ABSTRACT 4243

Hematologic Improvement–Neutrophil and –Platelet in the MEDALIST Trial: Multilineage Data From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Anemia in Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes With Ring Sideroblasts Who Require Red Blood Cell Transfusions

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INTRODUCTION

- Lower-risk myelodysplastic syndromes (LR-MDS) are characterized by ineffective erythropoiesis, which leads to anemia and red blood cell (RBC) transfusion dependence[1,2]
- Additional cytopenias in patients with lower-risk MDS may complicate treatment and contribute to infections and bleeding events[3,4]
- Effective treatments for anemia in transfusion-dependent patients with lower-risk MDS are lacking and may exacerbate specific cytopenias[1,2]
  - For example, in patients with non-del(5q) lower-risk MDS, lenalidomide was associated with grade 3 or 4 neutropenia and thrombocytopenia[5]
- 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[6]
- MEDALIST is a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of luspatercept in patients with lower-risk MDS with ring sideroblasts (RS) who require RBC transfusions[7]
  - The primary endpoint, RBC transfusion independence ≥ 8 weeks (during Weeks 1–24) was achieved by 37.9% of patients in the luspatercept arm and 13.2% of patients in the placebo arm ($P < 0.0001$)[7]

OBJECTIVE

- To report hematologic improvement (HI) outcomes for patients in the MEDALIST trial

METHODS

Study Design

- MEDALIST is an ongoing phase 3, randomized, double-blind, placebo-controlled trial (NCT02631070)
- Patients were randomized between March 2016 and June 2017 at 65 sites
- Eligible patients had anemia due to Revised International Prognostic Scoring System-defined Very low-, Low-, or Intermediate-risk MDS with RS; were refractory to, intolerant of, or unlikely to respond to (serum erythropoietin > 200 U/L) erythropoiesis-stimulating agents; and required RBC transfusions
- Patients were randomized 2:1 to receive luspatercept (starting dose 1.0 mg/kg, with titration up to 1.75 mg/kg, if needed) or placebo subcutaneously every 3 weeks for ≥ 24 weeks
- Platelet and neutrophil counts were assessed by the central laboratory

MEDALIST Multilineage Analysis

- Data cutoff for this analysis was July 1, 2019
- Secondary endpoints were defined according to International Working Group (IWG) 2006 criteria,[8] and included:
  - HI–erythroid (HI-E) response during Weeks 1–24 and Weeks 1–48
  - HI–neutrophil (HI-N) response during Weeks 1–24 and Weeks 1–48
  - HI–platelet (HI-P) response during Weeks 1–24 and Weeks 1–48
- Additional analyses included:
  - Mean neutrophil and platelet changes from baseline
  - Absolute increases in neutrophil and platelet counts
  - Safety

RESULTS

Patients

- Mean baseline absolute neutrophil count was 2.8×10^9/L in patients receiving luspatercept and 2.7×10^9/L in patients receiving placebo (Table 1)
  - Baseline neutropenia (per IWG 2006 criteria,[8] baseline neutrophils $< 1 \times 10^9$/L) was confirmed in 15 (9.8%) and 10 (13.2%) patients in the luspatercept and placebo arms, respectively
- Mean baseline platelet count was 259.3×10^9/L in patients receiving luspatercept and 251.7×10^9/L in patients receiving placebo (Table 1)
  - Baseline thrombocytopenia (per IWG 2006 criteria,[8] baseline platelets $< 100 \times 10^9$/L) was confirmed in 8 (5.2%) and 6 (7.9%) patients in the luspatercept and placebo arms, respectively

Table 1. Baseline Patient and Treatment Characteristics

Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
MDS WHO 2008 classification, n (%)		
MDS RCMD-RS	145 (94.8)	74 (97.4)
MDS RARS	7 (4.6)	2 (2.6)
Other[a]	1 (0.7)	0
Absolute neutrophil count, mean (SD), $\times 10^9$/L	2.8 (2.1)	2.7 (2.0)
Absolute neutrophil count category, n (%)		
$< 0.5 \times 10^9$/L	1 (0.7)	0
0.5 to $< 1.0 \times 10^9$/L	14 (9.2)	10 (13.2)
$\geq 1.0 \times 10^9$/L	138 (90.2)	66 (86.8)
Platelet count, mean (SD), $\times 10^9$/L	259.3 (122.6)	251.7 (123.9)
Platelet count category, n (%)		
$< 100 \times 10^9$/L	8 (5.2)	6 (7.9)
$100–400 \times 10^9$/L	128 (83.7)	61 (80.3)
$> 400 \times 10^9$/L	17 (11.1)	9 (11.8)
Patients with baseline neutropenia,[b] n (%)	15 (9.8)	10 (13.2)
Patients with baseline thrombocytopenia,[c] n (%)	8 (5.2)	6 (7.9)
Prior therapy with G-CSF,[d] n (%)	51 (33.3)	22 (28.9)
Mutated *SF3B1*,[e] n (%)	138 (93.2)	64 (86.5)

[a] 1 patient was diagnosed locally with MDS-RS and multilineage dysplasia.
[b] Baseline neutrophil count $< 1 \times 10^9$/L.
[c] Baseline platelet count $< 100 \times 10^9$/L.
[d] In combination with erythropoiesis-stimulating agents.
[e] 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%.
G-CSF, granulocyte colony-stimulating factor; MDS, myelodysplastic syndromes; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts; SD, standard deviation; WHO, World Health Organization.

HI Endpoints

- HI-E was achieved in 90 of 153 (58.8%) patients in the luspatercept arm and 13 of 76 (17.1%) patients in the placebo arm during Weeks 1–48 (Table 2)
- Of patients evaluable for HI-N (baseline neutrophil count $< 1 \times 10^9$/L), 3 of 15 (20.0%) patients receiving luspatercept and 1 of 10 (10.0%) patients receiving placebo achieved HI-N during Weeks 1–48 (Table 2)
- Of patients evaluable for HI-P (baseline platelet count $< 100 \times 10^9$/L), 5 of 8 (62.5%) receiving luspatercept and 2 of 6 (33.3%) receiving placebo achieved HI-P during Weeks 1–48 (Table 2)
  - None of the patients in the luspatercept arm who achieved HI-P received platelet transfusions

Changes in Neutrophils

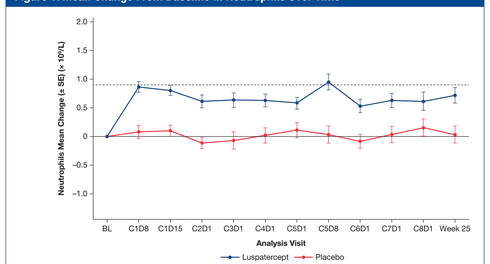
- By Cycle 5, Day 8, mean change from baseline in neutrophils was 0.95×10^9/L in the luspatercept arm and 0.04×10^9/L in the placebo arm (Figure 1)
  - Early increases were observed in the luspatercept arm by Cycle 1, Day 8 (C1D8) (0.86×10^9/L vs 0.08×10^9/L for placebo)

Table 2. Patients Achieving HI-E, HI-N, and HI-P

Endpoint	Luspatercept	Placebo
Achieved HI-E[a] (Weeks 1–24), n/N (%)	81/153 (52.9)	9/76 (11.8)
Reduction of ≥ 4 RBC units/8 weeks[b]	52/107 (48.6)	8/56 (14.3)
Mean Hb increase of ≥ 1.5 g/dL[c]	29/46 (63.0)	1/20 (5.0)
Achieved HI-E[a] (Weeks 1–48), n/N (%)	90/153 (58.8)	13/76 (17.1)
Reduction of ≥ 4 RBC units/8 weeks[b]	58/107 (54.2)	12/56 (21.4)
Mean Hb increase of ≥ 1.5 g/dL[c]	32/46 (69.6)	1/20 (5.0)
Achieved HI-N (Weeks 1–24), n/N (%)[d]	2/15 (13.3)	0/10 (0)
Achieved HI-N (Weeks 1–48), n/N (%)[d]	3/15 (20.0)	1/10 (10.0)
Achieved HI-P (Weeks 1–24), n/N (%)[e]	4/8 (50.0)	2/6 (33.3)
Achieved HI-P (Weeks 1–48), n/N (%)[e]	5/8 (62.5)	2/6 (33.3)

HI-N and HI-P responses were not associated with erythroid response.
[a] Defined as the proportion of patients meeting the modified HI-E criteria per IWG 2006 criteria,[8] sustained over a consecutive 56-day period during the indicated treatment period: for patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks, a reduction of ≥ 4 units RBC transfusion; for patients with baseline RBC transfusion burden of < 4 units/8 weeks, mean Hb increase of ≥ 1.5 g/dL. [b] Based on the number of patients with baseline transfusion burden of ≥ 4 units/8 weeks. [c] Based on the number of patients with baseline RBC transfusion burden of < 4 units/8 weeks. [d] Defined as the proportion of patients meeting the HI-N criteria per IWG criteria.[8] [e] Defined as the proportion of patients meeting the HI-P criteria per IWG criteria.[8]
Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HI-N, hematologic improvement–neutrophil; HI-P, hematologic improvement–platelet; IWG, International Working Group; RBC, red blood cell.

Figure 1. Mean Change From Baseline in Neutrophils Over Time



Number of patients:

Luspatercept	148	139	149	143	140	137	119	128	123	109	121
Placebo	70	72	73	74	67	70	64	68	68	67	62

Dotted line indicates a mean change from baseline of 0.9×10^9/L.
BL, baseline; C, Cycle; D, Day; SE, standard error.

- 124 (81.0%) patients in the luspatercept arm achieved a mean absolute increase in neutrophils of $\geq 0.5 \times 10^9$/L versus 39 (51.3%) in the placebo arm (Table 3)

Changes in Platelets

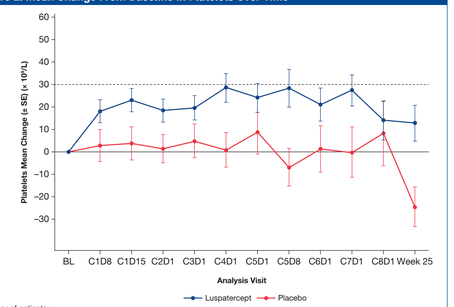
- By Cycle 4, Day 1, mean change from baseline in platelets was 28.7×10^9/L in the luspatercept arm and 0.9×10^9/L in the placebo arm (Figure 2)
  - Early increases were observed in the luspatercept arm by C1D8 (18.3×10^9/L vs 2.9×10^9/L for placebo) (Figure 2)
- 108 (70.6%) patients in the luspatercept arm achieved a mean absolute increase in platelets of $\geq 30 \times 10^9$/L versus 32 (42.1%) in the placebo arm (Table 3)

Table 3. Patients Achieving Mean Absolute Neutrophil and Platelet Increases

Parameter	Luspatercept (n = 153)	Placebo (n = 76)
Patients with mean absolute neutrophil increase $\geq 0.5 \times 10^9$/L, n (%)[a]	124 (81.0)	39 (51.3)
Patients with mean absolute platelet increase $\geq 30 \times 10^9$/L, n (%)[a]	108 (70.6)	32 (42.1)

[a] For ≥ 56 consecutive days, compared with baseline.

Figure 2. Mean Change From Baseline in Platelets Over Time



Number of patients:

Luspatercept	148	139	151	146	141	137	120	131	125	109	122
Placebo	71	73	74	74	70	72	65	70	69	67	64

Dotted line indicates mean change from baseline of 30×10^9/L.
BL, baseline; C, Cycle; D, Day; SE, standard error.

Hematological Toxicities

- Treatment-emergent grade 3 or 4 neutropenia was reported in 13 patients (7 [4.6%] patients receiving luspatercept and 6 [7.9%] receiving placebo) (Table 4)
- No grade 3 or 4 treatment-emergent thrombocytopenia was reported in either treatment arm
- 1 patient in the luspatercept arm who achieved HI-N or HI-P progressed to High-risk MDS
- None of the patients who achieved HI-N or HI-P progressed to acute myeloid leukemia (AML)
- Infection was reported in 4 of 9 luspatercept-treated patients and 3 of 7 placebo-treated patients experiencing neutropenia on study
- Bleeding was not reported in any luspatercept- or placebo-treated patients experiencing thrombocytopenia on study

Table 4. Safety Summary

Parameter	Luspatercept (n = 153)	Placebo (n = 76)
Incidence of treatment-emergent grade 3 or 4 neutropenia, n (%)	7 (4.6)	6 (7.9)
Incidence of treatment-emergent grade 3 or 4 thrombocytopenia, n (%)	0	0

CONCLUSIONS

- A greater proportion of patients in the luspatercept arm achieved HI-E during Weeks 1–48 than those in the placebo arm (58.8% vs 17.1%)
- Of patients evaluable for HI-N (n = 25), 20.0% achieved HI-N in the luspatercept arm during Weeks 1–48 versus 10.0% in the placebo arm
- Of patients evaluable for HI-P (n = 14), 62.5% achieved HI-P in the luspatercept arm during Weeks 1–48 compared with 33.3% in the placebo arm
- Mean increases from baseline in neutrophils and platelets were observed early following treatment initiation with luspatercept and stabilized over time
  - For patients with normal baseline levels, mean neutrophil and platelet increases did not exceed the upper limit of normal and were not clinically meaningful
  - For the few patients with baseline neutropenia or thrombocytopenia in the MEDALIST trial, treatment with luspatercept did not exacerbate these cytopenias
  - Mean neutrophil and platelet increases occurred independently of erythroid response to luspatercept
- None of the patients who achieved HI-N or HI-P progressed to AML
- Further research is needed during the future development of luspatercept to assess HI-N and HI-P in LR-MDS patients with severe neutropenia or thrombocytopenia

REFERENCES

1. Adès L, et al. *Lancet*. 2014;383:2239-2252.
2. Fenaux P, Adès L. *Blood*. 2013;121:4280-4286.
3. Toma A, et al. *Haematologica*. 2012;97:1459-1470.
4. Bryan J, et al. *Semin Hematol*. 2010;47:274-280.
5. Santini V, et al. *J Clin Oncol*. 2016;34:2988-2996.
6. Suragani RN, et al. *Nat Med*. 2014;20:408-414.
7. MEDALIST authors. *Blood*. 2018;132:abstract 1.
8. Cheson BD, et al. *Blood*. 2006;108:419-425.

ACKNOWLEDGEMENTS

We thank all the patients who participated in the study. This study was sponsored by Celgene Corporation, Summit, NJ, USA. The authors received editorial assistance and printing support in the preparation of this poster from Excerpta Medica (Emily Poulin, PhD), supported by Celgene Corporation. The authors are fully responsible for all content and editorial decisions.

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DISCLOSURES

G.J.M.: Celgene Corporation, Cellectis – membership on board of directors or advisory committee, research funding; Celgene Corporation – speakers bureau. P.F.: Astex Pharmaceuticals, Celgene Corporation, Jazz Pharmaceuticals – honoraria, research funding; Aprea Therapeutics – research funding. R.B.: Celgene Corporation, Takeda – research funding; Celgene Corporation – consultancy, honoraria. V.S.: Celgene Corporation, Johnson & Johnson, Novartis – honoraria; Acceleron, Amgen, Celgene Corporation, Menarini, Novartis – membership on board of directors or advisory committee. M.D.-C.: Celgene Corporation, Novartis – consultancy, membership on board of directors or advisory committee, research funding. C.F.: Celgene Corporation, Janssen, Novartis – consultancy, speakers bureau; Celgene Corporation – research funding. M.A.S.: Celgene Corporation, Millennium Pharmaceuticals, Syros – membership on board of directors or advisory committee. A.F.L.: Celgene Corporation – membership on board of directors or advisory committee, research funding. A.L., R.I., J.Z., A.R., D.S.: Celgene Corporation – employment, equity ownership. P.G.L.: Acceleron Pharma – employment; Abbott Laboratories, Acceleron Pharma, Fibrogen – equity ownership. U.P.: AbbVie, Celgene Corporation, Novartis – consultancy, honoraria. R.S.K.: Alexion, Jazz Pharmaceuticals, Novartis – speakers bureau; Agios, Celgene Corporation, Daiichi Sankyo, Incyte, Janssen, Pfizer – consultancy. G.G.-M., M.C., O.I.: no conflicts of interest to disclose.

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Presented at the 61th Annual Meeting of the American Society of Hematology (ASH); Orlando, FL, USA; December 7–10, 2019.