RESEARCH LETTER

blood advances

TO THE EDITOR:

Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes

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Anemia is the clinical hallmark of myelodysplastic syndromes (MDS) where majority of patients present with anemia, and more than half of the patients become red blood cell transfusion–dependent (RBC-TD) during course of the disease.[1] Erythroid stimulating agents (ESA) are the mainstay of treating anemia in lower-risk MDS (LR-MDS), with 30% to 40% response rates being reported.[2] ESA response can be predicted based on endogenous serum erythropoietin (EPO) level and transfusion burden.[3] Luspatercept, a TGF-B fusion trap protein, is a first-in-class erythroid-maturating agent approved by the Food and Drug Administration for treatment of RBC-TD LR-MDS with ring sideroblasts (RS) based on red blood cell–transfusion independence (RBC-TI) in 38% of 153 patients in the MEDALIST study.[4] Luspatercept neutralizes TGF-B ligands which negatively regulates terminal erythroid maturation.[5] ESA promote early stages of erythropoiesis, whereas, luspatercept enhances terminal erythroid maturation; thus, the combination of ESA and luspatercept may have synergistic effect, which provides the study rationale of evaluating the response rate for this combination.[6] Notably, there are overall minimal adverse events in MDS patients with either therapy and no concern of overlapping toxicities. To date, there have been no data presented on the safety and efficacy of the combination. We report data on the activity of combining luspatercept with ESA in LR-MDS patients.

We treated a consecutive cohort of LR-MDS patients at Moffitt Cancer Center, with ESA and luspatercept combination, if no response (1° failure) or loss of response (2° failure) was observed to luspatercept monotherapy as add-back strategy or upfront combination. Baseline RBC transfusion burden (TB) was defined as nontransfusion dependent (NTD) (0 units in 8 weeks before luspatercept), low TB (LTB) (1-5 units every 8 weeks) and high TB (HTB) (≥6 units every 8 weeks). A hematological response (HI) was defined as (1) an objective hemoglobin (Hgb) increase of >1.5 g/dL in NTD, (2) RBC-TI with Hgb increase of 1.5 g/dL, or RBC-TI without Hgb 1.5 g/dL increase, or >50% reduction in RBC TB among RBC-TD. Luspatercept dose escalation and choice of ESA/dosing was at the discretion of the treating physician. The study was performed with institutional review board approval and according to the Declaration of Helsinki.

Between February 2020 and September 2021, 28 consecutive patients were treated with luspatercept and ESA combination after no response (1° failure) (n = 18) or loss of initial response to luspatercept monotherapy (2° failure) (n = 7) with 10.9 (2.4-19.8) months median duration of response to luspatercept monotherapy, or as initial exploratory combination treatment (n = 3). Table 1 summarizes baseline characteristics. The median age was 72 years and 53.5% (15 of 28) had MDS-RS subtype; 96.4% (27 of 28) were intermediate- or lower-risk MDS by the revised international prognostic scoring system (IPSS-R). *SF3B1* somatic mutation was detected in 24 patients (85.7%). The mean Hgb level was 8 g/dL and 43% (12 of 28) were RBC-HTB dependent. The median serum EPO level, available for 18 patients at time referral, was 119.5 U/L. About 25 patients (89%) had an initial ESA treatment (25). In majority of the patients the previous ESA administered was epoetin (21/25 patients) of whom 5

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Data are available on request from the corresponding author, Rami S. Komrokji (rami.komrokji@moffitt.org).

Table 1. Baseline characteristics

Baseline characteristics (n = 28)	% (n)
Age (median) (y)	72 (51-94)
Gender (male)	68 (19)
Race (White)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dL	8 (6.6-9.4)
Platelets (mean) × 10^9/L	259 (16-814)
ANC (mean) × 10^9/L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n = 18)
RBC TB	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Previous ESA treatment	89 (24)
Previous HMA treatment	42 (12)
Previous lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

ANC, absolute neutrophil count; MLD, multi-lineage dysplasia; MPN myeloproliferative neoplasm; SLD, single lineage dysplasia.

received 40 000 units weekly and 16 received 60 000 units weekly, for at least 8 weeks. Four patients received darbepoeitin with minimum 200 mcg every 2 weeks dosing regimen, for at least 8 weeks. The hematological response rate to previous ESA therapy was 21.4% (6/25 patients). Furthermore, 12 patients (43%) had previous hypomethylating agent (HMA) and 11 patients (39%) had previous lenalidomide (Len) treatment.

The concurrent ESA used in combination with luspatercept was epoetin used in 17 patients and darbepoetin in 11 patients. Epoetin concurrent dose was 60 000 units weekly and darbepoeitin dose was 500 mcg every 3 weeks, respectively. The majority of patients (27/28; 96%) had luspatercept dose escalation, whereby 23 patients received 1.33 mg/kg, 25 received 1.75 mg/kg, and only 1 patient did not receive any luspatercept dose escalation.

The overall HI rate to luspatercept combined with ESA was 36% (10/28 patients). Table 2 summarizes detailed responses. HI according to baseline RBC-TB were observed in 33% NTD patients (1/3), 38% LTB patients (5/13) and 25% HTB patients (4/12), respectively ($P = .75$). Five out of 7 patients (71%) who responded originally to luspatercept alone (2° failure) responded to ESA add-on, whereas only 3 out of 18 patients (17%) who did not respond to luspatercept monotherapy (1° failure), responded when ESA was added. Two out of 3 patients responded to the upfront ESA/luspatercept combination.

None of the ESA naïve patients (n = 4) responded to ESA add-on after luspatercept monotherapy failure, which assures the combination response was not a response to ESA alone. All responders to combination therapy were at the highest dose luspatercept, except for 1 patient, who was at dose level 2. Out of 6 patients who initially responded to ESA alone (2° ESA failure), 3 responded to ESA add-on after luspatercept failure. Out of 22 patients with no response to ESA originally (1° ESA failure), 6 responded when ESA was added back to luspatercept.

Among responders, the median duration of response to luspatercept and ESA combination therapy was 16.6 months (range, 5.2-31.3). As of last follow-up, 15 patients (54%) discontinued treatment. Reason of discontinuation was lack of response in 12 patients and loss of response in 3 patients.

No response to combination ESA/luspatercept was observed among *SF3B1* wild-type patients (n = 4, 100%). Baseline serum EPO levels were available for 18 patients at the time of referral. None of the patients with serum EPO >500 U/L responded to addition of ESA; whereas, 25% of the patients (2/8) with serum EPO 200 to 500 U/L and 40% of the patients (4/10) with serum EPO <200 U/L, responded to addition of ESA.

There was a trend of higher response among HMA and Len naïve patients. The HI rate was 25% (3/12) after HMA failure, compared

Table 2. Detailed response rate

	% (n)
Overall response (n = 28)	**36 (10)**
Hgb increase >1.5 g/dL in NTD or Hgb increase >1.5 g/dL with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dL increase	14 (4/28)
>50% reduction in RBC-TB	4 (1/28)
Response in NTD (n = 3)	
Hgb increase >1.5 g/dL	33 (1/3)
Response in LTB (n = 13)	**38 (5/13)**
Hgb increase >1.5 g/dL and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dL increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n = 12)	**33 (4/12)**
Hgb increase >1.5 g/dL and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dL increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

with 44% (7/16) in HMA naïve patients ($P = .3$). However, after HMA failure, more patients (8/12; 67%) were RBC HTB, compared with 25% (4/16) in HMA naïve patients ($P = .05$). The HI rate was 18% (2/11 patients) for Len failure compared with 47% (8/17) Len naïve patients ($P = .1$). No difference in HTB was observed among Len naïve and Len-treated patients.

Our study represents a consecutive cohort of patients treated with combination of luspatercept and ESA. The limitations include small sample size, its exploratory nature, and dosing of luspatercept/ESA was based on physician choice. We did not collect detailed data on adverse events; however, no thromboembolic events or toxicity were reported previously with either drug alone.

To our knowledge, this is the first proof of principle data confirming clinical activity combining luspatercept and ESA. Predictors of response included previous response to luspatercept monotherapy, endogenous serum EPO levels <500 U/L, *SF3B1* mutation, lower RBC TB and being HMA/Len treatment naïve. These findings should guide future planned-combination studies, which are needed to confirm the benefit of this combination.

Contribution: R.S.K. and D.A.S. designed the study, wrote the manuscript, and contributed patients to the study; L.E.A. and N.H.A.A. collected data and conducted the analysis; and all other authors contributed patients to the study and reviewed and approved the final manuscript.

Conflict-of-interest disclosure: R.S.K. reported honoraria, membership on an entity's board of directors or advisory committees, and is a member of speaker's bureau for CTI BioPharma; honoraria and membership on an entity's board of directors or advisory committees from Taiho, Bristol Myers Squibb (BMS), Novartis, AbbVie, and Geron; and honoraria and is a member of speaker's bureau for PharmaEssentia, Servio, and Jazz. A.K. reported consultancy, honoraria, and is a member of the speaker's bureau PharmaEssentia, Imago Biosciences, Incyte, Blueprint, Novartis, AbbVie, and CTI BioPharma; consultancy, honoraria, research support, and is a member of speaker's bureau for GSK, Sierra Oncology and BMS; and research support from Prelude Pharmaceuticals, Morphosys, and Protagonist. K.S. reported consultancy, honoraria, and membership on an entity's board of directors or advisory committees for Gilead Sciences, Inc., Astellas, Curis, BMS, BerGenBio, Mablytics, AROG, and Novartis; consultancy, membership on an entity's board of directors or advisory committees, and research funding from Curis; and research funding from Incyte, Syntrix Pharmaceuticals, and Celgene/BMS. J.E.L. reported consultancy for Novartis, Boxer Capital, and Dava Oncology; and consultancy for Dedham Group, Jasper Therapeutics, Astellas, Agios/Servio, Jazz, BerGenBio, Millenium Pharma/Takeda, ElevateBio Management, Daiichi Sankyo, AbbVie, and Servier. E.P. reported research funding from BMS, Kura, Incyte, and Syntrix Pharmaceuticals and honoraria from Stemline. D.A.S. reported membership on an entity's board of directors or advisory committees for Syndax, Nemucore, AbbVie, Agios Kite, Shattuk Labs, and Intellia; is a member of speaker's bureau for Incyte; research funding from Syntrix Pharmaceuticals; consultancy and membership on an entity's board of directors or advisory committees for Novartis; consultancy for Magenta; membership on an entity's board of directors or advisory committees and is a member of speakers bureau for BMS; membership on an entity's board of directors or advisory committees and research funding from Aprea; consultancy for Takeda; and patents and royalties (LB-100) from Lixte. The remaining authors declare no competing financial interests.

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References

1. Volpe VO, Garcia-Manero G, Komrokji RS. Myelodysplastic syndromes: a new decade. *Clin Lymphoma Myeloma Leuk*. 2022;22(1):1-16.
2. Park S, Greenberg P, Yucel A, et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. *Br J Haematol*. 2019;184(2):134-160.
3. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol*. 2003;120(6):1037-1046.
4. 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.
5. Komrokji RS. Activin receptor II ligand traps: new treatment paradigm for low-risk MDS. *Curr Hematol Malig Rep*. 2019;14(4):346-351.
6. Verma A, Suragani RNVS, Aluri S, et al. Biological basis for efficacy of activin receptor ligand traps in myelodysplastic syndromes. *J Clin Invest*. 2020;130(2):582-589.