

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 trial³ 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](https://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 criteria⁷; met criteria for IPSS-R very low, low, or intermediate risk⁸; 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 chelating 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 2006⁹ 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

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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)	<.0001
5–7 Units/8 weeks, n (%)	22 (40.7)	
≥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)	<.0001
5–7 Units/8 weeks, n (%)	13 (24.1)	
≥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.

24 and 48 weeks of treatment, respectively. Mean change in serum ferritin concentration was $-518 \mu\text{g/L}$ (95%–801; -235) after the first 12 administrations of luspatercept (see Table S4). No correlation was found between the reduction in ferritin concentration and an increase in hemoglobin concentration.

During the first 24 weeks of treatment, 14 (6.9%) patients achieved a major erythroid response according to the IWG 2018 criteria. In the high transfusion burden subgroup, a minor erythroid response was observed in 76 (41.9%) patients (see Table S6). Additional data regarding trends in hemoglobin concentration, absolute neutrophil count and platelet count are provided in Figures S3, S6 and S7.

Multiple logistic regression analysis was performed to investigate the correlation between the probability of achieving a primary response and the baseline characteristics of the patients. A significant association was found between the baseline transfusion burden and the individual probability to achieve TI ($p < .001$). No correlation was observed with age, sex, IPSS-R risk, time since initial diagnosis, and time since first RBC transfusion.

We defined an optimal threshold for RBC transfusions with respect to the probability to achieve TI and, accordingly, we stratified our patient population in three subgroups: low (≤ 4 RBC units/8 weeks), intermediate (5–7 RBC units/8 weeks), and high transfusion burden (≥ 8 RBC units/8 weeks).

Such stratification identified groups with a different probability to achieve TI and different duration of TI, as shown in Table 1.

Median time on treatment was 294 days (21–526) and the median number of administered doses was 14 (2–25). At least one increase from the baseline recommended dose of 1 mg/kg occurred in 188 (93.5%) patients. Overall, 164 (81.6%) patients received the maximum allowed dose of 1.75 mg/kg at least once during the study period. The median dose of luspatercept at first TI response was 1.33 mg/kg. Although 41.8% [33 of 79] of patients who achieved TI had their first response at the starting dose (1.0 mg/kg), 58.2% had their first response after dose increases. The dose at first response was positively correlated with baseline transfusion burden.

During the study period, serious adverse events (SAE) occurred in 35 (17.4%) patients. The most frequently observed SAE were cardiac events (hypertension, acute heart failure, atrial fibrillation; $n = 11$), acute kidney injury ($n = 1$), infections ($n = 10$), COVID-19 pneumonia ($n = 4$), and falls leading to bone fractures ($n = 4$). Overall, 20 patients died during the study period. Grade 4 thrombocytopenia and neutropenia, according to the CTCAE v5, were observed in 1 and 8 patients, respectively. All were recorded in patients who showed low counts at baseline and were not correlated with disease progression or evolution.

Evolution to AML occurred in 5 (2.5%) patients (see Figure S2). All patients who showed evolution to AML were still being treated with luspatercept at the time of progression. Treatment discontinuation occurred in 87 (43.3%) patients. The main reasons for treatment discontinuation were lack of benefit or loss of response (64.4%), death (14.9%), and consent withdrawal (4.6%). Additional information regarding treatment exposure and treatment safety are provided in Tables S5 and S7.

Results of randomized clinical trials (RCTs) represent the basis for approving drugs or interventions for clinical use.¹⁰ However, RCTs

require subjects' selection that prevents participation of some patients to the study. Moreover, patients in RCT receive the intervention in highly controlled settings unlike those in clinical practice. Additionally, compliance in RCT far exceeds that observed outside of clinical trials. All these factors may generate gaps between evidence from RCT and real-world data, which could be particularly critical when interventions are complex, costly, and, as in case of MDS, involve older individuals with physical and cognitive frailty.

In this study, we were able to confirm that luspatercept was effective for treating transfusion-dependent anemia outside the setting of a clinical trial and we observed that the benefit extended beyond the achievement of TI, producing a significant reduction in the number of transfusions. Importantly, baseline transfusion burden can identify subgroups of patients with distinct probability to have a clinical benefit from the treatment.

As expected, our real-world MDS-RS population included subjects who were older when compared with the Medalist cohort and was enriched in significant concomitant comorbidities. Overall, we were faced with frail patients with potentially reduced treatment compliance, and in which the presence of comorbidity may concur to increase the severity of anemia. Despite that, we observed a response rate that was comparable to that of the Medalist study (see Table S3 for a direct comparison) and higher than what was previously reported in a real-world setting.⁴ We also observed a high compliance rate and a manageable tolerability profile. The incidence of AML was low and consistent with the natural history of MDS-RS.^{11–13}

Since only a proportion of patients achieve TI with luspatercept treatment, the identification of predictive factors associated with individual probability to achieve is of immediate clinical utility and could optimize patient management. Predictors of response previously published in other studies^{4,5} were not found to be significant in our analysis, which included a larger and more homogeneous cohort of MDS-RS patients. In our observations, patients with higher transfusion burden had a lower probability to obtain a clinical benefit from luspatercept. An accurate evaluation of patients' baseline characteristics is deemed mandatory to maximize the clinical benefit of luspatercept administration.

These findings may reinforce the hypothesis that luspatercept could be more effective in early disease phases when ineffective erythropoiesis represents a major driver of MDS-related anemia.

Overall, the results of the present study could be useful for both improving clinical management of patients and optimizing healthcare policies in MDS-RS with transfusion-dependent anemia.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Requests for access to data from the study should be addressed to FISiM scientific committee (please contact Matteo G Della Porta at matteo.della_porta@hunimed.eu). All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the FISiM scientific committee before data release.

Luca Lanino^{1,2} , Francesco Restuccia³ , Alessandra Perego⁴,
Marta Ubezio^{1,2}, Bruno Fattizzo⁵, Marta Riva⁶, Angela Consagra⁷,
Pellegrino Musto⁸, Daniela Cilloni⁹ , Esther Natalie Oliva¹⁰,
Raffaele Palmieri¹¹, Antonella Poloni¹² , Catello Califano¹³,
Isabella Capodanno¹⁴, Federico Itri¹⁵, Chiara Elena¹⁶,
Claudio Fozza¹⁷ , Fabrizio Pane¹⁸, Anna Maria Pelizzari¹⁹,
Massimo Breccia²⁰ , Francesco Di Bassiano²¹, Elena Crisà²²,
Dario Ferrero²³, Valentina Giai²³, Daniela Barraco²⁴,
Antonella Vaccarino²⁵, Davide Griguolo²⁶, Paola Minetto²⁷,
Martina Quintini²⁸, Stefania Paolini²⁹, Grazia Sanpaolo³⁰,
Mariarosaria Sessa³¹, Monica Bocchia³², Nicola Di Renzo³³,
Elisa Diral³⁴, Livia Leuzzi³⁵, Angelo Genua³⁶, Attilio Guarini³⁷,
Alfredo Molteni³⁸, Barbara Nicolino³⁹, Ubaldo Occhini⁴⁰,
Giulia Rivoli⁴¹, Roberto Bono⁴², Anna Calvisi⁴³, Andrea Castelli⁴⁴,
Eros Di Bona⁴⁵, Ambra Di Veroli⁴⁶, Felicetto Ferrara⁴⁷,
Luana Fianchi⁴⁸ , Sara Galimberti⁴⁹, Daniele Grimaldi⁵⁰,
Monia Marchetti⁵¹, Marianna Norata⁵², Marco Frigeni⁵³,
Rosaria Sancetta⁵⁴, Carmine Selleri⁵⁵, Iliara Tanasi⁵⁶, Patrizia Tosi⁵⁷,
Mauro Turrini⁵⁸ , Laura Giordano^{1,2}, Carlo Finelli²⁹, Paolo Pasini⁵⁹,
Iliara Naldi⁷ , Valeria Santini⁷ , Matteo Giovanni Della Porta^{1,2} 
on behalf of Fondazione Italiana Sindromi Mielodisplastiche (FISiM)
Clinical network (<https://www.fisimematologia.it/>)

¹IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

²Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

³Presidio Ospedaliero, Pescara, Italy

⁴Ospedale San Gerardo, ASST, Monza, Italy

⁵SC Ematologia, IRCCS Ca' Granda Ospedale Maggiore Policlinico & Dipartimento di Oncologia ed Emato-oncologia, University of Milan, Milan, Italy

⁶S.C. Ematologia, Dipartimento di Ematologia, Oncologia e Medicina Molecolare, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

⁷MDS Unit, Dipartimento Medicina Sperimentale e Clinica, AOU Careggi, Università di Firenze, Firenze, Italy

⁸Dipartimento di Medicina di Precisione e Rigenerativa e Area Ionica, Università degli Studi "Aldo Moro", AOU Consorziale Policlinico, Bari, Italy

⁹AO Ordine Mauriziano, Università degli Studi di Torino, Turin, Italy

¹⁰UOC Ematologia, Grande Ospedale Metropolitano Bianchi Melacrinò Morelli, Reggio Calabria, Italy

¹¹UOC Ematologia, Fondazione Policlinico Tor Vergata, Rome, Italy

¹²Università Politecnica Marche, UOC Ematologia, AOU Marche, Ancona, Italy

¹³U.O.C. Ematologia PO A, Tortora - Pagani, Italy

¹⁴Azienda Unità Sanitaria Locale- IRCCS di Reggio Emilia, Reggio Emilia, Italy

¹⁵AOU San Luigi Gonzaga, SCU Medicina Interna ad Indirizzo Ematologico, Università degli Studi di Torino, Torino, Italy

¹⁶UOC Ematologia1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

¹⁷Dipartimento di Medicina, Chirurgia e Farmacia, Università di Sassari, Sassari, Italy

¹⁸Dipartimento di Medicina Clinica e Chirurgia, Università di Napoli Federico II, Naples, Italy

¹⁹Comprehensive Cancer Center, ASST Spedali Civili di Brescia, Brescia, Italy

²⁰Università Sapienza, Rome, Italy

²¹A.O.O.R. "Villa Sofia - Cervello" -U.O.C. di Oncoematologia Palermo, Palermo, Italy

²²AOU Maggiore della Carità, Università del Piemonte Orientale, Novara, Italy

²³SC Ematologia, AOU Città della Salute e della Scienza, Torino, Italy

²⁴SC Ematologia, Ospedale di Circolo, ASST Sette Laghi, Varese, Italy

²⁵SSD Ematologia P.O. San Giovanni Bosco- ASL Città di Torino, Torino, Italy

²⁶UCO Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Ospedale Maggiore, Trieste, Italy

²⁷Clinica Ematologica, IRCCS-Policlinico San Martino, Genoa, Italy

²⁸Azienda Ospedaliera di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy

²⁹IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

³⁰UOC Ematologia e Trapianto di Cellule Staminali Emopoietiche - Ospedale Casa Sollievo della Sofferenza, IRCCS San Giovanni Rotondo, San Giovanni Rotondo, Italy

³¹Hematology Section, Department of Medical Sciences, Azienda Ospedaliero-Universitaria, Arcispedale S.Anna, University of Ferrara, Ferrara, Italy

³²UOC Ematologia, Azienda Ospedaliero Universitaria Senese, Università di Siena, Siena, Italy

³³UOC Ematologia e Trapianto di Cellule Staminali P.O. "Vito Fazzi" -ASL Lecce, Lecce, Italy

³⁴Unità di Ematologia e Trapianto di Midollo Osseo, IRCCS Ospedale San Raffaele, Milan, Italy

³⁵SC Oncologia, SS Oncoematologia, PO Fatebenefratelli, ASST Fatebenefratelli Sacco, Milan, Italy

³⁶AO Santa Maria, Trani, Italy

³⁷IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

- ³⁸UOC Ematologia e CTMO, ASST Cremona, Cremona, Italy
- ³⁹SSD Ematologia, ASLTO4 Presidio Ospedaliero di Ivrea, Ivrea, Italy
- ⁴⁰Ospedale San Donato, Hematology Unit, Arezzo, Italy
- ⁴¹IRCCS Ospedale Policlinico San Martino, U.O Ematologia e terapie Cellulari, Genoa, Italy
- ⁴²A.O.O.R Villa Sofia – Cervello, U.O.S.D. Unità Trapianti di Midollo Osseo, Palermo, Italy
- ⁴³U.O.C. Ematologia – CTMO Ospedale San Francesco, Nuoro, Italy
- ⁴⁴Hematology Unit, Ospedale Degli Infermi, Biella, Italy
- ⁴⁵Oncoematologia, AULSS 7 Pedemontana, Bassano del Grappa, Italy
- ⁴⁶UOC Ematologia Ospedale Belcolle Viterbo, Viterbo, Italy
- ⁴⁷Hematology, Ospedale Antonio Cardarelli, Naples, Italy
- ⁴⁸Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
- ⁴⁹Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Pisa, Italy
- ⁵⁰Hematology Division, AO S.Croce e Carle, Cuneo, Italy
- ⁵¹Hematology Unit, AO Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
- ⁵²Hematology Unit, IRCCS – Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori”, Meldola, Italy
- ⁵³Dipartimento di Oncologia ed Ematologia, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy
- ⁵⁴UO di Ematologia- Ospedale dell'Angelo, Mestre-Venezia, Italy
- ⁵⁵UOC Ematologia, AOU San Giovanni Dio e Ruggi d'Aragona, Università di Salerno, Salerno, Italy
- ⁵⁶U.O.C. di Ematologia Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy
- ⁵⁷UO Ematologia Ospedale Infermi Rimini, Rimini, Italy
- ⁵⁸Division of Hematology, Valduce Hospital, Como, Italy
- ⁵⁹AIPASIM (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](https://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>

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SUPPORTING INFORMATION

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