Benefit of continuing luspatercept therapy in patients with lower-risk myelodysplastic syndromes who did not achieve red blood cell transfusion independence by week 25 in the MEDALIST study

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Introduction

- Red blood cell (RBC) transfusion dependence among patients with anemia due to lower-risk myelodysplastic syndromes (LR-MDS) reduces health-related quality of life and increases mortality[1,2]
- Luspatercept, the first and only erythroid maturation agent, led to RBC transfusion independence (RBC-TI) for ≥ 8 of the first 24 weeks of treatment in a greater proportion of patients compared with placebo in the randomized, double-blind, placebo-controlled, phase 3 MEDALIST study (NCT02631070)[3]
  - 38% of patients (n = 58) receiving luspatercept achieved RBC-TI for ≥ 8 weeks compared with 13% of patients (n = 10) receiving placebo ($P < 0.001$) during the first 24 weeks of treatment[3]
- The potential benefits of continuing luspatercept treatment for patients with LR-MDS who may need longer than 24 weeks to achieve RBC-TI are not well understood

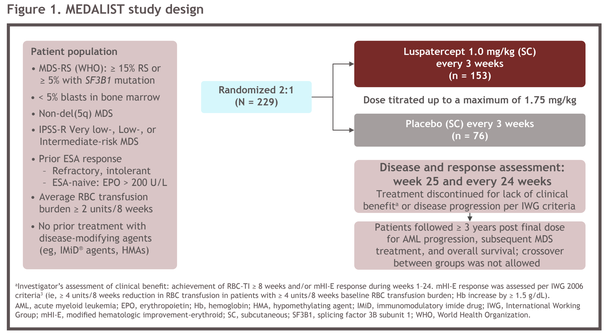
Objective

- To evaluate the benefits of continuing luspatercept treatment beyond the primary endpoint among patients who did not achieve RBC-TI for ≥ 8 weeks by week 25 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 (RS); 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

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[1] (ie, ≥ 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; EPO, erythropoietin; Hb, hemoglobin; HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IWG, International Working Group; mHI-E, modified hematologic improvement-erythroid; SC, subcutaneous; SF3B1, splicing factor 3B subunit 1; WHO, World Health Organization.

- 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 assessments were conducted every 24 weeks
  - The primary endpoint was evaluated at week 25, defined as 24 calendar weeks after the first dose, regardless of dose delays
- Patients without disease progression (IWG-MDS criteria) who showed clinical improvement (eg, decrease in RBC transfusion requirement compared to baseline or increase in Hb level compared to baseline) at week 25 could continue to receive luspatercept or placebo in a double-blind treatment extension phase until disease progression, unacceptable side effects, or withdrawal from the study
  - The extension phase consisted of 3-week cycles
- For this post hoc analysis, response indicators included RBC transfusion burden, serum ferritin (SF) levels, and hematologic improvement-erythroid (HI-E) response
  - Response indicators were assessed every 24 weeks up to the data cutoff of July 1, 2019
  - HI-E response was defined as:
    - A reduction in RBC transfusions of ≥ 4 units/8 weeks for patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks
    - An increase in Hb level of ≥ 1.5 g/dL over 8 weeks for patients with baseline RBC transfusion burden of < 4 units/8 weeks

Results

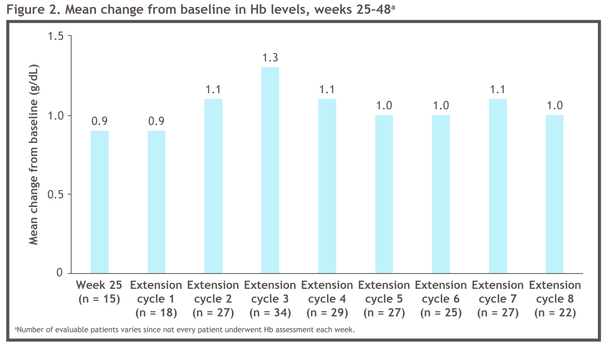
Patients

- Of 153 patients receiving luspatercept, 68 (44%) patients who did not achieve RBC-TI for ≥ 8 weeks by week 25 but continued treatment through week 48 were included in this analysis

Treatment extension phase: weeks 25-48

- 16% of patients (n = 11/68) achieved RBC-TI for ≥ 8 weeks
  - Of these, 3 patients achieved RBC-TI for ≥ 16 weeks
  - Median time to achieving RBC-TI for ≥ 8 weeks was 5 months
- Patients (n = 36) had a mean change from baseline in RBC units transfused of −1.3 units (standard deviation, 7.98)
- 26% of patients (n = 18/68) had reduced RBC transfusion burden from baseline
- 44% of patients (n = 30/68) had reduced SF levels from baseline
  - Of the patients who had an SF level ≥ 1000 µg/L at baseline (n = 39), 18% (n = 7/39) shifted to an SF level < 1000 µg/L by week 48
- Mean change from baseline in Hb levels are shown in **Figure 2**

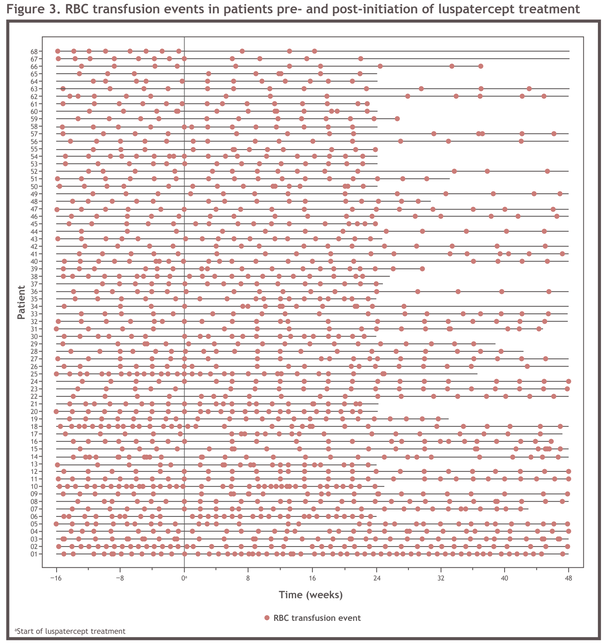
Figure 2. Mean change from baseline in Hb levels, weeks 25-48[a]



[a]Number of evaluable patients varies since not every patient underwent Hb assessment each week.

- RBC transfusion events in patients during the 16 weeks prior to and 48 weeks after the start of luspatercept treatment are shown in **Figure 3**

Figure 3. RBC transfusion events in patients pre- and post-initiation of luspatercept treatment

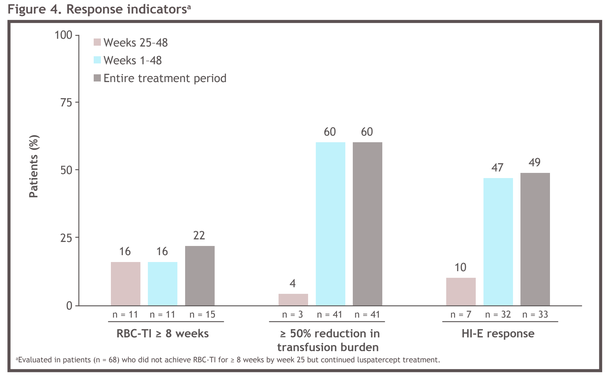


*Start of luspatercept treatment

Overall outcomes: weeks 1-48 and entire treatment period

- During weeks 1-48, 16% (n = 11/68) of patients continuing luspatercept treatment who had not achieved RBC-TI by week 25 achieved RBC-TI for ≥ 8 weeks
  - 60% (n = 41) achieved ≥ 50% reduction in RBC transfusion burden for ≥ 8 weeks from baseline
  - 47% (n = 32) achieved HI-E response
- During the entire treatment period, from baseline to the data cutoff date, 22% of patients (n = 15/68) achieved RBC-TI for ≥ 8 weeks
  - 60% (n = 41) achieved ≥ 50% reduction in RBC transfusion burden from baseline for ≥ 8 weeks
  - 49% (n = 33) achieved HI-E response
- Response indicators across analysis periods are shown in **Figure 4**

Figure 4. Response indicators[a]



[a]Evaluated in patients (n = 68) who did not achieve RBC-TI for ≥ 8 weeks by week 25 but continued luspatercept treatment.

Conclusions

- A considerable proportion of patients with LR-MDS in the MEDALIST study who did not achieve RBC-TI for ≥ 8 weeks by week 25, but continued to receive luspatercept experienced a broad range of clinical improvements at later time points
  - Clinical improvements observed after week 25 included RBC-TI for ≥ 8 weeks, reduced RBC transfusion burden, improved Hb levels, and reduced SF levels
- Continuing luspatercept treatment beyond week 25 may provide clinical benefit for a meaningful proportion of patients with LR-MDS
- These findings may inform clinical and population health decisions considering the timing of clinical benefit with continued luspatercept treatment

References

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