Neutrophil and platelet increases with luspatercept in lower-risk MDS: secondary endpoints from the MEDALIST trial

Guillermo Garcia-Manero (The University of Texas MD Anderson Cancer Center, United States) Ghulam Mufti (Guy's, King's and St. Thomas' School of Medicine, United Kingdom) Pierre Fenaux (hôpital St Louis, Paris, France) Rena Buckstein (Odette Cancer Center, Canada) Valeria Santini (University of Florence, Italy) Maria Diez-Campelo (HOSPITAL CLINICO SALAMANCA, Spain) Carlo Finelli (IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy, Italy) Osman Ilhan (Ankara University, ) Mikkael Sekeres (Sylvester Comprehensive Cancer Center, University of Miami, United States) Amer Zeidan (Yale University, United States) Rodrigo Ito (Bristol Myers Squibb, United States) Jennie Zhang (Bristol Myers Squibb, United States) Anita Rampersad (Bristol Myers Squibb, United States) Daniel Simsner (Formerly Bristol Myers Squibb (Academic Pharma, United States) Uwe Platzbecker (Department of Hematology and Cellular Therapy, Medical Clinic and Polyclinic I, Leipzig University Hospital, Germany) Rami Komrokji (H. Lee Moffitt Cancer Center, United States)

Abstract:

Conflict of interest:

COI notes: G.G.-M.: Acceleron Pharma, Astex Pharmaceuticals, Bristol Myers Squibb, Helsinn Therapeutics, and Jazz Pharmaceuticals - consulting or advisory role; AbbVie, Acceleron Pharma, Astex Pharmaceuticals, Bristol Myers Squibb, and Helsinn Therapeutics- honoraria; AbbVie, Amphivena Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, H3 Biomedicine, Helsinn Therapeutics, Merck, Novartis, and Onconova Therapeutics - research funding. G.J.M.: AbbVie and Novartis - consulting or advisory role; Bristol Myers Squibb and Novartis- research funding. P.F.: AbbVie, Bristol Myers Squibb, Janssen, and Jazz Pharmaceuticals - honoraria, consulting or advisory role; Jazz Pharmaceuticals - accommodations, expenses, travel. R.B.: Bristol Myers Squibb - honoraria, consulting or advisory role, research funding; TAIHO - honoraria, consulting or advisory role, research funding; Takeda - research funding. V.S.: Bristol Myers Squibb, and Novartis - honoraria; Astex, Bristol Myers Squibb, Geron, Gilead, Menarini, and Novartis - consulting or advisory role. M.D.-C.: Bristol Myers Squibb and Novartis - consulting or advisory role, honoraria, membership on an entity's board of directors or advisory committee, research funding. C.F.: Bristol Myers Squibb, Janssen, Novartis, and Takeda - consulting or advisory role, speakers' bureau; Bristol Myers Squibb - research funding. M.A.S.: Bristol Myers Squibb, Millennium, and Syros Pharmaceuticals - consulting or advisory role; Pfizer and Takeda- research funding. A.M.Z.: Abbvie, Acceleron Pharma, Agios, Astellas, Beyond Spring, Boehringer-Ingelheim, Bristol Myers Squibb, Cardiff Oncology, Cardinal Health, Daiichi Sankyo, Epizyme, Incyte, Ionis, Jazz Pharmaceuticals, Novartis, Pfizer, Otsuka, Seattle Genetics, Taiho, Takeda, and Trovagene - consulting or advisory role, honoraria; Abbvie, ADC Therapeutics, Aprea, Astex, Boehringer-Ingelheim, Bristol Myers Squibb, Incyte, MedImmune/AstraZeneca, Novartis, Pfizer, Takeda, and Trovagene; Cardiff Oncology, CCITLA, and Leukemia and Lymphoma Society - other. R.I.: Bristol Myers Squibb - ended employment in the past 24 months, stock and other ownership interests; Eli Lilly and Company - employment, stock and other ownership interests. J.2.: Bristol Myers Squibb - employment, stock and other ownership interests. D.S.: Bristol Myers Squibb - ended employment in the past 24 months, stock and other ownership interests. A.R.: Bristol Myers Squibb - employment, travel, accommodations, expenses, and stock and other ownership interests. J.T.B.: Acceleron Pharma - employment, stock and other ownership interests; Bristol Myers Squibb - stock and other ownership interests. U.P.: AbbVie, Bristol Myers Squibb, and Novartis - consultants, honoraria. R.S.K.: Agios, Bristol Myers Squibb, Daiichi Sankyo, Incyte, Janssen, Novartis, and Pfizer - consulting or advisory role; Alexion Pharmaceuticals, Jazz Pharmaceuticals, and Novartis - speakers bureau, AbbVie - stock and other ownership interests. O.I.: no conflicts of interest to disclose.

Preprint server: No;

Author contributions and disclosures: G.G.-M. V.S., U.P., R.S.K., designed the study. G.G.-M., G.J.M., P.F., R.B., V.S., M.D.-C., C.F., O.I., M.A.S., A.M.Z., U.P., R.S.K., collected data. G.G.-M., G.J.M., P.F., R.B., V.S., M.D.-C., C.F., O.I., M.A.S., A.M.Z., U.P., R.S.K., R.I., J.2., A.R., D.S., J.T.B., analysed and interpreted the data. R.I., A.R., supervised the clinical study. J.2., performed statistical analysis.
Non-author contributions and disclosures: Yes; We thank all the patients who participated in the study. This study was sponsored by Celgene, a Bristol-Myers Squibb Company, Princeton, NJ in collaboration with Acceleron Pharma. The authors received writing support in the preparation of this report from Karolina Lech, PhD, of Excerpta Medica, supported by Bristol Myers Squibb. The authors are fully responsible for all content and editorial decisions.

Agreement to Share Publication-Related Data and Data Sharing Statement: BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

Clinical trial registration information (if any): MEDALIST trial is registered at ClinicalTrials.gov, number: NCT02631070 and at EudraCT.ema.europa.eu, number: 2015-003454-41.
Letter to Blood

Neutrophil and platelet increases with luspatercept in lower-risk MDS: secondary endpoints from the MEDALIST trial

Guillermo Garcia-Manero,1 Ghulam J. Mufti,2 Pierre Fenaux,3 Rena Buckstein,4 Valeria Santini,5 María Diez-Campelo,6 Carlo Finelli,7 Osman Ilhan,8 Mikkael A. Sekeres,9 Amer M. Zeidan,10 Rodrigo Ito,11 Jennie Zhang,11 Anita Rampersad,11 Daniel Sinsimer,12 Jay T. Backstrom,13 Uwe Platzbecker,14* and Rami S. Komrokji15*

1Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; 2Department of Haemat-Oncology, King’s College London, London, United Kingdom; 3Service d’Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; 4Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 5MDS Unit, AOU Careggi, DMSC, University of Florence, Florence, Italy; 6Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; 7IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli” Bologna, Italy; 8Department of Hematology, Ankara University School of Medicine, Ankara, Turkey; 9Sylvester Cancer Center, University of Miami Miller School of Medicine, Miami, FL; 10Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT; 11Bristol Myers Squibb, Princeton, NJ; 12Formerly Bristol Myers Squibb, Princeton, NJ; 13Acceleron Pharma, Cambridge, MA; 14Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; 15Moffitt Cancer Center, Tampa, FL

*Co-senior authors

Correspondence:
Guillermo Garcia-Manero, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;
e-mail: ggarciam@mdanderson.org;

Main text word count: 1,196 [max 1,200]

Tables & figures: 1 & 1 [max 2]

References: 19 [max 25]
Myelodysplastic syndromes (MDS) result in abnormal blood cell development, cytopenias, and risk of progression to acute myeloid leukemia (AML). Most patients with lower-risk MDS (LR-MDS) have anemia, but patients can also have neutropenia and/or thrombocytopenia with significant clinical implications. Treatments for anemia include red blood cell (RBC) transfusions, erythropoiesis-stimulating agents (ESAs), hypomethylating agents (HMAs), or lenalidomide. However, RBC transfusions can result in iron overload, patients can become resistant to ESAs, and HMAs and lenalidomide have been associated with grade 3 or 4 neutropenia and thrombocytopenia. Luspatercept is a first-in-class erythroid maturation agent that binds several transforming growth factor-β (TGF-β) superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis. Its efficacy and safety were demonstrated in the phase 3 placebo-controlled MEDALIST trial in RBC transfusion-dependent patients with LR-MDS with ring sideroblasts (RS). In this study, significantly more luspatercept-treated patients achieved RBC transfusion independence for ≥8 weeks during Weeks 1-24 (37.9% vs 13.2%; P<.001). Significantly more patients in the luspatercept arm achieved hematologic improvement-erythroid (HI-E), as per 2006 International Working Group (IWG) criteria, during Weeks 1-24 (52.9% vs 11.8%; P<.001) and Weeks 1-48 (58.8% vs 17.1%; P<.001). Here, we report the effect of luspatercept on lineages outside the erythroid compartment, including platelets and neutrophils, and the HI for these lineages in MEDALIST patients cytopenic at baseline.

Full details of the MEDALIST trial (NCT02631070) have been published. Briefly, 229 adults with LR-MDS (defined as Very Low-, Low-, Intermediate-risk MDS per the Revised International Prognostic Scoring System [IPSS-R]) with RS (either ≥15% or ≥5% if SF3B1 mutation was present), who were refractory to, intolerant of, or unlikely to respond to ESAs (serum erythropoietin >200 U/L) and required RBC transfusions, were randomized 2:1 to receive luspatercept (n = 153) or placebo (n = 76) subcutaneously every 3 weeks for 24 weeks.

Data cutoff for the current analysis was July 1, 2019. The secondary endpoints reported are mean neutrophil and platelet counts; mean neutrophil and platelet changes from baseline; proportions of patients achieving absolute increases in neutrophil and platelet counts of ≥0.5 × 10⁹/L and ≥30 × 10⁹/L, respectively; proportions of patients achieving HI-neutrophil (HI-N) and HI-platelet (HI-P) during Weeks 1-24 and 1-48; and hematological toxicities (neutropenia and thrombocytopenia). HI-N is defined as neutrophil increase of >0.5 × 10⁹/L and ≥100% among patients with pretreatment levels <1 × 10⁹/L. HI-P is defined as platelet increase, without platelet transfusion, of ≥30 × 10⁹/L (>20 × 10⁹/L at baseline) or
>20 \times 10^9/L \text{ and } \geq 100\% \text{ increase (<20} \times 10^9/L \text{ at baseline)} \text{ among patients with pretreatment levels <100} \times 10^9/L.^{14}

Median age of patients in the MEDALIST trial was 71 years; 62.9\% were male.^{13} Most patients (95.6\%) had refractory cytopenia with multilineage dysplasia and RS (RCMD-RS) and 91.0\% of those with available data had $SF3B1$ mutations (Table 1).^{13}

Mean baseline ANC was $2.8 \times 10^9/L$ and 25 patients (10.9\%) had neutropenia (neutrophils <$1 \times 10^9/L$ per IWG 2006 criteria$^{14}$) – 15 (9.8\%) of the luspatercept and 10 (13.2\%) of the placebo arm (Table 1). Mean baseline platelet count was $257 \times 10^9/L$ and 14 (6.1\%) patients had thrombocytopenia (platelets <$100 \times 10^9/L$ per IWG 2006 criteria$^{14}$) – 8 (5.2\%) of the luspatercept and 6 (7.9\%) of the placebo arm (Table 1). Table 1 also lists characteristics of patients with baseline neutropenia or thrombocytopenia.

Among all randomized patients, 124 (81.0\%) versus 39 (51.3\%) patients in the luspatercept and placebo arms, respectively, achieved mean absolute increase in neutrophils of $\geq 0.5 \times 10^9/L$ for 56 consecutive days compared with baseline (Figure 1A). Similarly, 108 (70.6\%) versus 32 (42.1\%) patients in the luspatercept versus placebo arm achieved mean absolute increase in platelets of $\geq 30 \times 10^9/L$ (Figure 1B), maintained through Week 25. By Cycle 5, Day 8, mean change from baseline in neutrophils was $0.95 \times 10^9/L$ versus $0.04 \times 10^9/L$ in the luspatercept and placebo arm, respectively (Figure 1C). By Cycle 4, Day 1, mean change from baseline in platelets was $28.7 \times 10^9/L$ in the luspatercept and $0.9 \times 10^9/L$ in the placebo arm (Figure 1D). Mean neutrophil and platelet counts are presented in Figure 1E-F. While the increased levels of both neutrophils and platelets were maintained throughout luspatercept treatment (Weeks 1-24), they did not exceed the upper limits of normal values for adults to be considered a safety concern. The observed mean absolute increases in neutrophils and platelets were not dose-dependent.

Of the 25 patients evaluable for HI-N, more of those randomized to luspatercept versus placebo achieved HI-N during Weeks 1-24 (13.3\% vs 0.0\%) and Weeks 1-48 (20.0\% vs 10.0\%). Similarly, of the 14 patients evaluable for HI-P, more luspatercept- versus placebo-treated patients achieved HI-P during Weeks 1-24 (50.0\% vs 33.3\%) and Weeks 1-48 (62.5\% vs 33.3\%). These findings potentially support the use of luspatercept to treat patients with LR-MDS with RS who are often neutropenic and/or thrombocytopenic and anemic. However, the HI-N and HI-P responses in the placebo arm might highlight the normal oscillations seen in blood counts of patients with LR-MDS. Coupled with the low numbers of patients evaluable for HI-N and HI-P, these results should be interpreted with caution.

Treatment-emergent grade 3 or 4 neutropenia was infrequently reported, with lower incidence in the luspatercept versus the placebo group (7/153 [4.6\%] vs 6/76 [7.9\%]) and may have represented normal...
fluctuations in patients’ blood counts. No grade 3 or 4 treatment-emergent thrombocytopenia was reported in either treatment arm. These rates of grade 3 or 4 cytopenias are much lower than those observed with other therapies for MDS, including decitabine, azacytidine, and lenalidomide, which in a phase 3 randomized placebo-controlled trial in patients with lower-risk non-del(5q) MDS, showed high rates of grade 3 or 4 neutropenia (61.9% vs 12.7%) and thrombocytopenia (35.6% vs 3.8%).

Despite the increase in neutrophil counts, there was a slight increase in infection rate with luspatercept compared to placebo. Infection was reported in 4/9 (44.4%) and 3/7 (42.9%) luspatercept- and placebo-treated patients, respectively, who experienced neutropenia (any grade) during the study. Overall infection rates for luspatercept and placebo patients were 53.6% and 40.8%, respectively. The infections were not opportunistic and were mostly grade 1-2 in severity. The differences in infection rates were not assessed, as this study was not designed or powered for this purpose. Bleeding was not reported in any luspatercept- or placebo-treated patients who experienced thrombocytopenia (any grade) on study. Among patients who achieved HI-N or HI-P, 1 patient in the luspatercept arm progressed to higher-risk MDS, but none progressed to AML.

Although only a minority of patients were evaluable for HI-P/HI-N, luspatercept treatment resulted in a mean increase from baseline in platelet and neutrophil counts in most patients overall versus placebo. Mean neutrophil and platelet count increases were observed early on luspatercept treatment and persisted to Week 25. This could be associated with the positive effect of luspatercept on hematopoietic stem and progenitor cell expansion by modulating the structure of extracellular matrix or by direct inhibition of TGF-β signaling. In the 25 patients with baseline neutropenia and 14 patients with baseline thrombocytopenia, higher proportions of patients in the luspatercept versus placebo arms achieved HI-N and HI-P during Weeks 1-24 and 1-48. As meaningful statistical analyses were not possible due to small sample sizes, these results should be treated with caution.

All the patients in the MEDALIST study provided written informed consent.

Acknowledgments

We thank all the patients who participated in the study. This study was sponsored by Celgene, a Bristol-Myers Squibb Company, Princeton, NJ in collaboration with Acceleron Pharma. The authors received writing support in the preparation of this report from Karolina Lech, PhD, of Excerpta Medica, supported by Bristol Myers Squibb. The authors are fully responsible for all content and editorial decisions.
Contributions

G.G-M. V.S., U.P., R.S.K., designed the study. G.G-M., G.J.M., P.F., R.B., V.S., M.D-C., C.F., O.I., M.A.S., A.M.Z., U.P., R.S.K., collected data. G.G-M., G.J.M., P.F., R.B., V.S., M.D-C., C.F., O.I., M.A.S., A.M.Z., U.P., R.S.K., R.I., J.Z., A.R., D.S., J.T.B. analyzed and interpreted the data. R.I., A.R., supervised the clinical study. J.Z., performed statistical analysis.

Conflict-of-interest disclosure

G.G-M.: Acceleron Pharma, Astex Pharmaceuticals, Bristol Myers Squibb, Helsinn Therapeutics, and Jazz Pharmaceuticals - consulting or advisory role; AbbVie, Acceleron Pharma, Astex Pharmaceuticals, Bristol Myers Squibb, and Helsinn Therapeutics - honoraria; AbbVie, Amphivena Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, H3 Biomedicine, Helsinn Therapeutics, Merck, Novartis, and Onconova Therapeutics - research funding. G.J.M.: AbbVie and Novartis - consulting or advisory role; Bristol Myers Squibb and Novartis - research funding. P.F.: AbbVie, Bristol Myers Squibb, Janssen, and Jazz Pharmaceuticals - honoraria, consulting or advisory role; Jazz Pharmaceuticals - accommodations, expenses, travel. R.B.: Bristol Myers Squibb - honoraria, consulting or advisory role, research funding; TAIHO - honoraria, consulting of advisory role, research funding; Takeda - research funding. V.S.: Bristol Myers Squibb, and Novartis - honoraria; Astex, Bristol Myers Squibb, Geron, Gilead, Menarini, and Novartis - consulting or advisory role. M.D.-C.: Bristol Myers Squibb and Novartis - consulting or advisory role, honoraria, membership on an entity's board of directors or advisory committee, research funding. C.F.: Bristol Myers Squibb, Janssen, Novartis, and Takeda - consulting or advisory role, speakers' bureau; Bristol Myers Squibb - research funding. M.A.S.: Bristol Myers Squibb, Millennium, and Syros Pharmaceuticals - consulting or advisory role; Pfizer and Takeda - research funding. A.M.Z.: Abbvie, Acceleron Pharma, Agios, Astellas, Beyond Spring, Boehringer-Ingehelm, Bristol Myers Squibb, Cardiff Oncology, Cardinal Health, Daiichi Sankyo, Epizyme, Incyte, Ionis, Jazz Pharmaceuticals, Novartis, Pfizer, Otsuka, Seattle Genetics, Taiho, Takeda, and Trovagene - consulting or advisory role, honoraria; Abbvie, ADC Therapeutics, Aprea, Astex, Boehringer-Ingehelim, Bristol Myers Squibb, Incyte, MedImmune/AstraZeneca, Novartis, Pfizer, Takeda, and Trovagene; Cardiff Oncology, CCITLA, and Leukemia and Lymphoma Society - other. R.I.: Bristol Myers Squibb – ended employment in the past 24 months, stock and other ownership interests; Eli Lilly and Company – employment, stock and other ownership interests. J.Z.: Bristol Myers Squibb - employment, stock and other ownership interests. D.S.:
Bristol Myers Squibb - ended employment in the past 24 months, stock and other ownership interests.
A.R.: Bristol Myers Squibb - employment, travel, accommodations, expenses, and stock and other ownership interests. J.T.B.: Acceleron Pharma - employment, stock and other ownership interests; Bristol Myers Squibb - stock and other ownership interests. U.P.: AbbVie, Bristol Myers Squibb, and Novartis - consultancy, honoraria. R.S.K.: Agios, Bristol Myers Squibb, Daiichi Sankyo, Incyte, Janssen, Novartis, and Pfizer - consulting or advisory role; Alexion Pharmaceuticals, Jazz Pharmaceuticals, and Novartis - speakers bureau, AbbVie - stock and other ownership interests. O.I.: no conflicts of interest to disclose.

REFERENCES
1. Platzbecker U. Treatment of MDS. Blood. 2019; 133(10):1096-1107.
2. Bryan J, Jabbour E, Prescott H, Kantarjian H. Thrombocytopenia in patients with myelodysplastic syndromes. Semin Hematol. 2010;47(3):274-280.
3. Toma A, Fenaux P, Dreyfus F, Cordonnier C. Infections in myelodysplastic syndromes. Haematologica. 2012;97(10):1459-1470.
4. Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet. 2014;383(9936):2239-2252.
5. Fenaux P, Haase D, Santini V, et al. Myelodysplastic syndromes: Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(2):142-156
6. Greenberg PL, Stone RM, Al-Kali A, et al. Myelodysplastic syndromes, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(1):60-87.
7. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). Int J Hematol. 2018;107(1):55-63.
8. Moukalled NM, El Rassi FA, Temraz SN, Taher AT. Iron overload in patients with myelodysplastic syndromes: an updated overview. Cancer. 2018;124(20):3979-3989.
9. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. Blood. 2013;121(21):4280-4286.
10. Zeidan AM, Kharfan-Dabaja MA, Komrokji RS. Beyond hypomethylating agents failure in patients with myelodysplastic syndromes. Curr Opin Hematol. 2014;21(2):123-130.
11. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34(25):2988-2996.
12. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-beta superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014;20(4):408-414.
13. 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.

14. 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.

15. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2465.

16. Lübbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J Clin Oncol.* 2011;29(15):1987-1996.

17. Platzbecker U, Middeke JM, Sockel K, et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. *Lancet Oncol.* 2018;19(12):1668-1679.

18. Wobus M, Mies A, Magno V, et al. Altered structure and function of mesenchymal stromal cell-derived extracellular matrix in MDS can be restored by luspatercept. *Blood.* 2019;134(Supplement 1). Abstract 1699.

19. Kubasch AS, Fenaux P, Platzbecker U. Development of luspatercept to treat ineffective erythropoiesis. *Blood Adv.* 2021(5):1565-1575.
| Characteristic                                      | ITT population | Patients with neutropenia* | Patients with thrombocytopenia† |
|----------------------------------------------------|----------------|----------------------------|---------------------------------|
|                                                    | Luspatercept   | Placebo                    | Total                           | Luspatercept | Placebo | Total | Luspatercept | Placebo | Total |
|                                                    | (n = 153)      | (n = 76)                   | (n = 229)                       | (n = 15)      | (n = 10) | (n = 25) | (n = 8)      | (n = 6)  | (n = 14) |
| Age, median, years (range)                         | 71 (40–95)     | 72 (26–91)                 | 71 (26–95)                      | 69.5 (43–79) | 72 (43–86) | 72.5 (58–79) | 73.5 (65–80) | 73.5 (58–80) |
| Male, n (%)                                        | 94 (61.4)      | 50 (65.8)                  | 144 (62.9)                      | 9 (60.0)      | 6 (60.0)  | 15 (60.0) | 5 (62.5)     | 5 (83.3) | 10 (71.4) |
| MDS WHO 2008 classification, n (%)                 |                |                            |                                 |               |           |         |               |           |         |
| RS and multilineage dysplasia                      | 1 (0.7)        | 0                          | 1 (0.4)                         | NA            | NA        | NA      | NA            | NA        | NA      |
| RCMD-RS                                            | 145 (94.8)     | 74 (97.4)                  | 219 (95.6)                      | 15 (100.0)    | 9 (90.0)  | 24 (96.0) | 8 (100.0)    | 6 (100.0) | 14 (100.0) |
| RARS                                               | 7 (4.6)        | 2 (2.6)                    | 9 (3.9)                         | NA            | 1 (10.0)  | 1 (4.0)  | NA            | NA        | NA      |
| Mutated SF3B1, n/N with data (%)                   | 138/148(93.2)  | 64/74 (86.5)               | 202/222 (91.0)                  | 12 (80.0)     | 10 (100.0)| 22 (88.0) | 5 (62.5)     | 4 (66.7)  | 9 (64.3) |
| ANC, mean, × 10⁹/L (SD)                            | 2.8 (2.1)      | 2.7 (2.0)                  | 2.8 (2.0)                       | 0.8 (0.19)    | 0.8 (0.11)| 0.8 (0.16)| 3.6 (5.00)   | 1.8 (0.96) | 2.8 (3.83) |
| ANC category, n (%)                                |                |                            |                                 |               |           |         |               |           |         |
| <0.5 × 10⁹/L                                       | 1 (0.7)        | 0                          | 1 (0.4)                         | 1 (6.7)       | 0         | 1 (4.0)  | NA            | NA        | NA      |
| 0.5 to <1.0 × 10⁹/L                                | 14 (9.2)       | 10 (13.2)                  | 24 (10.5)                       | 14 (93.3)     | 10 (100.0)| 24 (96.0)| 2 (25.0)     | 2 (33.3)  | 4 (28.6) |
| ≥1.0 × 10⁹/L                                       | 138 (90.2)     | 66 (86.8)                  | 204 (89.1)                      | NA            | NA        | NA      | 6 (75.0)     | 4 (66.7)  | 10 (71.4) |
| Platelet count, mean, × 10⁹/L (SD)                 | 259 (123)      | 252 (124)                  | 257 (123)                       | 160.5 (58.13) | 179.1 (80.97)| 167.9 (67.20)| 78.1 (14.16)| 84.7 (12.74)| 80.9 (13.48) |
| Platelet count category, n (%)                     |                |                            |                                 |               |           |         |               |           |         |
| <100 × 10⁹/L                                       | 8 (5.2)        | 6 (7.9)                    | 14 (6.1)                        | 2 (13.3)      | 2 (20.0)  | 4 (16.0) | 8 (100.0)    | 6 (100.0) | 14 (100.0) |
| 100–400 × 10⁹/L                                    | 128 (83.7)     | 61 (80.3)                  | 189 (82.5)                      | 13 (86.7)     | 8 (80.0)  | 21 (84.0)| NA            | NA        | NA      |
| >400 × 10⁹/L                                       | 17 (11.1)      | 9 (11.8)                   | 26 (11.4)                       | NA            | NA        | NA      | NA            | NA        | NA      |
| ICT use, n (%) | 71 (46.4) | 40 (52.6) | 111 (48.5) | 10 (66.7) | 8 (80.0) | 18 (72.0) | 3 (37.5) | 5 (83.3) | 8 (57.1) |

ANC, absolute neutrophil count; ICT, iron chelation therapy; ITT, intention to treat; NA, not applicable; RARS, refractory anemia with ring sideroblasts; SD, standard deviation; WHO, World Health Organization.

*Patients from the ITT population with neutropenia defined per IWG2006 criteria as neutrophil level ≤1 × 10⁹/L.
†Patients from the ITT population with thrombocytopenia defined per IWG2006 criteria as platelet level ≤100 × 10⁹/L.
‡No patients with SF3B1 mutation had RS <15%.

**Figure 1. Neutrophil and platelet improvements.** Achievement of mean (A) absolute neutrophil increase ≥0.5 × 10⁹/L and (B) absolute platelet increase ≥30 × 10⁹/L. Mean change from baseline in (C) neutrophils and (D) platelets over time. Mean counts of (E) neutrophils and (F) platelets. Dashed lines indicate (C) a mean change from baseline of 0.9 × 10⁹/L and (D) a mean change from baseline of 30 × 10⁹/L. BL, baseline; C, Cycle; D, Day; SD, standard deviation; SE, standard error.
Figure 1. Neutrophil and platelet improvements. Achievement of mean (A) absolute neutrophil increase $\geq 0.5 \times 10^9/L$ and (B) absolute platelet increase $\geq 30 \times 10^9/L$. Mean change from baseline in (C) neutrophils and (D) platelets over time. Mean counts of (E) neutrophils and (F) platelets. Dashed lines indicate (C) a mean change from baseline of $0.9 \times 10^9/L$ and (D) a mean change from baseline of $30 \times 10^9/L$. BL, baseline; C, Cycle; D, Day; SD, standard deviation; SE, standard error.