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ORIGINAL PAPER

Haematological Malignancy – Clinical

Real-life experience of luspatercept in transfusion-dependent lower risk myelodysplastic syndrome patients

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Summary

Luspatercept has been approved for the treatment of anaemia in transfusion-dependent (TD) patients with lower risk (LR) myelodysplastic syndromes (MDS) after erythroid-stimulated agent (ESA) failure, according to the results of the MEDALIST trial. In this multicentre retrospective study, we report efficacy and safety data of luspatercept administered in 98 TD LR-MDS patients after ESA failure. The percentage of patients that stopped luspatercept due to adverse events was comparable to that reported in the MEDALIST study. Furthermore, we observed that 44.3% patients who had completed 24 weeks of follow-up achieved transfusion independence lasting longer than 8 weeks, compared to 38% in the MEDALIST trial. These positive results may be attributed to the inclusion of patients with lower transfusion needs in our study. All responses were observed within 8 months since luspatercept onset and many were long-lasting, even in the high-transfusion burden patient group. In addition, response to luspatercept and the presence of less than two mutations independently predicted for longer overall survival. Overall, our results confirm luspatercept's safety and efficacy in TD LR-MDS patients who have experienced ESA failure in a real-world setting.

KEYWORDS
lower risk MDS, luspatercept, response, survival, transfusion dependence

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematopoietic malignancies characterized by peripheral blood cytopenias, clonal haematopoiesis, and bone marrow dysplasia with a variable risk of transformation to acute myeloid leukaemia (AML).[1]

Prognostically, patients with MDS are distinguished into lower and higher risk groups, according to the revised International Prognostic Scoring System (IPSS-R), which

For affiliations refer to page 108.

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combines multiple parameters. The lower risk (LR) group is further divided into very low (0–1.5 points), low (2–3 points) and intermediate (3.5–4.5 points) risk groups.[2] Advances in molecular diagnostics, with next-generation sequencing (NGS), and the recognition of the prognostic value of mutations in various genes led to the development of the new molecular IPSS (IPSS-M).[3]

The majority of patients diagnosed with MDS are classified as LR based on the IPSS-R. The main goals of treatment in patients with LR-MDS are to restore cytopenias and improve quality of life,[4,5] while constantly reassessing for possible transformation to higher risk MDS or AML. In LR-MDS, symptomatic anaemia is the predominant problem, with patients often requiring regular red blood cell (RBC) transfusions. In addition, transfusion dependence (TD) and its severity are another factors that not only reduce the quality of life but also increase morbidity and mortality in MDS patients.[6] Moreover, prolonged TD can lead to significant iron overload, which also adversely impacts patient outcomes and survival.[7,8] Therefore, an essential goal of treatment in LR-MDS is transfusion independence (TI), improving haemoglobin levels and restoring effective erythropoiesis.

Although erythroid-stimulated agents (ESAs) have been the mainstay of LR-MDS anaemia treatment since their approval in 2017, their effectiveness and duration of response (DOR) are limited.[9,10] In particular, many patients receiving ESAs do not respond, and most patients who initially respond will eventually relapse and become TD. Until recently, treatment options were limited for patients who were not eligible for ESAs or for whom ESAs had failed. A recent breakthrough in treating anaemia in LR-MDS patients is the transforming growth factor beta (TGF-β) pathway blockers.

Luspatercept is a recombinant fusion protein that acts as a ligand trap for TGF-β superfamily members, inhibiting SMAD2/3 signalling and promoting the maturation of RBCs. It was initially approved for the treatment of TD LR-MDS patients who had high percentages of bone marrow ring sideroblasts (RS) or a low percentage of RS and an *SF3B1* mutation (*SF3B1*^{mut}) and had failed an ESA, based on the findings of the MEDALIST trial.[11]

SF3B1 mutation is the most common splicing factor mutation in MDS, and it is strongly associated with the presence of bone marrow RS.[12] In the current WHO classification, MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*) has replaced the previous MDS-RS category.[13] Recently, luspatercept has also gained approval as a first-line treatment for TD LR-MDS, irrespective of the presence of RS or *SF3B1* mutations, according to the results of the COMMANDS trial.[14] The aim of our study was to assess the safety and efficacy of luspatercept in TD LR-MDS patients after failure of ESAs, in a real-world setting.

METHODS

This retrospective, multicentre study was approved by the local ethics committee (EBΔ721/25-10-2023) and it was conducted according to the declaration of Helsinki. We studied TD LR-MDS patients who had received luspatercept after ESA failure either as monotherapy or in combination with ESA according to physician choice for at least 8 weeks. Patient demographic and baseline disease characteristics, including age, sex, the presence of bone marrow RS, cytogenetics and gene mutations, were recorded. Blood counts and serum ferritin levels were recorded at baseline and at the time point of response and the most recent date of luspatercept administration. The maximum treatment dose and number of cycles, as well as adverse events leading to treatment discontinuation, were recorded. Records of patients' transfusion history were reviewed thoroughly. Transfusion burden (TB) was defined as high (HTB), intermediate (ITB) and low (LTB) if they had received ≥8, 3–7 or 1–2 RBC transfusions in the last 16 weeks before luspatercept onset respectively. Luspatercept was administered subcutaneously once every 3 weeks, starting at a dose of 1.0 mg/kg, which was increased stepwise to 1.33 mg/kg and then to a maximum of 1.75 mg/kg if required.

Response was defined as TI for at least 8 weeks after luspatercept initiation. Therefore, the date of response was set at 8 weeks after the date of the last recorded transfusion or after the date of luspatercept onset, if no RBC transfusions were administered thereafter. Loss of response (LOR) was defined as the re-emergence of RBC transfusion needs. However, if LOR was noted before the completion of 16 weeks, the response was not considered meaningful. All variables were reported as median [5%–95% range] and all estimates were

TABLE 1 Patient baseline characteristics.

Number of patients	98
Age (years), median [range]	75 [59–88]
Male/female	59/39
Luspatercept monotherapy/combination with ESA	81/17
BM blasts (%), median [range]	1 [0–4]
IPSS-R cytogenetic risk group (*N*) very good/good/intermediate/poor/no metaphases	1/75/15/4/3
IPSS-R score: 2/2.5/3/3.5/4/4.5/NA	19/30/12//18/6/10/3
IPSS-R risk category: low/intermediate/NA	61/34/3
BM RS present/absent (*N*)	80/18
HTB/ITB/LTB	48/37/13
Hb (g/dL)	7.7 [5.8–9.1]
Neutrophils (×10^3/μL)	2.605 [0.629–6.610]
Lymphocytes (×10^3/μL)	1.495 [0.575–2.765]
Monocytes (×10^3/μL)	0.420 [0.080–0.957]
Platelets (×10^3/μL) (*N* = 90)	250 [42–584]
Patients with platelets (<50 ×10^3/μL) (*N*)	6/98
Ferritin (ng/dL) (*N* = 88)	901 [42–3704]

Abbreviations: BM, bone marrow; ESA, erythroid-stimulated agen; Hb, haemoglobin; HTB, high transfusion burden; IPSS-R, revised International Prognostic Scoring System; ITB, intermediate transfusion burden; LTB, Low transfusion burden; *N*, number informative; NA, not available; continuous variables are presented as median [5%–95%] range; RS, ring sideroblasts.

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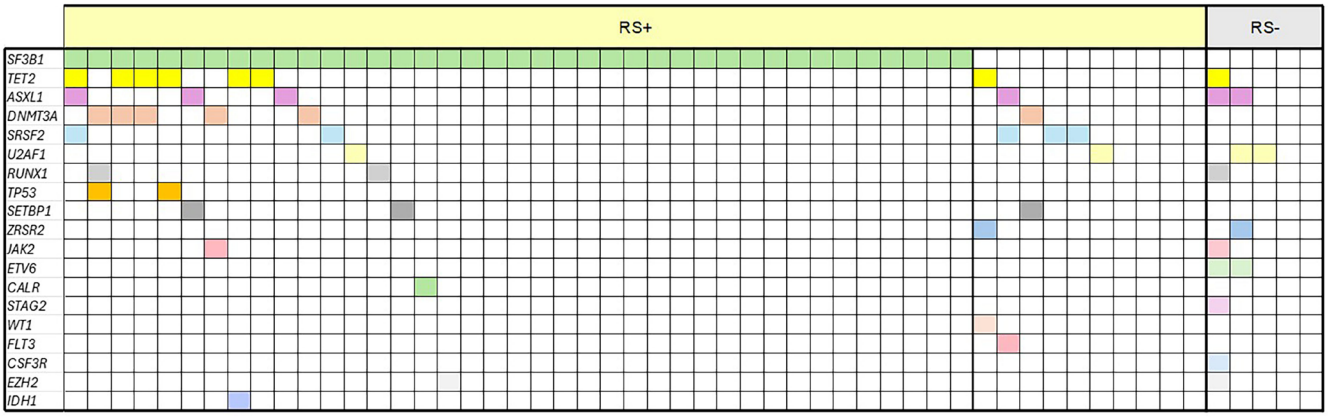


FIGURE 1 Mutation plot at baseline. In the RS+ group, 39 patients were *SF3B1*^{mut} and 10 were *SF3B1*^{wt}. In the RS− group, no patient was *SF3B1*^{mut}. Seventeen of 39 *SF3B1*^{mut} patients carried additional mutations. Six patients had no mutations. RS, ring sideroblasts.

reported as median [5%–95% confidence interval (CI)]. Fisher's exact test and Wilcoxon matched-pairs signed-rank test were performed for comparison of categorical and continuous variables, respectively, and the Kaplan–Meier method with Cox proportional hazard models was applied to analyse time-to-event data. Statistical analysis was performed using Stata (18, StataCorp LLC, College Station, TX).

RESULTS

A total of 98 patients from 15 Greek and 2 Turkish sites were included in the study, with treatment initiation dates ranging from October 2020 to April 2024, and the data collection cut-off was in August 2024. The median follow-up was 13.1 [4.2–39.8] months. Our study included TD-MDS patients, with a median age of 75 [59–88] years and a male predominance. Patients belonged to the low or intermediate IPSS-R risk category. The baseline characteristics are depicted in detail in Table 1. Baseline NGS panel mutational data were available for 54 patients and are represented in Figure 1.

Regarding luspatercept exposure, 74 patients received the maximum dose (1.75 mg/kg), 12 received the intermediate dose (1.33 mg/kg) and 12 received the minimum dose (1 mg/kg). The median number of luspatercept cycles was 14 [4–54]. During follow-up, 57 patients discontinued treatment: eight due to adverse events as shown in Table 2, eight patients because of death unrelated to treatment, two patients proceeded to allogeneic transplantation and 36 patients due to inadequate response. Notably, three patients stopped because of a persistent haemoglobin level greater than 11 g/dL.

Throughout the observation period, four patients progressed to MDS with increased blasts 5%–10% (one with fibrosis) and one patient progressed to chronic myelomonocytic leukaemia. No cases of AML transformation were recorded. Overall, a total of 20 patients succumbed to causes related to MDS, but unrelated to treatment. Table S1 depicts causes of death in our patient cohort.

TABLE 2 Adverse events that led to treatment discontinuation.

Adverse event (*N*) (%)	(8) (8.2%)
Musculoskeletal pain	2
Vertigo	1
Hypertension	1
Orthostatic hypotension	1
Soft tissue infections	1
Bleeding disorder	1
Undetermined	1

Forty-two of 98 patients (42.9%) responded to treatment, 12/48 (25%) in the HTB group, 21/37 (56.8%) in the ITB group and 9/13 (69.2%) in the LTB group respectively ($p = 0.002$) (Figure 2). Among the 88 patients who had completed 24 weeks of follow-up after luspatercept onset, 39 (44.3%) achieved TI lasting longer than 8 weeks. All LTB patients who became TI also exhibited >1.5 g/dL increase in haemoglobin level. There was a trend for better response in the *SF3B1* mutated group than the *SF3B1* unmutated group (19/39; 48.7% vs. 3/15; 20%, respectively, $p = 0.069$). There was no difference in response for patients with bone marrow RS (36/80; 45%) compared to patients without bone marrow RS (6/18; 33.3%), $p = 0.366$. In addition, there was no difference in the response rates between patients carrying up to one mutation (14/32; 43.8%) compared to patients carrying more than one mutation (8/22; 36.4%), $p = 0.59$. Finally, we did not observe any difference in response rates between patients receiving luspatercept as monotherapy (36/81; 44.4%) compared to patients treated with a combination of luspatercept and ESA (6/17; 35.3%), $p = 0.59$.

Twenty-nine of 42 responders had ferritin levels available upon response, showing a significant decrease compared to baseline (691 [52–4375] vs. 880 [93, 6291] ng/dL, $p = 0.008$). An overall increase in neutrophil counts was observed for the entire patient population, with baseline counts of 2.605 [0.629–6.610] $\times 10^3/\mu L$ compared to 2.850 [531, 8.855] $\times 10^3/\mu L$, $p = 0.003$. Three of 11 patients (27.3%) with baseline

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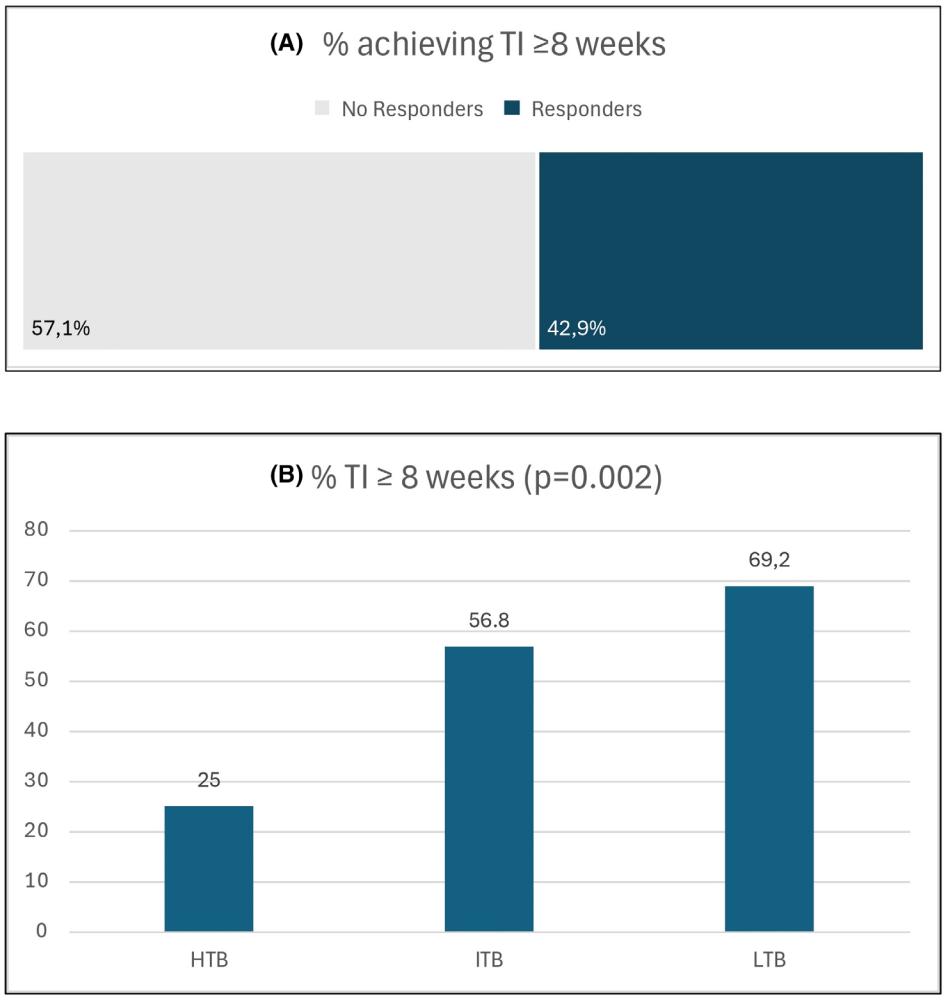


FIGURE 2 (A) Percentage of patients achieving response. (B) Percentage of patients achieving response within each transfusion category. Forty-two of 98 patients. HTB, high transfusion burden; ITB, intermediate transfusion burden; LTB, Low transfusion burden; TI, transfusion independence.

neutrophil counts $<10^3$/μL had a neutrophil response as per IWG 2018 response criteria—HI-N.[15] No significant change in the platelet count was observed (baseline counts of 250 [42–584] $\times10^3$/μL compared to 240 [23–543] $\times10^3$/μL, $p=0.324$). However, 4 of 15 patients (26.7%) with baseline platelet counts <100 $\times10^3$/μL had a platelet response as per IWG 2018 response criteria—HI-P.[15]

All 42 responders achieved a response within 8 months of luspatercept treatment with a median time to response of 3.7 [2–7.5] months (Figure 3A). The median DOR using the Kaplan–Meier method was reached at 32 months. Ten of 42 patients lost response after having experienced TI for a median time of 14.8 [2.58–35.5] months. Time to LOR is represented in Figure 3B. Notably, within the HTB group, seven of 12 responders exhibited responses that lasted longer than 6 months (Figure 4).

Finally, variables that could possibly affect overall survival (OS) were investigated. No difference in hazard ratios (HR) for OS was observed for sex, age >75 versus ≤75 years, HTB versus non-HTB and IPSS-R cytogenetic risk group (with very good or good risk categories comprising the low-risk cytogenetic group and intermediate- and poor-risk categories comprising the high-risk cytogenetic group). Patients who achieved response had an increased probability of survival, with an OS rate at 2 years of 83.3% for responders compared to 62.5% for non-responders (HR: 0.37 [0.14–0.99], $p=0.048$) (Figure 5A). The number of mutations (≥2 vs. 0–1) negatively affected OS (HR: 3.33 [1.11–9.98], $p=0.032$) (Figure 5B). Moreover, in multivariable Cox regression analysis, response to luspatercept and the number of mutations (0–1 vs. ≥2) were independent predictive factors for OS. Results of univariate and multivariate Cox regression analysis are shown in Table 3.

DISCUSSION

In this retrospective, multicentre study, we have demonstrated substantial efficacy of luspatercept in a real-world population, consisting of TD LR-MDS patients with previous ESA failure. The main finding of our study was that patients with lower TB exhibit higher rates of response to luspatercept compared to patients with higher TB. Therefore, it can be assumed that early treatment

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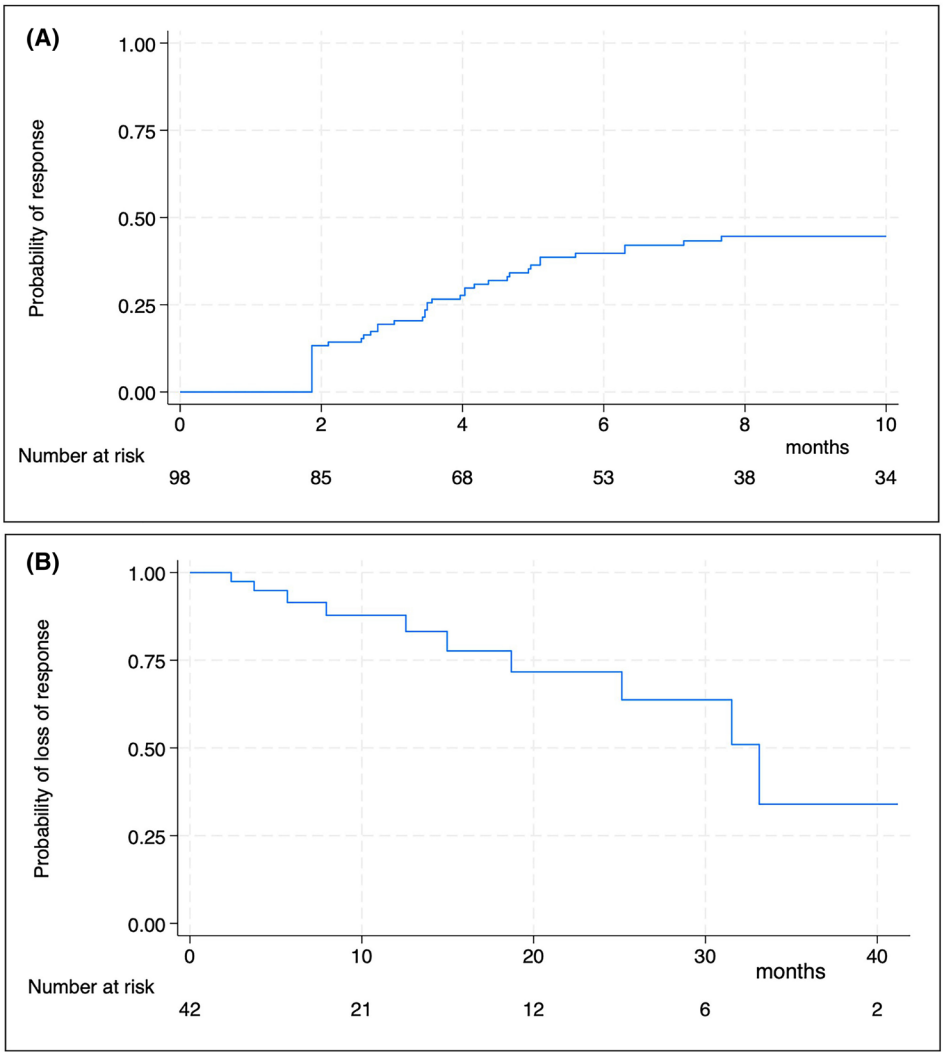


FIGURE 3 (A) Time to response (months). (B) Time to loss of response (months) in the 42 patients who had achieved a response.

initiation with luspatercept may be beneficial for anaemic LR-MDS patients. In fact, the ongoing ELEMENT study (NCT05949684) that compares ESAs against luspatercept in the first-line treatment in anaemic non-TD LR-MDS patients is expected to validate the above assumption. Response rates in our study appear to be higher than those in the MEDALIST study. In the MEDALIST study, 38% of patients achieved 8-week TI in the first 24 weeks of the study, while the respective response rate in our study was 44.3%. It is rather surprising for a real-world study to exceed the response rates of a clinical trial. The higher response rates can be attributed, at least in part, to the lower TB of patients at baseline. In the MEDALIST trial, only patients who received ≥2 RBC units per 8 weeks in the 16 weeks prior to randomization were included. The same inclusion criteria were adopted in a prospective real-world study that included 201 TD LR-MDS patients after ESA failure. Interestingly, only 30.8% of patients achieved 8-week TI in the first 24 weeks of the study.[15]

Our cohort included patients with less than four RBC units in the 16 weeks prior to treatment onset. Notably, there were 13 patients who had only received one to two RBC units in the above period. This patient population is not clearly defined by the IWG2018 criteria,[16] so we had to adjust this category accordingly. This category was defined as the LTB group in our study.

Our results in terms of response to luspatercept are in concordance with other retrospective real-life studies which also included patients with lower TB, and patients who received a combination of luspatercept with ESAs following ESA failure.[17–19] Of note, the study of Jonasova et al.[17] had a retrospective multicentre design, while the studies by Mukherjee et al.[18] and Andritsos et al.[19] were based on electronic records of the USA population. The results of these studies and ours are not directly comparable since they comprise heterogeneous patient populations in terms of TB, prior ESA failure and combination treatment of luspatercept with ESAs. However, they all share a common feature: the inclusion of a significant proportion of lower TB MDS patients that may explain the higher response rates observed in real-life studies than the MEDALIST trial.

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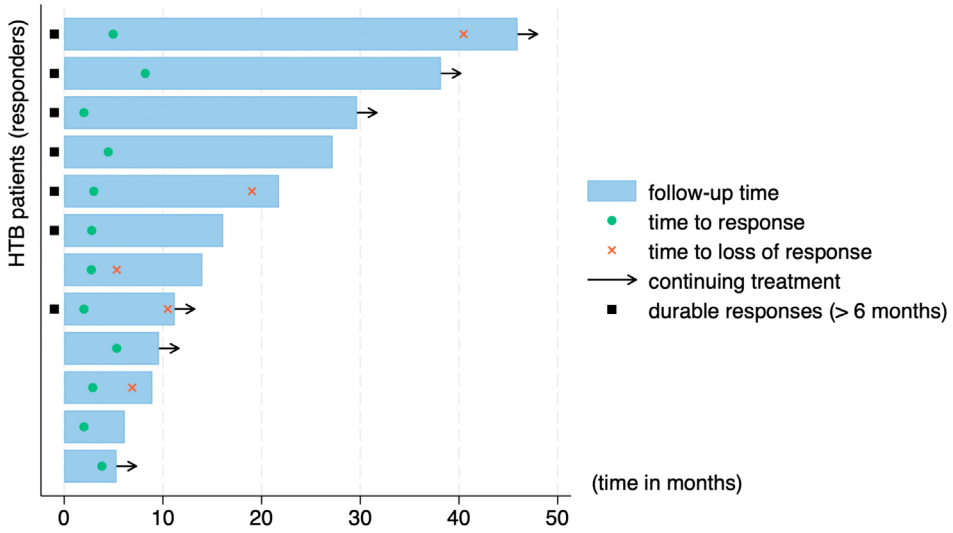


FIGURE 4 Durable responses within the HTB group. HTB, high transfusion burden.

In our study, we did not observe a difference in response rates between patients receiving luspatercept monotherapy and patients receiving combination treatment with ESAs, but the small number of patients receiving combination treatment may hinder safe conclusions. From a pathophysiological point of view, it would be interesting to exploit the synergistic effect of ESAs and luspatercept as the former acts at the earlier stages and the latter acts at the later stages of erythropoiesis.[20,21] This combination has shown positive effects in everyday clinical practice[17]; however, randomized clinical trials are needed to establish its use.

The positive effect of bone marrow RS in the response rates in luspatercept-treated patients is not consistent across studies.[17,19,22] We found no correlation between the presence of RS and response to treatment in our study. We did, however, observe a trend for a higher response rate in the *SF3B1*^{mut} patient group. This may indicate that *SF3B1* mutation status is a more reliable predictor of response to luspatercept than the presence of RS. Moreover, the number of mutations (0–1 compared to ≥2) did not affect response to treatment. This is in agreement with a post hoc analysis of the COMMANDS trial suggesting that mutation load may not have an adverse impact on outcome in TD LR-MDS treated with luspatercept.[23] However, the COMMANDS trial included TD LR-MDS patients treated in a front-line setting. The role of mutation load in response to luspatercept after ESA failure has not been examined thoroughly.

The vast majority of our patients (74/98) received the maximum luspatercept dose. Dose escalation has been shown to favour responses in clinical practice, as previously reported.[24]

In our cohort, all responses were observed within 8 months of treatment and were long-lasting even in the subset of difficult-to-treat HTB patients. More specifically, DOR for patients achieving TI ≥8 weeks was extended, reaching a median time of 32 months. In the MEDALIST trial, median DOR was 20.2 months for patients achieving TI ≥8 weeks in the first 6 months of treatment, also taking into account multiple responses, defined as the occurrence of new periods of TI lasting ≥8 weeks.[25] However, even in that study, longer median DOR has been reported in a subset of patients with lower transfusion needs.[26]

Luspatercept has been known to exhibit multilineage effects. In the MEDALIST trial, neutrophil and platelet counts were increased in the entire luspatercept-treated population, whereas in the COMMANDS trial, more neutrophil and platelet responses were reported in the luspatercept compared to the ESA-treated arm.[27,28] An interesting finding of our study is the increase of neutrophil counts in the entire population of patients treated with luspatercept, confirming similar results from the MEDALIST trial. Interestingly, two out of seven patients with baseline neutrophil counts $<\times 10^3$/μL had HI-N. Even though we did not observe significant changes in platelet counts in our study population, we observed HI-P in 4 of 13 patients with baseline platelet counts $<100 \times 10^3$/μL.

Furthermore, we report a significant decrease in ferritin levels among patients who responded to treatment, at the time of response. Luspatercept has been reported to decrease ferritin levels in the MEDALIST trial,[11] as well as in responders in a real-world data,[29] but the exact mechanism remains unclear. Since all responses occurred in less than 8 months in our cohort, it is more likely that ferritin decrease upon response is associated with the improvement of haematopoiesis rather than the reduction of TB in these patients.

The safety profile of luspatercept was anticipated and manageable in our study population; moreover, no patient progressed to AML. Additionally, the percentage of patients who discontinued the treatment was 8.2% and was comparable to that of MEDALIST (8%).

The number of mutations (≥2 compared to 0–1) predicted an inferior OS in our patient cohort. This suggests that luspatercept may not be able to change the clinical course of the

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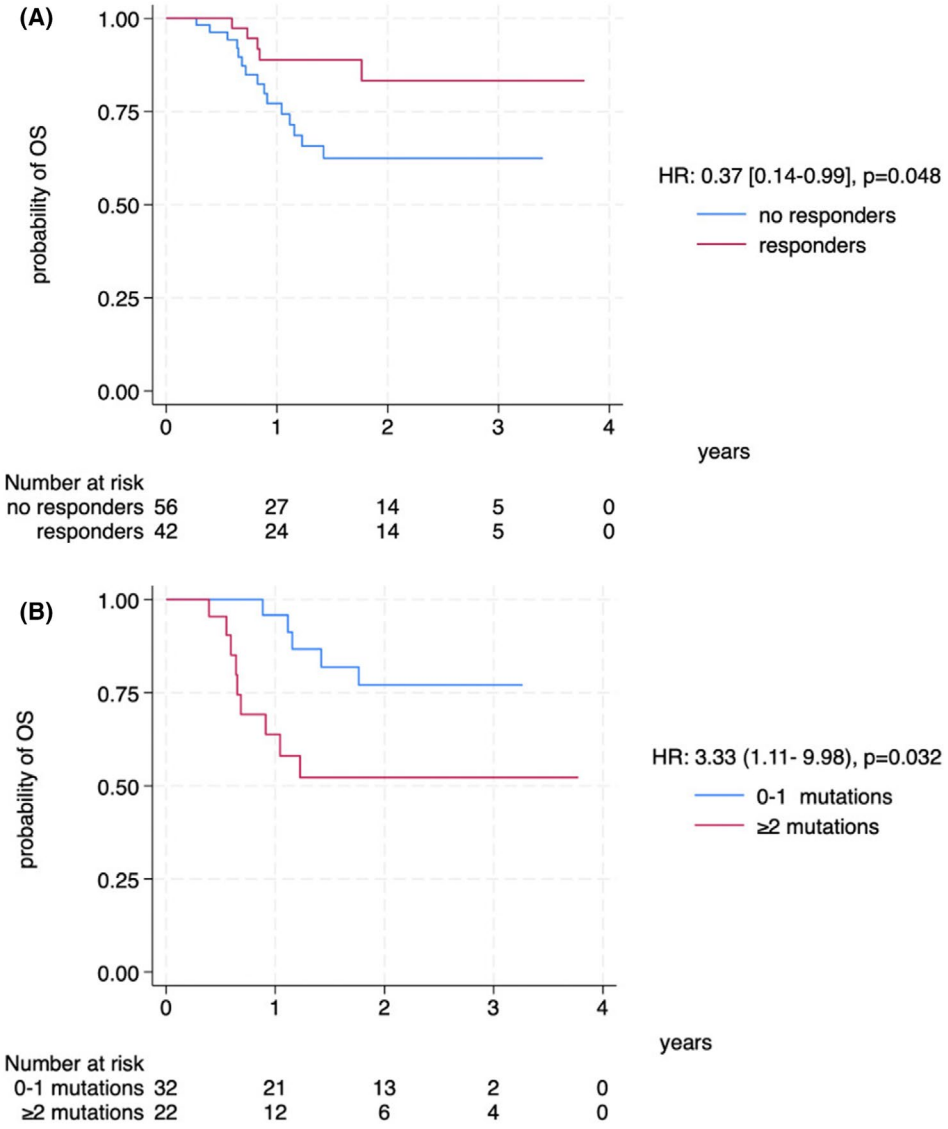


FIGURE 5 (A) Overall survival (OS) probability according to response. (B) OS probability according to mutation burden. HR, hazard ratio.

TABLE 3 Results of Cox regression analysis for the association between patient variables and OS.

	Univariate analysis		Multivariate analysis	
Variables	**HR [95% CI]**	***p*-value**	**HR [95% CI]**	***p*-value**
Male sex	0.74 [0.31–1.79]	0.508		
Age >75	2.44 [0.93–6.37]	0.069		
High-risk cytogenetics	1.21 [0.40–3.62]	0.741		
HTB	1.69 [0.66–3.86]	0.299		
≥2 mutations	3.33 [1.11–9.98]	**0.032**	3.49 [1.16–10.52]	**0.026**
Response	0.37 [0.14–0.99]	**0.048**	0.21 [0.47–0.94]	**0.041**

Note: Highlighted (bold) *p*-values denote statistically significant results.

Abbreviations: CI, confidence interval; HR, hazard ratio; HTB, high transfusion burden; OS, overall survival.

disease. However, we were able to observe a survival benefit in the patients who responded to luspatercept, as previously reported in the MEDALIST trial.[25] This effect was independent of the number of mutations, highlighting the overall benefit of luspatercept in TD LR-MDS patients in a real-world setting.

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Several limitations of our study should be acknowledged. First, the retrospective nature of the study introduces potential selection and information bias. Second, molecular data were available for only 54 of 98 patients, which may have limited our ability to fully assess the impact of genetic factors on treatment outcomes. Furthermore, the relatively short median follow-up time of 13.1 months may not have captured the full long-term efficacy and safety profile of luspatercept in this population. Finally, our study lacks a thorough description of side effects beyond those leading to drug discontinuation.

The inclusion of patients receiving combination therapy with ESAs, while reflecting real-world practice, created additional heterogeneity in our study population. Although we found no significant difference in outcomes between monotherapy and combination therapy groups, the small number of patients receiving combination therapy limits our ability to draw definitive conclusions about the relative efficacy of these approaches.

In summary, we have confirmed luspatercept's safety and efficacy in TD LR-MDS in the real-life setting. Response rates are higher in lower TD patients, suggesting that early treatment initiation of luspatercept may be beneficial in LR-MDS patients.

AUTHOR CONTRIBUTIONS

All authors performed the research and reviewed the manuscript. Anthi Bouchla and Vasiliki Pappa designed the research study and analysed the data. Anthi Bouchla and Sotirios G. Papageorgiou wrote the paper.

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SUPPORTING INFORMATION

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

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