Abstract: P763

Title: LUSPATERCEPT IMPROVES HEMATOPOIESIS IN LOWER-RISK MYELODYSPLASTIC SYNDROMES (MDS): COMPARATIVE BIOMARKER ANALYSIS OF RING SIDEROBLAST-POSITIVE AND -NEGATIVE SUBGROUPS FROM THE PHASE 3 COMMANDS STUDY

Abstract Type: Poster Presentation

Topic: Myelodysplastic syndromes - Biology & translational research

Background:

MDS are characterized by ineffective hematopoiesis and commonly anemia, often requiring regular RBC transfusions. Luspatercept was superior to epoetin alfa (an erythropoiesis-stimulating agent [ESA]) in RBC transfusion independence (RBC-TI; hemoglobin [Hb] increase 60.4% vs 34.8%; *P*<0.0001) in patients (pts) with lower-risk (LR) MDS in the phase 3 COMMANDS trial (NCT03682536; Garcia-Manero G, et al. *Blood* 2023;142[Suppl 1]:193).

Aims:

To analyze biomarkers in luspatercept and ESA responders by ring sideroblast (RS) status in COMMANDS.

Methods:

The primary endpoint was RBC-TI for ≥12 wk with a concurrent mean Hb increase ≥1.5 g/dL (wk 1–24). Complete blood counts, targeted genomics, bone marrow mononuclear cell (BMMC) RNA-sequencing, and serum cytokine analyses were previously described (Hayati S, et al. *Blood* 2023;142[Suppl 1]:1845). BMMC proteomic analysis was done using liquid chromatography-tandem mass spectrometry.

Results:

At baseline (BL), 320/350 pts had ≥1 somatic gene mutations (11 pts missing data); the most common in RS+ vs RS− pts were *SF3B1* (82% vs 5%), *TET2* (38% vs 26%), *ASXL1* (19% vs 29%), *DNMT3A* (16% vs 18%), *U2AF1* (7% vs 22%), *SRSF2* (7% vs 16%), and *EZH2* (7% vs 5%). Most mutations had a variant allelic frequency (VAF) of 3–50%; higher VAFs were observed in RS+ vs RS− pts for *SF3B1*, *TET2*, *DNMT3A,* and *U2AF1* (*P*<0.05). Primary endpoint response rates were superior with luspatercept vs ESA when stratified by mutation type (risk difference [RD] 0.25 [95% CI 0.15–0.35]), VAF >10% (RD 0.36 [95% CI 0.28–0.44]), and IPSS-M risk groups (RD 0.26 [95% CI 0.14–0.37]). This superiority was also observed in RS+ pts. Only comparable responses rates were seen in RS− pts in both treatment arms, probably in part due to more luspatercept pts with a higher mutation burden vs ESA pts (median 2 mutations vs 1; *P*=0.08). Despite this, longer RBC-TI duration was seen with luspatercept vs ESA both in RS+ and RS− pts, respectively. Luspatercept-treated pts showed improvements at wk 24 and 48 not only in Hb (*P*<0.001), but also total leukocyte (*P*<0.05), neutrophil (*P*<0.05), and lymphocyte (*P*<0.05) counts. Platelets and monocytes remained unchanged (Fig. A). Compared with BL, BMMC transcriptomics at wk 24 showed downregulated inflammatory, apoptosis, TGFβ signaling, and mRNA splicing pathways in luspatercept-treated pts. Parallel BMMC proteomic analysis confirmed downregulation of inflammatory (LAIR, IL6, IL2, IL20, IFNγ), apoptosis, and epithelial-to-mesenchymal transition pathways, and upregulation of protein translation, nonsense-mediated decay, and oxidative phosphorylation pathways (*P*<0.05) with luspatercept (Fig. B). Consistently, luspatercept-treated pts had reductions in serum inflammation biomarkers. Importantly, reduced N-terminal pro-brain natriuretic peptide (NT-proBNP, a biomarker of cardiac stress), at wk 24 vs BL (*P*<0.05) was noted with luspatercept but not with ESA; NT-proBNP decreases were seen in primary endpoint responders irrespective of RS status (*P*<0.05) (Fig. C).

Summary/Conclusion:

Along with positive effects on erythropoiesis, luspatercept improved overall hematopoiesis and decreased

inflammatory biomarkers. The primary responses were favorable to luspatercept and agnostic to RS status by mutational type, VAF cutoff, IPSS-M classification, and longer duration of response. Such improvements were not observed in ESA-treated pts. These results indicate broader positive effects of luspatercept on hematopoiesis, while reducing inflammation and cardiac damage, in part due to its inhibitory action on SMAD2/3 signaling in LR-MDS.

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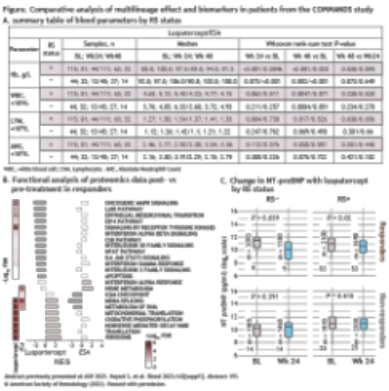

Keywords: Hematopoiesis, Bone marrow microenvironment, Myelodysplastic syndrome