Exploring REBLOZYL: A Breakthrough Therapy for Anemia in MDS

1. **New indication**

The FDA approved REBLOZYL for the treatment of anemia without previous erythropoiesis-stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

2. **NCCN update**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend luspatercept-aamt (REBLOZYL®) as a first-line treatment option for symptomatic anemia in lower-risk MDS*

3. **COMMANDS study**

Link to Lancet publication:  
Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial - The Lancet

**Background**

Erythropoiesis-stimulating agents (ESAs) have been the standard-of-care treatment for anemia in most patients with lower-risk myelodysplastic syndromes but responses are limited and transient. Luspatercept promotes late-stage erythroid maturation and has shown durable clinical efficacy in patients with lower-risk myelodysplastic syndromes. In this study, we report the results of a prespecified interim analysis of luspatercept versus epoetin alfa for the treatment of anemia due to lower-risk myelodysplastic syndromes in the phase 3 COMMANDS trial.

**Study Design**

COMMANDS is a global phase 3, open-label, randomized controlled trial.

- Eligible patients were aged 18 years or older with a diagnosis of myelodysplastic syndromes with very low, low, or intermediate risk per the Revised International Prognostic Scoring System (IPSS-R)
- Patients were ESA-naïve and required 2–6 packed red blood cell (RBC) units per 8 weeks for ≥8 weeks immediately before randomization.
- Patients on both the luspatercept and epoetin alfa arms were stratified by
  - baseline RBC transfusion burden: <4 RBC units/8 weeks vs ≥4 units/8 weeks
  - endogenous serum erythropoietin concentration: ≤200 U/L vs >200 to <500 U/L
  - ring sideroblast status: positive vs negative

**Study Endpoints**

- The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL (weeks 1–24), assessed in the intention-to-treat population.
- Safety was assessed in patients who received at least one dose of study treatment. The COMMANDS trial was registered with ClinicalTrials.gov, NCT03682536 (active, not recruiting).

**Drug Administration**
Luspatercept was administered subcutaneously once every 3 weeks starting at 1.0 mg/kg body weight with possible titration up to 1.75 mg/kg.

Epoetin alfa was administered subcutaneously once a week starting at 450 IU/kg body weight with possible titration up to 1050 IU/kg (maximum permitted total dose of 80 000 IU).

### Study Findings

- The interim efficacy analysis was done for 301 patients (147 in the luspatercept group and 154 in the epoetin alfa group) who completed 24 weeks of treatment or discontinued earlier.
- Median treatment exposure for patients receiving luspatercept was 42 weeks (IQR 20–73) versus 27 weeks for the patients receiving epoetin alfa (IQR 19–55).
- 59% (86/147) of the patients in the luspatercept arm achieved the primary endpoint vs 31% (48/154) of the patients in the epoetin alfa arm (p<0.0001).

Images are from the COMMANDS Oral Presentation at ASCO**

- Duration of transfusion independence of >12 weeks was 127 weeks in the luspatercept arm vs 77 weeks in the epoetin alfa arm with a hazard ratio of 0.456 (0.260 - 0.798)
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- Safety: The most common suspected treatment-related adverse events in the luspatercept group (≥3% patients, with the most common event occurring in 5% patients) were fatigue, asthenia, nausea, dyspnea, hypertension, and headache; and none (≥3% patients) in the epoetin alfa group.
Interpretation
In this interim analysis, luspatercept was superior to epoetin alfa with a longer duration of response. Luspatercept improved the rate at which red blood cell transfusion independence and increased hemoglobin were achieved compared with epoetin alfa in ESA-naive patients with lower-risk myelodysplastic syndromes. Long-term follow-up and additional data will be needed to confirm these results and further refine findings in other subgroups of patients with lower-risk myelodysplastic syndromes, including non-mutated SF3B1 or ring sideroblast-negative subgroups. The full COMMANDS analysis will be presented at ASH 2023 in San Diego.

- **Podcast**: A podcast hosted by Blood Cancers Today to discuss recent clinical updates in lower-risk MDS data with Dr. Garcia Manero, Professor of Medicine, Department of Leukemia at MD Anderson.
- **Short video (Komrokji)**: A short video by Blood Cancers Today featuring Dr. Komrokji, Vice Chair of Malignant Hematology at Moffitt Cancer Center, to discuss recent clinical updates in lower-risk MDS.
- **Short video (Garcia Manero)**: A short video by Blood Cancers Today featuring Dr. Garcia Manero, Professor of Medicine, Department of Leukemia at MD Anderson, to discuss recent clinical updates in lower-risk MDS.

Footnotes:
*For patients with IPSS-R very low-, low-, or intermediate-risk MDS non-del(5q) +/- other cytogenetic abnormalities. For patients with RS <15% (or RS <5% with an SF3B1 mutation), this recommendation is only for those with sEPO ≤ 500 MU/mL.

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