were missing for 1 patient in the luspatercept arm. [e] Baseline hemoglobin was defined as the last value measured on or before the date and time of first dose.

EPO, erythropoietin; SD, standard deviation.

MEDALIST authors. Blood. 2018;132:abstract 1.

RBC-TI ≥ 8 WEEKS ACHIEVED ANY TIME DURING TREATMENT PERIOD



- **Primary endpoint previously reported:** **37.9%** luspatercept versus **13.2%** placebo patients achieved RBC-TI ≥ 8 weeks during Weeks 1–24 (*P* < 0.0001)[1]

[a] Determined using a Cochran-Mantel-Haenszel test stratified for average baseline transfusion requirement (≥ 6 U/8 weeks vs < 6 U/8weeks) and baseline IPSS-R score (Very low or Low vs Intermediate).

CI, confidence interval; OR, odds ratio.

1. MEDALIST authors. Blood. 2018;132:abstract 1.

Data cutoff: July 1, 2019.

RBC-TI ≥ 8 WEEKS ACHIEVED DURING THE ENTIRE TREATMENT PERIOD
RESPONSE BY BASELINE TRANSFUSION BURDEN

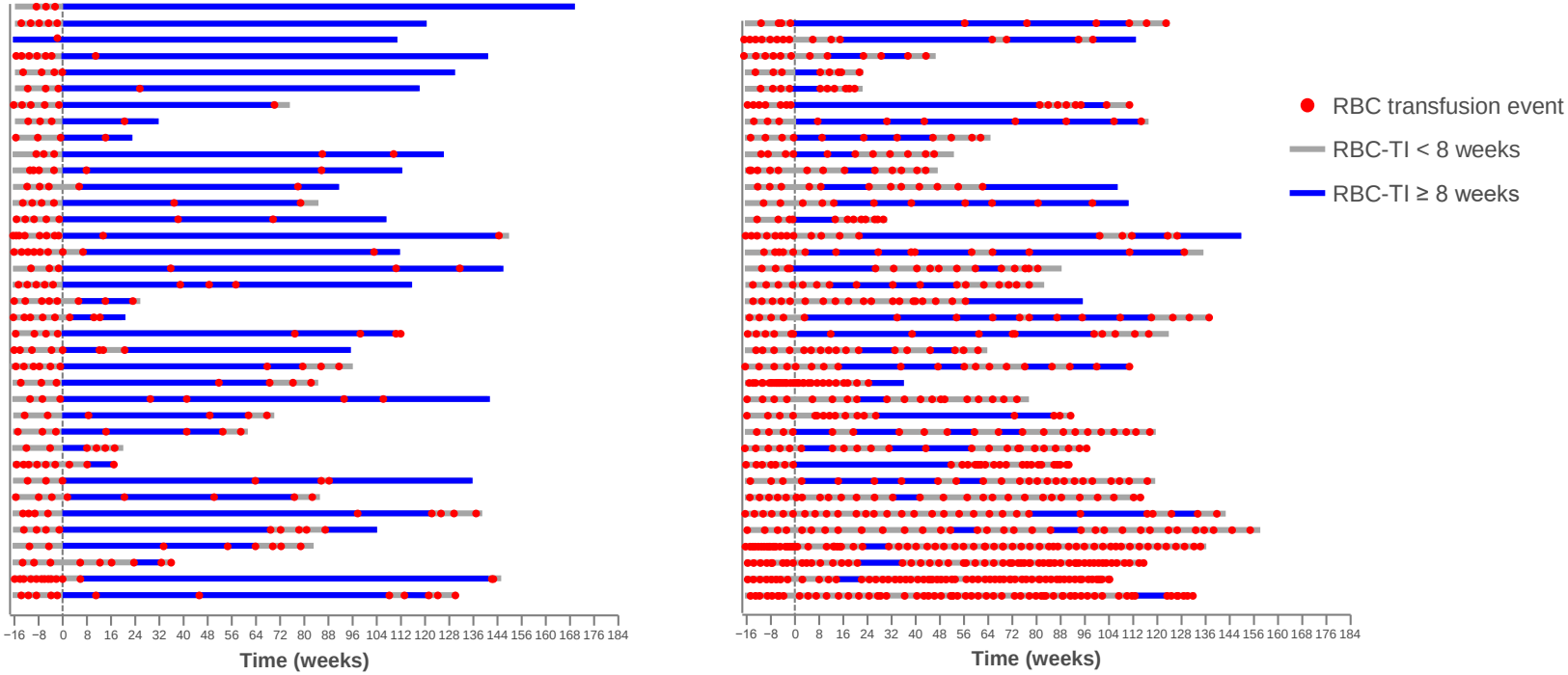
RBC-TI ≥ 8 Weeks Over the Entire Treatment Period	Luspatercept (n = 153)	Placebo (n = 76)	Luspatercept Minus Placebo	
			OR (95%CI)[a]	*P* Value[a]
Average baseline RBC transfusion requirement, n/N (%)				
≥ 6 U/8 weeks	14/66 (21.2)	2/33 (6.1)	4.17 (0.89–19.60)	0.0547
≥ 4 to < 6 U/8 weeks	20/41 (48.8)	2/23 (8.7)	10.00 (2.07–48.28)	0.0013
< 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)	8.36 (2.51–27.83)	0.0002

[a] Determined using a Cochran-Mantel-Haenszel test.

- Higher RBC-TI ≥ 8 weeks for luspatercept versus placebo regardless of baseline transfusion burden

Data cutoff: July 1, 2019.

LUSPATERCEPT PATIENTS ACHIEVING RBC-TI ≥ 8 WEEKS (N = 73)
ANALYSIS OF MULTIPLE RESPONSE PERIODS

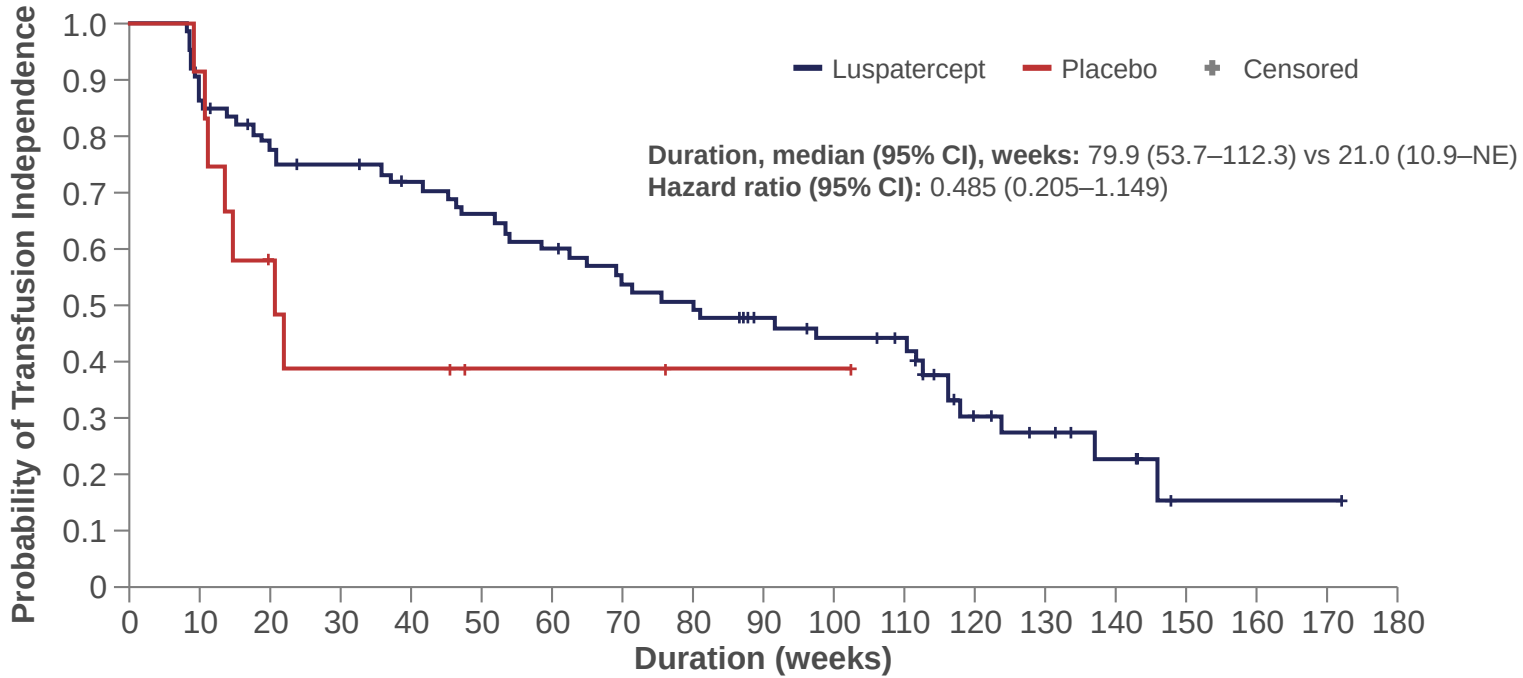


- Of the 73 luspatercept-treated patients achieving RBC-TI ≥ 8 weeks during the entire treatment period:
  - 51 (69.9%) had ≥ 2 separate response periods
  - 28 (38.4%) had ≥ 3 separate response periods
  - 15 (20.5%) had ≥ 4 separate response periods

Response according to IWG 2006 criteria.
Transfusion events are not representative of changes in RBC units transfused.

Data cutoff: July 1, 2019.

CUMULATIVE DURATION OF RBC-TI ≥ 8 WEEKS[a] IN ALL RESPONDERS



Number of patients[b]

Luspatercept	73	63	55	52	48	44	40	35	32	27	24	22	11	8	5	1	1	1
Placebo	12	11	7	4	4	2	2	2	1	1	1							

[a] Cumulative duration of RBC-TI ≥ 8 weeks is defined as the sum of all durations of RBC-TI for patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase.
[b] In the intent-to-treat population; patients who maintained response were censored from the analysis.

NE, not estimable.

Data cutoff: July 1, 2019.

TREATMENT EXPOSURE AND CUMULATIVE DURATION OF RESPONSE

Parameter	Luspatercept (n = 153)	Placebo (n = 76)
Treatment duration, median (range), weeks	50.9 (6.0–172.0)	24.0 (7.0–103.0)
In patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase	109.1 (18.0–172.0)[a]	53.6 (24.0–103.0)[b]
Patients remaining on treatment as of July 1, 2019 data cutoff, n (%)	41 (26.8)	0
Cumulative duration of RBC-TI ≥ 8 weeks (sum of all periods of RBC-TI ≥ 8 weeks),[c] median (95% CI), weeks	79.9 (53.7–112.3)[a]	21.0 (10.9–NE)[b]

[a] In the 73 patients in the luspatercept arm who achieved RBC-TI ≥ 8 weeks during the entire treatment phase. [b] In the 12 patients in the placebo arm who achieved RBC-TI ≥ 8 weeks during the entire treatment phase. [c] Cumulative duration of RBC-TI ≥ 8 weeks is defined as the sum of all durations of RBC-TI for patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase.

- Of the 153 luspatercept-treated patients, 12 (7.8%) remained transfusion free after the first dose of luspatercept through Week 48
- Patients receiving luspatercept had longer duration of treatment, duration of the longest single period of RBC-TI ≥ 8 weeks, and cumulative duration of RBC-TI ≥ 8 weeks

Data cutoff: July 1, 2019.

ACHIEVEMENT AND DURATION OF CLINICAL BENEFIT OVER THE ENTIRE TREATMENT PERIOD

Clinical Benefit and Duration	Luspatercept	Placebo
Clinical benefit[a] – all patients, n/N (%)	**98/153 (64.1)**	**20/76 (26.3)**
Baseline transfusion burden ≥ 6 U/8 weeks	37/66 (56.1)	9/33 (27.3)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	22/41 (53.7)	3/23 (13.0)
Baseline transfusion burden < 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)
Duration of clinical benefit[b] – all patients, median (range), weeks	**92.3 (8–172)**	**26.8 (8–103)**
Baseline transfusion burden ≥ 6 U/8 weeks	66.0 (8–148)	23.9 (8–103)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	96.1 (13–150)	45.7 (45–51)
Baseline transfusion burden < 4 U/8 weeks	91.7 (21–172)	26.8 (18–76)

[a] Defined as achieving RBC-TI ≥ 8 weeks and/or mHI-E per IWG 2006 criteria[1] over the entire treatment phase.
[b] Duration of clinical benefit is defined as the time from start of response (RBC-TI ≥ 8 weeks and/or mHI-E) to end of treatment.

- Durable clinical benefit with luspatercept was achieved regardless of baseline transfusion burden

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

Data cutoff: July 1, 2019.

SAFETY
SUMMARY

Summary of TEAEs, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	134 (87.6)	63 (82.9)
Patients with ≥ 1 TEAE resulting in treatment discontinuation	21 (13.7)	6 (7.9)
Specific TEAEs[a] resulting in discontinuation		
Fatigue	2 (1.3)	0
Diarrhea	0	0
Asthenia	1 (0.7)	0
Dizziness	0	0
Nausea	0	0
Back pain	0	0
Headache	1 (0.7)	0
Dyspnea	0	0

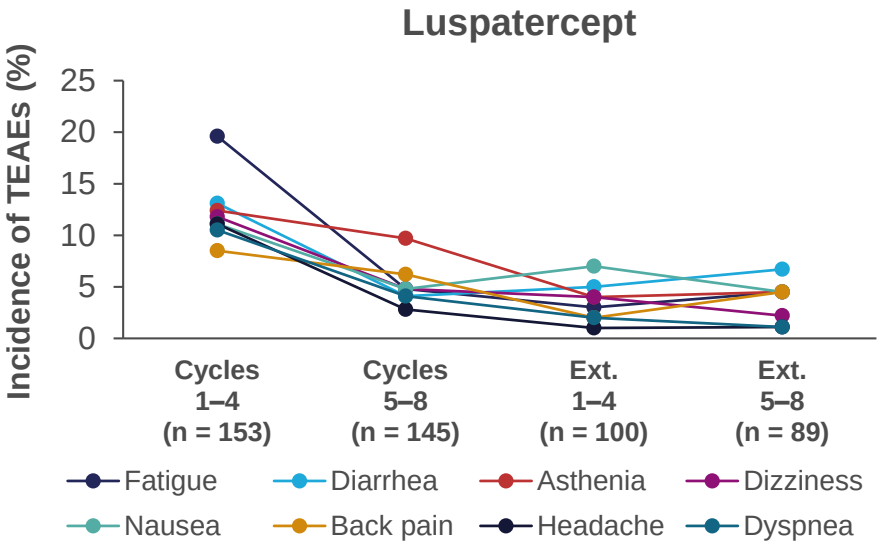
[a] TEAEs occurring more frequently in the luspatercept arm.

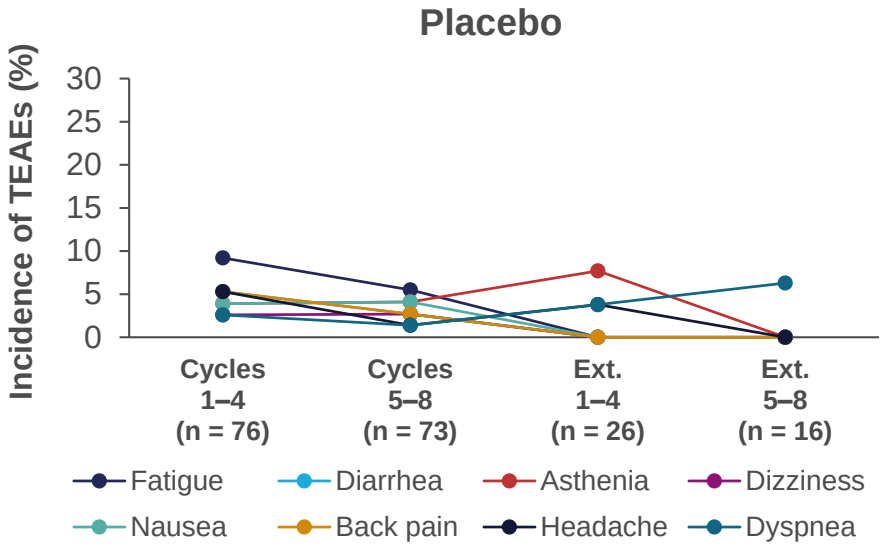
- The overall frequency of SAEs was 41.8% in the luspatercept arm and 30.3% in the placebo arm
  - After adjusting for exposure, the incidence of SAEs per 100 patient-years was comparable between the luspatercept (EAIR 42.3/100 patient-years) and placebo (EAIR 55.7/100 patient-years) arms
  - The overall EAIR of SAEs was comparable between the luspatercept arm and placebo arm
- Incidence of grade 3 TEAEs was balanced between treatment arms

EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Data cutoff: July 1, 2019.

SAFETY
FREQUENT TEAEs (ANY GRADE) BY TREATMENT CYCLE





- New onset of TEAEs generally decreased over time in both treatment arms during the first 24 weeks of the study

Includes disease assessment at Week 25. TEAEs included AEs that started on or after the day of the first dose and on or before 42 days after the last dose. The onset date of the AE was used to determine the cycle. AEs with a duration overlapping multiple cycles were only counted in the first overlapped cycle. If an AE occurred multiple times in different cycles, it was counted once in each cycle. If an AE occurred multiple times within the same cycle, it was counted only once. If a patient experienced multiple events under the same preferred term, then the patient was counted only once for that preferred term.

AE, adverse event; Ext., extension cycle.

Data cutoff: July 1, 2019.

SAFETY
DISEASE PROGRESSION

Summary of Disease Progression, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Progression to HR-MDS or AML	8 (5.2)	4 (5.3)
HR-MDS	5 (3.3)	2 (2.6)
AML	3 (2.0)	2 (2.6)

AML, acute myeloid leukemia; HR-MDS, higher-risk myelodysplastic syndromes.

Data cutoff: July 1, 2019.

SUMMARY

- In this longer-term analysis of the MEDALIST study, more luspatercept-treated patients achieved RBC-TI ≥ 8 weeks any time during treatment versus placebo (47.7% vs 15.8%)
  - Approximately 70% of responders in the luspatercept arm had multiple response periods
- Luspatercept-treated patients had durable cumulative duration of RBC-TI and clinical benefit regardless of baseline transfusion burden

SUMMARY (cont.)

- Those TEAEs occurring more frequently with luspatercept resulted in very few discontinuations and decreased in incidence over time
- Luspatercept is a potential new therapy for the treatment of anemia in patients with LR-MDS with RS
  - The COMMANDS study is currently evaluating the efficacy and safety of luspatercept versus epoetin alfa in untreated RBC transfusion-dependent patients with LR-MDS

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