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Zeidan AM et al. ASH 2025 [Abstract 789]

Clinical benefit of luspatercept in erythropoiesis-stimulating agent-naive patients with early disease characteristics and very low-, low-, or intermediate-risk myelodysplastic syndromes: a post-hoc analysis from the COMMANDS trial

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ASH 2025, Abstract 792

Background and objective

- Luspatercept demonstrated superiority over epoetin alfa in the phase 3 COMMANDS trial (NCT03682536) in ESA-naive TD patients with LR-MDS[1]
  - In this study, luspatercept offered durable clinical benefit, with higher rates of RBC-TI versus epoetin alfa[1,2]
  - These results supported its approval as first-line treatment for anemia in adults with LR-MDS who may require RBC transfusions and are ESA-naive[3]
- In LR-MDS, patient disease characteristics can help predict response and define the optimal time to initiate therapy[4,5]
  - Higher Hb, lower sEPO, and lower TB are characteristics that may identify patients with less advanced LR-MDS and a higher likelihood of treatment responsiveness[6-8]
  - Recognizing characteristics of disease may help identify patients most likely to benefit from treatment

Objective: to evaluate treatment outcomes with luspatercept and epoetin alfa in patients with less advanced versus more advanced disease characteristics

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; RBC-TI, red blood cell-transfusion independence; sEPO, serum erythropoietin; TB, transfusion burden; TD, transfusion-dependent.

1. Della Porta MG et al. *Lancet Hematol*. 2024;11:e646–e658. 2. Garcia-Manero G et al. *Adv Ther*. 2025;42:3576-3589. 3. Reblozyl® (luspatercept-aamt). Package insert. Bristol Myers Squibb; May 2024. 4. Park S et al. *Leuk Res*. 2010;34:1430-1436. 5. Greenberg PL et al. *Blood*. 2012;120:2454-2465. 6. Jabbour E et al. *Clin Lymphoma Myeloma Leuk*. 2013;13:131-138. 7. Park S et al. *Ann Hematol*. 2020;99:7-19. 8. Boccia R et al. *J Clin Med*. 2024;13:2702.

Study design

COMMANDS (NCT03682536) is a global, phase 3, open-label, randomized controlled trial[1]

Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low-, or intermediate-risk MDS (with or without RS) by WHO 2016 classification, with < 5% BM blasts[a]
- Required RBC transfusions (2–6 pRBC U/8 weeks, minimum of 8 weeks prior to randomization)
- ESA-naive
- Endogenous sEPO < 500 U/L

R 1:1

Luspatercept
1.0 mg/kg SC Q3W
titration up to 1.75 mg/kg
(n = 182)

Epoetin alfa[b]
450 IU/kg SC QW
titration up to 1050 IU/kg
(n = 181)

Response assessments at Day 169 and then every 24 weeks thereafter

End of treatment

- Due to lack of clinical benefit[c] or disease progression per IWG 2006 criteria

Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, and survival for 5 years from first dose

Primary endpoint

- RBC-TI for ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (Weeks 1-24)

Select secondary endpoints

- RBC-TI for ≥ 12 weeks (Weeks 1-24)
- Duration of RBC-TI ≥ 12 weeks (Week 1-EOT)
- OS
- Progression to AML
- Safety

Post-hoc efficacy outcomes (data cutoff: February 7, 2025)

- RBC-TI ≥ 12 weeks (Week 1-EOT)
- Duration of RBC-TI ≥ 12 weeks (Week 1-EOT)
- HI-E[d] (Week 1-EOT)

Outcomes stratified by baseline Hb (≥ 8 and < 8 g/dL), sEPO (≤ 100, > 100 to ≤ 200, and > 200 U/L), and TB (= 2 and ≥ 4 pRBC U/8 weeks)

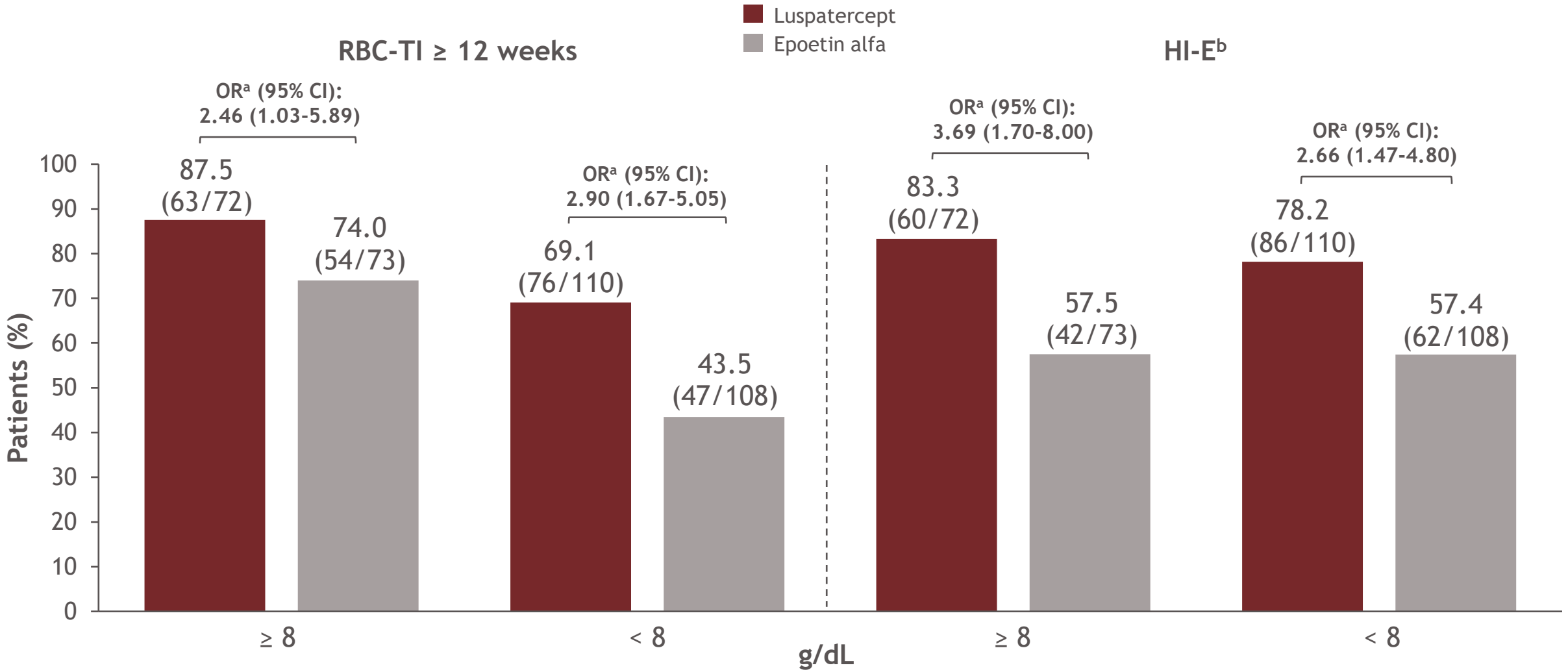
AML, acute myeloid leukemia; BM, bone marrow; EOT, end of treatment; HI-E, hematologic improvement-erythroid; HR-MDS, higher-risk myelodysplastic syndromes; IPSS-R, International Prognostic Scoring System-Revised; IU, international units; IWG, International Working Group; MDS, myelodysplastic syndromes; OS, overall survival; pRBC, packed red blood cell; Q3W, every 3 weeks; QW, once weekly; R, randomized; RS, ring sideroblast; SC, subcutaneously; U, units; WHO, World Health Organization.

[a]Patients with del(5q) were excluded. [b]Two patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose. [c]Clinical benefit was defined as transfusion reduction of ≥ 2 pRBC U/8 weeks versus baseline. [d]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 pRBC U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 pRBC U/8 weeks.

1. Della Porta MG et al. *Lancet Hematol*. 2024;11:e646-e658.

Santini V et al. ASH 2025 [Abstract 792]

Achievement of RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline Hb



Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1–65) months for luspatercept and 28.8 (0–69) months for epoetin alfa.
OR, odds ratio.
[a]OR is based on an unstratified Cochran–Mantel–Haenszel test. [b]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 U/8 weeks.

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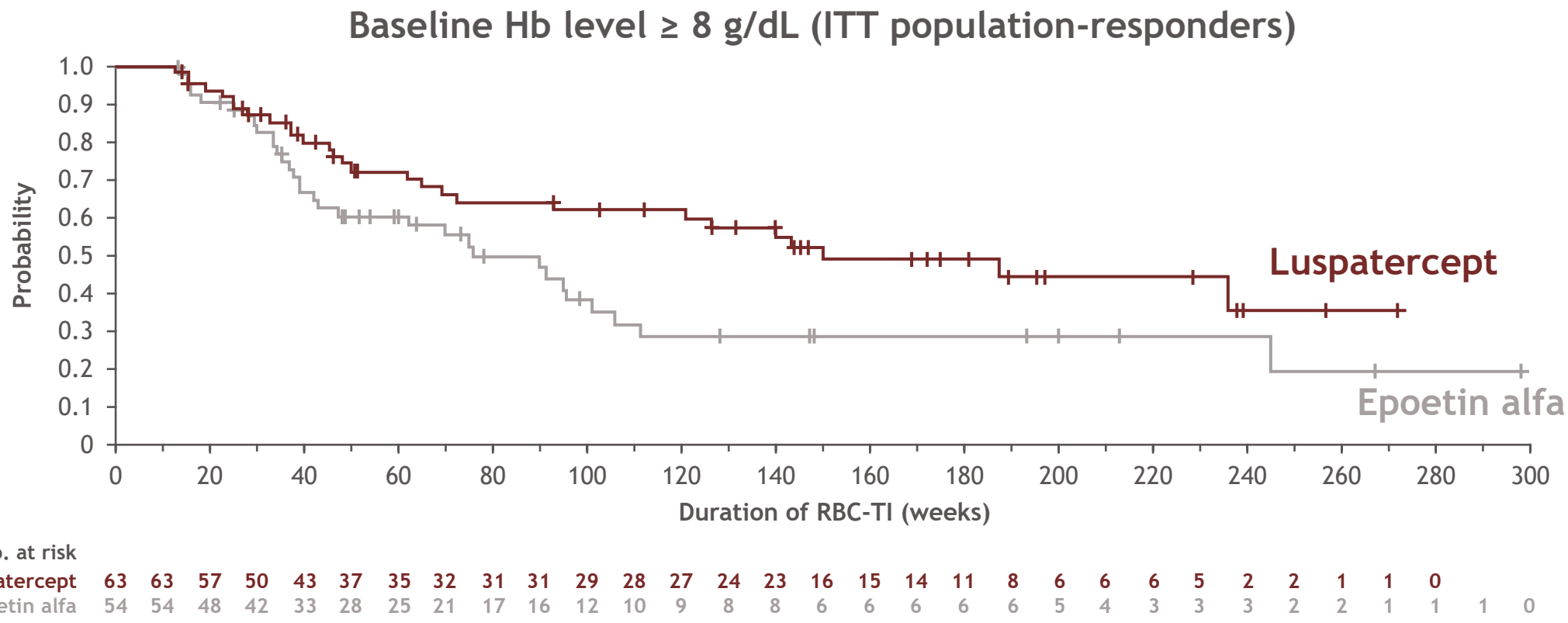
Duration of RBC-TI ≥ 12 weeks (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline Hb



Median (95% CI) duration,[a] weeks	Luspatercept	Epoetin alfa	HR[b] (95% CI)
Hb, g/dL			
≥ 8	150.0 (72.0-NE)	75.6 (41.9-101.1)	0.600 (0.359-1.002)
< 8	108.3 (53.7-132.6)	86.7 (37.3-186.1)	1.042 (0.636-1.706)

Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
ITT, intent-to-treat; NE, not estimable.
[a]Median is from an unstratified Kaplan-Meier method. [b]HR is calculated by an unstratified Cox proportional hazard model.

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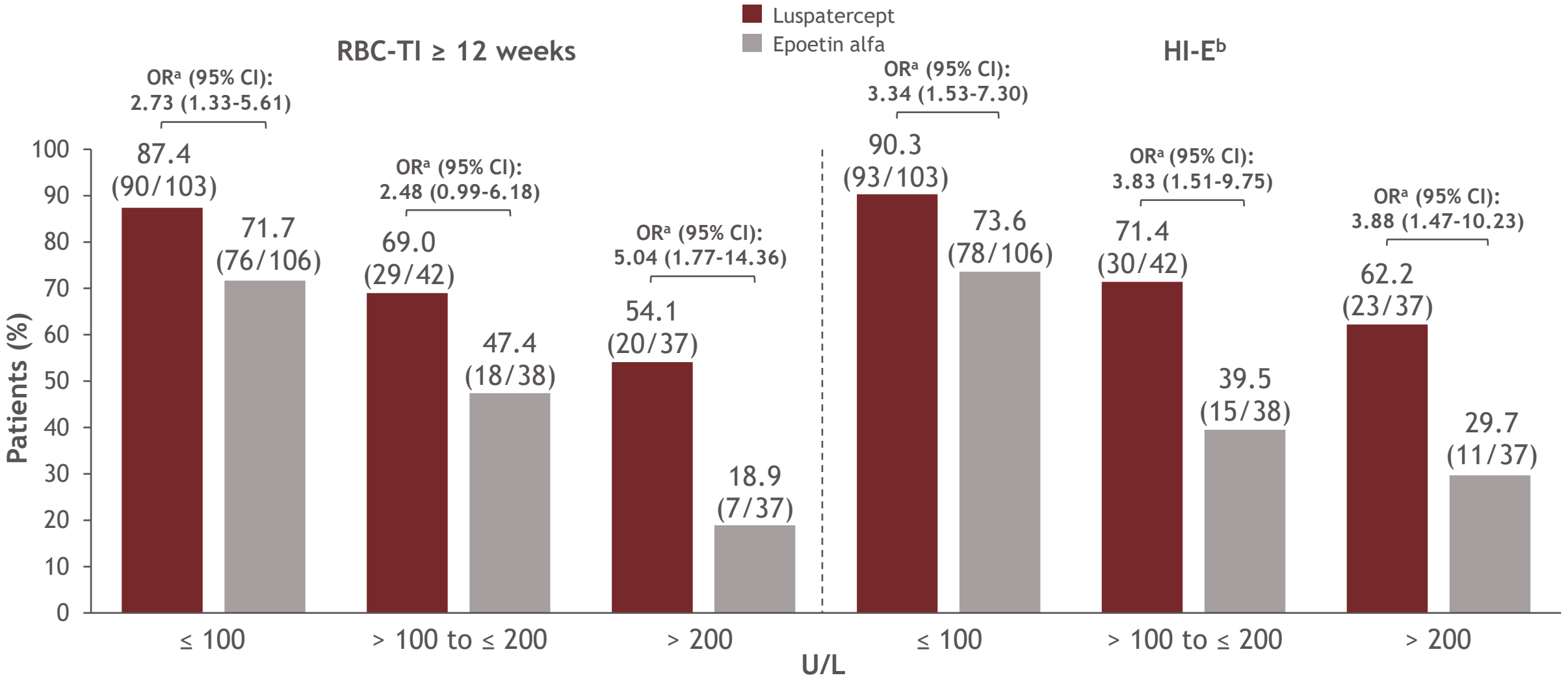
Achievement of RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline sEPO



Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1–65) months for luspatercept and 28.8 (0–69) months for epoetin alfa.
[a]OR is based on an unstratified Cochran–Mantel–Haenszel test. [b]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 U/8 weeks.

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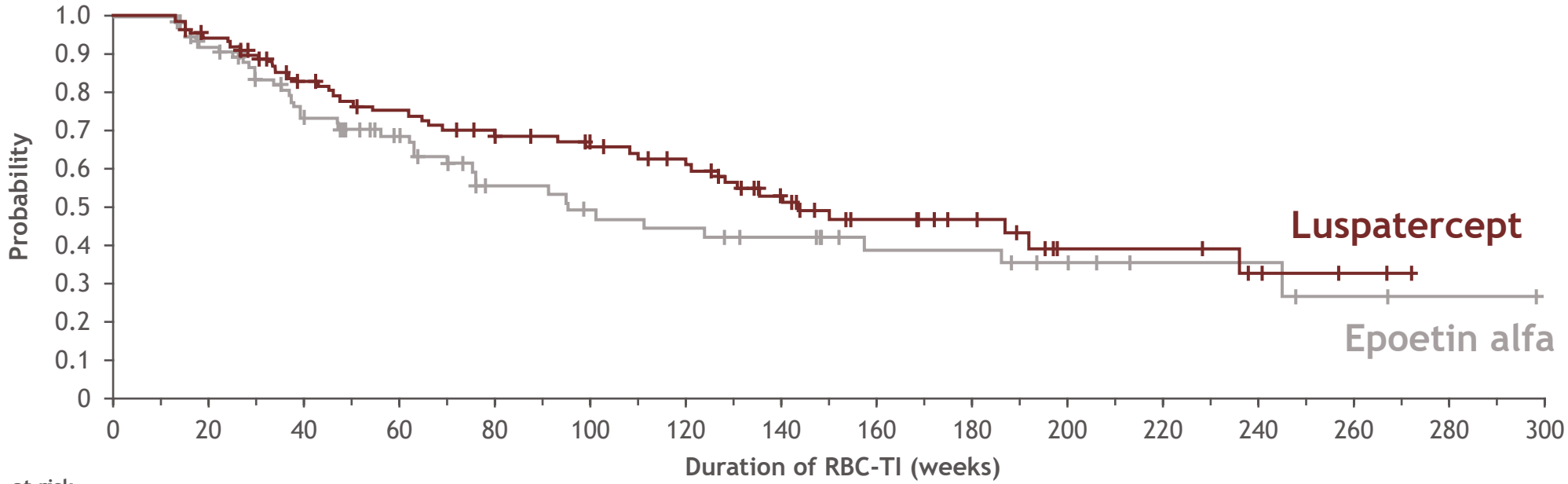
Duration of RBC-TI ≥ 12 weeks (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline sEPO

Baseline sEPO ≤ 100 U/L (ITT population-responders)



No. at risk

Luspatercept	90	90	83	77	67	61	58	54	51	49	45	43	40	34	29	21	18	16	14	11	7	7	7	6	4	3	2	1	0
Epoetin alfa	76	76	67	58	50	44	39	32	26	26	21	20	19	16	15	13	11	11	11	9	8	6	4	4	4	2	2	1	1	1	0

Median (95% CI) duration,[a] weeks	Luspatercept	Epoetin alfa	HR[b] (95% CI)
sEPO, U/L			
≤ 100	143.3 (120.1-235.9)	95.1 (69.7-186.1)	0.753 (0.484-1.171)
> 100 to ≤ 200	66.9 (31.1-154.1)	33.1 (26.9-89.7)	0.512 (0.246-1.067)
> 200	48.3 (26.3-132.6)	24.6 (14.9-NE)	0.848 (0.300-2.394)

Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Median is from an unstratified Kaplan-Meier method. [b]HR is calculated by an unstratified Cox proportional hazard model.

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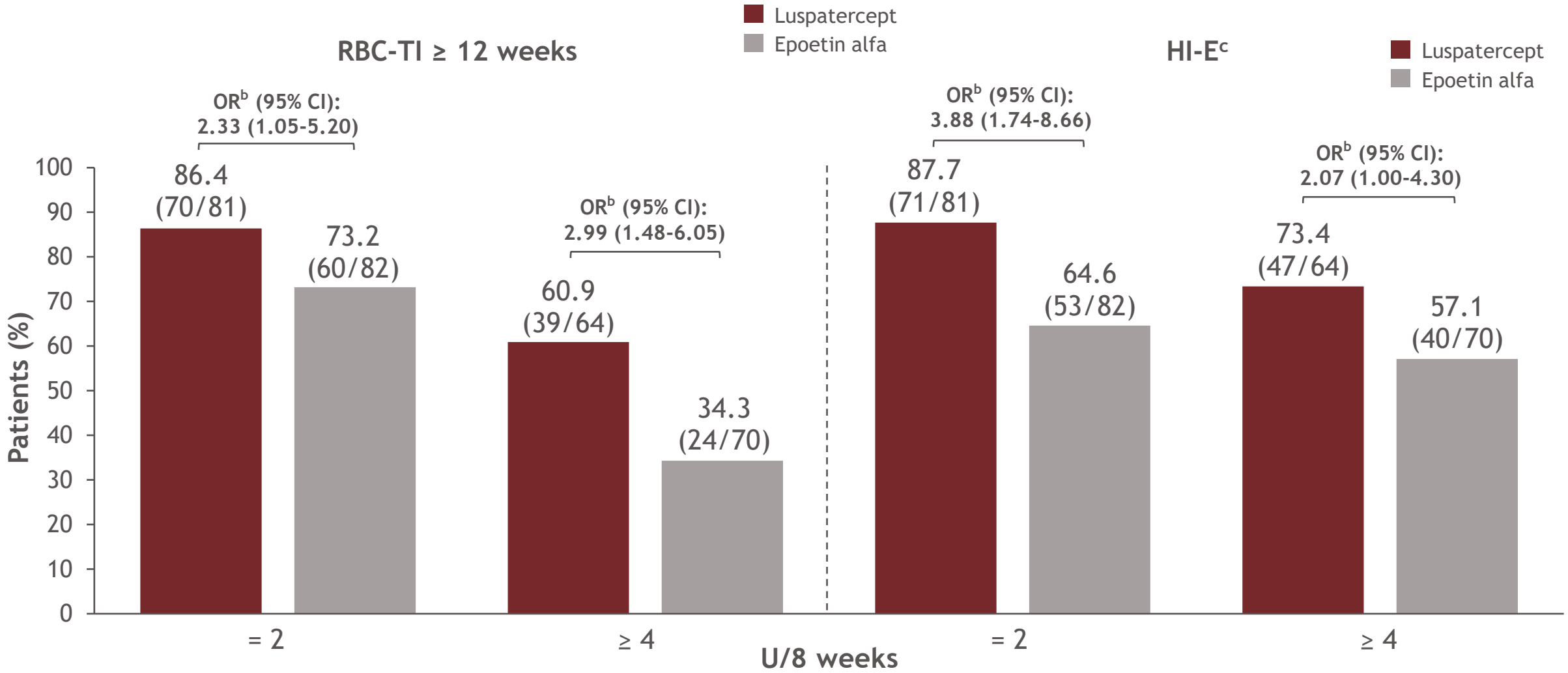
Achievement of RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline TB[a]



Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1–65) months for luspatercept and 28.8 (0–69) months for epoetin alfa.
[a]RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) for TB < 4 U/8 weeks were 84.7% (100/118) and 83.9% (99/118) for luspatercept, and 69.4% (77/111) and 57.7% (64/111) for epoetin alfa, respectively. In this subgroup, 32 luspatercept patients and 25 epoetin alfa patients had TB = 3 U/8 weeks; 5 luspatercept patients and 3 epoetin alfa patients had TB = 1 U/8 weeks; and 1 epoetin alfa patient had a TB = 0 U/8 weeks. [b]OR is based on an unstratified Cochran–Mantel–Haenszel test. [c]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 U/8 weeks.

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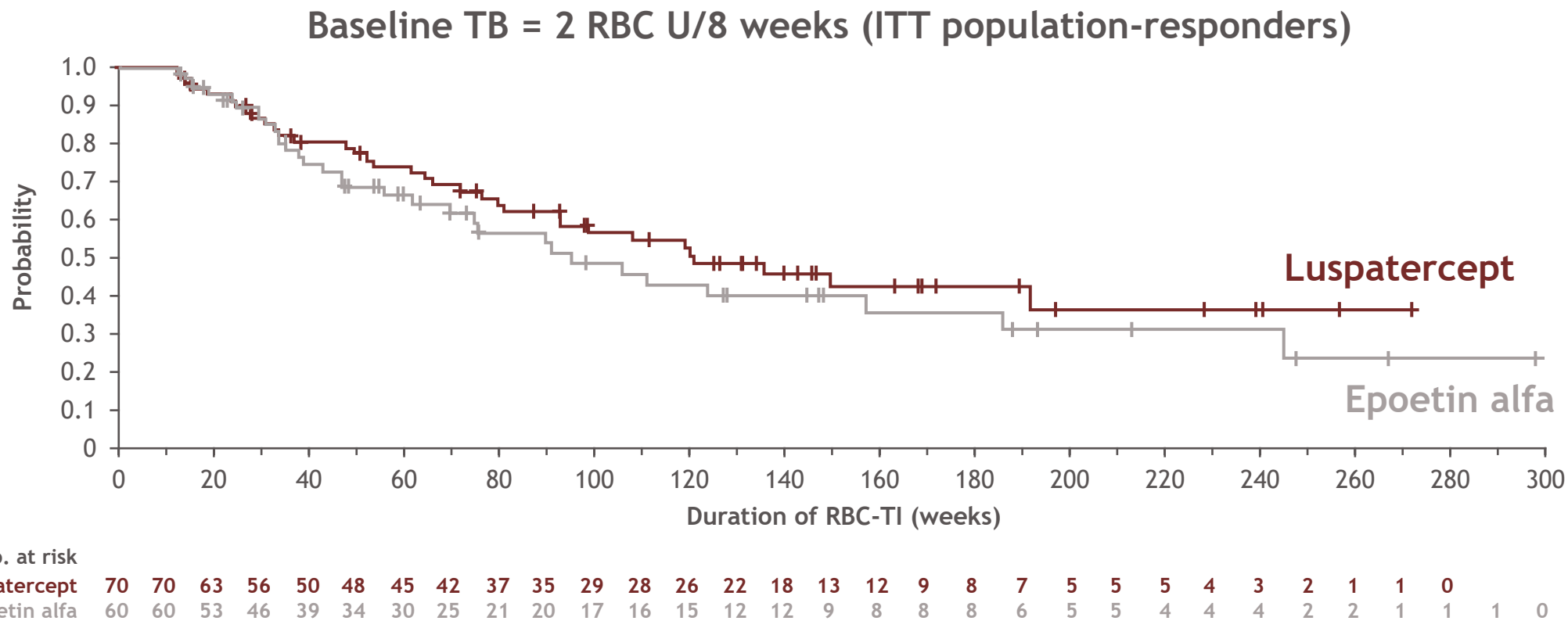
Duration of RBC-TI ≥ 12 weeks (Week 1-EOT) with **luspatercept and epoetin alfa**, stratified by baseline TB



Median (95% CI) duration,[a] weeks	Luspatercept	Epoetin alfa	HR[b] (95% CI)
TB, U/8 weeks			
= 2	120.9 (81.0-NE)	95.1 (61.9-186.1)	0.796 (0.488-1.298)
≥ 4	110.0 (43.4-184.4)	62.9 (26.9-NE)	0.904 (0.464-1.764)

Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Median is from an unstratified Kaplan-Meier method. [b]HR is calculated by an unstratified Cox proportional hazard model.

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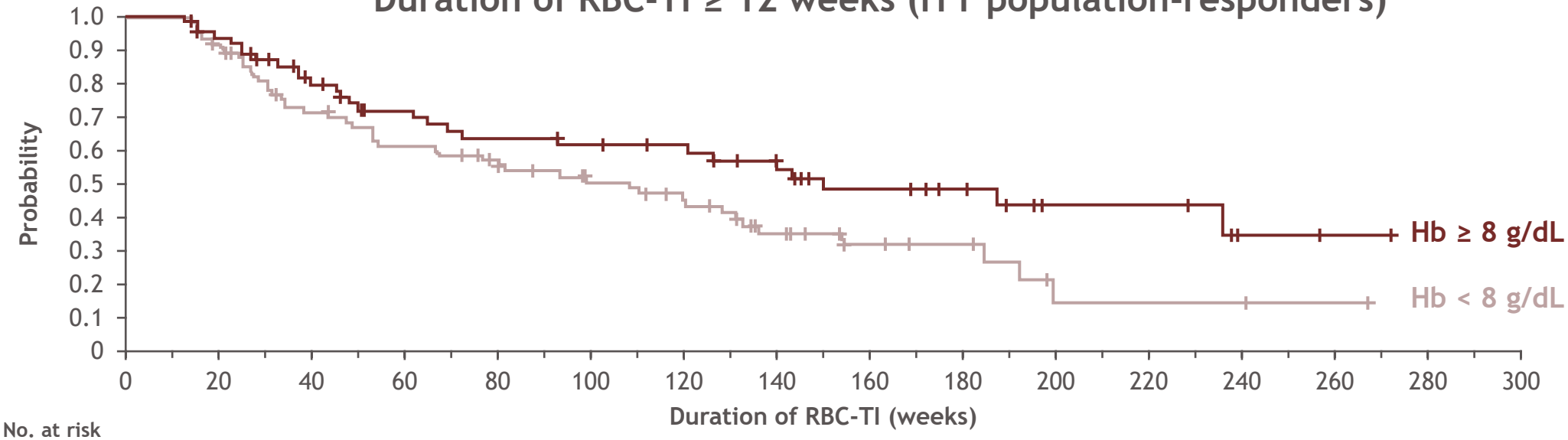
RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept**, stratified by baseline Hb

	Luspatercept		OR[a]/HR[b] (95% CI)
	Hb ≥ 8 g/dL	Hb < 8 g/dL	
RBC-TI ≥ 12 weeks (Week 1-EOT), % (n/N)	87.5 (63/72)	69.1 (76/110)	OR, 3.1 (1.4-7.0)
HI-E (Week 1-EOT),[c] % (n/N)	83.3 (60/72)	78.2 (86/110)	OR, 1.4 (0.6-3.0)
Median (95% CI) duration of RBC-TI ≥ 12 weeks,[d] weeks	150.0 (72.0-NE)	108.3 (53.7-132.6)	HR, 0.623 (0.389-0.999)

Duration of RBC-TI ≥ 12 weeks (ITT population-responders)



No. at risk

Hb ≥ 8 g/dL	63	63	57	50	43	37	35	32	31	31	29	28	27	24	23	16	15	14	11	8	6	6	6	5	2	2	1	1	0
Hb < 8 g/dL	76	76	69	58	51	47	43	41	36	33	29	28	24	21	15	12	9	7	7	5	2	2	2	2	2	1	1	0	

Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

[a]OR is based on an unstratified Cochran-Mantel-Haenszel test. [b]HR is calculated by an unstratified Cox proportional hazard model. [c]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 U/8 weeks. [d]Median is from an unstratified Kaplan-Meier method.

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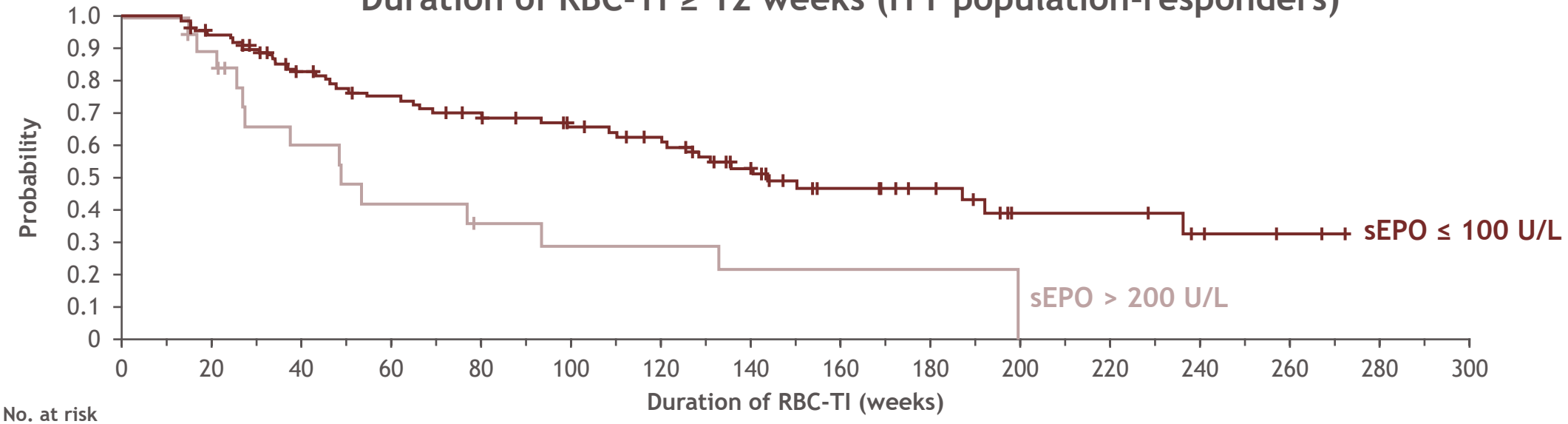
RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept**, stratified by baseline sEPO

	Luspatercept		OR[a]/HR[b] (95% CI)
	sEPO ≤ 100 U/L	sEPO > 200 U/L	
RBC-TI ≥ 12 weeks (Week 1-EOT), % (n/N)	87.4 (90/103)	54.1 (20/37)	OR, 5.9 (2.5-14.0)
HI-E (Week 1-EOT),[c] % (n/N)	90.3 (93/103)	62.2 (23/37)	OR, 5.7 (2.2-14.4)
Median (95% CI) duration of RBC-TI ≥ 12 weeks,[d] weeks	143.3 (120.1-235.9)	48.3 (26.3-132.6)	HR, 0.406 (0.220-0.748)

Duration of RBC-TI ≥ 12 weeks (ITT population-responders)



No. at risk

sEPO ≤ 100 U/L	90	90	83	77	67	61	58	54	51	49	45	43	40	34	29	21	18	16	14	11	7	7	7	6	4	3	2	1	0
sEPO > 200 U/L	20	20	17	11	10	8	7	7	5	5	4	4	4	4	3	2	2	1	1	1	0								

Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

[a]OR is based on an unstratified Cochran-Mantel-Haenszel test. [b]HR is calculated by an unstratified Cox proportional hazard model. [c]HI-E was defined as the proportion of patients with a mean Hb increase ≥ 1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or ≥ 4 U reduction in transfusions for patients with baseline TB ≥ 4 U/8 weeks. [d]Median is from an unstratified Kaplan-Meier method.

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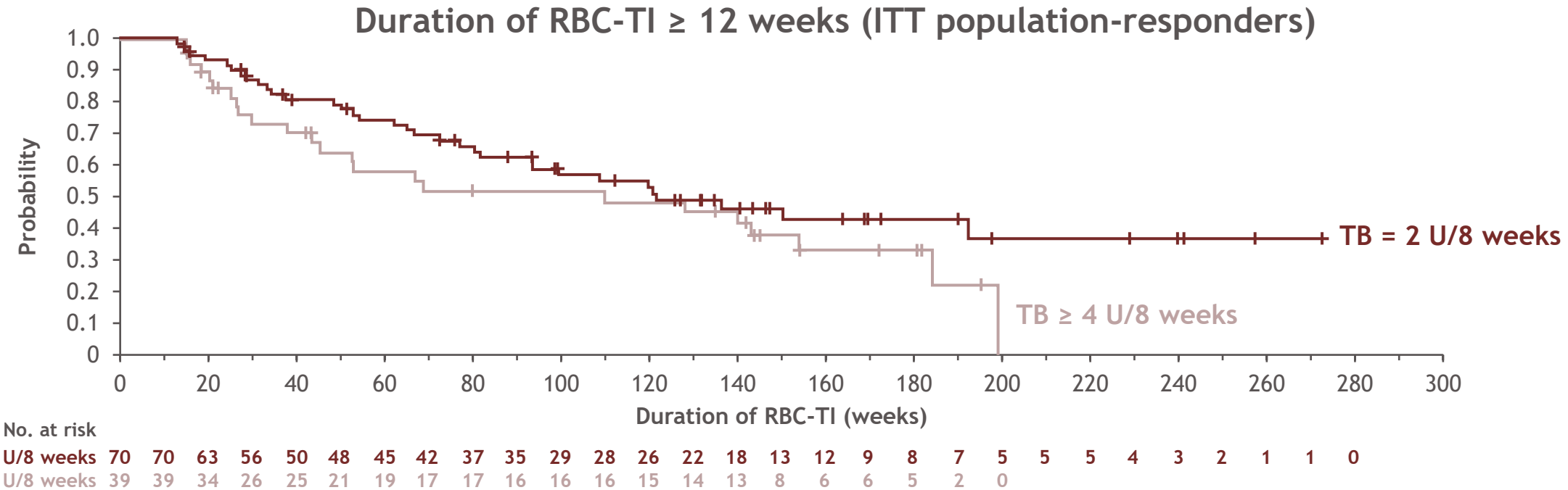
RBC-TI ≥ 12 weeks and HI-E (Week 1-EOT) with **luspatercept**, stratified by baseline TB

	Luspatercept		OR[a]/HR[b] (95% CI)
	TB = 2 U/8 weeks	TB ≥ 4 U/8 weeks	
RBC-TI ≥ 12 weeks (Week 1-EOT), % (n/N)	86.4 (70/81)	60.9 (39/64)	OR, 4.1 (1.8-9.2)
HI-E (Week 1-EOT),[c] % (n/N)	87.7 (71/81)	73.4 (47/64)	OR, 2.6 (1.1-6.1)
Median (95% CI) duration of RBC-TI ≥ 12 weeks,[d] weeks	120.9 (81.0-NE)	110.0 (43.4-184.4)	HR, 0.699 (0.413-1.181)



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Summary

- In the COMMANDS trial, luspatercept consistently yielded higher response rates and longer response duration than epoetin alfa across all clinically relevant subgroups (Hb, sEPO, and TB), supporting luspatercept as a preferred first-line therapy in TD LR-MDS
- Patients with higher Hb, lower sEPO, and lower TB, indicative of less advanced disease, achieved greater clinical benefit with luspatercept than those with more advanced disease
- Given these results, initiation of luspatercept early in the disease course of LR-MDS may lead to higher rates and a longer duration of transfusion independence

This COMMANDS post-hoc analysis supports early luspatercept use in TD LR-MDS, including in patients with less advanced disease characteristics

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- All authors contributed to and approved the presentation
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