Supplemental Materials

Methods

Study design

Details of the ongoing phase 3, randomized, double-blind, placebo-controlled MEDALIST trial (NCT02631070) have been published previously.[1] Transfusion-dependent patients with lower-risk myelodysplastic syndromes (LR-MDS) and ring sideroblasts (LR-MDS-RS) were randomized 2:1 to subcutaneous luspatercept or placebo every 3 weeks for 24 weeks at 65 sites in 11 countries from March 2016 through June 2017 (supplemental Figure 2). The starting dose of luspatercept was 1.0 mg/kg, which was titrated up (to a maximum of 1.75 mg/kg) according to transfusion requirements and adverse events.

The trial was conducted in accordance with the laws of applicable authorities. Institutional review boards or ethics committees approved the protocol. All patients provided written informed consent. All authors had access to the study data.

Endpoints

Details of the primary endpoint (achievement of red blood cell transfusion independence [RBC-TI] for ≥8 weeks during weeks 1-24) along with various secondary endpoints during weeks 1-24 and 1-48 have been published previously.[1] Outcomes were initially assessed at week 25, after which patients with clinical benefit (as assessed by the investigators) and no disease progression (by International Working Group [IWG] 2006 criteria[2]) could remain on their randomized treatment during the extension phase, while other patients discontinued treatment and entered follow-up.

In this article, we report RBC-TI for ≥8 weeks; RBC-TI for ≥12 weeks; RBC-TI for ≥16 weeks (as per IWG 2018 criteria); the number of patients TI 1 year after treatment commencement; achievement of modified hematologic improvement-erythroid (mHI-E) (defined below); ≥50% and ≥75% reductions in RBC units transfused from baseline for ≥24 weeks; mean change in RBC units from baseline; transfusion events and treatment-emergent adverse events (TEAEs) during weeks 1-48; time to achievement and duration of response; and progression to acute myeloid leukemia (AML). These analyses were carried out for the overall population, and separately for patients with high transfusion burden (HTB) or low transfusion burden (LTB), except for RBC-TI for ≥16 weeks, which was only performed on the overall patient population.

Statistical analyses

The data cutoff date for the current post hoc analyses was July 1, 2019. All efficacy analyses were performed on the intention-to-treat population. The proportions of all patients who achieved RBC-TI for ≥8 weeks during the entire assessment period were compared using a Cochran-Mantel-Haenszel (CMH) test stratified for average baseline RBC transfusion requirement (≥6 vs <6 units of RBC per 8 weeks) and baseline revised International Prognostic Scoring System (IPSS-R) score (very low- or low- vs intermediate-risk) at a two-sided significance level of 0.05. In the HTB and LTB subpopulations, unstratified CMH tests were used. For comparisons of mHI-E achievement, unstratified CMH tests were used.

Achievement of ≥50% and ≥75% reductions in transfusion burden in the overall population were compared using a CMH test stratified for average baseline RBC transfusion requirement (≥6 vs <6 units of RBC per 8 weeks) and baseline IPSS-R score (very low- or low- vs intermediate-risk). In the HTB and LTB subpopulations, unstratified CMH tests were used. The median durations of ≥50% and ≥75% reductions in transfusion burden were estimated using an unstratified Kaplan–Meier method, with *P* values from the log-rank test used to compare luspatercept and placebo with RBC transfusion requirement (≥6 units vs <6 units/8 weeks) and baseline IPSS-R (very low- or low- vs intermediate-risk) as covariates.

For the comparisons of RBC units and transfusion events during weeks 1-48, least squares means (LSMs) were calculated for the luspatercept and placebo populations. LSM differences, 95% confidence intervals (CIs), and two-sided *P* values from analysis of covariance adjusting for baseline transfusion burden were calculated.

Data sharing statement

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Supplementary Results

Patients

Of the 229 patients randomized to luspatercept (N = 153) or placebo (N = 76), 99 (43.2%) had HTB and 130 (56.8%) had LTB. Median hemoglobin levels were similar in patients with HTB or LTB, but mean serum erythropoietin was higher among HTB patients (Figure 1A).

Among patients who entered the primary double-blind treatment phase, 100 of 153 (65.4%) patients receiving luspatercept and 26 of 76 (34.2%) receiving placebo entered the double-blind extension phase and continued on their assigned treatment.[1]LTB patients remained on luspatercept longer than HTB patients (median, 18.6 vs 7.6 months, respectively), while HTB and LTB patients both remained on placebo for a median of 5.5 months. The maximum luspatercept dose (1.75 mg/kg) was received by similar proportions of patients with HTB or LTB (68.2% vs 66.7%, respectively).

Rates of RBC-TI for ≥12 weeks

RBC-TI for ≥12 weeks was achieved by 52/153 (34.0%) patients receiving luspatercept during weeks 1-48, including 45/87 (51.7%) LTB and 7/66 (10.6%) HTB patients and 9/76 (11.8%) patients receiving placebo, including 7/43 (16.3%) LTB and 2/33 (6.1%) HTB patients. Similarly, in the primary analysis during weeks 1-48, 51 patients (33.0%) receiving luspatercept achieved RBC-TI for ≥12 weeks, suggesting sustained treatment effect.

Time to and duration of RBC-TI and mHI-E response

Overall, the median (range) time to first RBC-TI ≥8 weeks response was 0.29 (0.1-33.1) weeks for patients receiving luspatercept and 3.21 (0.1-34.4) weeks for placebo (Figure 1C). Median (range) time to first response for HTB patients receiving luspatercept was 15.36 (0.1-25.1) weeks and not estimable due to the small number of patients for placebo, and 0.14 (0.1-33.1) weeks and 3.21 (0.1-26.4) weeks for LTB patients receiving luspatercept and placebo, respectively. Overall, the Kaplan–Meier estimates of median time to RBC-TI ≥8 weeks response for patients randomized to luspatercept vs placebo were not reached (NR) (95% CI: 21.86, NR) vs NR (95% CI: NR, NR; hazard ratio [HR]: 3.47, 95% CI: 1.88, 6.42; $P < .0001$) (supplemental Figure 3A); NR (95% CI: NR, NR) vs NR (95% CI: 34.43, NR; HR: 3.45, 95% CI: 0.77, 15.48; $P = .0853$) for HTB patients (supplemental Figure 3B); and 4.00 weeks (95% CI: 0.43, 18.00) vs NR (95% CI: NR, NR; HR: 3.98, 95% CI: 2.03, 7.81; $P < .0001$) for LTB patients (supplemental Figure 3C).

Overall, the median (range) time to RBC-TI ≥16 weeks response was 0.29 (0.14-27.57) weeks for patients receiving luspatercept and 6.71 (0.14-26.43) weeks for placebo. Median (range) time to first RBC-TI ≥16 weeks response for HTB patients receiving luspatercept was 7.14 (0.14-22.14) weeks and 0.14 (0.14-0.14) for placebo, and 0.14 (0.14-27.57) weeks and 9.14 (0.14-26.43) weeks for LTB patients receiving luspatercept and placebo, respectively. Overall, the median (range) duration of RBC-TI ≥16 weeks response was 38.71 (16.00-48.00) weeks for patients receiving luspatercept and 22.29 (20.00-48.00) weeks for placebo. Median (range) duration of RBC-TI ≥16 weeks response for HTB patients receiving luspatercept was 39.79 (26.00-48.00) weeks and 48.00 (48.00-48.00) for placebo, and 37.71

(16.00-48.00) weeks and 22.00 (20.00-36.57) weeks for LTB patients receiving luspatercept and placebo, respectively

Overall, the median (range) time to first mHI-E response was 0.43 (0.1-38.1) weeks for patients receiving luspatercept and 11.57 (0.1-39.4) weeks for those receiving placebo. Median (range) time to first response for HTB patients receiving luspatercept was 0.43 (0.1-31.0) weeks and 8.29 (0.1-29.1) for placebo, and 0.29 (0.1-38.1) weeks and 19.00 (3.1-39.4) weeks for LTB patients receiving luspatercept and placebo, respectively (Figure 1C). Overall, the Kaplan–Meier estimates of median time to mHI-E response for patients randomized to luspatercept vs placebo were 13.14 weeks (95% CI: 4.00, 27.57) vs NR (95% CI: 39.43, NR; HR: 4.67, 95% CI: 2.61, 8.37; *P* < .0001) (supplemental Figure 3D);11.14 weeks (95% CI: 4.86, NR) vs NR (95% CI: 29.14, NR; HR: 2.76, 95% CI: 1.33, 5.75; *P* = .0042) for HTB patients (supplemental Figure 3E); and 15.00 weeks (95% CI: 3.14, 32.14) vs NR (95% CI: 39.43, NR; HR: 8.98, 95% CI: 3.25, 24.85; *P* < .0001]) for LTB patients (supplemental Figure 3F).

Overall, the Kaplan–Meier estimates of median duration of mHI-E response were 15.14 weeks (95% CI: 12.00, 22.14) for patients randomized to luspatercept and 15.86 weeks (95% CI: 8.86, 55.71) for placebo (*P* = .7472). The Kaplan–Meier estimates of median duration of mHI-E response for HTB patients randomized to luspatercept were 12.21 weeks (95% CI: 9.86, 23.57) and 15.86 weeks (95% CI: 8.14, 31.00) for placebo (*P* = .972), and 15.86 weeks (95% CI: 13.43, 29.86) and 35.29 weeks (95% CI: 11.86, NE) for LTB patients randomized to luspatercept and placebo, respectively (*P* = .5789).

Reduction in transfusion burden

During the entire treatment phase, a significantly greater proportion of patients treated with luspatercept achieved ≥50% reduction in RBC transfusion burden over ≥24 weeks when compared with placebo, both overall (50.3% vs 14.5%; *P* < .001) and among patients with HTB (34.8% vs 9.1%) or LTB (62.1% vs 18.6%) (Figure 2A).

Among patients who received luspatercept, the most common dose level at which a ≥50% reduction in RBC transfusion burden over ≥24 weeks was first achieved was 1.0 mg/kg. Overall, the median time to first achievement of a ≥50% reduction in RBC transfusion burden over ≥24 weeks was 6.9 months (95% CI: 2.59, NE) for the 77 responders treated with luspatercept and NE for the 11 responders randomized to placebo. The median time to first achievement was 0.3 months (95% CI: 0.1, NE) and 23.6 months (95% CI: 6.5, NE) for patients with LTB and HTB, respectively.

The Kaplan–Meier estimates of the median longest durations of ≥50% reduction in RBC transfusion burden for ≥24 weeks were 30.3 months (95% CI: 16.6, NE) for patients randomized to luspatercept and NE (95% CI: 5.5, NE) for placebo (P = .206). Overall, the longest duration of response was significantly longer in patients treated with luspatercept compared with those treated with placebo (19.9 months vs 10.7 months; P = .0034). The longest duration of response was longer in patients with LTB (21.5 months vs 9.1 months) compared with patients with HTB (16.2 months vs 14.7 months).

The Kaplan–Meier estimates of the median (95% CI) longest durations of ≥75% reduction in RBC transfusion burden for ≥24 weeks were 114.7 (75.4, 144.1) weeks for patients randomized to luspatercept and NE (NE, NE) for placebo. Among HTB patients, the longest durations of ≥75% reduction in RBC transfusion burden for ≥24 weeks were 144.1 (26.9, 144.1) and NE (NE, NE) weeks for luspatercept and placebo, respectively. Luspatercept-treated patients achieved significantly greater reductions in the requirement for RBC transfusions vs placebo, receiving ~12 fewer RBC units (over 6 transfusion visits) in the first year of treatment.

Among patients who received luspatercept, the most common dose level at which a ≥75% reduction in RBC transfusion burden over ≥24 weeks was first achieved was 1.0 mg/kg. Overall, the median time to first achievement of a ≥75% reduction in RBC transfusion burden over ≥24 weeks was NE for the 53 responders treated with luspatercept and NE for the 5 responders treated with placebo. The median time to first achievement was 11.2 months (95% CI: 2.5, NE) and NE (95% CI: 16.4, NE) for patients with LTB and HTB, respectively.

During weeks 1-48, patients in the luspatercept arm received significantly fewer RBC units compared with placebo (mean [standard deviation; SD]: 22.9 [19.07] RBC units vs 35.6 [17.39] RBC units; LSM difference [95% CI]: −11.5 [−15.1, −8.0]; P < .0001) and attended fewer transfusion visits (mean [SD]: 12.9 [10.24] visits vs 19.3 [9.87] visits; LSM difference [95% CI]: −6.0 [−8.1, −3.8]; P < .0001). This was also the case for RBC units received by LTB patients (mean [SD]: 13.4 [12.79] units vs 27.4 [13.02] units) and HTB patients (mean [SD]: 35.5 [18.75] units vs 46.4 [16.61] units). Fewer transfusion visits were undertaken by both LTB and HTB patients receiving luspatercept compared with placebo (LTB patients: mean [SD]: 8.0 [7.59] visits vs 15.7 [8.76] visits; HTB patients: mean [SD]: 19.5 [9.63] visits vs 24.2 [9.25] visits) (supplemental Table 1).

Safety

Overall, 13.7% vs 9.1% of patients receiving luspatercept vs placebo reported a TEAE that led to permanent study drug discontinuation. LTB and HTB patients receiving luspatercept reported comparable rates of discontinuation due to TEAEs (11.5% vs 16.7%, respectively).

Although 53% of the HTB patients in the current analysis had ≥1 grade 3 or 4 TEAE, the rates were comparable across the luspatercept and placebo arms (53.0% and 54.5%, respectively).

Overall, 3/153 (2.0%) patients (2 HTB, 1 LTB) in the luspatercept group progressed to AML vs 2/76 (2.6%) patients (both LTB) in the placebo group. Time from MDS diagnosis to AML progression ranged from 57.2 to 223.6 months in the 3 patients receiving luspatercept and was 30.1 to 32.7 months in the 2 patients receiving placebo.

References

1. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2):140-151.
2. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425.

Supplemental Tables and Figures

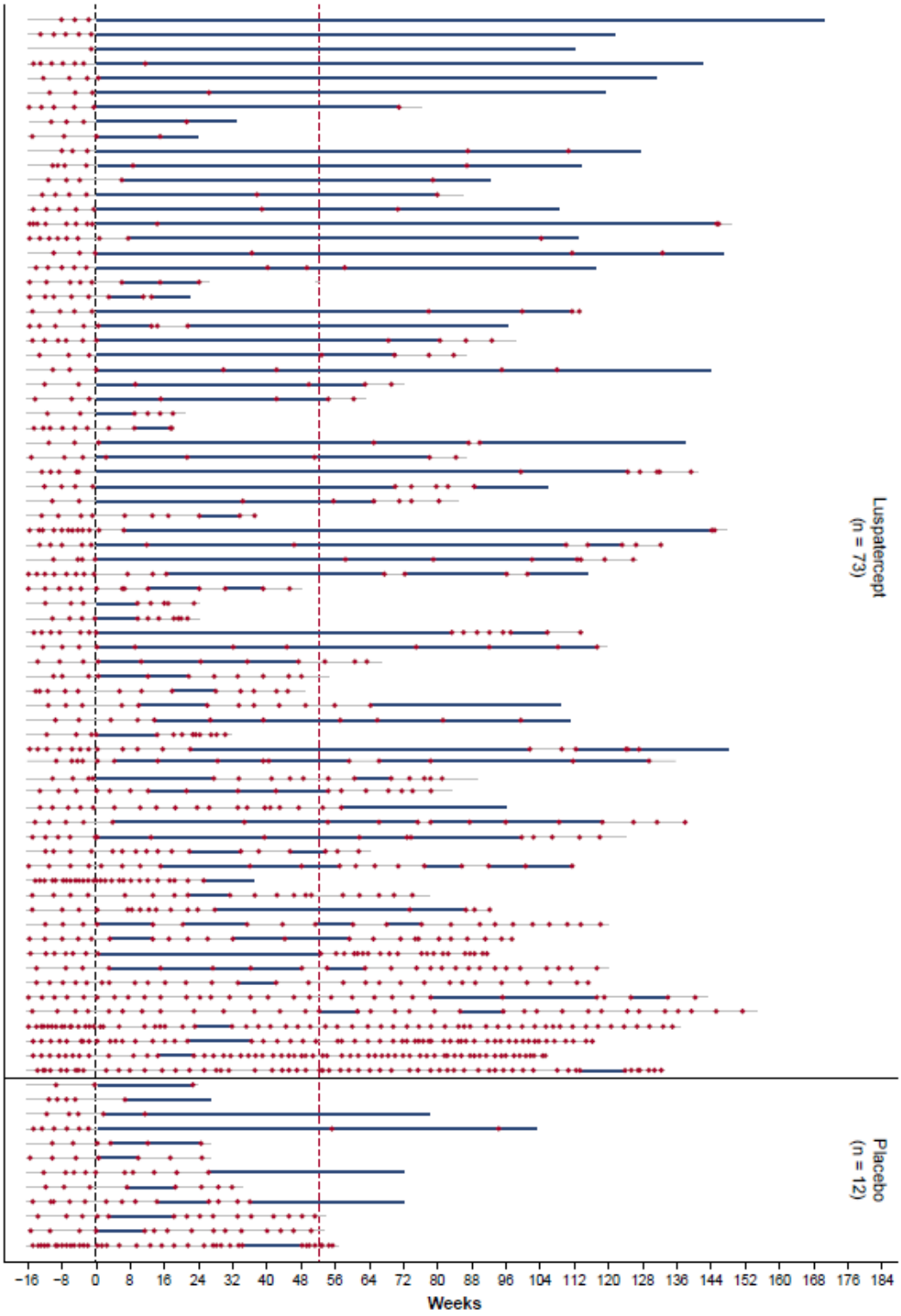
Table 1. Number of RBC units transfused and transfusion visits during weeks1-48 in the overall population and according to transfusion burden

	Overall		LTB		HTB	
	Luspatercept (N = 153)	**Placebo (N = 76)**	**Luspatercept (n = 87)**	**Placebo (n = 43)**	**Luspatercept (n = 66)**	**Placebo (n = 33)**
RBC units transfused during weeks 1-48						
Mean (SD)	22.9 (19.07)	35.6 (17.39)	13.4 (12.79)	27.4 (13.02)	35.5 (18.75)	46.4 (16.61)
LSM (SE)	23.3 (1.05)	34.9 (1.49)				
LSM difference (95% CI)	−11.5 (−15.1, −8.0)					
*P**	< .0001					
Number of transfusion visits during weeks 1-48						
Mean (SD)	12.9 (10.24)	19.3 (9.87)	8.0 (7.59)	15.7 (8.76)	19.5 (9.63)	24.2 (9.25)
LSM (SE)	13.1 (0.62)	19.05 (0.88)				
LSM difference (95% CI)	−6.0 (−8.1, −3.8)					
*P**	< .0001					

ANCOVA, analysis of covariance; CI, confidence interval; HTB, high transfusion burden; LSM, least squares mean; LTB, low transfusion burden; RBC, red blood cell; SD, standard deviation; SE, standard error.

*Two-sided *P* value from ANCOVA adjusting for baseline transfusion burden.

Figure 1: Swimmer plot of transfusions and RBC-TI ≥8 weeks responses during the entire treatment phase for patients who achieved RBC-TI ≥8 weeks at any time during the entire treatment period

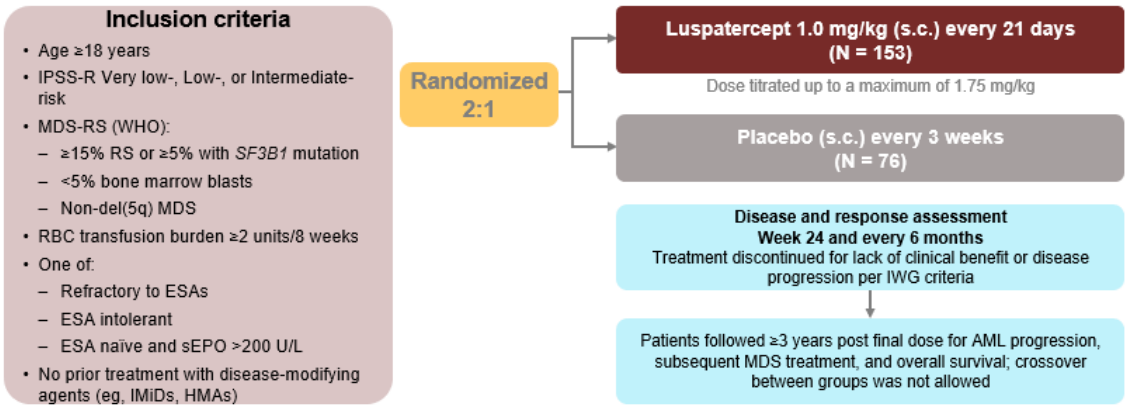


Red dots denote a transfusion event

Blue bars represent the time during RBC-TI is maintained for patients who achieved RBC-TI ≥8 weeks at any time during the entire treatment period

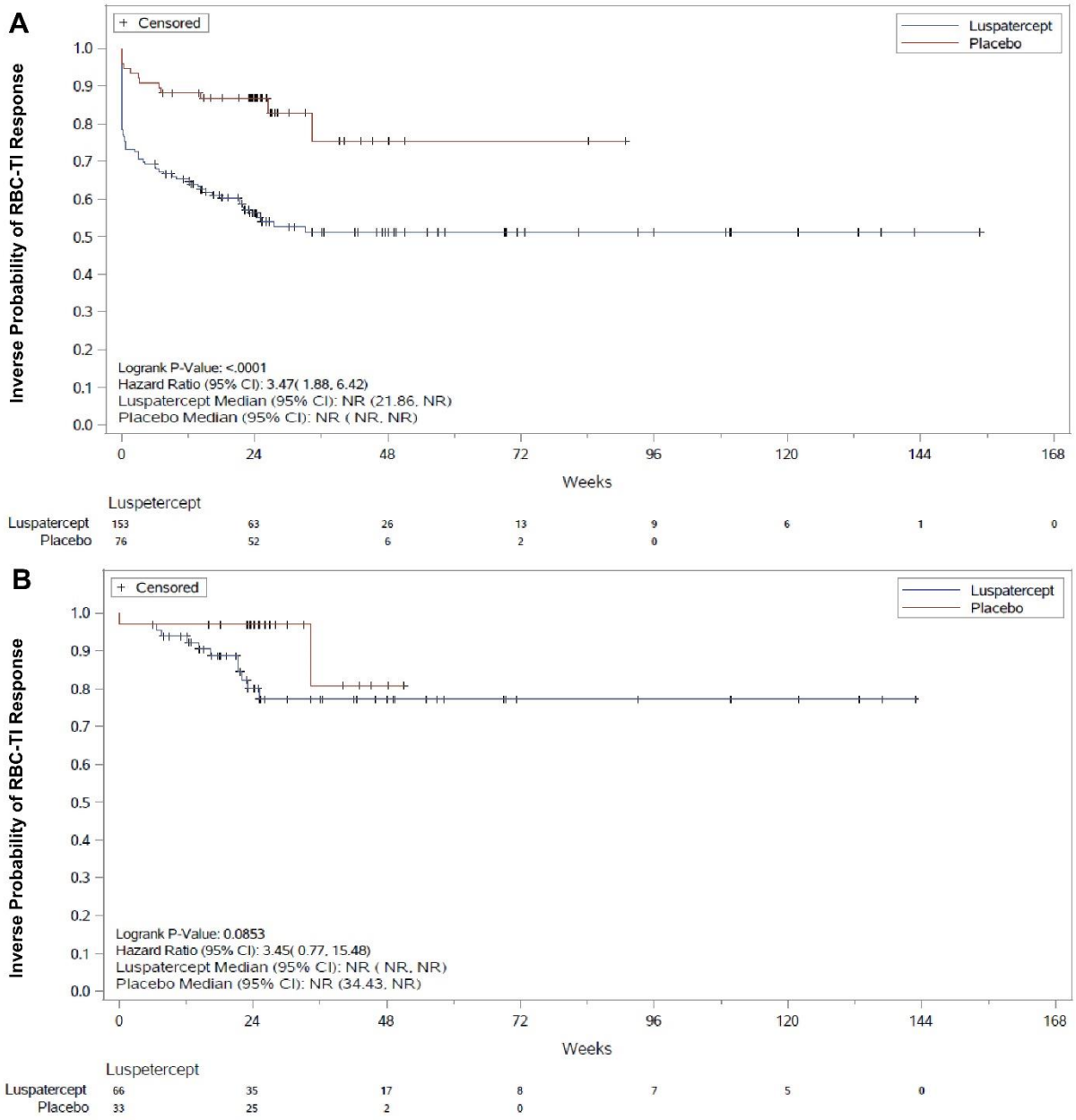
Red dashed line indicates 1 year post treatment initiation

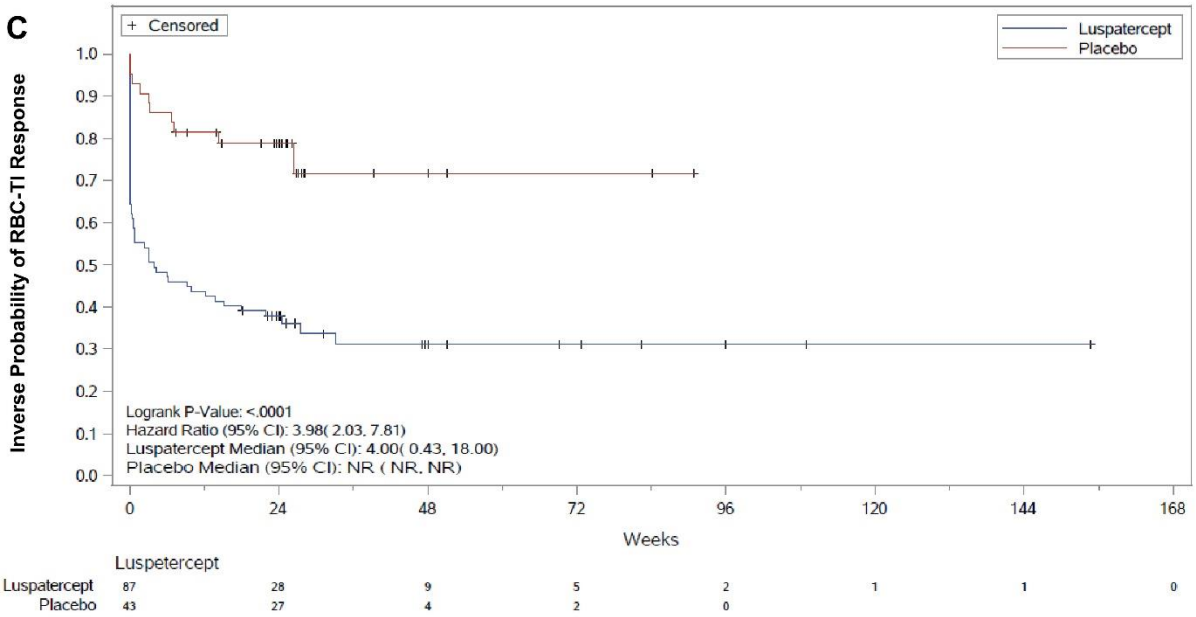
Figure 2. Study design of the MEDALIST trial.

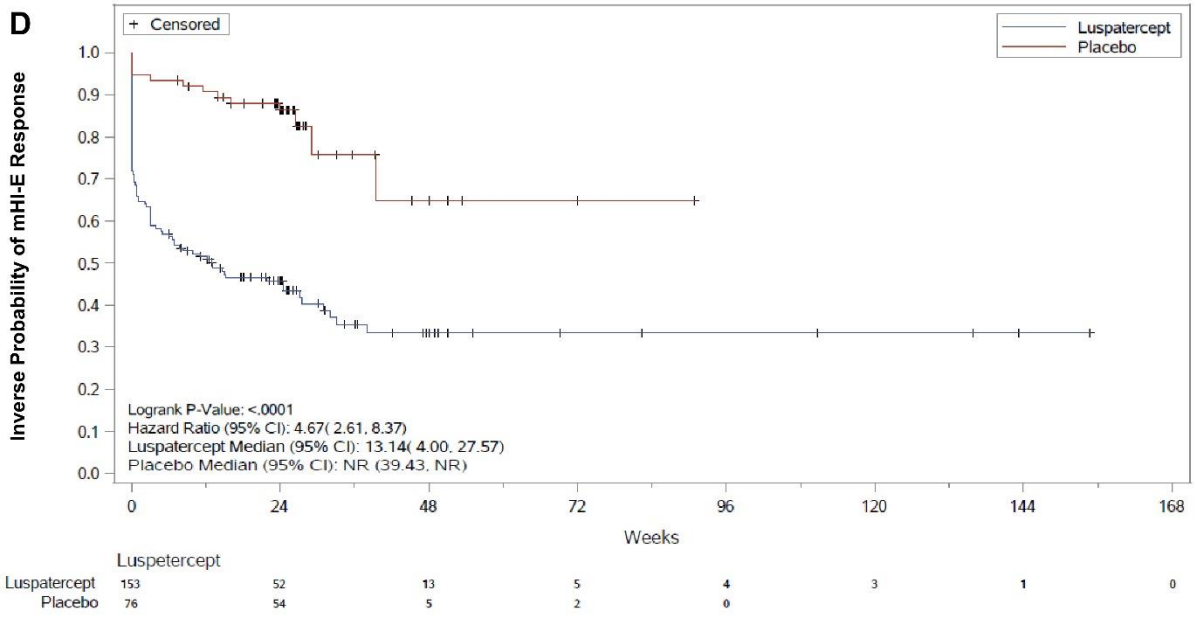


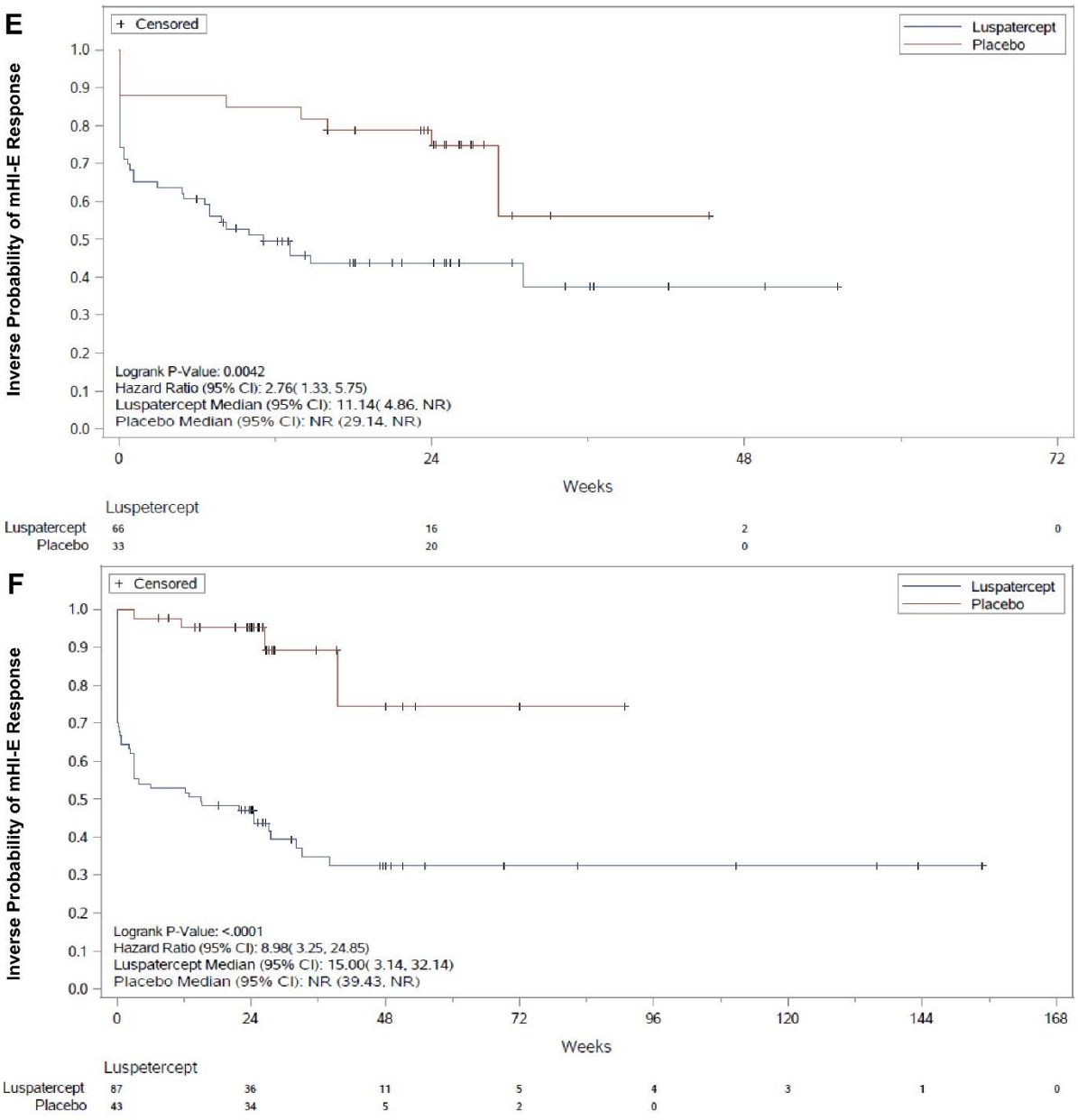
AML, acute myeloid leukemia; ESA, erythroid-stimulating agent; HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IPSS-R, revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblasts; s.c., subcutaneous; sEPO, serum erythropoietin; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

Figure 3. Kaplan–Meier curves for time to RBC-TI ≥8 weeks (A-C) and time to mHI-E (D-F) response for overall (A and D), HTB (B and E), and LTB (C and F) patients.




C
+ Censored
Luspatercept
Placebo
Inverse Probability of RBC-TI Response
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Logrank P-Value: <.0001
Hazard Ratio (95% CI): 3.98(2.03, 7.81)
Luspatercept Median (95% CI): 4.00(0.43, 18.00)
Placebo Median (95% CI): NR (NR, NR)
0
24
48
72
96
120
144
168
Weeks
Luspetercept
Luspatercept 87 28 9 5 2 1 1 0
Placebo 43 27 4 2 0


D
+ Censored
Luspatercept
Placebo
Inverse Probability of mHI-E Response
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Logrank P-Value: <.0001
Hazard Ratio (95% CI): 4.67(2.61, 8.37)
Luspatercept Median (95% CI): 13.14(4.00, 27.57)
Placebo Median (95% CI): NR (39.43, NR)
0
24
48
72
96
120
144
168
Weeks
Luspetercept
Luspatercept 153 52 13 5 4 3 1 0
Placebo 76 54 5 2 0



CI, confidence interval; HR, hazard ratio; HTB, high transfusion burden; LTB, low transfusion burden; mHI-E, modified hematologic improvement-erythroid; NR, not reached; RBC-TI, red blood cell transfusion independence.