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-naive 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).

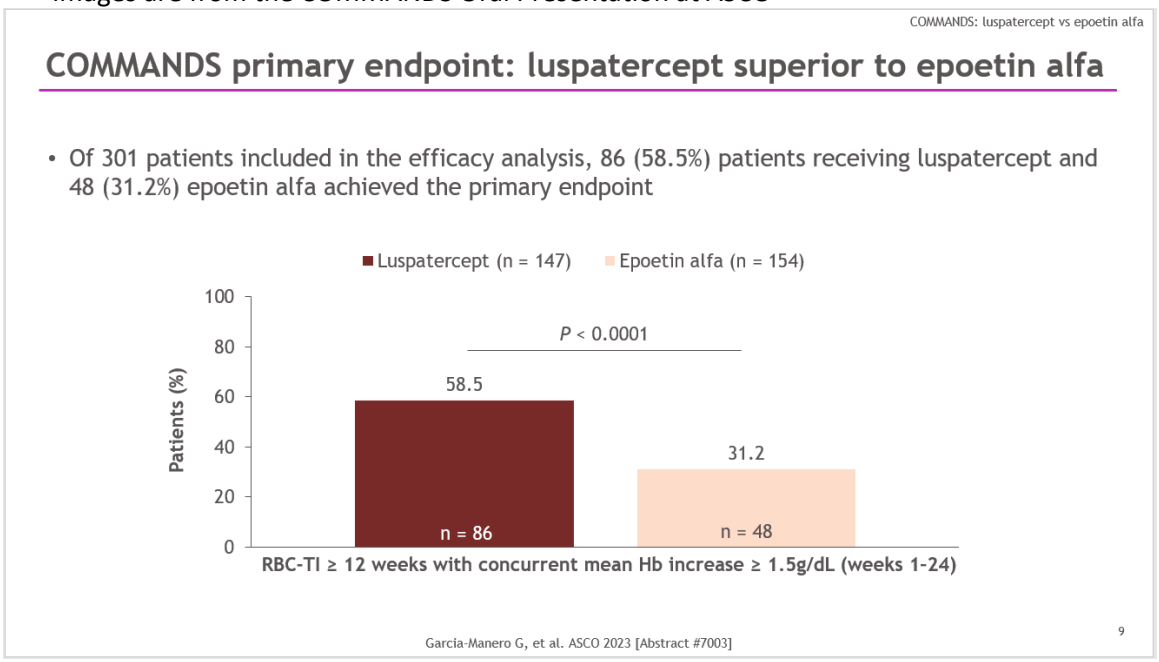
Drug Administration

- 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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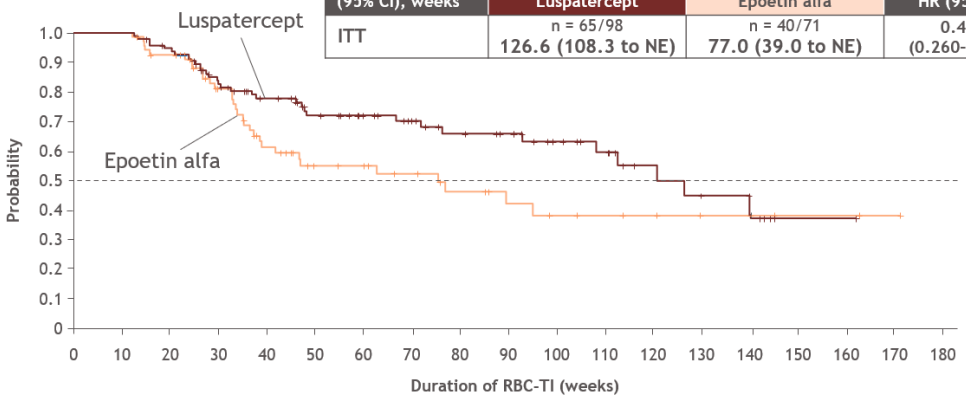
COMMANDS: luspatercept vs epoetin alfa

RBC-TI ≥ 12 weeks in luspatercept and epoetin alfa patients

Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
ITT	n = 65/98 126.6 (108.3 to NE)	n = 40/71 77.0 (39.0 to NE)	0.456 (0.260-0.798)



No. at risk

Luspatercept	98	98	91	74	61	49	42	37	31	28	21	17	11	8	6	1	1	0
Epoetin alfa	71	71	63	47	33	24	23	19	15	11	9	8	7	5	5	2	2	1	0

CI, confidence interval; NE, not estimable.
During week 1-EOT.

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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.

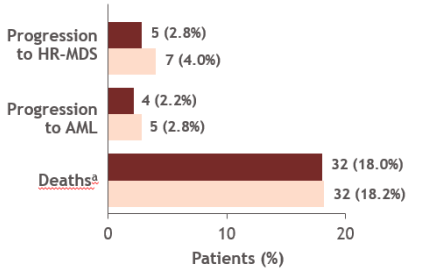
COMMANDS: luspatercept vs epoetin alfa

COMMANDS: safety

Patients, n (%)	Luspatercept (n = 178)		Epoetin alfa (n = 176)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

TEAEs of any grade
164 (92.1%) luspatercept
150 (85.2%) epoetin alfa

Treatment duration, median (range), weeks
41.6 (0-165) luspatercept
27.0 (0-171) epoetin alfa



Safety data are not exposure-adjusted.
[a]Deaths during treatment period and post-treatment period.

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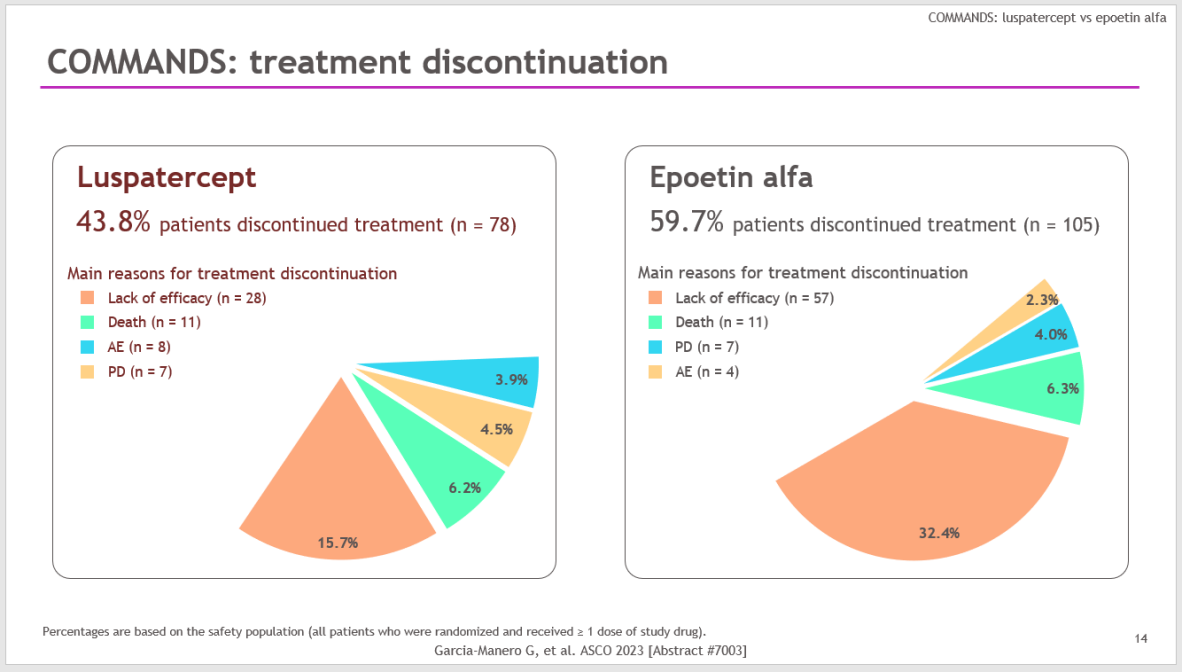

Interpretation

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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