# Luspatercept reduces red blood cell transfusions in patients with lower-risk myelodysplastic syndromes regardless of baseline transfusion burden in the MEDALIST study

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Guillermo Garcia-Manero,[1] Pierre Fenaux,[2] Uwe Platzbecker,[3] Rena Buckstein,[4] Valeria Santini,[5] María Díez-Campelo,[6] Derek Tang,[7] Rodrigo Ito,[7] Shannon Fabre,[7] Emily Mantovani,[7] Roberto Zoffoli,[8] Dimana Miteva,[7] Christina Hughes,[7] Wasiulla Khan,[7] Rami S. Komrokji,[9] Ulrich Germing[10]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [3]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [6]Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; [7]Bristol Myers Squibb, Princeton, NJ, USA; [8]Bristol Myers Squibb, Braine-l'Alleud, Belgium; [9]Moffitt Cancer Center, Tampa, FL, USA; [10]University Hospital of Düsseldorf, Düsseldorf, Germany

## Introduction

- Observational studies have suggested an inverse relationship between ongoing red blood cell (RBC) transfusion burden (TB) and survival in patients with anemia due to lower-risk myelodysplastic syndromes (LR-MDS), even among those with low initial RBC TB[1,2]
- Luspatercept, the first and only erythroid maturation agent, demonstrated red blood cell transfusion independence (RBC-TI) in patients with LR-MDS for ≥ 8 of the first 24 weeks of treatment in the randomized, double-blind, placebo-controlled, phase 3 MEDALIST study (NCT02631070)[3]
  - By achieving an erythroid response with associated increases in hemoglobin (Hb) levels, luspatercept reduced the severity of anemia in patients who were receiving regular RBC transfusions
- Understanding the efficacy of luspatercept to reduce RBC TB in the context of low or high pretreatment RBC TB levels may be useful in clinical and health policy decision-making

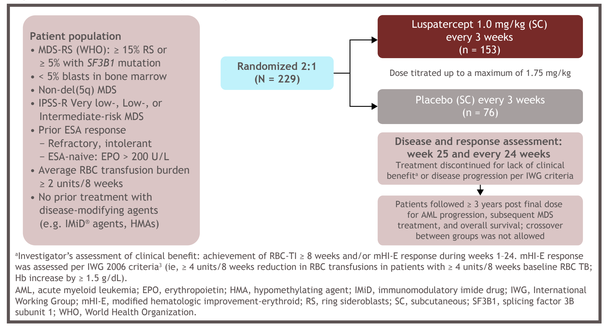
## Objective

- To evaluate the effect of luspatercept on the cumulative number of RBC transfusion units and visits according to baseline RBC TB levels among patients with LR-MDS in the MEDALIST study

## Methods

- The methods and primary findings of the MEDALIST study have been reported previously[3]
  - Eligible patients were ≥ 18 years of age; had LR-MDS according to Revised International Prognostic Scoring System (IPSS-R) criteria with ring sideroblasts; were refractory, intolerant, or unlikely to respond to erythropoiesis-stimulating agents (ESAs); and required regular RBC transfusions (≥ 2 units/8 weeks) in the 16 weeks prior to randomization
  - A total of 229 patients were randomized 2:1 to receive either luspatercept (n = 153) or placebo (n = 76) every 3 weeks (**Figure 1**)
  - Disease and response assessments were conducted every 24 weeks
    - The primary endpoint assessment was at week 25, defined as 24 calendar weeks after the first dose, regardless of dose delays
- The primary endpoint of the MEDALIST study was the achievement of RBC-TI for ≥ 8 weeks during weeks 1-24
  - Patients receiving luspatercept who achieved RBC-TI for ≥ 8 weeks by week 25 were defined as luspatercept responders
  - Patients receiving luspatercept who did not achieve RBC-TI for ≥ 8 weeks by week 25, but continued treatment were defined as luspatercept non-responders
- This secondary analysis evaluated the cumulative number of RBC transfusion units or RBC transfusion visits through 144 weeks of treatment according to patients' baseline RBC TB level
  - Low and high baseline RBC TB categories were defined as having < 6 RBC transfusion units or ≥ 6 RBC transfusion units over 8 weeks, respectively
- Cumulative mean number of RBC transfusion units or RBC transfusion visits were estimated using Nelson-Aalen nonparametric estimators with robust variance estimate for each treatment group with 95% confidence intervals (CIs)
  - Luspatercept responders were also compared with luspatercept non-responders

**Figure 1. MEDALIST study design**




[a]Investigator's assessment of clinical benefit: 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] (ie, ≥ 4 units/8 weeks reduction in RBC transfusions in patients with ≥ 4 units/8 weeks baseline RBC TB; Hb increase by ≥ 1.5 g/dL).
AML, acute myeloid leukemia; EPO, erythropoietin; HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IWG, International Working Group; mHI-E, modified hematologic improvement-erythroid; RS, ring sideroblasts; SC, subcutaneous; SF3B1, splicing factor 3B subunit 1; WHO, World Health Organization.

## Results

- Of the 153 patients randomized to receive luspatercept, 87 (57%) were classified as having low baseline RBC TB and 66 (43%) as high baseline RBC TB
  - Proportions were identical in the placebo group
    - 57% (n = 43/76) were classified as having low baseline RBC TB
    - 43% (n = 33/76) were classified as having high baseline RBC TB
- At week 25, patients receiving luspatercept had lower mean cumulative RBC transfusion units (**Table 1**) and RBC transfusion visits (**Table 2**) than placebo across both baseline RBC TB categories
  - Luspatercept responders had the lowest mean cumulative RBC transfusion units and RBC transfusion visits regardless of baseline RBC TB category

**Table 1. Mean cumulative RBC transfusion units through 24 weeks**

| | Luspatercept (N = 153)[a] | Luspatercept responders (N = 58)[a] | Luspatercept non-responders (N = 95)[a] | Placebo (N = 76)[a] |
|---|---|---|---|---|
| Low baseline RBC TB (< 6 units/8 weeks) | 6.8 (5.6-8.4) n = 81[b] | 2.7 (2.0-3.7) n = 49[b] | 13.0 (11.4-14.9) n = 32[b] | 13.2 (11.5-15.2) n = 38[b] |
| High baseline RBC TB (≥ 6 units/8 weeks) | 17.2 (15.1-19.6) n = 47[b] | 3.7 (1.8-7.4) n = 6[b] | 18.9 (16.9-21.1) n = 41[b] | 24.2 (21.3-27.4) n = 30[b] |

[a]Number of patients in the intention-to-treat population.
[b]Number of patients with RBC transfusion data up to 24 weeks.

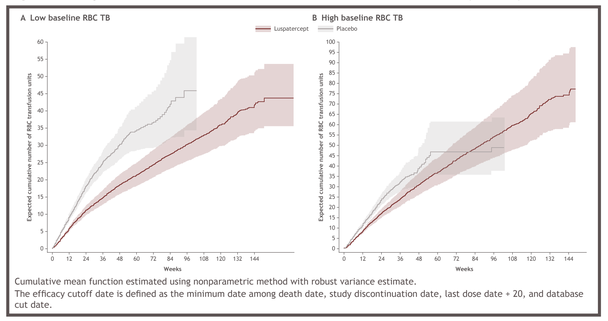
**Table 2. Mean cumulative RBC transfusion visits through 24 weeks**

| | Luspatercept (N = 153)[a] | Luspatercept responders (N = 58)[a] | Luspatercept non-responders (N = 95)[a] | Placebo (N = 76)[a] |
|---|---|---|---|---|
| Low baseline RBC TB (< 6 units/8 weeks) | 4.0 (3.3-4.8) n = 81[b] | 1.7 (1.2-2.2) n = 49[b] | 7.5 (6.5-8.6) n = 32[b] | 7.2 (6.3-8.3) n = 38[b] |
| High baseline RBC TB (≥ 6 units/8 weeks) | 9.4 (8.3-10.7) n = 47[b] | 2.0 (1.0-4.0) n = 6[b] | 10.3 (9.2-11.5) n = 41[b] | 12.5 (11.0-14.2) n = 30[b] |

[a]Number of patients in the intention-to-treat population.
[b]Number of patients with RBC transfusion data up to 24 weeks.

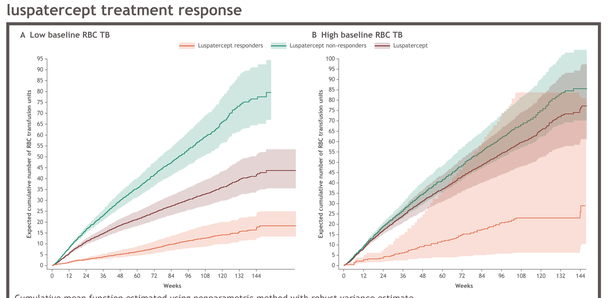
- Patients receiving luspatercept had a lower cumulative number of RBC transfusion units through 144 weeks compared with placebo, particularly those with low baseline RBC TB (**Figure 2**)
- Luspatercept responders continued to show a reduction in mean cumulative RBC transfusion units relative to luspatercept non-responders regardless of baseline RBC TB category (**Figure 3**, **Table 3**)
  - Luspatercept responders had a median follow-up of 26 months

**Figure 2. Expected cumulative number of RBC transfusion units (95% CI)**




Cumulative mean function estimated using nonparametric method with robust variance estimate.
The efficacy cutoff date is defined as the minimum date among death date, study discontinuation date, last dose date + 20, and database cut date.

**Figure 3. Expected cumulative number of RBC transfusion units (95% CI) by luspatercept treatment response**



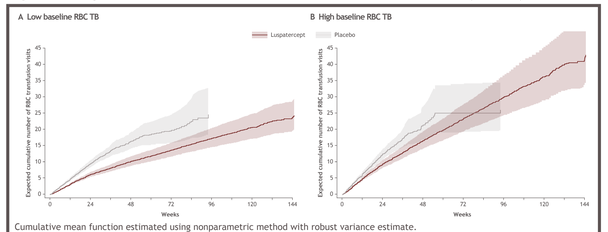

Cumulative mean function estimated using nonparametric method with robust variance estimate.
The efficacy cutoff date is defined as the minimum date among death date, study discontinuation date, last dose date + 20, and database cut date.

**Table 3. Mean cumulative RBC transfusion units by luspatercept treatment response**

| | RBC transfusion units (95% CI) | |
|---|---|---|
| Low baseline RBC TB (< 6 units/8 weeks) | Responders (N = 52) | Non-responders (N = 35) |
| 48 weeks | 4.7 (3.5-6.3) n = 43 | 22.8 (20.1-25.8) n = 15 |
| 144 weeks | 15.2 (11.5-20.0) n = 5 | 57.1 (50.5-64.6) n = 1 |
| High baseline RBC TB (≥ 6 units/8 weeks) | Responders (N = 6) | Non-responders (N = 60) |
| 48 weeks | 9.3 (3.5-25.0) n = 6 | 34.7 (29.6-40.7) n = 21 |
| 144 weeks | 26.1 (8.3-81.9) n = 1 | 85.6 (70.1-104.5) n = 1 |

- Patients receiving luspatercept had a lower cumulative number of RBC transfusion visits through 144 weeks compared with placebo, particularly those with low baseline RBC TB (**Figure 4**)

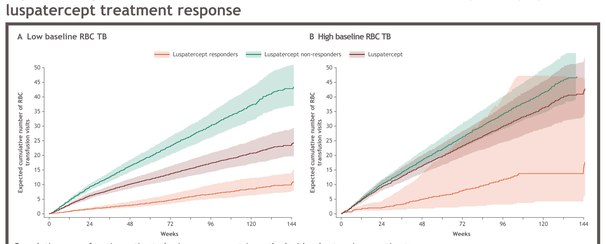
**Figure 4. Expected cumulative number of RBC transfusion visits (95% CI)**




Cumulative mean function estimated using nonparametric method with robust variance estimate.
The efficacy cutoff date is defined as the minimum date among death date, study discontinuation date, last dose date + 20, and database cut date.

- Luspatercept responders continued to show a reduction in mean cumulative RBC transfusion visits relative to luspatercept non-responders regardless of baseline RBC TB category (**Figure 5**, **Table 4**)

**Figure 5. Expected cumulative number of RBC transfusion visits (95% CI) by luspatercept treatment response**




Cumulative mean function estimated using nonparametric method with robust variance estimate.
The efficacy cutoff date is defined as the minimum date among death date, study discontinuation date, last dose date + 20, and database cut date.

**Table 4. Mean cumulative RBC transfusion visits by luspatercept treatment response**

| | RBC transfusion units (95% CI) | |
|---|---|---|
| Low baseline RBC TB (< 6 units/8 weeks) | Responders (N = 52) | Non-responders (N = 35) |
| 48 weeks | 2.8 (2.1-3.7) n = 43 | 13.1 (11.8-14.6) n = 15 |
| 144 weeks | 9.3 (7.2-12.2) n = 5 | 33.4 (28.8-38.9) n = 1 |
| High baseline RBC TB (≥ 6 units/8 weeks) | Responders (N = 6) | Non-responders (N = 60) |
| 48 weeks | 5.0 (1.8-13.5) n = 6 | 18.5 (16.1-21.2) n = 21 |
| 144 weeks | 15.5 (5.2-46.3) n = 1 | 47.0 (39.1-56.5) n = 1 |

## Conclusions

- Luspatercept showed a consistent benefit in reducing RBC TB within the first 24 weeks of treatment among patients with LR-MDS in the MEDALIST study, regardless of baseline RBC TB levels
- Patients who responded by week 25 continued to show benefit of luspatercept in terms of reduction in cumulative RBC transfusion units and RBC transfusion visits over a median follow-up of 26 months
- These findings may inform clinical and health policy decisions considering luspatercept treatment for patients with high or low pretreatment RBC TB

### References

1. de Swart L, et al. *Haematologica* 2020;105:632-639.
2. Sangerman MA, et al. *Blood* 2019;134(suppl 1). Abstract 3013.
3. Fenaux P, et al. *N Engl J Med* 2020;382:140-151.

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Email: ggarciam@mdanderson.org