



# The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

### 636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

#### Luspatercept Modulates Inflammation in the Bone Marrow, Restores Effective Erythropoiesis/Hematopoiesis, and Provides Sustained Clinical Benefit Versus Epoetin Alfa (EA): Biomarker Analysis from the Phase 3 COMMANDS Study

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**Introduction:** Anemia is common in patients (pts) with myelodysplastic syndromes (MDS) due to ineffective erythropoiesis, characterized by increased dysplastic erythroid precursors (EPs) and abortive differentiation in the bone marrow (BM). Insufficient red blood cells (RBCs) lead to chronic anemia and heart failure due to oxygen deprivation. Luspatercept is approved to treat anemia after erythropoiesis-stimulating agent (ESA) failure in pts with transfusion-dependent, lower-risk MDS (LR-MDS). In the phase 3 COMMANDS trial (NCT03682536), 58.5% of ESA-naïve luspatercept treated pts with LR-MDS experienced RBC transfusion independence for  $\geq 12$  wk with concurrent mean hemoglobin (Hb) increase  $\geq 1.5$  g/dL during wk 1-24, vs 31.2% of EA-treated pts.

**Aims:** To differentiate the mechanism of action of luspatercept from EA and determine its correlation with clinical benefit in the COMMANDS study.

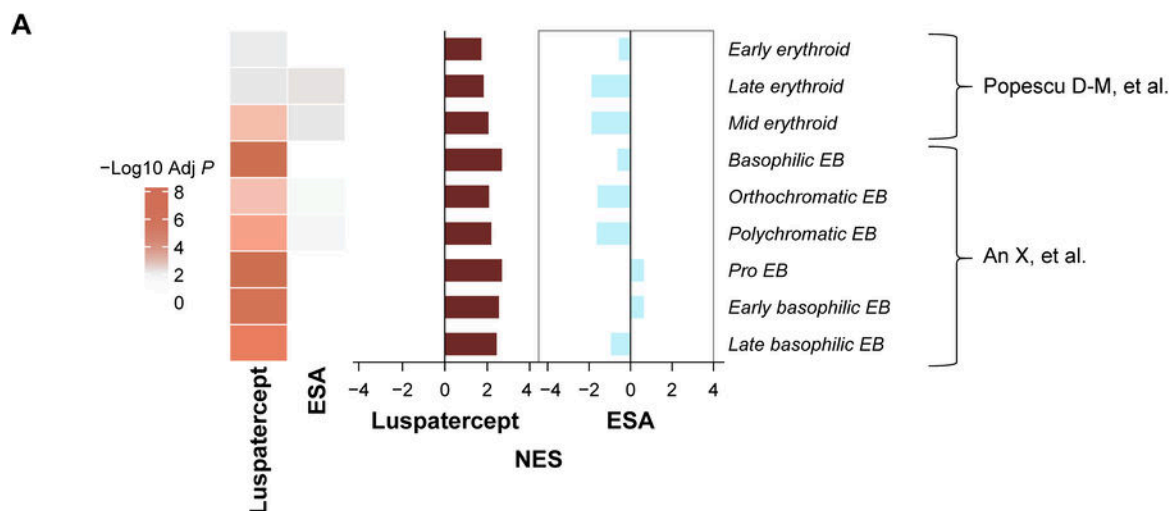
**Methods:** Cytomorphology assessments were performed on BM aspirates at baseline, wk 24 and 48. Complete blood count, Hb, and reticulocytes (retics) were measured in peripheral blood. BM mononuclear cells (BMMC) were subjected to bulk RNA-seq. Serum cytokine analysis was performed at screening and wk 24 using Rules-Based Medicine's Human Inflammation MAP ® v.1.1 and a custom Human MAP ELISA panel.

**Results:** In ITT population, EPs, retics, and Hb were increased vs baseline in the luspatercept arm at wk 24 ( $P < 0.001$ ) and wk 48 ( $P < 0.005$ ). EPs, retics, and Hb were increased in the EA arm at wk 24 ( $P < 0.01$ ), but this was not sustained to wk 48. Subgroup analysis showed similar trends for ring sideroblast (RS)+ pts in both arms. While RS– pts in the EA arm showed similar trends to the ITT population, luspatercept RS– pts showed trends of EP expansion post-wk 24 only. Retics increased significantly in RS– luspatercept pts at wk 24 ( $P < 0.005$ ). Hb increased more significantly at wk 24 with EA ( $P < 0.003$ ) but at wk 48 with luspatercept ( $P < 0.005$ ). Gene set enrichment analysis of BMMC revealed enrichment of early, mid, and late EP genes at baseline favored response to luspatercept, but enrichment of mid and late EP genes was unfavorable for EA (Figure A). Significant downregulation of REACTOME IL-1 signaling (normalized enrichment score [NES] =  $-2.27$ ; adjusted [Adj]  $P < 0.0001$  [vs EA = not significant (ns)]), BIOCARTE IL-6 pathway (NES =  $-1.99$ ; Adj  $P = 0.0025$  [vs EA = ns]) and IFN $\alpha$  response (NES:  $-2.26$ ; Adj  $P < 0.0001$  [vs EA = ns]) was observed with luspatercept. BIOCARTE IL-1R pathway was more significantly reduced with luspatercept (NES =  $-1.78$ ; Adj  $P = 0.0073$ ) compared with EA (NES =  $-1.79$ ; Adj  $P = 0.0172$ ), as was IL-10 signaling (luspatercept NES =  $-2.39$ ; Adj  $P < 0.001$  vs EA NES =  $-1.82$ ; Adj  $P = 0.0125$ ). TGF- $\beta$ , apoptosis, and spliceosome pathways down regulation was also observed with luspatercept. At wk 24, luspatercept responders had a median 640 pg/mL decrease ( $P = 0.0035$ ) of N-terminal pro-brain natriuretic peptide (NT-proBNP), produced by the heart, compared with a

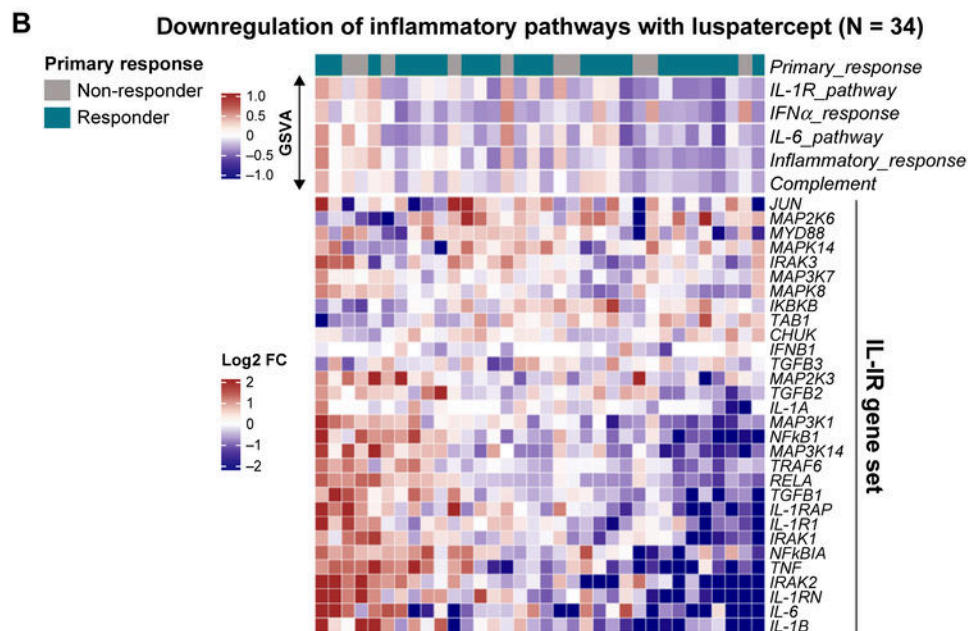
median 360 pg/mL decrease in EA arm responders ( $P = 0.37$ ). At wk 24, non-responders had a median increase of 775 pg/mL ( $P = 0.0032$ ) in the EA arm and 31.5 pg/mL ( $P = 0.95$ ) in the luspatercept arm.

**Conclusions:** Multiplatform analysis of primary BM samples from a phase 3 trial of luspatercept revealed novel response-associated biomarkers. Compared with EA, luspatercept led to sustained increase of EPs and retics over 48 wk with a concomitant Hb increase. RS— pts showed Hb accumulation peaked at wk 24 in the EA arm. Conversely, luspatercept in RS— pts significantly increased retics at wk 24 and EPs past wk 24 with concomitant peaking of Hb at wk 48, suggesting gradual and sustained clinical benefit. Unlike EA, which plays a role in early differentiation of hematopoietic stem cells (HSCs), luspatercept acts on different erythroid stages, leading to EP expansion and maturation. Furthermore, downregulation of IL-1, IL-1R, IFN $\alpha$ , IL-6 pro-inflammatory (Figure B), and IL-10 anti-inflammatory signaling with luspatercept suggests modulation of the BM inflammatory environment in MDS to restore HSC function for normal hematopoiesis (Wang J, et al. *Front Immunol* 2022;13:951937). Additionally, decreased or static levels of NT-proBNP with luspatercept suggest a positive effect in mitigating cardiac damage. These novel insights obtained from analysis of a large controlled clinical trial mechanistically differentiate the superior clinical benefit of luspatercept from EA in treating anemia due to MDS.

**Disclosures Hayati:** Bristol Myers Squibb: Current Employment, Current equity holder in publicly-traded company. **Zeidan:** Celgene/BMS: Consultancy, Honoraria; Servier: Consultancy, Honoraria; Foran: Consultancy, Research Funding; Gilead: Consultancy, Honoraria; ALX Oncology: Consultancy, Honoraria; Novartis: Consultancy, Honoraria; Daiichi Sankyo: Consultancy, Honoraria; Shattuck Labs: Research Funding; Otsuka: Consultancy, Honoraria; Geron: Consultancy, Honoraria; Kura: Consultancy, Honoraria; Taiho: Consultancy, Honoraria; Agios: Consultancy, Honoraria; Tyme: Consultancy, Honoraria; Regeneron: Consultancy, Honoraria; Syndax: Consultancy, Honoraria; Incyte: Consultancy, Honoraria; Jazz: Consultancy, Honoraria; Notable: Consultancy, Honoraria; Epizyme: Consultancy, Honoraria; Boehringer-Ingelheim: Consultancy, Honoraria; BioCryst: Consultancy, Honoraria; Mendus: Consultancy, Honoraria; Astex: Research Funding; Amgen: Consultancy, Honoraria; Chiesi: Consultancy, Honoraria; Genentech: Consultancy, Honoraria; BeyondSpring: Consultancy, Honoraria; Seattle Genetics: Consultancy, Honoraria; Schrödinger: Consultancy, Honoraria; Astellas: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; Zentalis: Consultancy, Honoraria; Takeda: Consultancy, Honoraria; Ionis: Consultancy, Honoraria; Pfizer: Consultancy, Honoraria; Orum: Consultancy, Honoraria; AbbVie: Consultancy, Honoraria; Syros: Consultancy, Honoraria; Lox Oncology: Consultancy, Honoraria. **Garcia-Manero:** AbbVie: Research Funding; Genentech: Research Funding; Bristol Myers Squibb: Other: Medical writing support, Research Funding. **Platzbecker:** Servier: Consultancy, Honoraria, Research Funding; Syros: Consultancy, Honoraria, Research Funding; Amgen: Consultancy, Research Funding; Jazz: Consultancy, Honoraria, Research Funding; Merck: Research Funding; Curis: Consultancy, Research Funding; Novartis: Consultancy, Honoraria, Research Funding; Bristol Myers Squibb: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; Silence Therapeutics: Consultancy, Honoraria, Research Funding; Takeda: Consultancy, Honoraria, Research Funding; MDS Foundation: Membership on an entity's Board of Directors or advisory committees; Roche: Research Funding; Celgene: Honoraria; AbbVie: Consultancy; Fibrogen: Research Funding; Janssen Biotech: Consultancy, Research Funding; Geron: Consultancy, Research Funding; BeiGene: Research Funding; BMS: Research Funding. **Verma:** Curis: Research Funding; GSK: Research Funding; Incyte: Research Funding; Medpacto: Research Funding; Eli Lilly: Research Funding; Novartis: Consultancy; Acceleron: Consultancy; Throws Exception: Current equity holder in private company; Celgene: Consultancy; Janssen: Honoraria; Prelude: Research Funding; Bakx: Consultancy, Current equity holder in private company; Stelexis: Consultancy, Current equity holder in private company, Honoraria; Bristol Myers Squibb: Research Funding. **Guerrero:** Bristol Myers Squibb: Current Employment. **Gandhi:** Bristol Myers Squibb: Current Employment, Current equity holder in publicly-traded company. **Suragani:** Bristol Myers Squibb: Current Employment, Current equity holder in publicly-traded company. **Vodala:** Bristol Myers Squibb: Current Employment; Mabgenex: Membership on an entity's Board of Directors or advisory committees.



Gene signatures reported by Popescu D-M, et al. (*Nature* 2019;574:365–371), and An X, et al. (*Blood* 2014; 22:3466–3477). For Popescu DM et al., the adjusted *P* value for early, mid, and late erythroid with luspatercept was: 0.023, 0.001, and 0.011, respectively; and with ESA was: 1, 0.012, and 0.0075, respectively. For An X et al., the Adj *P* value from top to bottom with luspatercept was: < 0.001, < 0.001, 0.0014, and 0.00028, respectively; and with ESA was: 1, 0.99, 0.88, 0.16, and 0.13, respectively.



Heatmap shows IL-1R gene set expression FC on log<sub>2</sub> scale. Top annotations represent: a) primary response b) GSVA scores of inflammatory-related pathways at wk 24 for 34 patients with paired baseline and wk 24 RNA-Seq data from bone marrow mononuclear cells. Red indicates upregulation and blue represents downregulation of genes and pathways.

Adj *P*, adjusted *P* value; CHUK, conserved helix-loop-helix ubiquitous kinase; EB, erythroblast; ESA, erythropoiesis-stimulating agent; FACS, fluorescence-activated cell sorting; FC, fold change; GSVA, gene set variation analysis; IFN, interferon; IKBKB, inhibitor of NF $\kappa$ B kinase subunit beta; IL, interleukin; IL1RAP, IL-1 receptor accessory protein; IRAK, IL-1 receptor-associated kinase; MAPK, mitogen activated protein kinase; MAP2K, mitogen activated protein kinase 2; MAP3K, mitogen activated protein kinase 3; MYD88, myeloid differentiation primary response 88; NES, normalized enrichment score; NF $\kappa$ B, nuclear factor kappa B; NF $\kappa$ BIA, NF $\kappa$ B inhibitor alpha; R, receptor; RELA, RELA proto-oncogene NF $\kappa$ B subunit; Seq, sequencing; TAB, TGF $\beta$  activated kinase 1; TGF $\beta$ , transforming growth factor beta; TNF, tumor necrosis factor; TRAF, TNF receptor associated factor; wk, week.

**Figure 1**

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