## CORRESPONDENCE

# Real-world efficacy and safety of luspatercept and predictive factors of response in patients with lower risk myelodysplastic syndromes with ring sideroblasts

To the Editor:

Myelodysplastic syndromes (MDS) are myeloid malignancies predominating in the elderly, characterized by ineffective hematopoiesis and risk of progression to acute myeloid leukemia (AML).[1] In lower risk MDS, anemia is the pathological hallmark of the disease and a high proportion of patients eventually become dependent on red blood cell (RBC) transfusions. Transfusion-dependent anemia was found to be associated with reduced quality of life and shorter survival, mainly because of an increased risk of cardiovascular complications and death.

Erythropoiesis-stimulating agents (ESA) are the first-line treatment for anemia in MDS.[2] Limited options are available to treat transfusion-dependent anemia after ESA failure, and therefore most patients will continue to receive RBC transfusions only. Recently, a phase 3 randomized placebo-controlled trial[3] provided evidence for the efficacy of luspatercept in treating transfusion-dependent anemia in patients with lower risk MDS-RS who were refractory to ESA treatment. First results of real-world use of luspatercept were recently published.[4–6] Fondazione Italiana Sindromi Mielodisplastiche (FISiM) promoted a multicenter, observational trial to collect and analyze data on the efficacy and safety of luspatercept in a population of adult patients who were treated in a compassionate use program. This study was registered at ClinicalTrials.gov (NCT05520749). The Ethics Committees of all involved Hospitals approved the study.

Eligible patients were 18 years of age or older and had MDS-RS according to 2016 WHO criteria[7]; met criteria for IPSS-R very low, low, or intermediate risk[8]; were receiving regular RBC transfusions (i.e., ≥2 units/8 weeks during the 16 weeks before enrollment); and were refractory to or unlikely to respond to ESA therapy. Main exclusion criteria included prior treatment with hypomethylating agents or lenalidomide; an absolute neutrophil count $<0.5 \times 10^9/L$; and a platelet count $<50 \times 10^9/L$. Additional inclusion and exclusion criteria are listed in Table S1.

Luspatercept was administered according to label instructions. No restrictive transfusion policy was implemented, and treatment with an iron cheating agent was administered according to currently available guidelines.[2]

The statistical plan of the Medalist trial was replicated in our analysis to evaluate the effectiveness of luspatercept administration outside of a clinical trial. The primary endpoint was transfusion independence (TI) for ≥8 weeks during weeks 1–24. The main secondary endpoints were TI for ≥12 weeks, during weeks 1–24 and 1–48. All the outcome measures are reported in Appendix S1.

The efficacy analyses were performed in all enrolled patients who received at least one dose of luspatercept. A regression model was used to identify the optimal baseline transfusion burden thresholds for patients' stratification.

Overall, 215 patients were screened for enrollment in the Italian luspatercept compassionate use program, and 201 received at least one dose of the study drug between November 1, 2020, and January 30, 2022. Reasons for screening failure included disease, neutropenia, and thrombocytopenia. The cutoff date for patients' data collection was August 31, 2022. The median follow-up was 377 days (21–534).

Median age at enrollment was 74 years (31–89). At least one comorbidity requiring ongoing treatment was present in 134 (66.7%) patients, and at least three were present in 43 (21.4%). Baseline median transfusion burden was 7 units/8 weeks (2–22). The complete baseline characteristics of the patients are listed in Table S2.

Transfusion independence (TI) for ≥8 weeks in the first 24 weeks was achieved in 62 (30.8%) patients. The percentage of patients who met the primary outcome measure increased to 39.3% when the observation period included the first 48 weeks. Among patients who had a primary response (n = 79), 23 (29.1%) had multiple TI intervals lasting 8 weeks or longer, and 12 (15.2%) had at least three or more TI intervals.

A primary response was achieved at the starting dose level (1 mg/kg) in 33 (41.8%) subjects, while dose increases at 1.3 mg/kg and 1.75 mg/kg were performed in 24.1% and 34.1% of primary responders, respectively. The median longest duration of primary response was 23.9 weeks (8–70). At data cutoff, 34 patients were still in a TI interval (see Figures S1, S4 and S5).

An erythroid response according to IWG 2006[9] criteria was observed in 71 (35.3%) patients during the first 24 weeks of treatment. A mean increase in the hemoglobin level of 1.5 g/dL or more was observed in 28 (13.9%) and 44 (21.9%) patients in the first

**TABLE 1** Evaluation of primary and secondary endpoints and erythroid response in the FISiM-luspatercept population stratified according to baseline transfusion burden.

| | FISiM study ($n = 201$) | *p*-value |
|---|---|---|
| Primary endpoint | | |
| RBC-TI ≥8 weeks during Weeks 1–24, *n* (%) | 61 (30.3) | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | 27 (51.9) | <.0001 |
| 5–7 Units/8 weeks, *n* (%) | 19 (37.3) | |
| ≥8 Units/8 weeks, *n* (%) | 13 (16.7) | |
| TI duration, median, weeks | 23.9 | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, median (IQR) | 33.9 (18–49) | .0045 |
| 5–7 Units/8 weeks, median (IQR) | 27.0 (11–41) | |
| ≥8 Units/8 weeks, median (IQR) | 13.9 (9–24) | |
| Secondary endpoints | | |
| RBC-TI ≥8 weeks, weeks 1–48, *n* (%) | 79 (39.3) | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | 29 (55.8) | |
| 5–7 Units/8 weeks, *n* (%) | 22 (40.7) | <.0001 |
| ≥8 Units/8 weeks, *n* (%) | 20 (25.6) | |
| RBC-TI ≥12 weeks, weeks 1–24, *n* (%) | 38 (18.9) | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | 16 (30.8) | |
| 5–7 Units/8 weeks, *n* (%) | 13 (24.1) | <.0001 |
| ≥8 Units/8 weeks, *n* (%) | 7 (9.0) | |
| RBC-TI ≥ 12 weeks, weeks 1–48, *n* (%) | 59 (29.4) | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | 22 (42.3) | <.0001 |
| 5–7 Units/8 weeks, *n* (%) | 18 (33.3) | |
| ≥8 Units/8 weeks, *n* (%) | 12 (15.4) | |
| Erythroid response | | |
| Reduction of ≥70% in total RBC units transfused during Weeks 1–24 | | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | 17 (32.1) | .1050 |
| 5–7 Units/8 weeks, *n* (%) | 18 (31.6) | |
| ≥8 Units/8 weeks, *n* (%) | 17 (18.7) | |
| Dose at first RBC-TI ≥8 weeks, weeks 1–48, *n* (%) | | |
| Baseline transfusion requirements | | |
| ≤4 Units/8 weeks, *n* (%) | | |
| 1.00 mg/kg | 17/33 (51.5) | .0490 |
| 1.33 mg/kg | 11/33 (33.3) | |
| 1.75 mg/kg | 5/33 (15.2) | |
| 5–7 Units/8 weeks, *n* (%) | | |
| 1.00 mg/kg | 7/19 (36.8) | |
| 1.33 mg/kg | 5/19 (26.3) | |
| 1.75 mg/kg | 7/19 (36.9) | |
| ≥8 Units/8 weeks, *n* (%) | | |
| 1.00 mg/kg | 7/27 (25.9) | |
| 1.33 mg/kg | 6/27 (22.2) | |
| 1.75 mg/kg | 14/27 (51.9) | |

*Note*: *p*-values calculated with Fisher's exact test for categorical variables and ANOVA for continuous variables.
Abbreviation: RBC-TI, red blood cell transfusions independence.

Luca Lanino[1,2] , Francesco Restuccia[3] , Alessandra Perego[4], Marta Ubezio[1,2], Bruno Fattizzo[5], Marta Riva[6], Angela Consagra[7], Pellegrino Musto[8], Daniela Cilloni[9] , Esther Natalie Oliva[10], Raffaele Palmieri[11], Antonella Poloni[12] , Catello Califano[13], Isabella Capodanno[14], Federico Itri[15], Chiara Elena[16], Claudio Fozza[17] , Fabrizio Pane[18], Anna Maria Pelizzari[19], Massimo Breccia[20] , Francesco Di Bassiano[21], Elena Crisà[22], Dario Ferrero[23], Valentina Giai[23], Daniela Barraco[24], Antonella Vaccarino[25], Davide Griguolo[26], Paola Minetto[27], Martina Quintini[28], Stefania Paolini[29], Grazia Sanpaolo[30], Mariarosaria Sessa[31], Monica Bocchia[32], Nicola Di Renzo[33], Elisa Diral[34], Livia Leuzzi[35], Angelo Genua[36], Attilio Guarini[37], Alfredo Molteni[38], Barbara Nicolino[39], Ubaldo Occhini[40], Giulia Rivoli[41], Roberto Bono[42], Anna Calvisi[43], Andrea Castelli[44], Eros Di Bona[45], Ambra Di Veroli[46], Felicetto Ferrara[47], Luana Fianchi[48] , Sara Galimberti[49], Daniele Grimaldi[50], Monia Marchetti[51], Marianna Norata[52], Marco Frigeni[53], Rosaria Sancetta[54], Carmine Selleri[55], Ilaria Tanasi[56], Patrizia Tosi[57], Mauro Turrini[58] , Laura Giordano[1,2], Carlo Finelli[29], Paolo Pasini[59], Ilaria Naldi[7] , Valeria Santini[7] , Matteo Giovanni Della Porta[1,2] 
on behalf of Fondazione Italiana Sindromi Mielodisplastiche (FISiM) Clinical network (https://www.fisimematologia.it/)

[1]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[3]Presidio Ospedaliero, Pescara, Italy
[4]Ospedale San Gerardo, ASST, Monza, Italy
[5]SC Ematologia, IRCCS Ca' Granda Ospedale Maggiore Policlinico & Dipartimento di Oncologia ed Emato-oncologia, University of Milan, Milan, Italy
[6]S.C. Ematologia, Dipartimento di Ematologia, Oncologia e Medicina Molecolare, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[7]MDS Unit, Dipartimento Medicina Sperimentale e Clinica, AOU Careggi, Università di Firenze, Firenze, Italy
[8]Dipartimento di Medicina di Precisione e Rigenerativa e Area Ionica, Università degli Studi "Aldo Moro", AOU Consorziale Policlinico, Bari, Italy
[9]AO Ordine Mauriziano, Università degli Studi di Torino, Turin, Italy
[10]UOC Ematologia, Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Reggio Calabria, Italy
[11]UOC Ematologia, Fondazione Policlinico Tor Vergata, Rome, Italy
[12]Università Politecnica Marche, UOC Ematologia, AOU Marche, Ancona, Italy
[13]U.O.C. Ematologia PO A, Tortora – Pagani, Italy
[14]Azienda Unità Sanitaria Locale- IRCCS di Reggio Emilia, Reggio Emilia, Italy
[15]AOU San Luigi Gonzaga, SCDU Medicina Interna ad Indirizzo Ematologico, Università degli Studi di Torino, Torino, Italy
[16]UOC Ematologia1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[17]Dipartimento di Medicina, Chirurgia e Farmacia, Università di Sassari, Sassari, Italy
[18]Dipartimento di Medicina Clinica e Chirurgia, Università di Napoli Federico II, Naples, Italy
[19]Comprehensive Cancer Center, ASST Spedali Civili di Brescia, Brescia, Italy
[20]Università Sapienza, Rome, Italy
[21]A.O.O.R. " Villa Sofia – Cervello"-U.O.C. di Oncoematologia Palermo, Palermo, Italy
[22]AOU Maggiore della Carità, Università del Piemonte Orientale, Novara, Italy
[23]SC Ematologia, AOU Città della Salute e della Scienza, Torino, Italy
[24]SC Ematologia, Ospedale di Circolo, ASST Sette Laghi, Varese, Italy
[25]SSD Ematologia P.O. San Giovanni Bosco- ASL Città di Torino, Torino, Italy
[26]UCO Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Ospedale Maggiore, Trieste, Italy
[27]Clinica Ematologica, IRCCS-Policlinico San Martino, Genoa, Italy
[28]Azienda Ospedaliera di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy
[29]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy
[30]UOC Ematologia e Trapianto di Cellule Staminali Emopoietiche – Ospedale Casa Sollievo della Sofferenza, IRCCS San Giovanni Rotondo, San Giovanni Rotondo, Italy
[31]Hematology Section, Department of Medical Sciences, Azienda Ospedaliero-Universitaria, Arcispedale S.Anna, University of Ferrara, Ferrara, Italy
[32]UOC Ematologia, Azienda Ospedaliero Universitaria Senese, Università di Siena, Siena, Italy
[33]UOC Ematologia e Trapianto di Cellule Staminali P.O. "Vito Fazzi" -ASL Lecce, Lecce, Italy
[34]Unità di Ematologia e Trapianto di Midollo Osseo, IRCCS Ospedale San Raffaele, Milan, Italy
[35]SC Oncologia, SS Oncoematologia, PO Fatebenefratelli, ASST Fatebenefratelli Sacco, Milan, Italy
[36]AO Santa Maria, Trani, Italy
[37]IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

[38]UOC Ematologia e CTMO, ASST Cremona, Cremona, Italy

[39]SSD Ematologia, ASLTO4 Presidio Ospedaliero di Ivrea, Ivrea, Italy

[40]Ospedale San Donato, Hematology Unit, Arezzo, Italy

[41]IRCCS Ospedale Policlinico San Martino, U.O Ematologia e terapie Cellulari, Genoa, Italy

[42]A.O.O.R Villa Sofia – Cervello, U.O.S.D. Unità Trapianti di Midollo Osseo, Palermo, Italy

[43]U.O.C. Ematologia – CTMO Ospedale San Francesco, Nuoro, Italy

[44]Hematology Unit, Ospedale Degli Infermi, Biella, Italy

[45]Oncoematologia, AULSS 7 Pedemontana, Bassano del Grappa, Italy

[46]UOC Ematologia Ospedale Belcolle Viterbo, Viterbo, Italy

[47]Hematology, Ospedale Antonio Cardarelli, Naples, Italy

[48]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

[49]Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Pisa, Italy

[50]Hematology Division, AO S.Croce e Carle, Cuneo, Italy

[51]Hematology Unit, AO Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

[52]Hematology Unit, IRCCS – Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori'', Meldola, Italy

[53]Dipartimento di Oncologia ed Ematologia, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

[54]UO di Ematologia- Ospedale dell'Angelo, Mestre-Venezia, Italy

[55]UOC Ematologia, AOU San Giovanni Dio e Ruggi d'Aragona, Università di Salerno, Salerno, Italy

[56]U.O.C. di Ematologia Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

[57]UO Ematologia Ospedale Infermi Rimini, Rimini, Italy

[58]Division of Hematology, Valduce Hospital, Como, Italy

[59]AIPASIM (Associazione Italiana Pazienti con Sindrome Mielodisplastica), ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

**Correspondence**

Matteo Giovanni Della Porta, Center for Accelerating Leukemia/Lymphoma Research (CALR), Comprehensive Cancer Center, IRCCS Humanitas Clinical and Research Center and Department of Biomedical Sciences, Humanitas University, Via Manzoni 56, 20089 Rozzano, Milan, Italy.
Email: matteo.della_porta@hunimed.eu

A preliminary analysis of the study was presented at the 2022 ASH Annual Meeting in New Orleans.

This study was registered at ClinicalTrials.gov (NCT05520749). The Ethics Committees of all involved Hospitals approved the study.

## ORCID

*Luca Lanino* https://orcid.org/0000-0003-2404-8829
*Francesco Restuccia* https://orcid.org/0000-0002-4583-651X
*Daniela Cilloni* https://orcid.org/0000-0001-6346-4791
*Antonella Poloni* https://orcid.org/0000-0002-4221-4125
*Claudio Fozza* https://orcid.org/0000-0001-7253-5432
*Massimo Breccia* https://orcid.org/0000-0003-1163-6162
*Luana Fianchi* https://orcid.org/0000-0002-7113-7202
*Mauro Turrini* https://orcid.org/0000-0001-5299-8456
*Ilaria Naldi* https://orcid.org/0000-0001-9585-6108
*Valeria Santini* https://orcid.org/0000-0002-5439-2172
*Matteo Giovanni Della Porta* https://orcid.org/0000-0002-6915-5970

## REFERENCES

1. Cazzola M. Myelodysplastic syndromes. Longo DL, ed. *N Engl J Med*. 2020;383(14):1358-1374.
2. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood J Am Soc Hematol*. 2013;122(17):2943-2964.
3. 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.
4. Farrukh F, Chetram D, Al-Kali A, et al. Real-world experience with luspatercept and predictors of response in myelodysplastic syndromes with ring sideroblasts. *Am J Hematol*. 2022;97(6):E210-E214.
5. Gangat N, Chetram D, McCullough K, et al. Limited activity of luspatercept in myelofibrosis and myeloid neoplasms other than myelodysplastic syndromes with ring sideroblasts. *Am J Hematol*. 2022;97(12):E474-E477.
6. Komrokji RS, Aguirre LE, Al-Ali N, et al. Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes. *Blood Adv*. Published online April 14, 2023. doi:10.1182/bloodadvances.2023009781
7. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
8. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.
9. Cheson BD. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425.
10. Armstrong KA, Metlay JP. Annals clinical decision making: translating population evidence to individual patients. *Ann Intern Med*. 2020;172(9):610-616.
11. Cazzola M, Barosi G, Gobbi PG, Invernizzi R, Riccardi A, Ascari E. Natural history of idiopathic refractory sideroblastic anemia. *Blood*. 1988;71(2):305-312.
12. Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. *J Clin Oncol Off J Am Soc Clin Oncol*. 2021;39(11):1223-1233.
13. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the international working Group for the Prognosis of MDS. *Blood*. 2020;136(2):157-170.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.