Luspatercept restores effective erythropoiesis and provides superior and sustained clinical benefit versus epoetin alfa: biomarker analysis from the phase 3 COMMANDS study

MDS-071

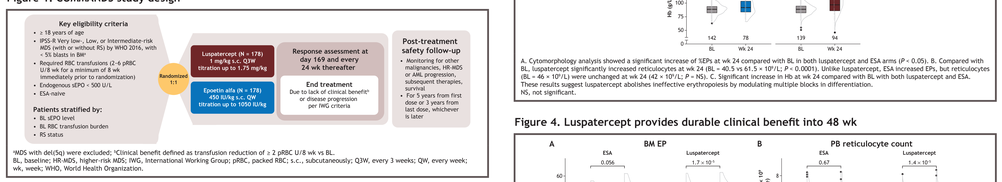
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Introduction

- Myelodysplasic syndromes (MDS) are a heterogeneous group of clonal hematopoietic neoplasms characterized by ineffective erythropoiesis
- MDS is characterized by cytopenia(s), the most frequent being anemia which 80% of patients experience, and bone marrow (BM) dysplasia (> 10% in ≥ 1 cell lineage)[1]
- The global annual incidence rate of MDS has been estimated as 0.06-0.26 per 100,000 persons[2]
- Progressive anemia is the most common complication of lower-risk MDS (LR-MDS; ~ 80% of cases) which eventually leads to a requirement of red blood cell (RBC) transfusions[3]
- Complications related to blood transfusions and inflammation negatively affect quality of life and increase the mortality rate in patients with LR-MDS
- ~30% of patients with LR-MDS progress to acute myeloid leukemia (AML)[4]
- Luspatercept is a novel receptor fusion protein consisting of a modified extracellular domain of human activin receptor type IIB (ActRIIB) linked to a human immunoglobulin G1 (IgG1) Fc domain
- Luspatercept binds several transforming growth factor beta (TGFB) superfamily ligands (activin B, growth differentiation factor [GDF] 11, GDF8, bone morphogenetic protein [BMP] 6, and BMP10) resulting in enhanced late-stage erythroid maturation[5]
- Luspatercept is approved in the US for the treatment of anemia in adult patients with Β-thalassemia who require regular RBC transfusions, and in erythropoiesis-stimulating agent (ESA)-naive patients with anemia due to LR-MDS, or with MDS/myeloproliferative neoplasm with ring sideroblasts (RS) and thrombocytosis, based on the results from the BELIEVE and MEDALIST phase 3 trials[6,7]
- ESAs are the standard of care in LR-MDS with symptomatic anemia
- ESAs increase BM erythropoiesis by increasing the percentage of BM erythroid precursor (EP) production, and by activating JAK-STAT, phosphoinositide 3-kinase (PI_3K), and MAPK-PKC signaling pathways
- ESA efficacy and duration of response is limited in patients with LR-MDS, with only a third responding with a response duration of 6-18 months
- Studies suggest a lower probability of response to ESAs (< 10%) in patients with high RBC transfusion burden and serum erythropoietin (sEPO) levels of > 500 U/mL, and in those with ≥ 2 mutated genes[1]
- ESAs promote proliferation of EPs, whereas luspatercept enhances late-stage EP maturation
- The COMMANDS study (NCT03682536) is a global, phase 3, open-label, randomized trial comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R-defined LR-MDS in ESA-naive patients who require RBC transfusions (**Figure 1**)

Figure 1. COMMANDS study design



[a]MDS with del(5q) were excluded; [b]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC U/8 wk vs BL.
BL, baseline; HR-MDS, higher-risk MDS; IWG, International Working Group; pRBC, packed RBC; s.c., subcutaneously; Q3W, every 3 weeks; QW, every week; wk, week; WHO, World Health Organization.

- The COMMANDS study met its primary endpoint of RBC-transfusion independence (TI) ≥ 12 wk and concurrent mean hemoglobin (Hb) increase ≥ 1.5 g/dL during wk 1-24, significantly in favor of luspatercept versus epoetin alfa, herein referred to as "ESA" (58.5% vs 31.2%; $P < 0.0001$)

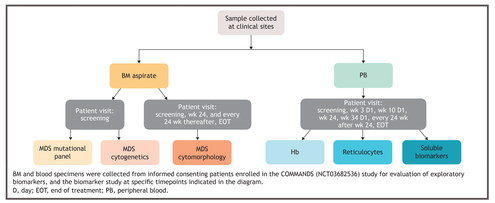
Objective

- To differentiate the mechanism of action (MOA) of luspatercept from ESAs and determine its correlation with clinical benefit

Methods

- Cytomorphology assessments were performed on BM aspirates at BL, wk 24, and wk 48 (**Figure 2**)
- Complete blood count, Hb, and reticulocytes were measured in PB
- BM mononuclear cells (BMMC) at BL and wk 24 were subjected to bulk RNA sequencing (RNA-Seq)
- Serum levels of erythroferrone (ERFE), GDF11, GDF15, and hepcidin were measured by ELISA at BL and wk 24
- All statistical analyses were conducted using the R statistical platform version 4.0.5, 2021-03-31
- The ggplot2 (v.3.3.3) package was used for data visualization
- Distribution of continuous variables between 2 subgroups were compared using the Wilcoxon rank-sum test

Figure 2. Sample collection during the COMMANDS study

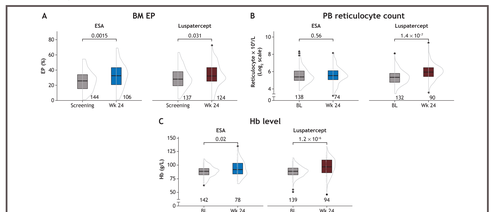


BM and blood specimens were collected from informed consenting patients enrolled in the COMMANDS (NCT03682536) study for evaluation of exploratory biomarkers, and the biomarker study at specific timepoints indicated in the diagram.
D, day; EOT, end of treatment; PB, peripheral blood.

Results

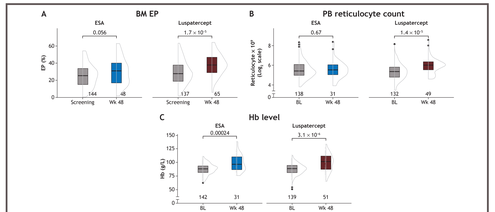
- There was gradual and sustained increase in BM EP, PB reticulocytes, and Hb with luspatercept (**Figures 3 and 4**)

Figure 3. Luspatercept restores ineffective erythropoiesis and provides superior clinical benefit compared with ESA



A. Cytomorphology analysis showed a significant increase of %EPs at wk 24 compared with BL in both luspatercept and ESA arms ($P < 0.05$). B. Compared with BL, luspatercept significantly increased reticulocytes at wk 24 (BL ~ 40.5 vs 61.5 × 10^9/L; $P < 0.0001$). Unlike luspatercept, ESA increased EPs, but reticulocytes (BL ~ 46 × 10^9/L) were unchanged at wk 24 (42 × 10^9/L; $P = NS$). C. Significant increase in Hb at wk 24 compared with BL with both luspatercept and ESA. These results suggest luspatercept abolishes ineffective erythropoiesis by modulating multiple blocks in differentiation.
NS, not significant.

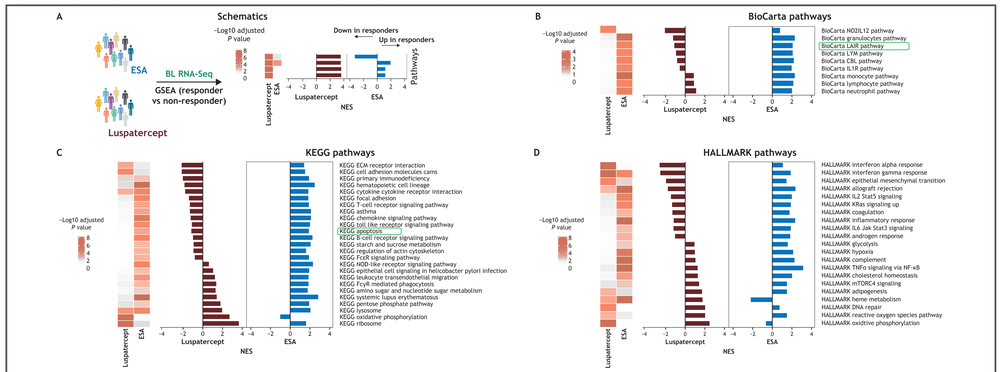
Figure 4. Luspatercept provides durable clinical benefit into 48 wk



A. A significant increase of %EPs at wk 48 compared with BL only with luspatercept ($P < 0.001$). B. Luspatercept significantly increased reticulocytes at wk 48 compared with BL (BL ~ 40.5 vs 63×10^9/L; $P < 0.0001$). C. Significant increase in Hb at wk 48 with both luspatercept and ESA. These results suggest durable hematologic improvement-erythroid with luspatercept.

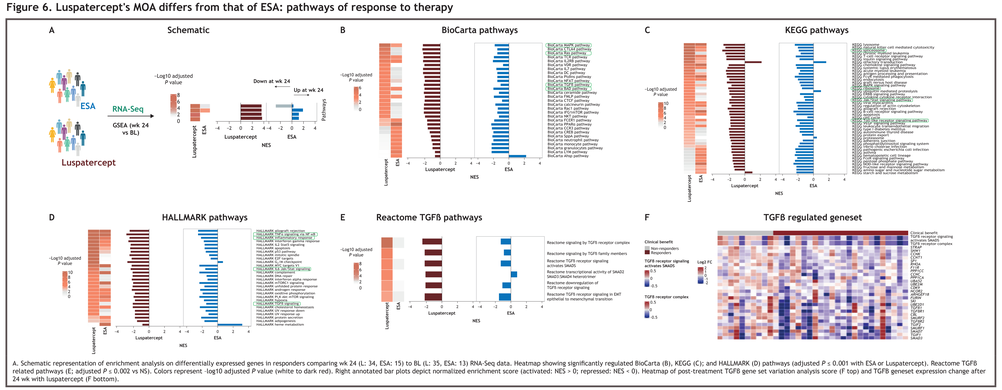
- Treatment-specific and non-specific pathways as predictors of erythroid response, luspatercept suppresses TGFB-associated pathways (**Figures 5 and 6**)
- GSEA of BM EP genes is favorably predictive of response to luspatercept, with the opposite trend for ESA treatment (**Figure 7**)[8,9]

Figure 5. Luspatercept's MOA differs from that of ESA: predictive pathways of clinical benefit



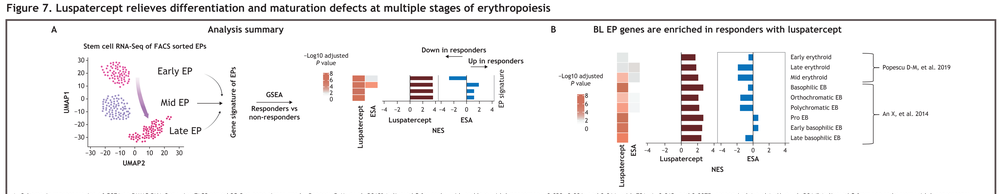
A. Schematic representation of GSEA based on BL BMMC differentially expressed genes comparison of responders (L: 35, ESA: 13) to non-responders (L: 22, ESA: 31). Heatmaps depict significantly regulated BioCarta (B), KEGG (C); and HALLMARK (D) pathways (adjusted $P \leq 0.005$ with ESA or luspatercept). Colors represent −log10 adjusted P value (white to dark orange). Right annotated bar plots show normalized enrichment score (activated in responders: NES > 0; NES < 0 repressed in responders). ECM, extracellular matrix; GSEA, gene set enrichment analysis; L, luspatercept; NES, normalized enrichment score.

Figure 6. Luspatercept's MOA differs from that of ESA: pathways of response to therapy



A. Schematic representation of enrichment analysis on differentially expressed genes in responders comparing wk 24 (L: 34, ESA: 15) to BL (L: 35, ESA: 13) RNA-Seq data. Heatmap showing significantly regulated BioCarta (B), KEGG (C); and HALLMARK (D) pathways (adjusted $P \leq 0.001$ with ESA or Luspatercept). Reactome TGFB related pathways (E; adjusted $P \leq 0.002$ vs NS). Colors represent −log10 adjusted P value (white to dark red). Right annotated bar plots depict normalized enrichment score (activated: NES > 0; repressed: NES < 0). Heatmap of post-treatment TGFB gene set variation analysis score (F top) and TGFB geneset expression change after 24 wk with luspatercept (F bottom).

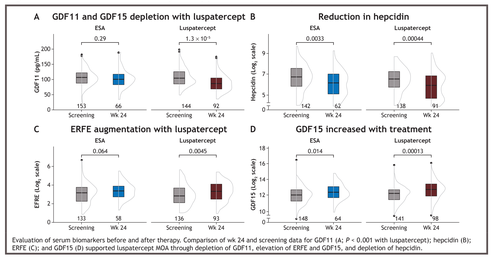
Figure 7. Luspatercept relieves differentiation and maturation defects at multiple stages of erythropoiesis



A. Schematic representation of GSEA on BMMC RNA-Seq using FACS sorted SC Seq gene signatures by Popescu D-M, et al. 2019[8] (adjusted P for early, mid, and late with luspatercept: 0.023, 0.001, and 0.011; with ESA: 1, 0.012, and 0.0075, respectively) and An X, et al. 2014[9] (adjusted P from top to bottom with luspatercept: < 0.001, < 0.001, < 0.001, 0.0014, and 0.00028; with ESA: 1, 0.99, 0.88, 0.16, and 0.13, respectively) B. Favorable predictability of BL early, mid, and late EPs with luspatercept and unfavorable trend with enrichment of mid and late EPs with ESA. FACS, fluorescence-activated cell sorting.

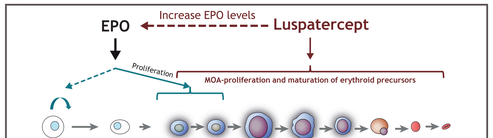
- A decrease in serum GDF11 with luspatercept indicated the treatment's pharmacokinetics (**Figure 8**)
- Serum ERFE increased (median 7.2, 10.1 ng/mL; $P < 0.05$; vs median 9.1, 10.4 ng/mL; NS) as did GDF15 levels (median 5.0, 7.0 ng/mL vs median 4.5, 5.4 ng/mL; $P < 0.05$), further suggesting expansion of EPs
- The reduction of serum hepcidin is a potential indicator of efficient iron redistribution

Figure 8. Serum biomarker analysis supports luspatercept MOA



Evaluation of serum biomarkers before and after therapy. Comparison of wk 24 and screening data for GDF11 (A; $P < 0.001$ with luspatercept); hepcidin (B); ERFE (C); and GDF15 (D) supported luspatercept MOA through depletion of GDF11, elevation of ERFE and GDF15, and depletion of hepcidin.

Figure 9. Proposed MOA of luspatercept in LR-MDS



Schematic representation of proposed MOA of luspatercept. EPO leads to proliferation and terminal differentiation of erythroid precursors in the early phases of erythropoiesis. However, EPO does not relieve maturation defects present at various stages of erythropoiesis. In contrast, luspatercept leads to durable expansion and maturation of erythroid precursors leading to significant increase in reticulocytes. Moreover, luspatercept acts at multiple stages of erythropoiesis, including early, mid, and late stages, to relieve erythroid maturation defects.
Baso E, basophilic erythroblast; BFU-E, burst forming unit erythroid; CFU-E, colony forming unit-erythroid; CFU-E-GEMM, CFU-E granulocyte, erythrocyte, monocyte, megakaryocyte; EPO, erythropoietin; Ortho E, orthochromatophilic erythroblast; Poly E, polychromatophilic erythroblast; Pro E, proerythroblast; retic, reticulocytes.

Conclusions

- Compared with ESA, luspatercept treatment led to more significant increases of EPs and reticulocytes at wk 24 suggesting restoration of ineffective erythropoiesis
- Compared with ESA, changes in EPs and reticulocytes were significant and sustained to wk 48
- Luspatercept treatment has a differential effect leading to expansion and maturation of EPs to provide sustained clinical benefit (**Figure 9**)
- Luspatercept acts on multiple erythroid stages, including early-, mid-, and late-stage EPs to relieve erythroid maturation defects
- These findings underscore novel insights into the mechanistic differentiation of luspatercept versus ESAs and the luspatercept-dependent, durable expansion and maturation of EPs that leads to sustained RBC-TI in patients with LR-MDS

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