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637.MYELODYSPLASTIC SYNDROMES-CLINICAL STUDIES | NOVEMBER 5, 2020

The Commands Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in Erythropoiesis Stimulating Agent-Naive Patients Who Require RBC Transfusions

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Introduction: Anemia is the predominant cytopenia observed in patients with myelodysplastic syndromes (MDS), with many patients requiring regular red blood cell (RBC) transfusions.

Erythropoiesis-stimulating agents (ESAs) remain a standard of care among patients with lower-risk MDS (LR-MDS), defined by International Prognostic Scoring System-Revised (IPSS-R) as Very Low-, Low-, or Intermediate-risk MDS, and endogenous serum erythropoietin (sEPO) levels ≤ 500 U/L. Recent studies of epoetin alfa and darbepoetin alfa have demonstrated efficacy among patients with LR-MDS, but the patient population in whom a clinically significant effect is seen may be limited (Fenaux P, et al. *Leukemia* 2018;32:2648-2658; Platzbecker U, et al. *Leukemia* 2017;31:1944-1950). A novel therapeutic option that increases the frequency of response and the duration of RBC transfusion independence (TI) in patients with LR-MDS would provide an important clinical benefit in this patient population.

Luspatercept is a first-in-class erythroid maturation agent with a mechanism of action distinct from ESAs (Suragani RNVS, et al. *Nat Med* 2014;20:408-414). It is now approved in both the US and EU for patients

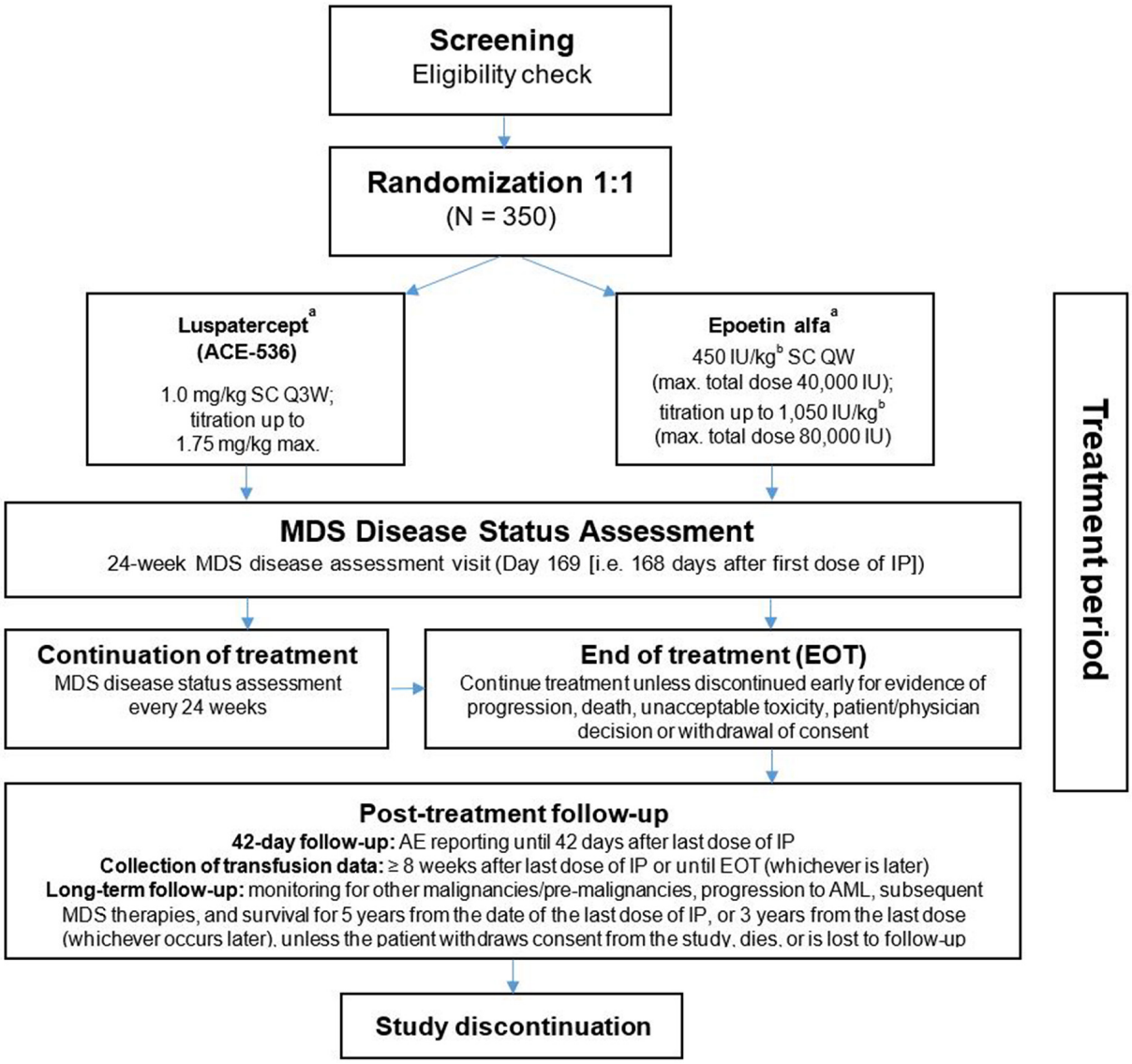
with LR-MDS with ring sideroblasts (RS) who require RBC transfusions and are refractory, intolerant, or ineligible to receive ESAs on the basis of results from a phase 3 study (Fenaux P, Platzbecker U, et al. *N Engl J Med* 2020;382:140-151). Luspatercept may also be beneficial in treating anemia in patients with ESA-naive, LR-MDS who require RBC transfusions. In a phase 2 study in anemic patients with LR-MDS, 63% of patients receiving luspatercept (0.75-1.75 mg/kg) achieved a modified hematologic improvement - erythroid (mHI-E) response (Platzbecker U, et al. *Lancet Oncol* 2017;18:1338-1347); when analyzed by RS status, 69% of patients with ≥ 15% RS and 43% of patients with < 15% RS achieved mHI-E response.

Study Design and Methods: The COMMANDS trial is a phase 3, open-label randomized study to compare the efficacy and safety of luspatercept versus epoetin alfa in anemic patients with IPSS-R defined LR-MDS, either with or without ≥ 15% RS, who are ESA naive, and who require regular RBC transfusions. Eligible patients must be aged ≥ 18 years at time of consent, have a documented diagnosis of IPSS-R defined LR-MDS with < 5% blasts in the bone marrow, have sEPO levels < 500 U/L, and require RBC transfusions (defined as an average transfusion requirement of 2-6 RBC units/8 weeks for ≥ 8 weeks immediately prior to randomization). Exclusion criteria include prior use of ESAs (≤ 2 doses of prior epoetin alfa permitted if ≥ 8 weeks from randomization date and sEPO confirmed as ≤ 500 U/L), granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), unless given for the treatment of febrile neutropenia; disease-modifying agents (e.g. lenalidomide), or hypomethylating agents; and presence of del(5q) cytogenetic abnormality.

A total of approximately 350 eligible patients will be randomized in a 1:1 ratio to receive either luspatercept (starting dose 1.0 mg/kg with titration up to 1.75 mg/kg) subcutaneously (SC) once every 3 weeks or epoetin alfa (starting dose 450 IU/kg with titration up to 1,050 IU/kg) SC once every week, for a minimum of 24 weeks (Figure). Best supportive care, including RBC transfusions, may be used in combination with study treatment in both arms. Randomization will be stratified by baseline RBC transfusion burden (< 4 vs ≥ 4 RBC units per 8 weeks), RS status (with RS+ defined as RS ≥ 15%, or ≥ 5% [but < 15%] if *SF3B1* mutation is present), and baseline sEPO level (≤ 200 U/L versus > 200 U/L). In addition, ≥ 40% and ≤ 60% of randomized patients will be RS+, and ≥ 25% will have sEPO > 200 U/L. The primary endpoint is the proportion of patients who achieve RBC-TI for 12 weeks within the first 24 weeks on study, with a concurrent mean hemoglobin (Hb) increase of ≥ 1.5 g/dL compared with baseline. Key secondary endpoints include duration of RBC-TI, change in Hb levels, achievement of HI-E response

per International Working Group (IWG) 2006 criteria, and safety. The COMMANDS trial is registered at ClinicalTrials.gov (NCT03682536) and EudraCT (number 2017-003190-34).

Figure. COMMANDS study design.



Disclosures

Platzbecker: *Takeda:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Geron:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Amgen:* Honoraria, Research Funding; *BMS:* Consultancy, Honoraria. **Santini:** *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Johnson & Johnson:* Honoraria; *Acceleron:* Consultancy; *Takeda:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Menarini:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *Takeda:*

Membership on an entity's Board of Directors or advisory committees. **Garcia-Manero:** *Celgene:* Consultancy, Honoraria, Research Funding; *Genentech:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Acceleron Pharmaceuticals:* Consultancy, Honoraria; *H3 Biomedicine:* Research Funding; *AbbVie:* Honoraria, Research Funding; *Helsinn Therapeutics:* Consultancy, Honoraria, Research Funding; *Amphivena Therapeutics:* Research Funding; *Astex Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Novartis:* Research Funding; *Jazz Pharmaceuticals:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Onconova:* Research Funding; *Merck:* Research Funding. **Komrokji:** *Geron:* Honoraria; *Novartis:* Honoraria; *Incyte:* Honoraria; *JAZZ:* Honoraria, Speakers Bureau; *AbbVie:* Honoraria; *Agios:* Honoraria, Speakers Bureau; *Acceleron:* Honoraria; *BMS:* Honoraria, Speakers Bureau. **Ito:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Fenaux:** *BMS:* Honoraria, Research Funding; *Jazz:* Honoraria, Research Funding; *Novartis:* Honoraria, Research Funding; *Abbvie:* Honoraria, Research Funding.

Author notes

* Asterisk with author names denotes non-ASH members.