

# **Lower-Risk MDS: Current Standards and Emerging Therapies**

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# Disclosures

- **Research: Garcia-Manero's work is supported by BMS, Astex, Taiho, Genentech, Abbvie, Curis, Novartis, Rigel, Zentalis and Chordia**
- **Advisor and speaker: BMS, Kurome, Curis, GSK, Astex and Taiho**

# Agenda

- **Discuss definition of LR-MDS**
- **US approach to LR-MDS**
- **Future approaches to LR-MDS**
  - **The case for “early intervention”**
  - **Role of allogeneic stem cell transplantation**
  - **New agents**

# Definition of lower risk MDS

- **CHIP/CCUS?**
- **IPSS: low and int-1**
- **IPSS-R: very low, low and some intermediate**
- **IPSS-M: very low, low, mod-low**
- **Pre or post HMA failure**

# Goals of therapy in lower risk MDS

- **Improvement in transfusion requirements**
- **Quality of life**
- **Survival: OS, EFS**
- **Delayed time to transformation**
  - **Major molecular endpoints that can serve as surrogates? CR, CCGR, MMR?**
- **Can we target co-morbidities?**

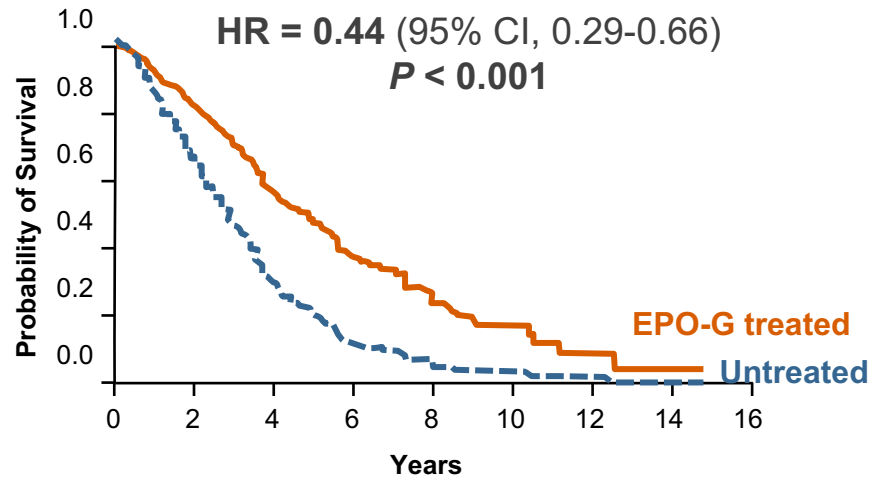
# Treatment algorithm 2025 LR MDS in the US

Entity	First line	Second line
<b>Del5q- MDS isolated anemia</b>	<b>lenalidomide</b>	<b>HMA, alloSCT</b>
<b>Isolated anemia, very low risk features</b>	<b>Growth factors Luspatercept</b>	<b>Imetelstat, HMA, len, alloSCT</b>
<b>RARS post ESA</b>	<b>luspatercept</b>	<b>HMA, len, alloSCT</b>
<b>Other lower risk MDS (bilineal cytopenia)</b>	<b>HMA</b>	<b>alloSCT</b>
<b>IDH1, IDH2, p53, SF3B1</b>	<b>Consider targeted approach, ivosidenib</b>	

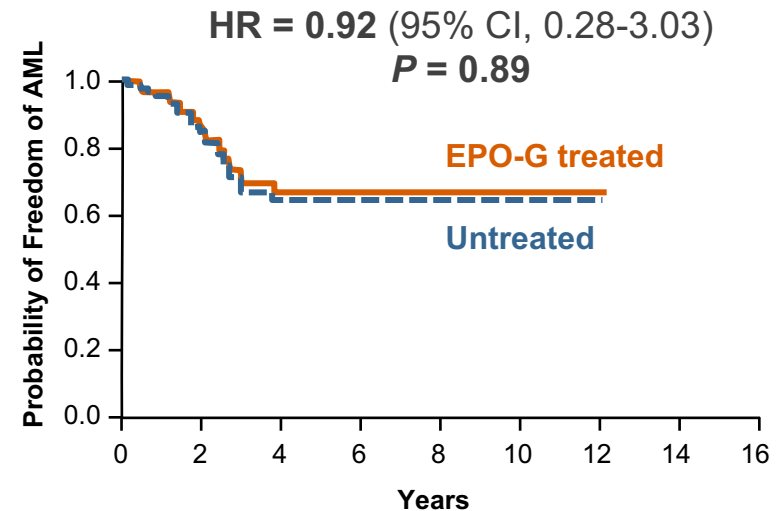
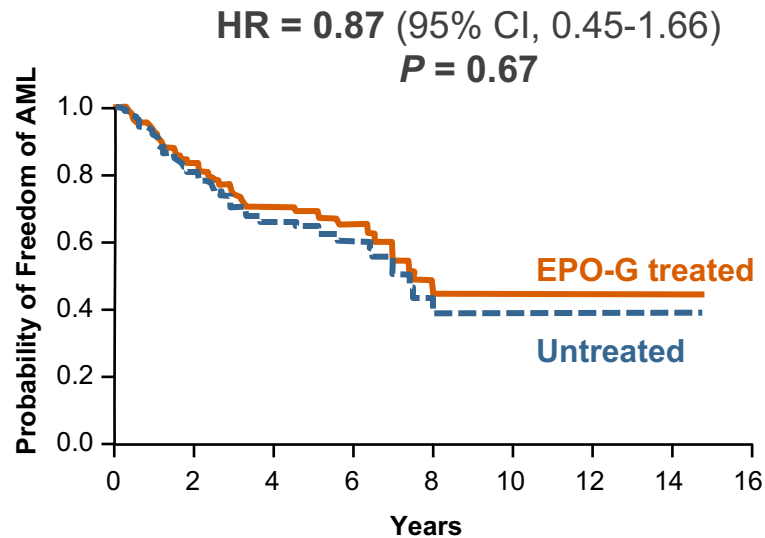
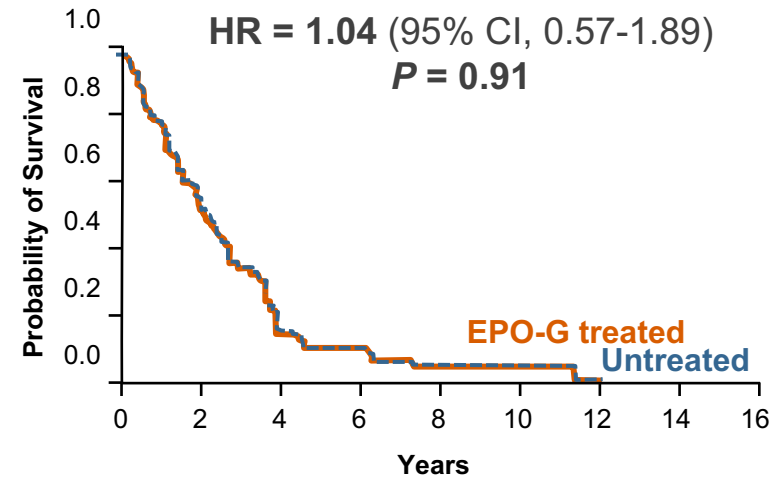
Based on NCCN guidelines

# EPO + GCSF May Improve Survival in MDS with Low RBC Tx Needs

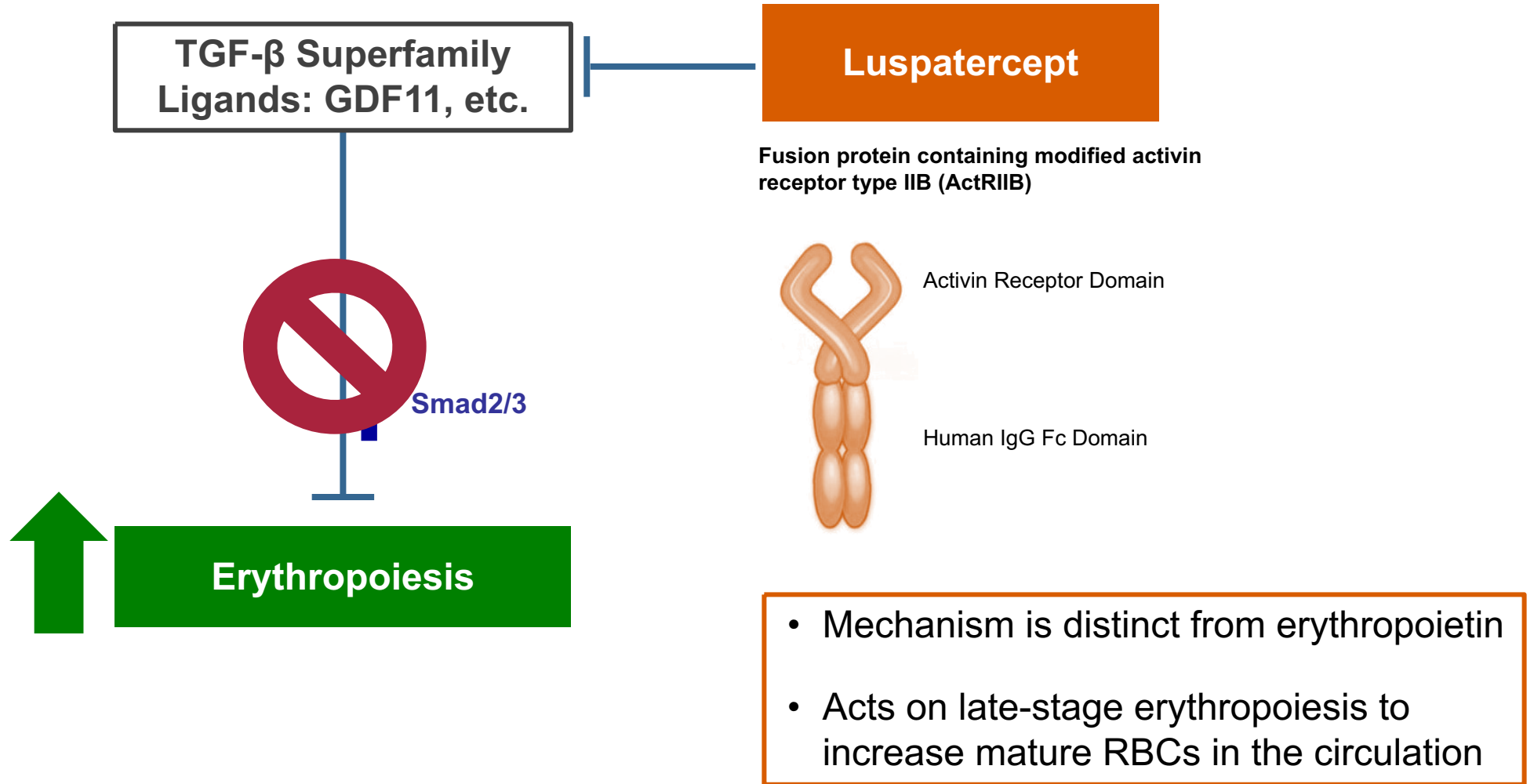
≤ 1 Unit PRBC per Month



≥ 2 Units PRBC per Month

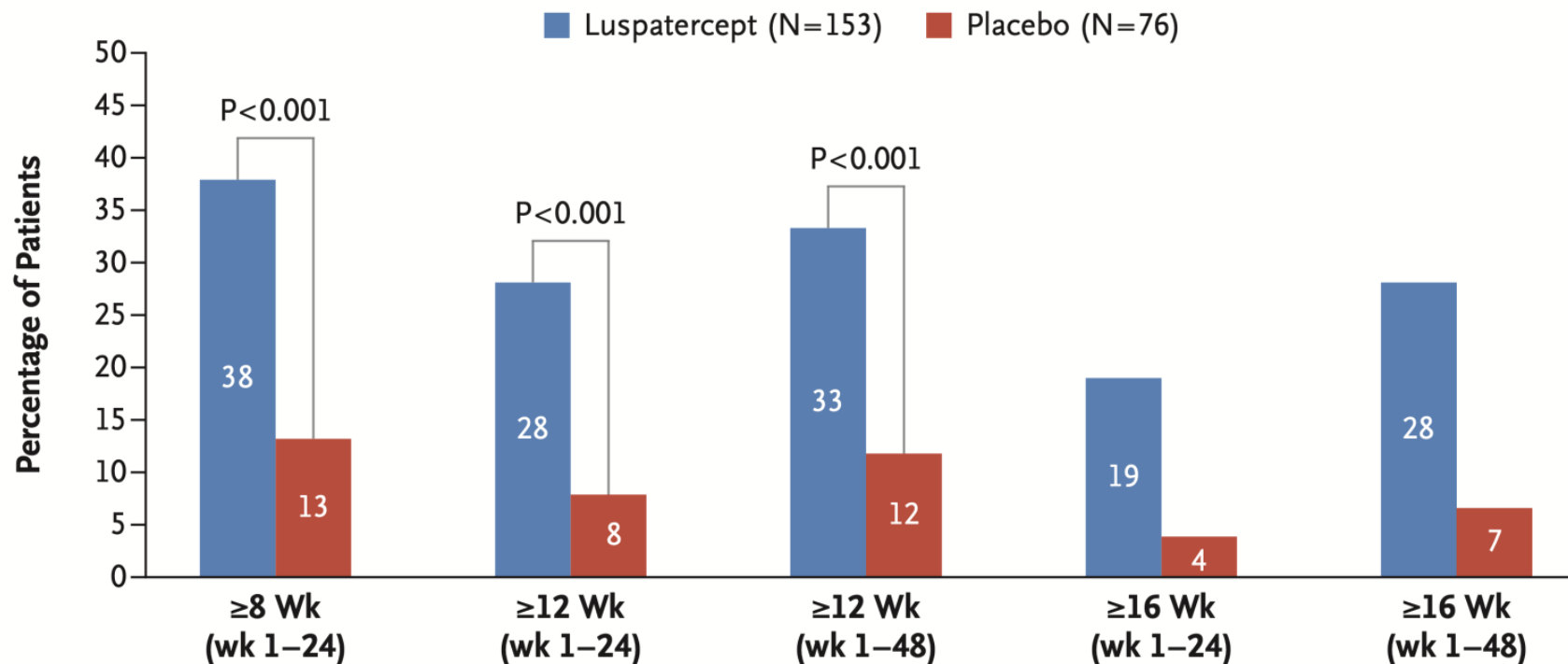


# Luspatercept in MDS: Background



# MEDALIST : achievement of primary endpoint in ITT population and subgroups

- The superiority of the luspatercept group to the placebo group was demonstrated in the percentage of patients who achieved RBC transfusion independence for  $\geq 8$  consecutive weeks within 24 weeks ( $p < 0.0001$ , stratified CMH test, significance level: one-sided 0.025, confirmatory analysis items).



## No. of Patients with Response (% [95% CI])

	$\geq 8$ Wk (wk 1-24)	$\geq 12$ Wk (wk 1-24)	$\geq 12$ Wk (wk 1-48)	$\geq 16$ Wk (wk 1-24)	$\geq 16$ Wk (wk 1-48)
Luspatercept	58 (38 [30-46])	43 (28 [21-36])	51 (33 [26-41])	29 (19 [13-26])	43 (28 [21-36])
Placebo	10 (13 [6-23])	6 (8 [3-16])	9 (12 [6-21])	3 (4 [1-11])	5 (7 [2-15])

# COMMANDS: study design

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

## Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R Very low-, Low-, or Intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow<sup>a</sup>
- Required RBC transfusions (2-6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

## Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status

R 1:1

Luspatercept (N = 182)  
1.0 mg/kg s.c. Q3W  
titration up to 1.75 mg/kg

Epoetin alfa (N = 181)<sup>b</sup>  
450 IU/kg s.c. QW  
titration up to 1050 IU/kg

Response assessment at  
day 169 and every  
24 weeks thereafter

End treatment  
Due to lack of clinical benefit<sup>c</sup>  
or disease progression  
per IWG 2006 criteria

## Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

<sup>a</sup>MDS patients with del(5q) were excluded; <sup>b</sup>2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; <sup>c</sup>Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline.

AML, acute myeloid leukemia; HR-MDS, higher-risk MDS; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; R, randomized; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

# COMMANDS: study endpoints

## Primary endpoint (weeks 1-24)

RBC-TI for  $\geq 12$  weeks WITH CONCURRENT mean Hb increase  $\geq 1.5$  g/dL

## Secondary endpoints (weeks 1-24)

- HI-E response  $\geq 8$  weeks per IWG 2006 criteria
- RBC-TI
  - 24 weeks
  - $\geq 12$  weeks
- Preplanned exploratory analysis of RBC-TI  $\geq 24$  weeks (weeks 1-48)

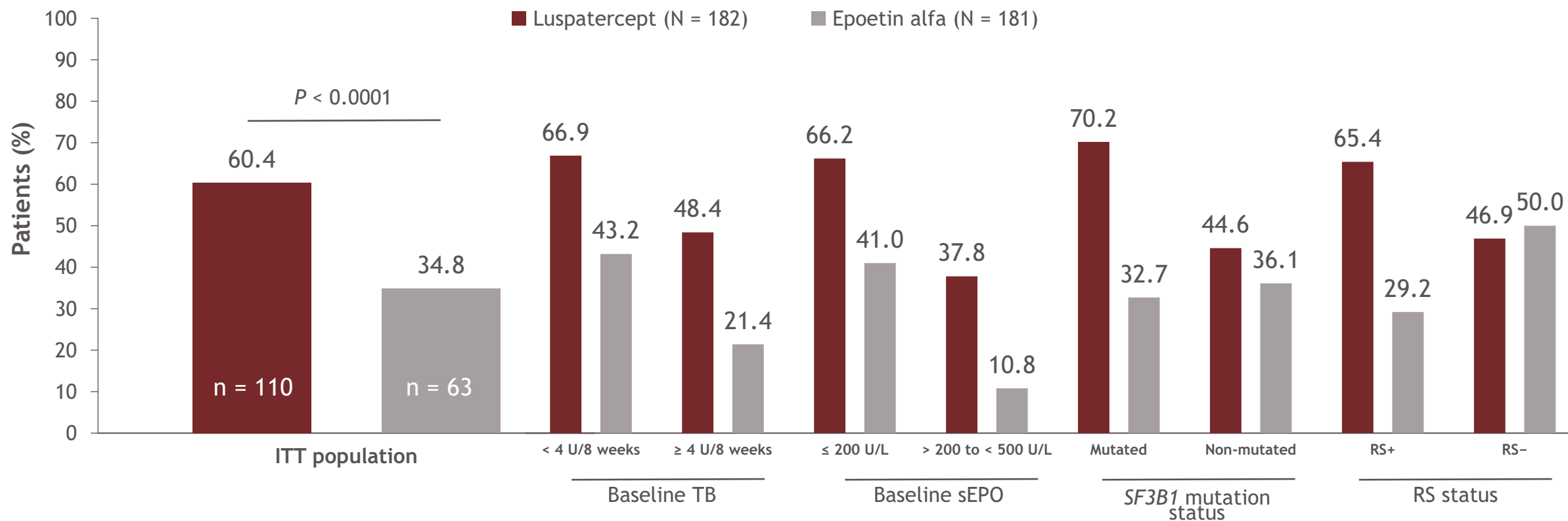
## Safety assessment

- TEAEs, EOI<sup>a</sup>
- AML progression
- Rates of on- and post-treatment deaths

<sup>a</sup>EOI are safety events selected based on findings from nonclinical or clinical phase 2 and 3 luspatercept trials.  
EOI, events of interest; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; RBC-TI, RBC transfusion independence; TEAE, treatment-emergent adverse event.

# COMMANDS: achievement of primary endpoint in ITT population and subgroups

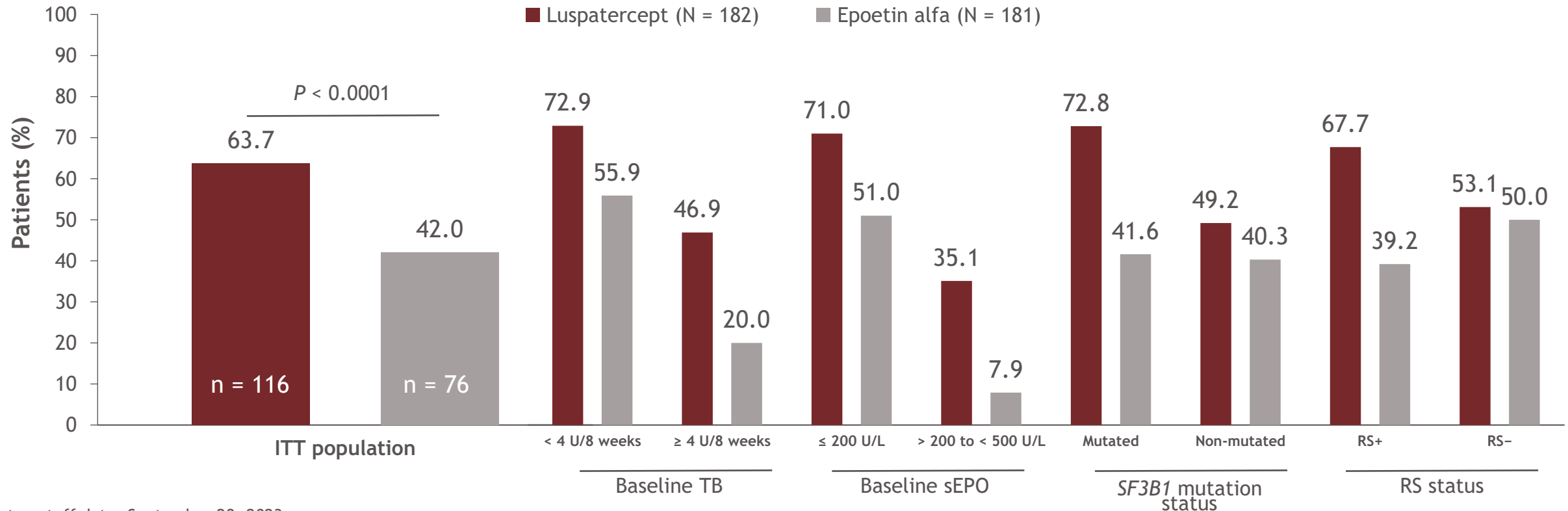
- The primary endpoint was achieved by 110 (60.4%) patients in the luspatercept arm versus 63 (34.8%) patients in the epoetin alfa arm ( $P < 0.0001$ )
  - Subgroup analysis of the primary endpoint showed greater response rates with luspatercept regardless of baseline TB, sEPO category, or *SF3B1* mutation status



Data cutoff date: March 31, 2023.  
ITT, intent to treat.

# COMMANDS: preplanned exploratory analysis of RBC-TI for $\geq 24$ weeks (weeks 1-48)

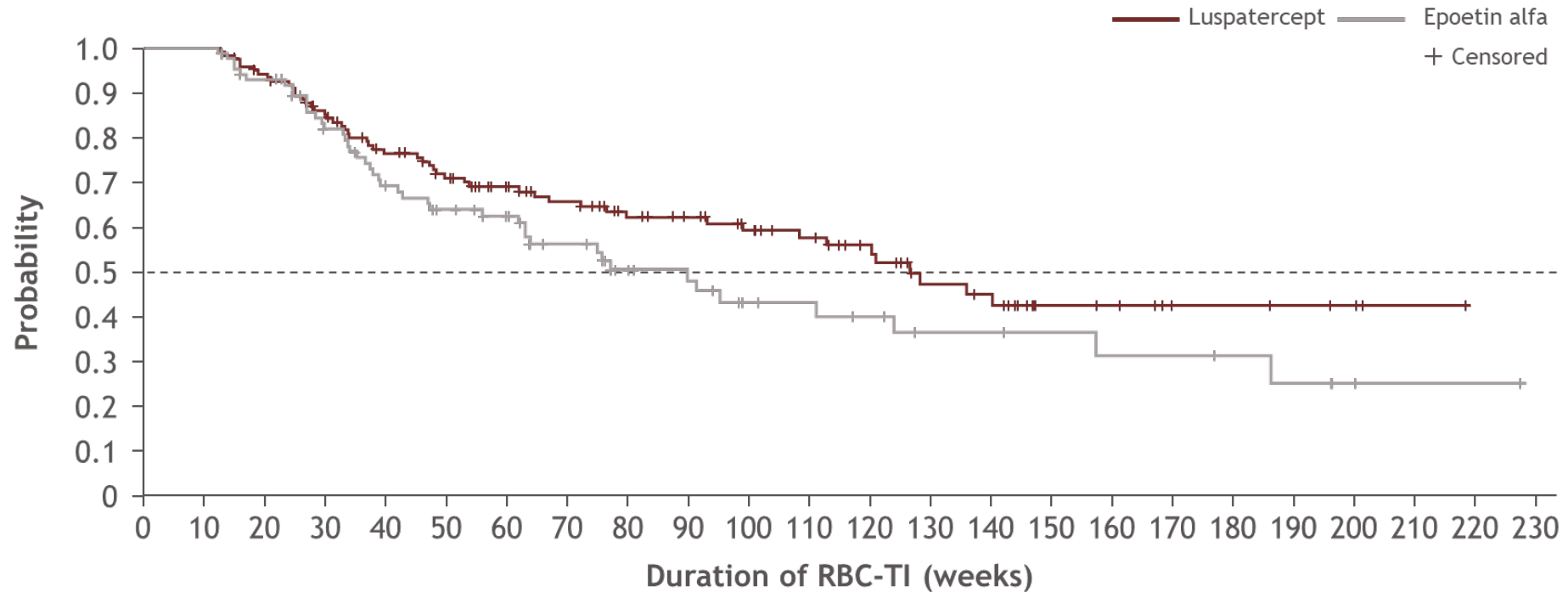
- Response rates of the preplanned exploratory analysis of RBC-TI for  $\geq 24$  weeks (weeks 1-48) were greater with luspatercept versus epoetin alfa regardless of baseline TB, sEPO category, or *SF3B1* mutation status



Data cutoff date: September 28, 2023.

# COMMANDS: duration of RBC-TI $\geq$ 12 weeks (week 1-EOT)

Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
ITT	126.6 (99.0-NE)	89.7 (61.9-123.9)	0.586 (0.380-0.904)



No. at risk

Luspatercept	124	124	115	100	86	76	67	59	50	46	40	35	28	20	18	10	9	5	5	4	3	1	
Epoetin alfa	88	88	79	65	54	47	43	32	23	20	15	14	12	9	9	7	6	6	5	4	2	1	1

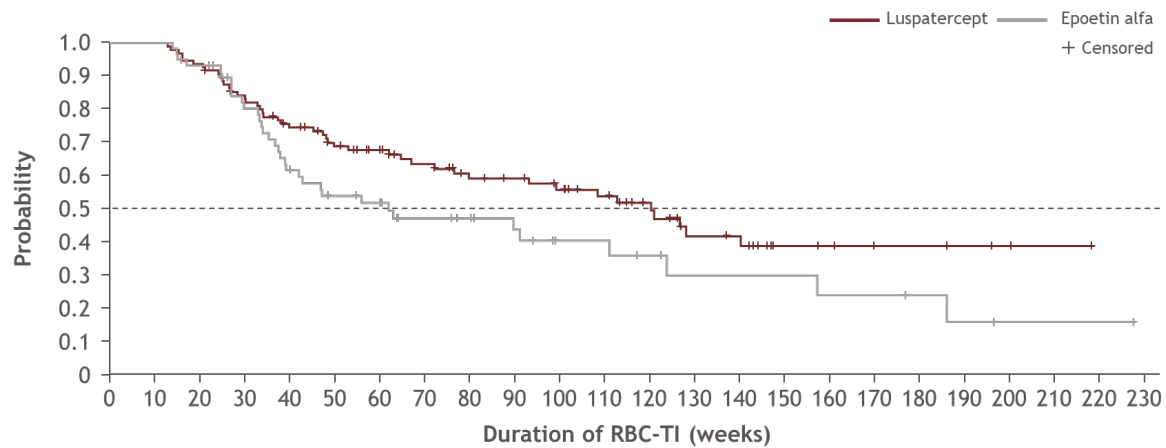
Data cutoff date: September 28, 2023.

CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not estimable.

# COMMANDS: duration of RBC-TI $\geq$ 12 weeks by RS subgroups (week 1-EOT)

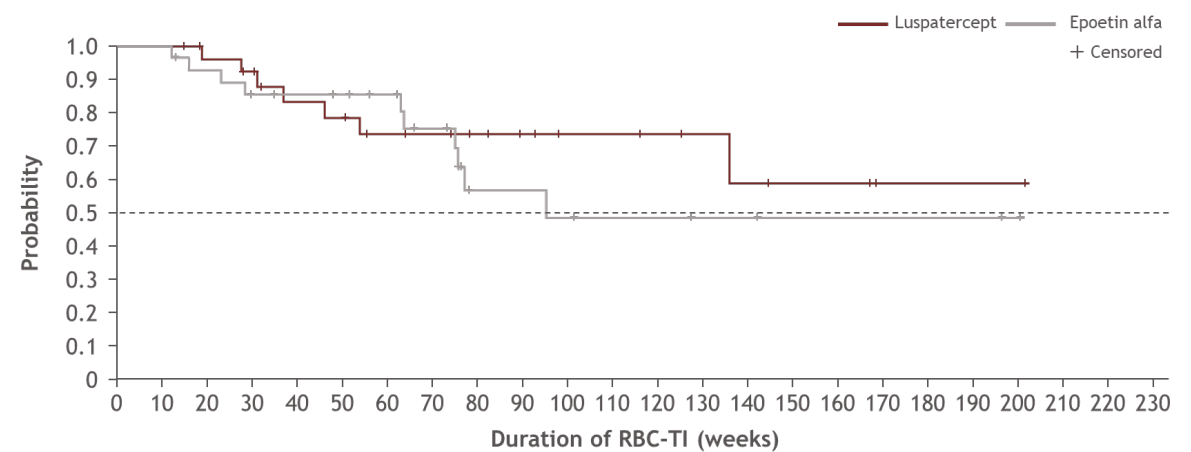
Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
RS+	120.1 (76.4-NE)	61.9 (38.9-123.9)	0.650 (0.415-1.018)
RS-	NE (135.9-NE)	95.1 (74.9-NE)	0.709 (0.269-1.866)

RS+



No. at risk	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230
Luspatercept	96	96	90	78	68	59	53	46	39	37	33	28	22	15	14	7	6	4	4	3	2	1		
Epoetin alfa	59	59	54	43	33	27	25	18	16	13	9	9	7	5	5	5	4	4	3	2	1	1		1

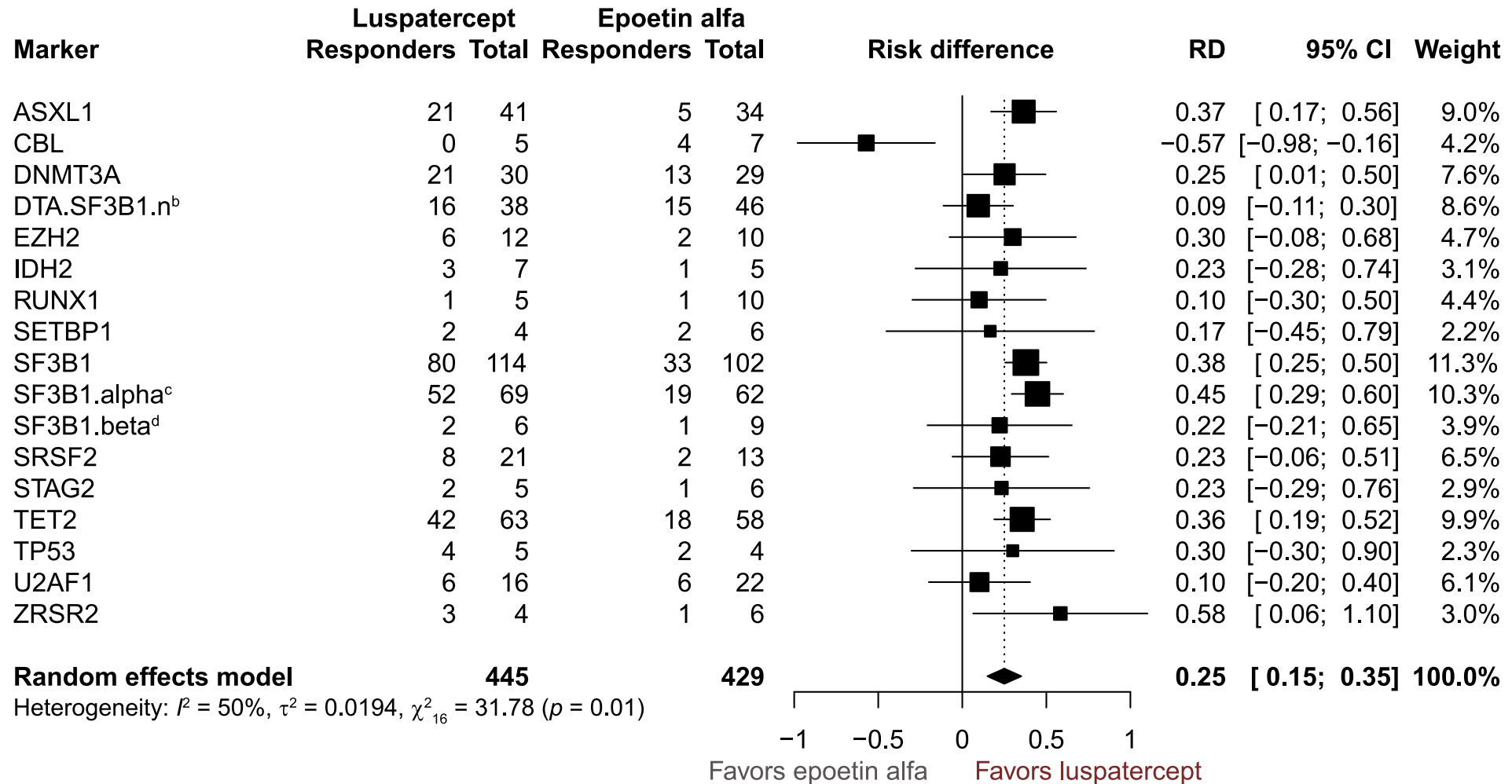
RS-



No. at risk	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230
Luspatercept	28	28	25	22	18	17	14	13	11	9	7	7	6	5	4	3	3	1	1	1	1			
Epoetin alfa	29	29	25	22	21	20	18	14	7	7	6	5	5	4	4	2	2	2	2	2	2	1		1

Data cutoff date: September 28, 2023.

# Luspatercept showed broad activity across multiple MDS-associated mutations in the primary analysis of the COMMANDS study<sup>a</sup>



Solid vertical line represents absence of treatment effect (no favorability or benefit with treatment); dotted line represents overall favorability based on the random effects model. <sup>a</sup>Patients who received treatment; <sup>b</sup>DTA.SF3B1.n = SF3B1 wt + DNMT3A mut or TET2 mut or ASXL1 mut; <sup>c</sup>SF3B1.alpha = SF3B1 mut + DNMT3A mut or TET2 mut or ASXL1 mut; <sup>d</sup>SF3B1.beta = SF3B1 mut + BCOR mut or BCORL1 mut or NRAS mut or RUNX1 mut or SRSF2 mut or STAG2 mut.

MDS, myelodysplastic syndromes; mut, mutation; RD, risk difference; wt, wild type.

# Luspatercept led to larger mean increases in neutrophils and platelets during the entire treatment period

Figure 3. Mean change from baseline in neutrophils in ITT population (weeks 1-EOT)

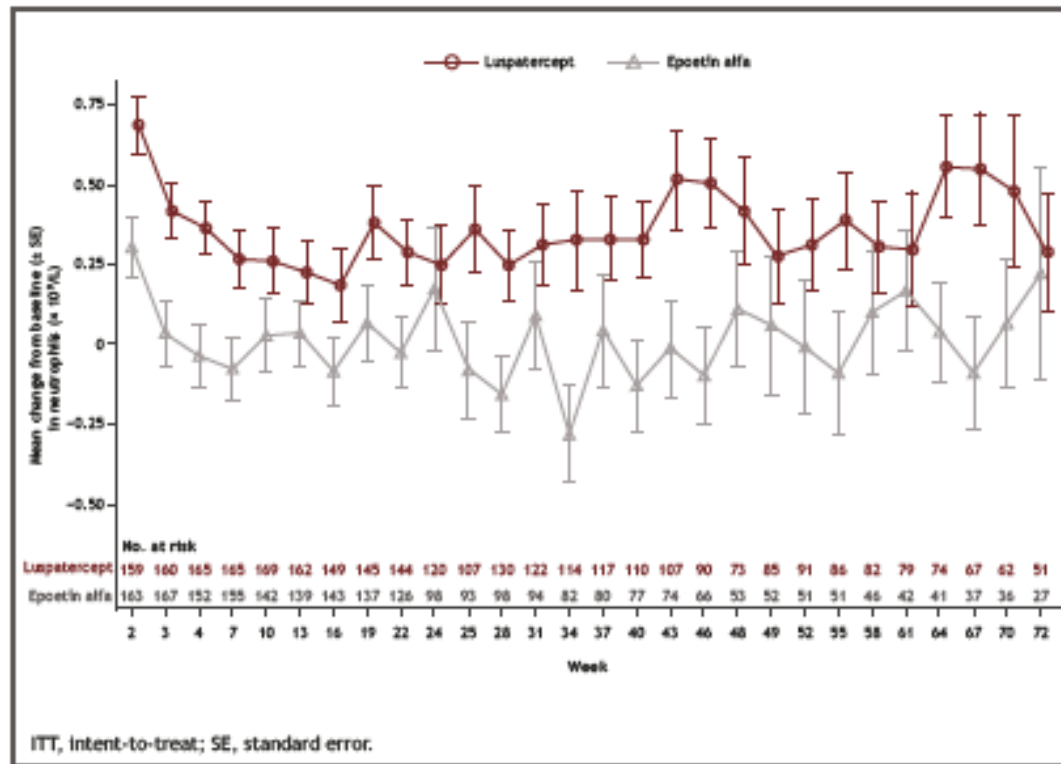
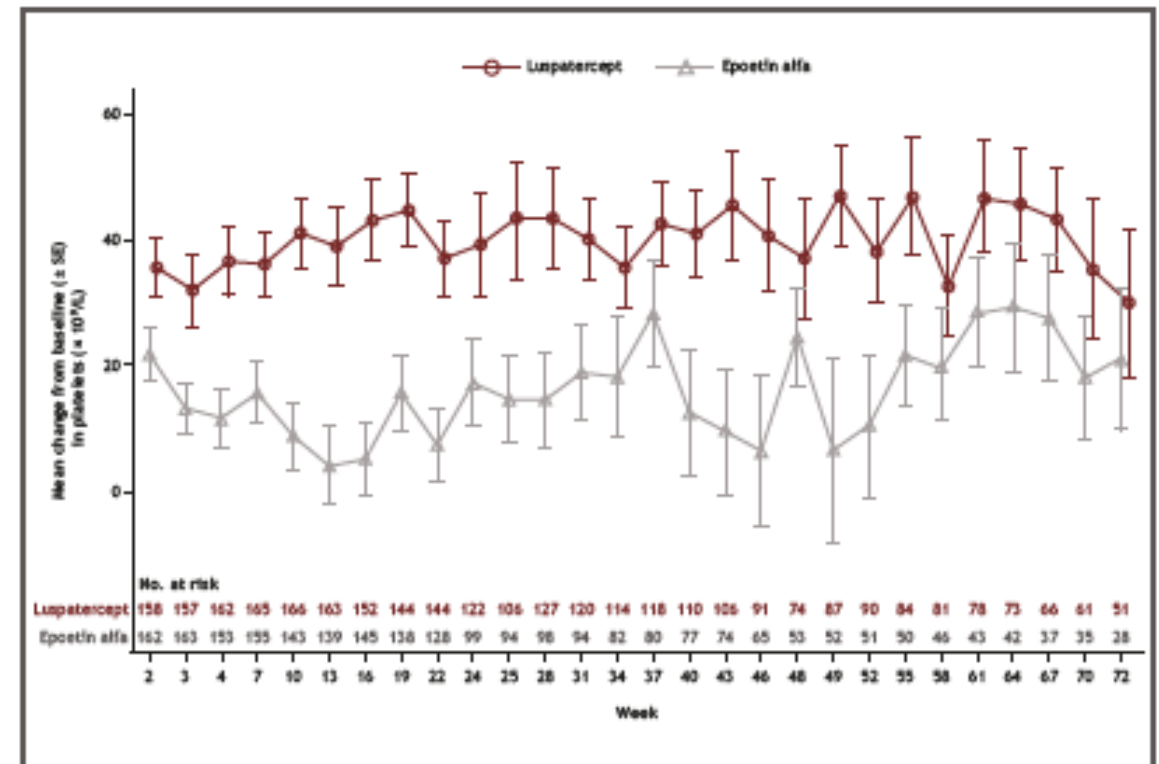


Figure 4. Mean change from baseline in platelets in the ITT population (weeks 1-EOT)



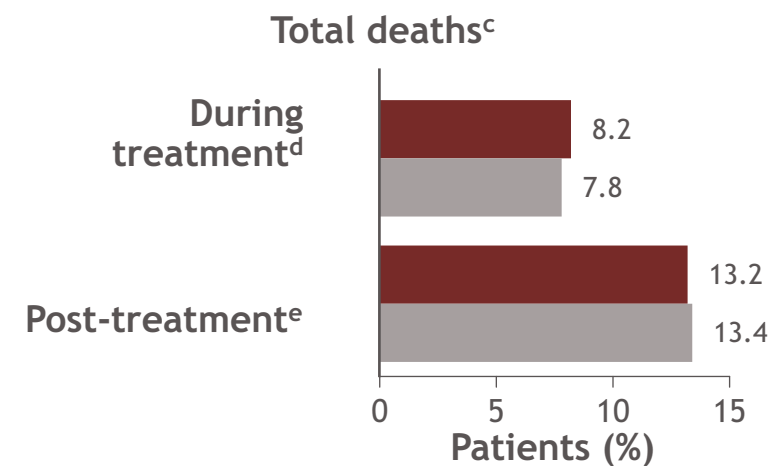
# COMMANDS: summary of safety<sup>a</sup>

- The median (range) duration of treatment was longer in the luspatercept arm compared with the epoetin alfa arm: 51.3 (3-196) weeks versus 37.0 (1-202) weeks
  - 143 (78.6%) of luspatercept patients and 146 (81.6%) of epoetin alfa patients had  $\geq 1$  dose escalation<sup>a</sup>
- Similar proportions of patients in the luspatercept and epoetin alfa arms died at any time during the study
- Rates of progression to AML<sup>b</sup> were low (2.7% vs 3.3% of patients for luspatercept versus epoetin alfa)

Most common TEAEs in $\geq 10\%$ of patients	Luspatercept (N = 182)	Epoetin alfa (N = 179)
Diarrhea	32 (17.6)	25 (14.0)
Fatigue	32 (17.6)	13 (7.3)
COVID-19	27 (14.8)	28 (15.6)
Hypertension	27 (14.8)	16 (8.9)
Dyspnea	26 (14.3)	14 (7.8)
Nausea	26 (14.3)	15 (8.4)
Peripheral edema	26 (14.3)	14 (7.8)
Asthenia	25 (13.7)	29 (16.2)
Dizziness	23 (12.6)	16 (8.9)
Anemia	22 (12.1)	19 (10.6)
Back pain	22 (12.1)	16 (8.9)
Headache	20 (11.0)	15 (8.4)

## Follow-up duration,<sup>b</sup> median (range)

17.2 (1-46) months for luspatercept arm  
16.9 (0-46) months for epoetin alfa arm



Data cutoff date: March 31, 2023.

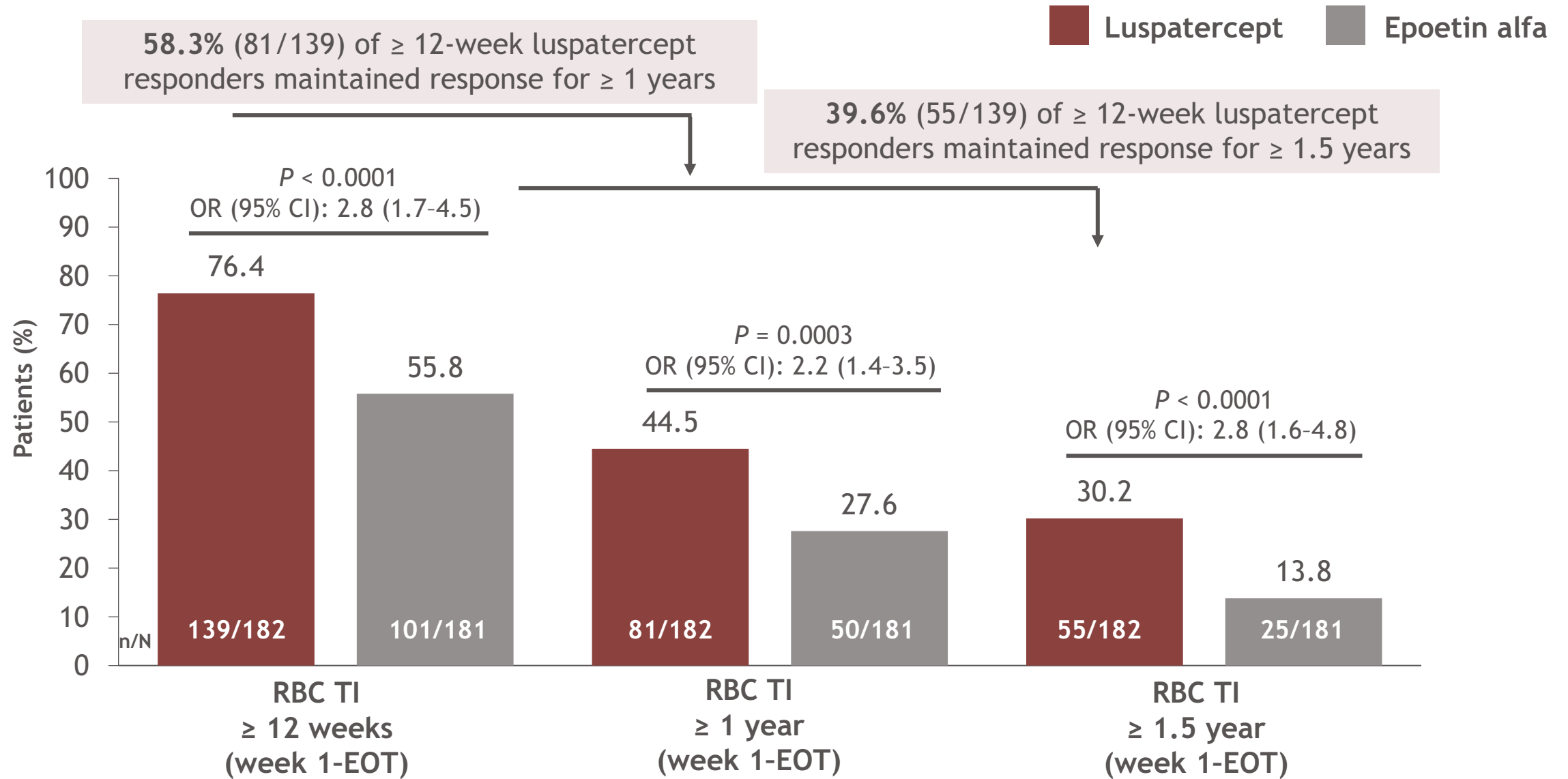
<sup>a</sup>Assessed in the safety population; <sup>b</sup>Median follow-up for overall survival assessed in the ITT population; <sup>c</sup>Total number of deaths includes number of deaths during treatment period and post-treatment period; <sup>d</sup>Any death that occurred on or after first dose of treatment until 42 days after the last dose of treatment; <sup>e</sup>Any death that occurred after 42 days of the last dose date of treatment.

# Long-term response analysis of transfusion independence in erythropoiesis stimulating agent-naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial

Guillermo Garcia-Manero,<sup>1</sup> Valeria Santini,<sup>2</sup> Amer M. Zeidan,<sup>3</sup> Rami S. Komrokji,<sup>4</sup> Veronika Pozharskaya,<sup>5</sup> Karen Keeperman,<sup>5</sup> Shelonitda Rose,<sup>5</sup> Yinzhi Lai,<sup>5</sup> Barkha Aggarwal,<sup>5</sup> Dimana Miteva,<sup>6</sup> David Valcárcel,<sup>7</sup> Pierre Fenaux,<sup>8</sup> Jake Shortt,<sup>9</sup> Matteo Giovanni Della Porta,<sup>10</sup> Uwe Platzbecker<sup>11</sup>

<sup>1</sup>MD Anderson Cancer Center, Houston, TX, USA; <sup>2</sup>MDS Unit, DMSC, University of Florence, AOUC, Florence; <sup>3</sup>Yale School of Medicine, New Haven, CT, USA; <sup>4</sup>Moffitt Cancer Center, Tampa, FL, USA; <sup>5</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>6</sup>Bristol Myers Squibb, Boudry, Switzerland; <sup>7</sup>Vall d'Hebron Hospital, Barcelona, Spain; <sup>8</sup>AP-HP St Louis, Paris, France; <sup>9</sup>Monash Health & Monash University, Clayton, VIC, Australia; <sup>10</sup>Humanitas University, Milan, Italy; <sup>11</sup>University Hospital Leipzig, Leipzig, Germany

# COMMANDS: RBC-TI responses of $\geq 12$ weeks, $\geq 1$ years, and $\geq 1.5$ years



# Overall survival and duration of response for transfusion independence in erythropoiesis-stimulating agent-naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial

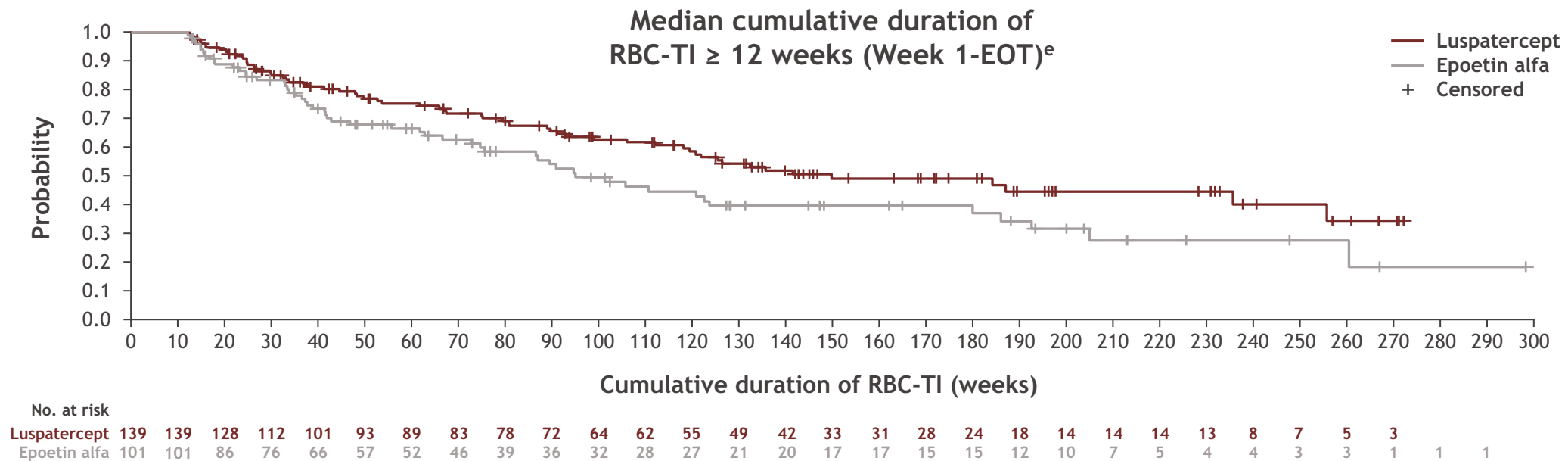
[Guillermo Garcia-Manero](#),<sup>1</sup> [Matteo Giovanni Della Porta](#),<sup>2</sup> [Amer M. Zeidan](#),<sup>3</sup> [Rami S. Komrokji](#),<sup>4</sup> [Veronika Pozharskaya](#),<sup>5</sup> [Shelonitda Rose](#),<sup>5,\*</sup> [Karen L. Keeperman](#),<sup>5</sup> [Yinzhi Lai](#),<sup>5</sup> [Sameer Kalsekar](#),<sup>6</sup> [Barkha Aggarwal](#),<sup>5</sup> [Dimana Miteva](#),<sup>7</sup> [David Valcárcel](#),<sup>8</sup> [Pierre Fenaux](#),<sup>9</sup> [Jake Shortt](#),<sup>10</sup> [Uwe Platzbecker](#),<sup>11</sup> [Valeria Santini](#)<sup>12</sup>

<sup>1</sup>University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; <sup>2</sup>Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; Humanitas University, Milan, Italy; <sup>3</sup>Yale University School of Medicine, New Haven, CT, USA; <sup>4</sup>Moffitt Cancer Center, Tampa, FL, USA; <sup>5</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>6</sup>Bristol Myers Squibb, Hyderabad, Telangana, India; <sup>7</sup>Bristol Myers Squibb, Boudry, Switzerland; <sup>8</sup>Hospital Universitari Vall d'Hebron, Barcelona, Spain; <sup>9</sup>Hôpital Saint-Louis, Université Paris 7, Paris, France; <sup>10</sup>Monash University and Monash Health, Melbourne, VIC, Australia; <sup>11</sup>University Hospital Leipzig, Leipzig, Germany; <sup>12</sup>University of Florence, DMSC, AOUC, Florence, Italy

\*At the time of the study.

# COMMANDS: RBC-TI ≥ 12 weeks with > 2.5 years of follow-up

	Luspatercept	Epoetin alfa	OR <sup>a</sup> /HR <sup>d</sup> (95% CI)
RBC-TI ≥ 12 weeks (Week 1-EOT) response rate, % (n/N)	76.4 (139/182)	55.8 (101/181)	OR, <sup>a</sup> 2.8 (1.7-4.5); <i>P</i> < 0.0001
Median (95% CI) duration of the longest RBC-TI ≥ 12-week period (Week 1-EOT), <sup>b,c</sup> weeks	126.6 (81.0-154.1)	86.7 (55.9-105.9)	HR, <sup>d</sup> 0.632 (0.434-0.919); <i>P</i> = 0.0156
Median (95% CI) cumulative duration of RBC-TI ≥ 12 weeks (Week 1-EOT), <sup>c,e</sup> weeks	150.0 (119.6-256.0)	95.1 (74.9-180.1)	HR, <sup>d</sup> 0.523 (0.353-0.777); <i>P</i> = 0.0011



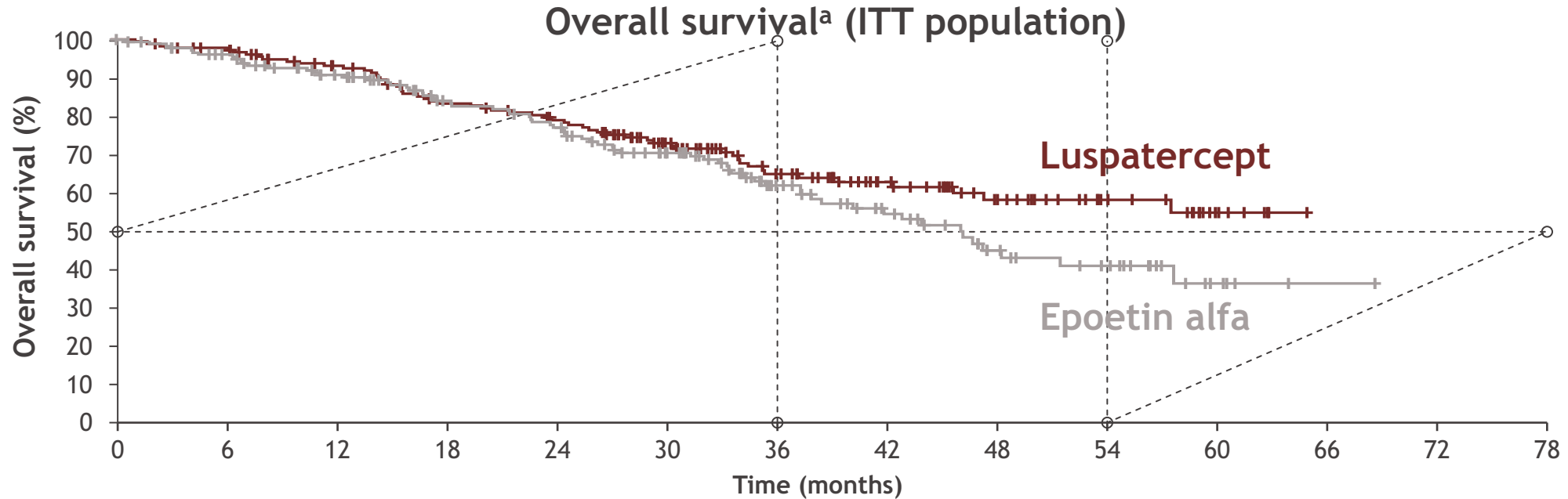
Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

EOT, end of treatment; OR, odds ratio.

<sup>a</sup>Based on Cochran-Mantel-Haenszel test stratified by baseline RBC TB, RS status, and sEPO levels. One-sided *P* value is presented. <sup>b</sup>Duration of RBC-TI ≥ 12 weeks is defined as the longest RBC-TI period from Week 1 to EOT. <sup>c</sup>Median is from an unstratified Kaplan-Meier method. <sup>d</sup>HR is calculated by a stratified Cox proportional hazard model. *P* value is from a stratified log-rank test.

<sup>e</sup>Cumulative duration is defined as the sum of all durations of RBC-TI ≥ 12-week episodes from Week 1 through EOT.

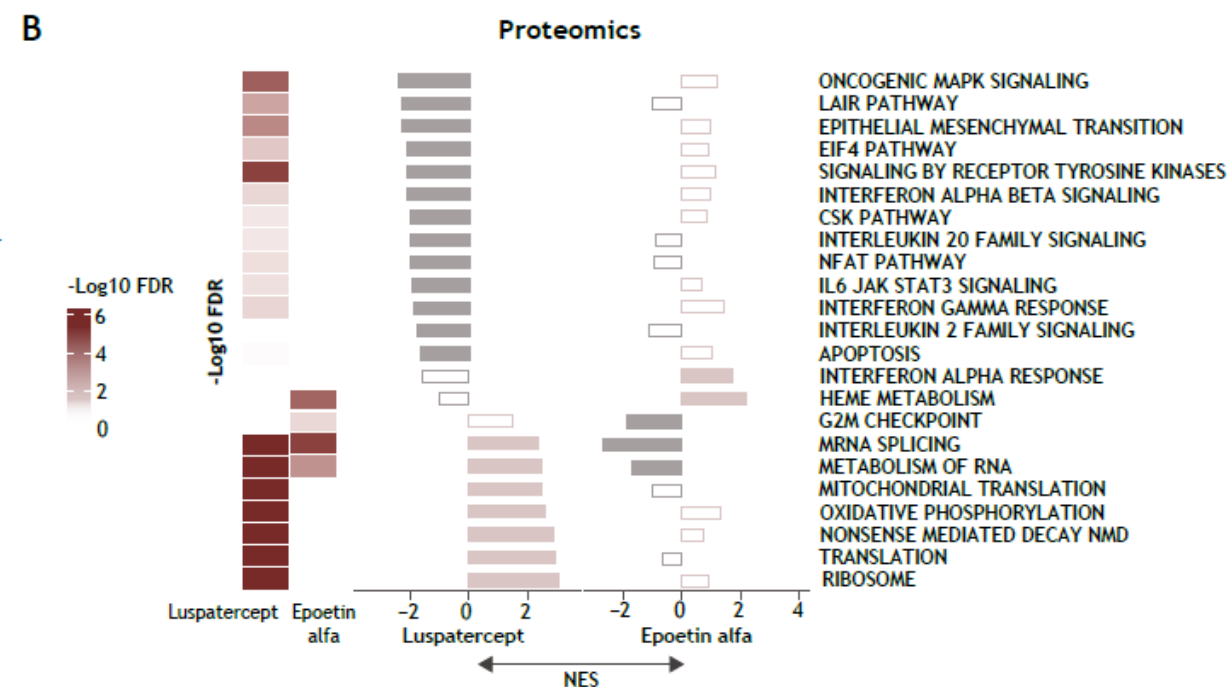
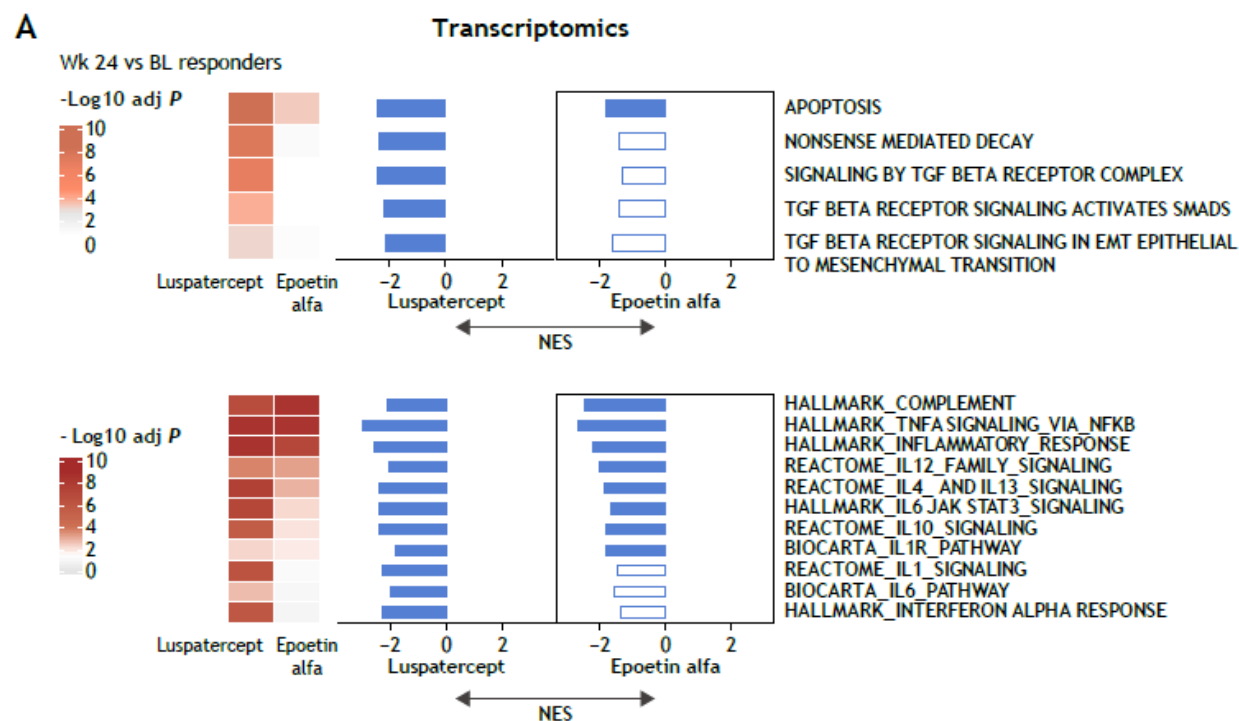
# COMMANDS: overall survival with > 2.5 years of follow-up



No. at risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78
Luspatercept	182	173	154	135	124	95	68	49	33	20	8				
Epoetin alfa	181	166	144	120	109	87	55	39	24	17	5	1			

	Luspatercept	Epoetin alfa	HR (95% CI) <sup>b</sup>
Median OS, <sup>c</sup> months	NR	46.0	0.805 (0.565-1.146)
Piecewise analysis Deaths, n/N (%), ≥ 36 months	6/68 (8.8)	15/55 (27.3)	0.330 (0.128-0.853); P = 0.0221

# BMMC transcriptomics and proteomics showed modulation of the dysregulated pathways associated with MDS: Luspatercept downregulated TGF $\beta$ signaling and inflammation associated pathways

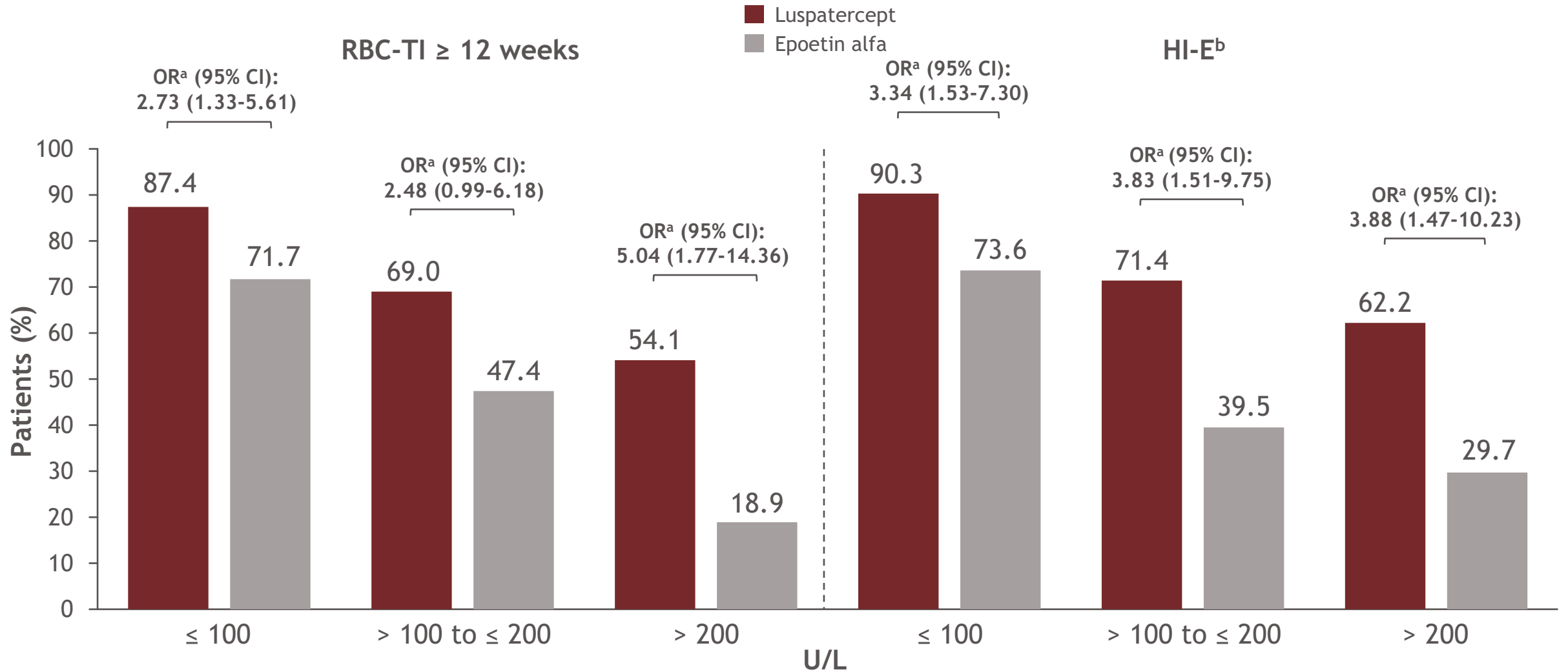


# Clinical benefit of luspatercept in erythropoiesis-stimulating agent-naive patients with early disease characteristics and very low-, low-, or intermediate-risk myelodysplastic syndromes: a post-hoc analysis from the COMMANDS trial

[Valeria Santini](#),<sup>1</sup> Matteo Giovanni Della Porta,<sup>2</sup> Rami S. Komrokji,<sup>3</sup> Veronika Pozharskaya,<sup>4</sup> Thalia Farazi,<sup>4</sup> Karen L. Keeperman,<sup>4</sup> Yinzhi Lai,<sup>4</sup> Dimana Miteva,<sup>5</sup> Tracy Krimmel,<sup>4</sup> Barkha Aggarwal,<sup>4</sup> David Valcárcel,<sup>6</sup> Pierre Fenaux,<sup>7</sup> Jake Shortt,<sup>8</sup> Uwe Platzbecker,<sup>9</sup> Guillermo Garcia-Manero,<sup>10</sup> Amer M. Zeidan<sup>11</sup>

<sup>1</sup>MDS Unit, Hematology, University of Florence, Florence, Italy; <sup>2</sup>Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; Humanitas University, Milan, Italy; <sup>3</sup>Moffitt Cancer Center, Tampa, FL, USA; <sup>4</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>5</sup>Bristol Myers Squibb, Boudry, Switzerland; <sup>6</sup>Hospital Universitari Vall d'Hebron, Barcelona, Spain; <sup>7</sup>Hôpital Saint-Louis, Université Paris 7, Paris, France; <sup>8</sup>Monash University and Monash Health, Melbourne, VIC, Australia; <sup>9</sup>University Hospital Leipzig, Leipzig, Germany; <sup>10</sup>University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; <sup>11</sup>Yale University School of Medicine, New Haven, CT, USA

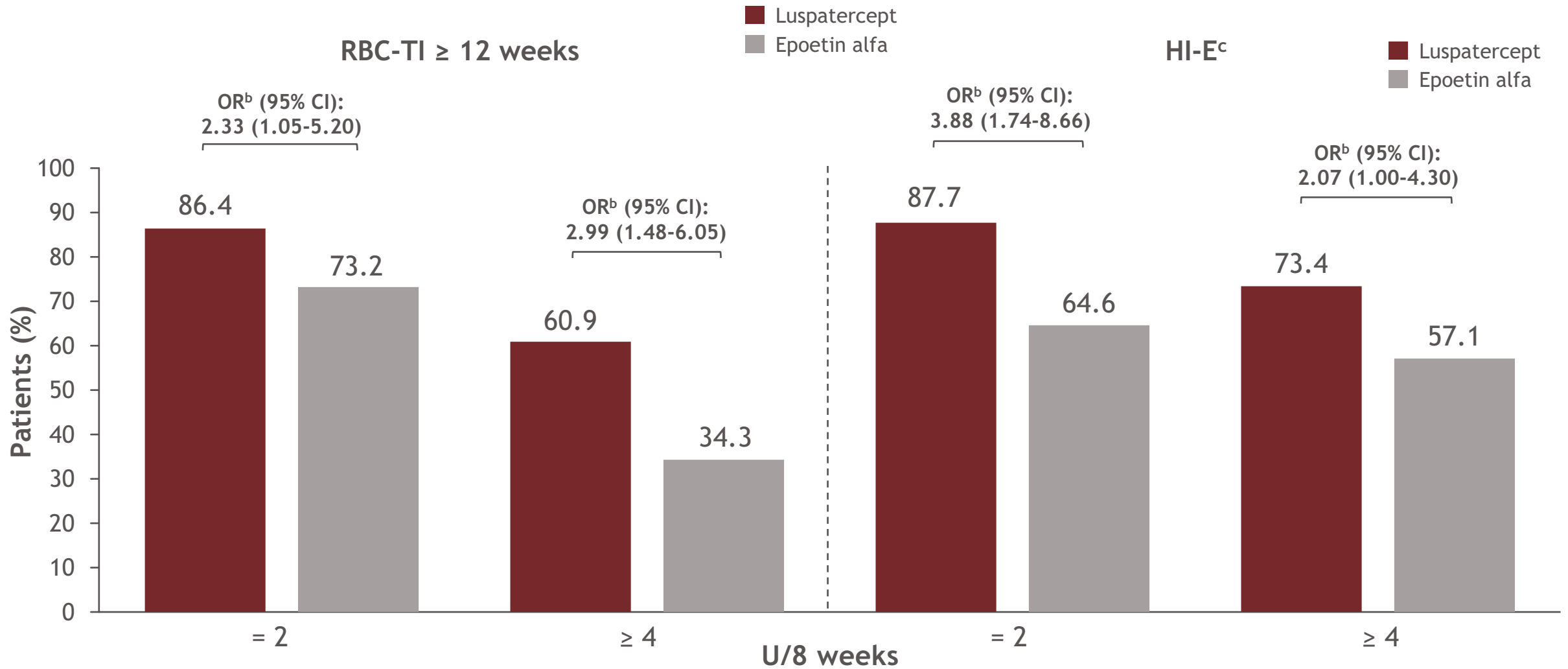
# Achievement of RBC-TI $\geq 12$ weeks and HI-E (Week 1-EOT) with luspatercept and epoetin alfa, stratified by baseline sEPO



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.

<sup>a</sup>OR is based on an unstratified Cochran-Mantel-Haenszel test. <sup>b</sup>HI-E was defined as the proportion of patients with a mean Hb increase  $\geq 1.5$  g/dL in the absence of transfusions for patients with baseline TB  $< 4$  U/8 weeks or  $\geq 4$  U reduction in transfusions for patients with baseline TB  $\geq 4$  U/8 weeks.

# Achievement of RBC-TI $\geq$ 12 weeks and HI-E (Week 1-EOT) with luspatercept and epoetin alfa, stratified by baseline TB<sup>a</sup>

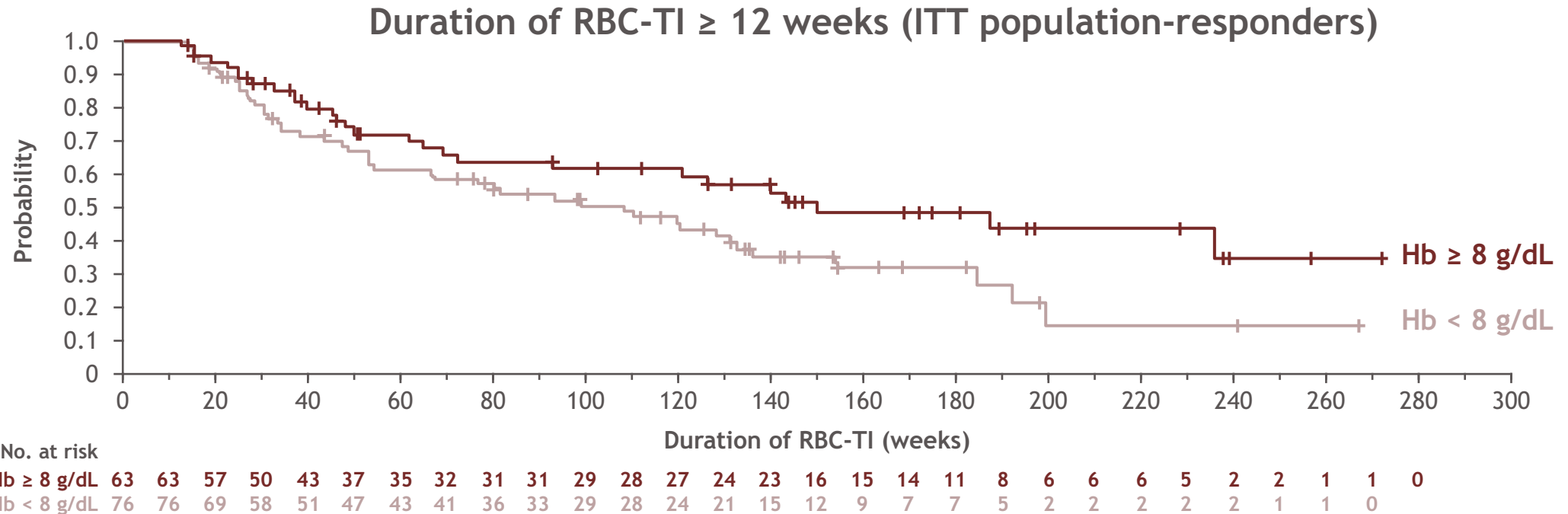


Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

<sup>a</sup>RBC-TI  $\geq$  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. <sup>b</sup>OR is based on an unstratified Cochran-Mantel-Haenszel test. <sup>c</sup>HI-E was defined as the proportion of patients with a mean Hb increase  $\geq$  1.5 g/dL in the absence of transfusions for patients with baseline TB < 4 U/8 weeks or  $\geq$  4 U reduction in transfusions for patients with baseline TB  $\geq$  4 U/8 weeks.

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

	Luspatercept		OR <sup>a</sup> /HR <sup>b</sup> (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), <sup>c</sup> % (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, <sup>d</sup> weeks	150.0 (72.0-NE)	108.3 (53.7-132.6)	HR, 0.623 (0.389-0.999)

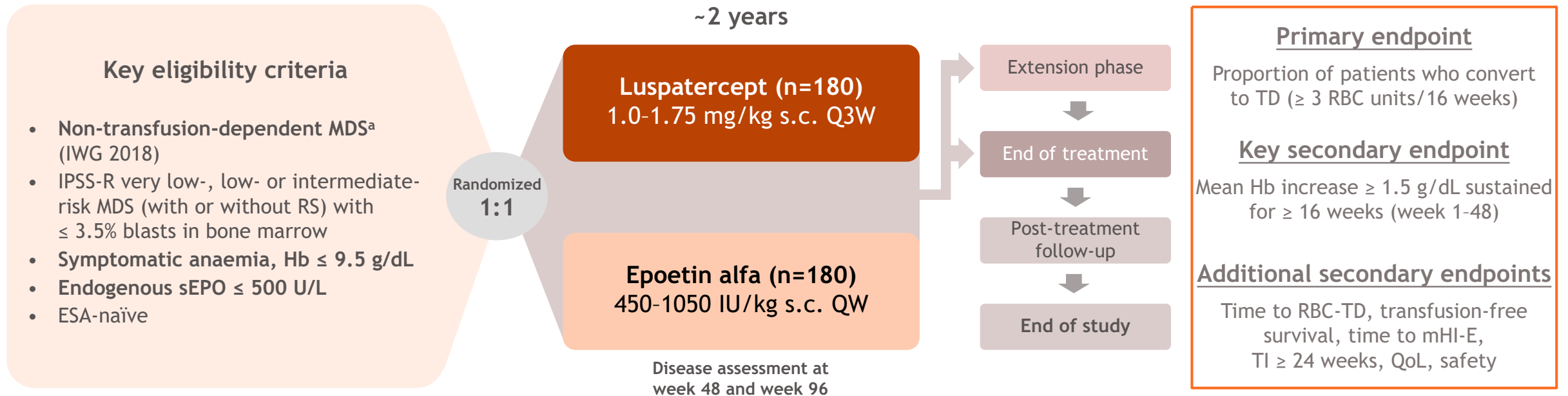


Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

<sup>a</sup>OR is based on an unstratified Cochran-Mantel-Haenszel test. <sup>b</sup>HR is calculated by an unstratified Cox proportional hazard model. <sup>c</sup>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. <sup>d</sup>Median is from an unstratified Kaplan-Meier method.

# Luspatercept: Wait for transfusion dependency?

## Ongoing: ELEMENT-MDS Phase 3 trial<sup>1,2</sup>

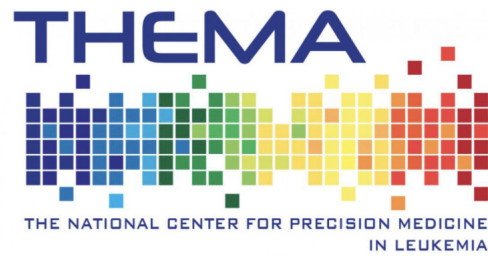


Luspatercept is not approved in Europe for patients with NTD anemia caused by lower-risk MDS

<sup>a</sup> 0 RBC units over 16 weeks prior to randomization; 1-2 RBC units within the 16 weeks prior to enrollment are allowed provided transfusion was administered for an acute event/illness (i.e. surgical procedure, bleeding, infection) or presence of comorbidity, and not for the treatment of low haemoglobin (with or without symptoms) alone.

ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; IPSS-R: International Prognostic Scoring System-Revised; IWG: International Working Group; MDS: myelodysplastic syndromes; mHI-E: modified haematological improvement - erythroid response; QoL, quality of life; QW: once a week; Q3W: once every 3 weeks; RBC: red blood cell; s.c.: subcutaneous; sEPO: serum erythropoietin; TD: transfusion dependency, TI: transfusion independence.

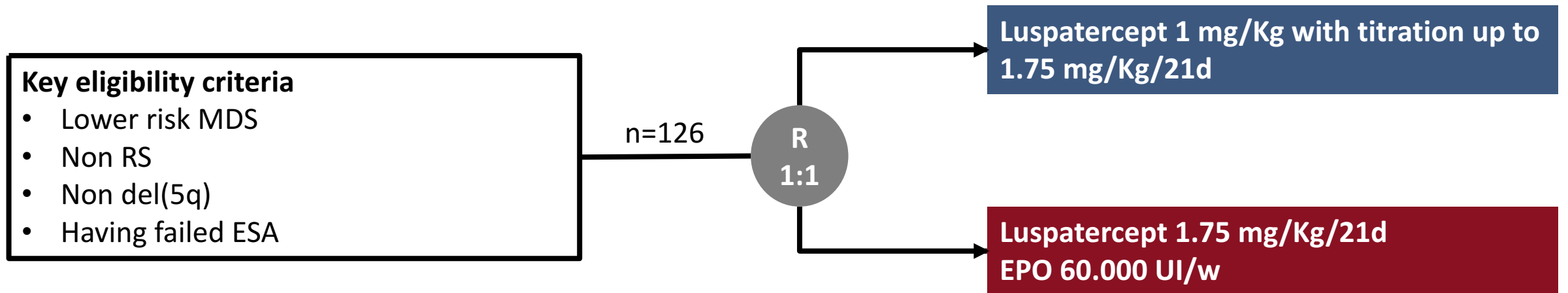
1. ClinicalTrials.gov. <https://clinicaltrials.gov/study/NCT05949684> (Accessed Jun 2024). 2. Zeidan AM, et al. *Blood* 2023;142(suppl.1):6503.



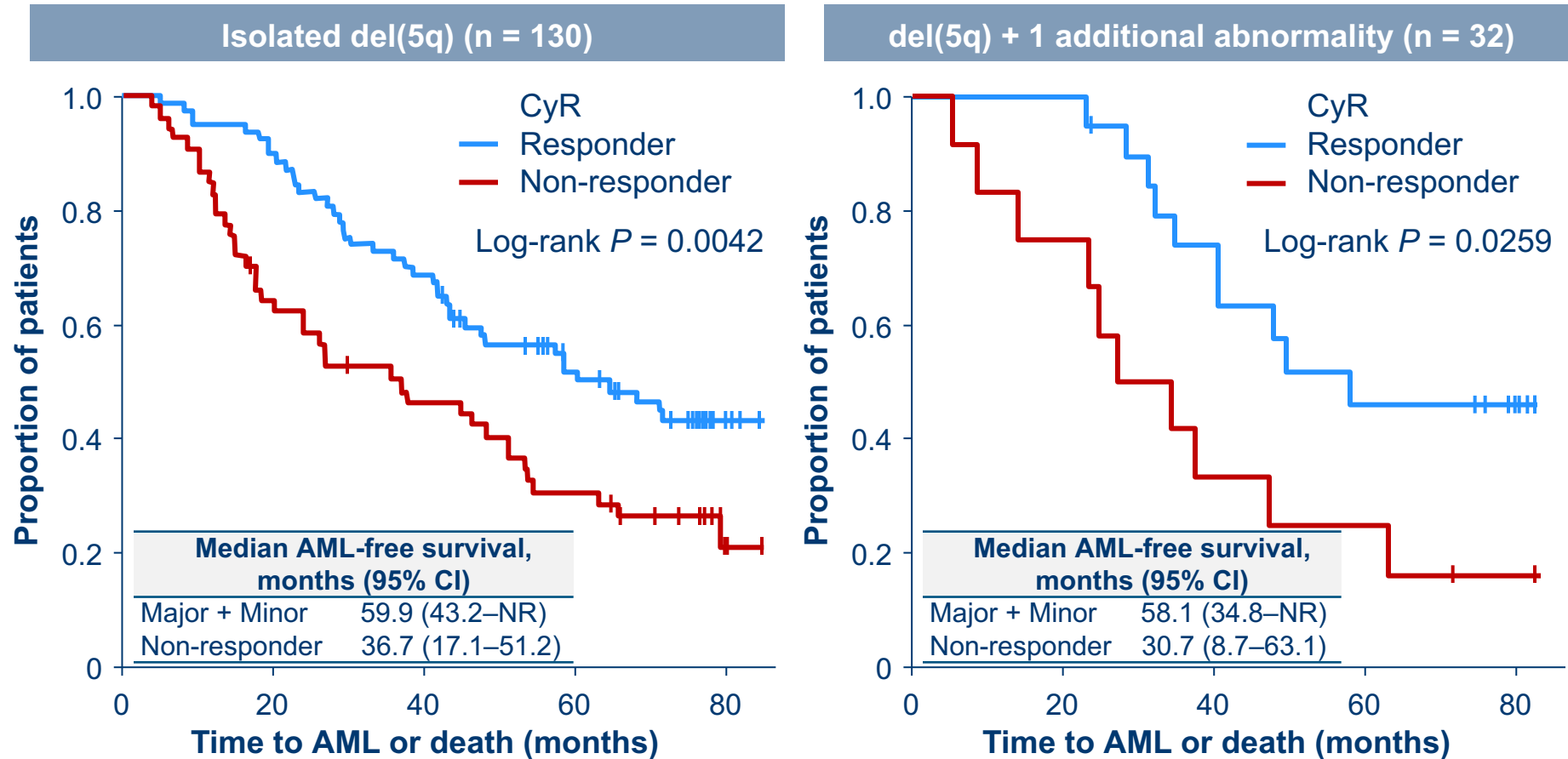
# Combining ESA and Luspatercept in Non-RS MDS Patients Having Failed ESA - Results of the Phase 1-2 Part a of the GFM Combola Study

*Lionel Adès, MD, PhD, Thomas Cluzeau, Thibault Comont, Lorea Aguinaga, Aspasia Stamatoullas, Mathieu Meunier, Emmanuel Gyan, Alice Garnier, Maud D'Aveni, Sylvain Thépot, Marie Sébert, Marius Moldovan, Anouk Walter Petrich, Karine Lemarié, Fatiha Chermat, Michaela Fontenay, Sylvie Chevret and Pierre Fenaux.*

# Combola Next step: Randomized part of the trial



# Results: AML-Free Survival by CyR in Patients With Isolated del(5q) and del(5q) + 1 Additional Abnormality

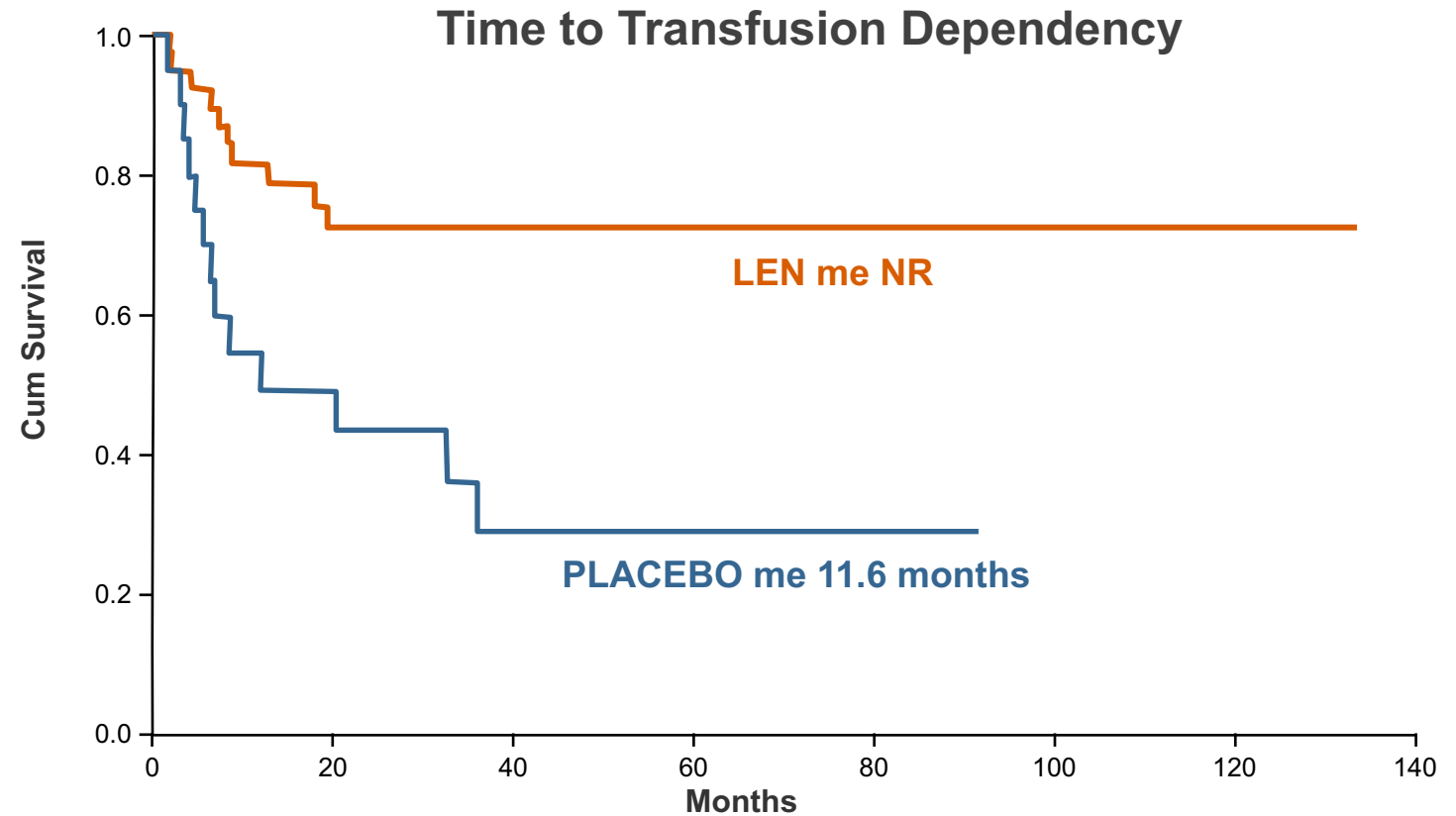


For the risk of AML transformation or death, CyR was associated with a 41% reduction (95% CI 0.38–0.92;  $P = 0.019$ ) in patients with isolated del(5q) and a 58% reduction (95% CI 0.17–1.02;  $P = 0.056$ ) in patients with del(5q) + 1 additional abnormality, compared with no CyR

# Sintra-Rev Trial

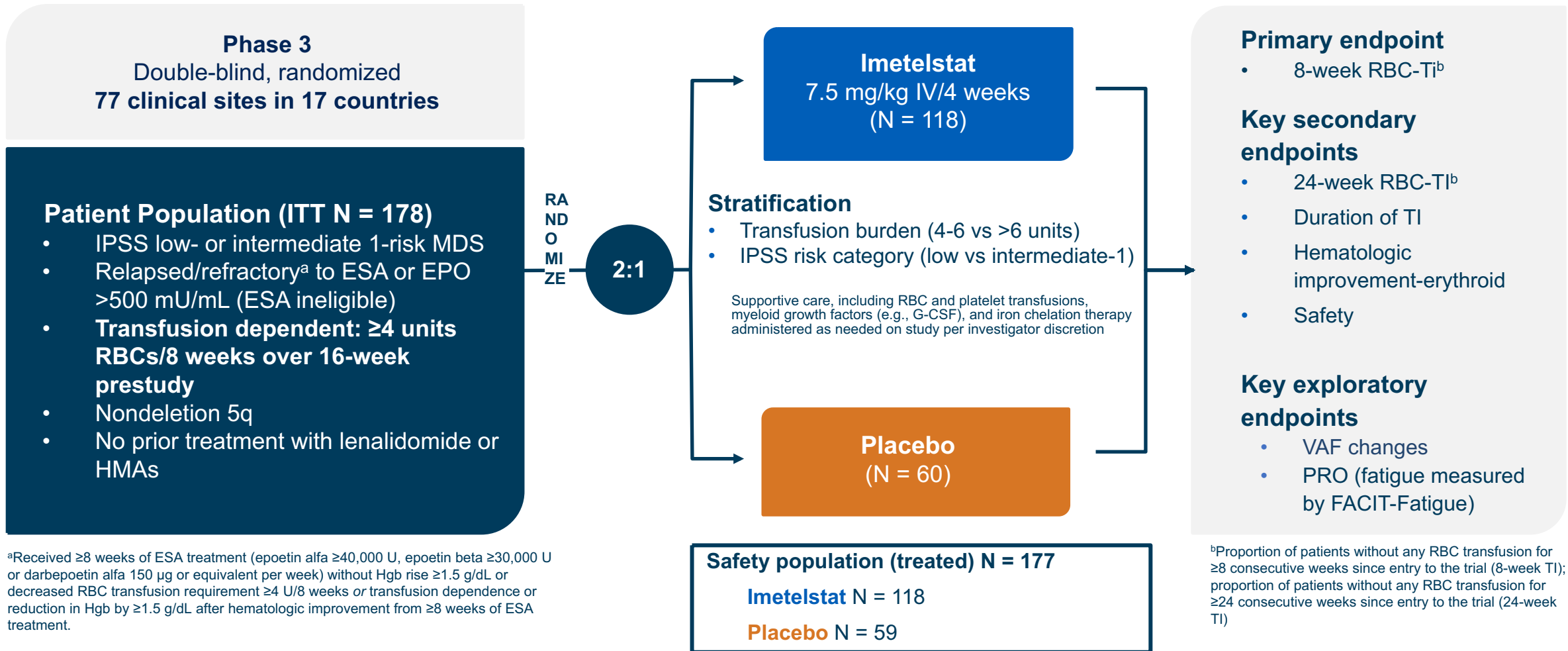
## Primary Objective: Efficacy (ITT, N=61)

- **Low doses of Len delayed and decreased transfusion dependency**
  - TD in 23 patients (38.3%):  
10 in Len (25%) vs 13 in placebo (65%)
  - Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692),  $P = 0.005$

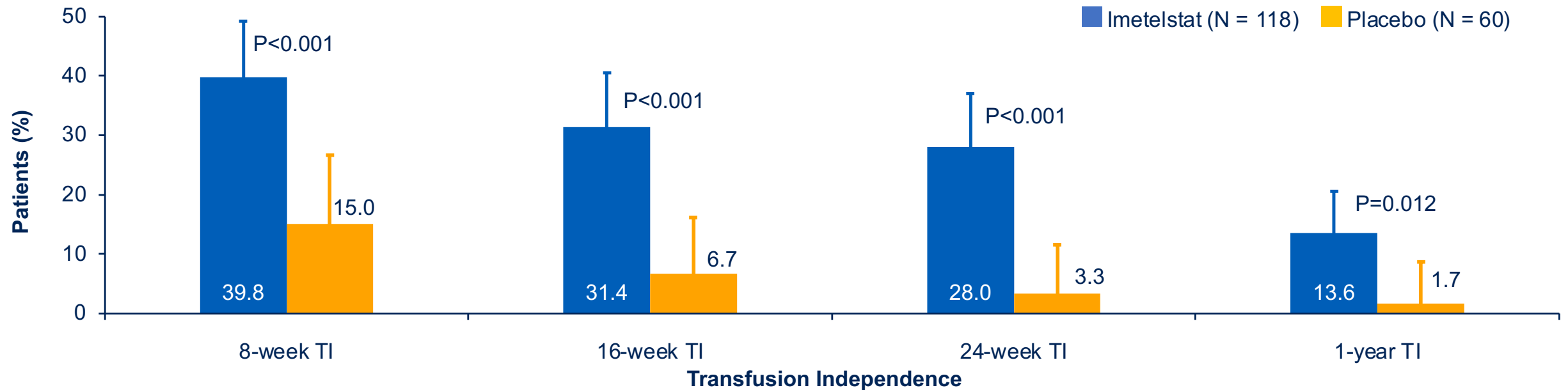


Median follow up 5.05y (0.3-11): 5.2 vs 4.85,  $P = ns$

# IMerge Phase 3 Trial: Imetelstat in Patients With LR-MDS Relapsed/Refractory to ESA or EPO<sup>1</sup>



# Higher Rates of Longer-Term Duration of RBC-TI Observed With Imetelstat vs Placebo<sup>1</sup>



## Patients With Response, n (% [95% CI])

<b>Imetelstat</b>	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
<b>Placebo</b>	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])



# A Randomized, Multicenter Trial of Shorter Durations of Hypomethylating Agents in Lower-Risk Myelodysplastic Syndromes

Ian M. Bouligny, MD<sup>1</sup>, Hetty Carraway, MD<sup>2</sup>, Mikkael A. Sekeres, MD<sup>3</sup>, Amy DeZern, MD<sup>4</sup>, Rami Komrokji, MD<sup>5</sup>, Richard Stone, MD<sup>6</sup>, Gail Roboz, MD<sup>7</sup>, Koji Sasaki, MD<sup>1</sup>, Guillermo Montalban-Bravo, MD<sup>1</sup>, Alex Bataller, MD<sup>1</sup>, Alexandre Bazinet, MD<sup>1</sup>, Danielle Hammond, MD<sup>1</sup>, Kelly Chien, MD<sup>1</sup>, Courtney D. DiNardo, MD<sup>1</sup>, Gautam Borthakur, MD<sup>1</sup>, Yesid Alvarado-Valero, MD<sup>1</sup>, Farhad Ravandi, MD,<sup>1</sup> Naval Daver, MD<sup>1</sup>, Tapan Kadia, MD<sup>1</sup>, Naveen Pemmaraju, MD<sup>1</sup>, Nicholas J. Short, MD<sup>1</sup>, Jane Waukau<sup>1</sup>, Matthew Rump<sup>2</sup>, Colin Huck<sup>4</sup>, Wei Qiao, PhD<sup>1</sup>, Xuelin Huang, PhD<sup>1</sup>, Elias Jabbour, MD<sup>1</sup>, Guillermo Garcia-Manero, MD<sup>1\*</sup>

<sup>1</sup>The University of Texas MD Anderson Cancer Center, Houston, TX

<sup>2</sup>Taussig Cancer Center, Cleveland Clinic, Cleveland, OH

<sup>3</sup>Sylvester Cancer Center, University of Miami, Miami, FL

<sup>4</sup>Sidney Kimmel Cancer Center, Johns Hopkins University, Baltimore, MD

<sup>5</sup>Moffitt Cancer Center, University of South Florida, Tampa, FL

<sup>6</sup>Dana-Farber Cancer Institute, Harvard University, Boston, MA

<sup>7</sup>Sandra and Edward Meyer Cancer Center, Cornell University, New York, NY

## Inclusion Criteria

≥18 years with **IPSS low- or intermediate-1-risk** MDS, CMML, or MDS/MPN

ECOG 0 to 3

Prior hypomethylating agent exposure **excluded**

## Cohorts

Transfusion dependent

3-day decitabine, 20 mg/m<sup>2</sup>  
3-day azacitidine, 75 mg/m<sup>2</sup>  
5-day azacitidine, 75 mg/m<sup>2</sup>

Transfusion independent

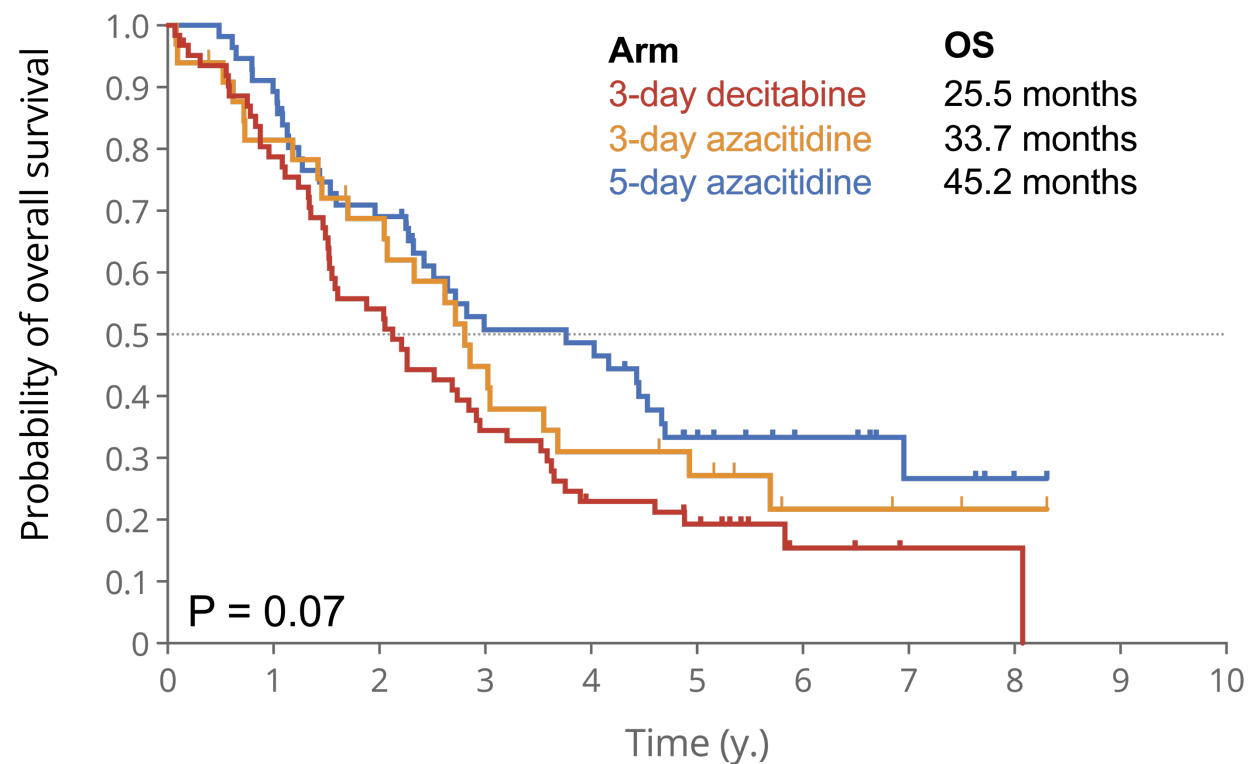
3-day decitabine, 20 mg/m<sup>2</sup>  
3-day azacitidine, 75 mg/m<sup>2</sup>  
5-day azacitidine, 75 mg/m<sup>2</sup>  
Best supportive care

Transfusion dependence was defined as requiring a RBC or platelet transfusion due to MDS **at any point** prior to therapy.

Bayesian randomization assigned patients to the arm with the **best EFS**.

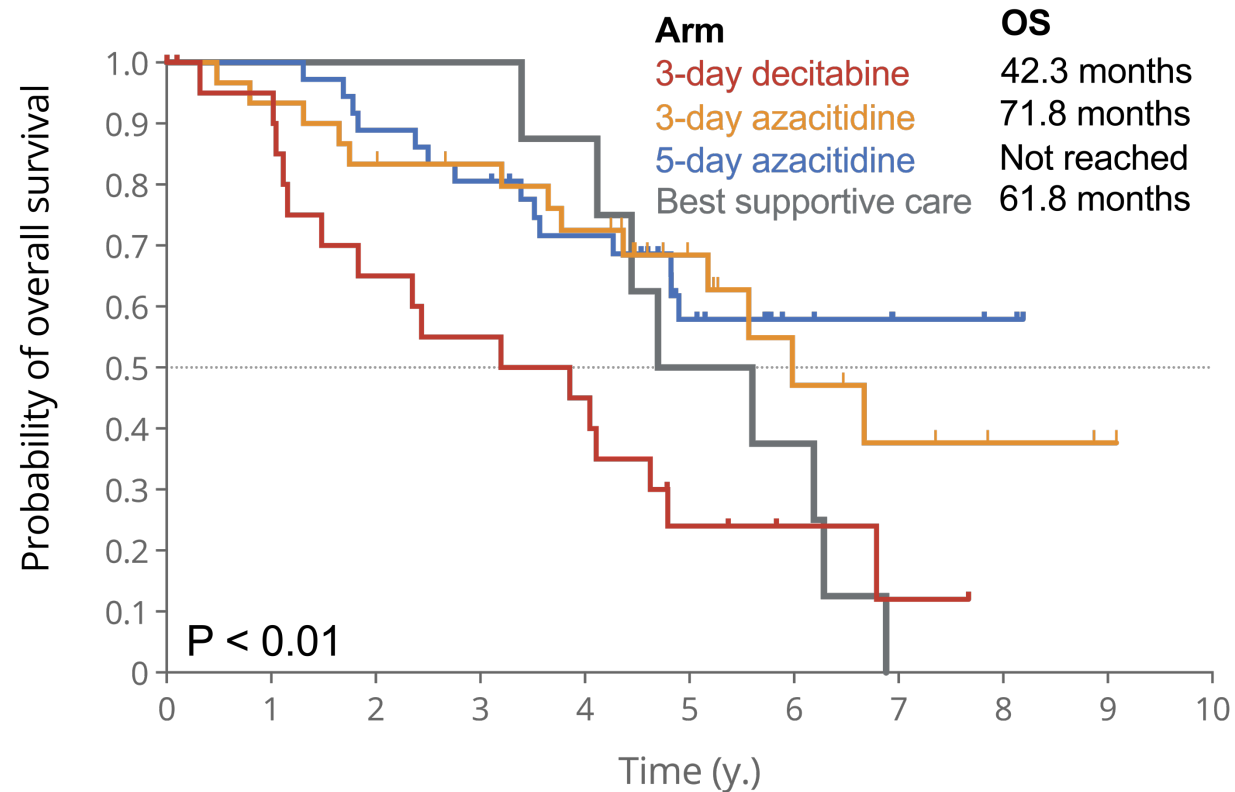
# Overall Survival

## Transfusion dependent



■	62	48	33	21	13	10	3	1	1	0	0
■	33	26	21	13	9	7	3	2	1	0	0
■	56	50	37	24	23	13	8	4	1	0	0

## Transfusion independent



■	22	19	13	11	9	4	2	1	0	0	0
■	30	28	25	23	20	12	6	4	2	1	0
■	36	36	32	29	24	15	6	3	2	0	0
■	8	8	8	8	7	4	3	0	0	0	0

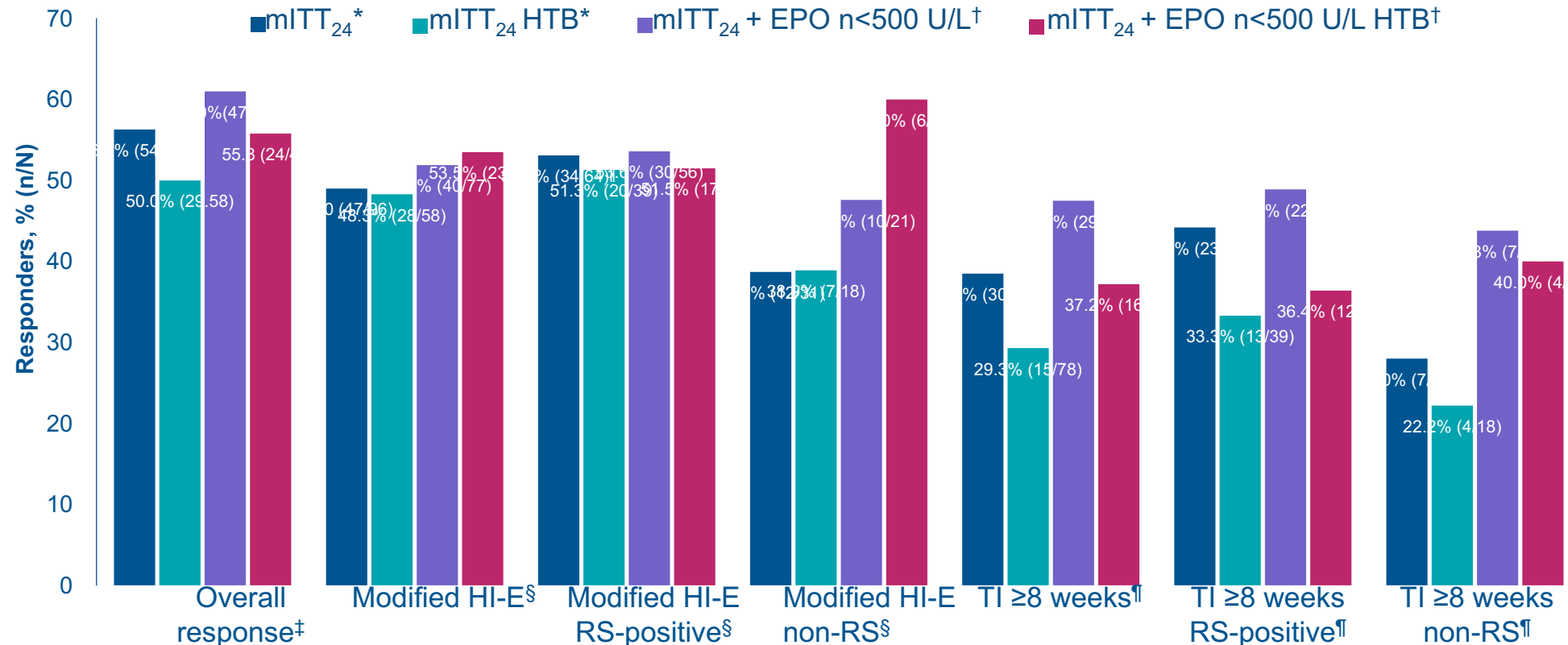


# Elritercept shows durable responses in lower-risk myelodysplastic neoplasms (LR-MDS) with transfusion dependence: updated results from an ongoing Phase 2 trial

Lynette Chee,<sup>1</sup> Shuh Ying Tan,<sup>2</sup> David Valcarcel Ferreiras,<sup>3</sup> Anish Puliyyayil,<sup>4</sup> Alejandro Arbelaez,<sup>5</sup> Montserrat Arnan Sangerman,<sup>6</sup> David M Ross,<sup>7</sup> Devendra Hiwase,<sup>8</sup> Teresa Bernal del Castillo,<sup>9</sup> Thomas Cluzeau,<sup>10</sup> Aristoteles Giagounidis,<sup>11</sup> Jen Salstrom,<sup>12</sup> Radha Ramesh,<sup>13</sup> Camden Bay,<sup>13</sup> Kevin Galinsky,<sup>13</sup> Leopold Sellner,<sup>13</sup> Kaveri Suryanarayan,<sup>13</sup> Maria Diez Campelo<sup>14</sup>

<sup>1</sup>The Royal Melbourne Hospital/ Peter MacCallum Cancer Centre, Department of Clinical Haematology, Melbourne, Australia; <sup>2</sup>St. Vincent's Hospital Melbourne, Fitzroy, Australia; <sup>3</sup>Vall d'Hebron University Hospital, Barcelona, Spain; <sup>4</sup>Border Medical Oncology and Haematology, Albury, Australia; <sup>5</sup>Tweed Valley Hospital, Cancer Care Services, Tweed Heads, Australia; <sup>6</sup>Institut Català d'Oncologia, Hospitalet de Llobregat, Barcelona, Spain; <sup>7</sup>Flinders Medical Centre, Adelaide, Australia; <sup>8</sup>The Royal Adelaide Hospital, Adelaide, Australia; <sup>9</sup>Hospital Universitario Central de Asturias, ISPA, IUOPA, Oviedo, Asturias, Spain; <sup>10</sup>CHU de Nice, Nice, France; <sup>11</sup>Marien Hospital Düsseldorf, Düsseldorf, Germany; <sup>12</sup>Keros Therapeutics, Lexington, United States; <sup>13</sup>Takeda Development Center Americas, Inc. (TDCA), Cambridge, United States; <sup>14</sup>Servicio de Hematología, Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain

# Responses were achieved by patients across a range of subgroups



\*Includes data for Weeks 0–24 for mITT<sub>24</sub> patients; †Includes data for Weeks 0–24 in mITT<sub>24</sub> patients with baseline EPO < 500 U/L, excluding one patient with del5q MDS; ‡Defined as achieving modified IWG 2006 HI-E and/or TI; §In patients with LBT, response was defined as a mean Hgb increase ≥1.5 g/dL during any 8-week treatment period. For patients with HTB, response was defined as a reduction in ≥4 units of RBC transfused during any 8-week study period compared with the 8-week period before C1D1; ¶RS Status missing in one patient; ¶Includes all responders who are MDS RP2D patients who have had 24 weeks of treatment or have discontinued before reaching week 24 at the data cutoff (mITT<sub>24</sub>) in addition to having ≥2 units of RBC transfusion at baseline. Hgb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LBT, low transfusion burden; MDS, myelodysplastic neoplasms; mITT<sub>24</sub>, modified intent-to-treat-24; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.



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## Safety and Efficacy Results from a Phase 1b Study of R289, a Dual IRAK 1/4 Inhibitor, in Patients with Relapsed/Refractory (R/R) Lower Risk Myelodysplastic Syndrome (LR-MDS)

**Guillermo Garcia-Manero, MD<sup>1</sup>**, Yazan F. Madanat, MD<sup>2</sup>, Mikkael A. Sekeres, MD, MS<sup>3</sup>, Hetty E. Carraway, MD<sup>4</sup>, Michael Cusnir, MD<sup>5</sup>, James McCloskey, MD<sup>6</sup>, Kiran Naqvi, MD, MPH<sup>7</sup>, Gary Schiller, MD<sup>8</sup>, Frank J. Hsu, MD<sup>9</sup>, Toufigh Gordi, PhD, MBA<sup>9</sup>, Lisa Rojkaer, MD<sup>9</sup>, Lewis R. Silverman, MD<sup>10</sup>

<sup>1</sup>Department of Leukemia, MD Anderson Cancer Center, University of Texas, Houston, TX; <sup>2</sup>Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; <sup>3</sup>Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; <sup>4</sup>Taussig Cancer Institute, Leukemia Program, The Cleveland Clinic, Cleveland, OH; <sup>5</sup>Mount Sinai Comprehensive Cancer Center (MSCCC), Miami Beach, FL; <sup>6</sup>Hackensack University Medical Center, John Theurer Cancer Center, Hackensack, NJ; <sup>7</sup>Division of Hematology/Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA; <sup>8</sup>David Geffen School of Medicine at UCLA, Los Angeles, CA; <sup>9</sup>Rigel Pharmaceuticals Inc. South San Francisco, CA; <sup>10</sup>Icahn School of Medicine at Mount Sinai, New York, NY

# Targeting Inflammatory Pathways in LR-MDS with R289, a Dual IRAK1/4 Inhibitor

- Interleukin receptor-associated kinases (IRAK) 1 and 4 are critical for downstream signaling of IL-1R family and most toll-like receptors (TLR) (Fig. 1), promoting proinflammatory cytokine production, bone marrow inflammation and cell death.<sup>1</sup>
- Co-targeting IRAK 1/4 may suppress inflammation and leukemic stem/progenitor cell function and restore hematopoiesis in MDS.
- R835 is a selective dual inhibitor of IRAK 1/4 that blocks TLR4 and IL-1R dependent cytokine release in vitro and in vivo<sup>2</sup> and substantially suppressed LPS-induced cytokine release compared to placebo in healthy subjects.<sup>3</sup>
- **We present dose escalation results from a phase 1b, open-label, single arm study evaluating the safety and preliminary efficacy of the oral IRAK 1/4 inhibitor R289, a prodrug of R835, in LR-MDS patients (NCT05308264).**

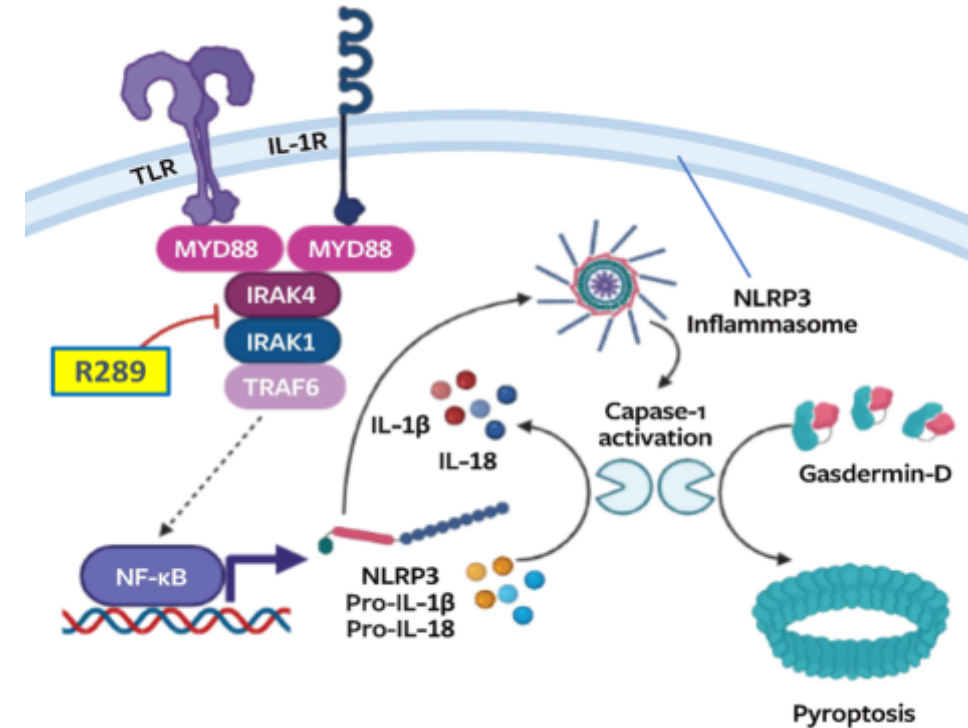


Fig 1: TLR/IL-1R Signaling Pathway

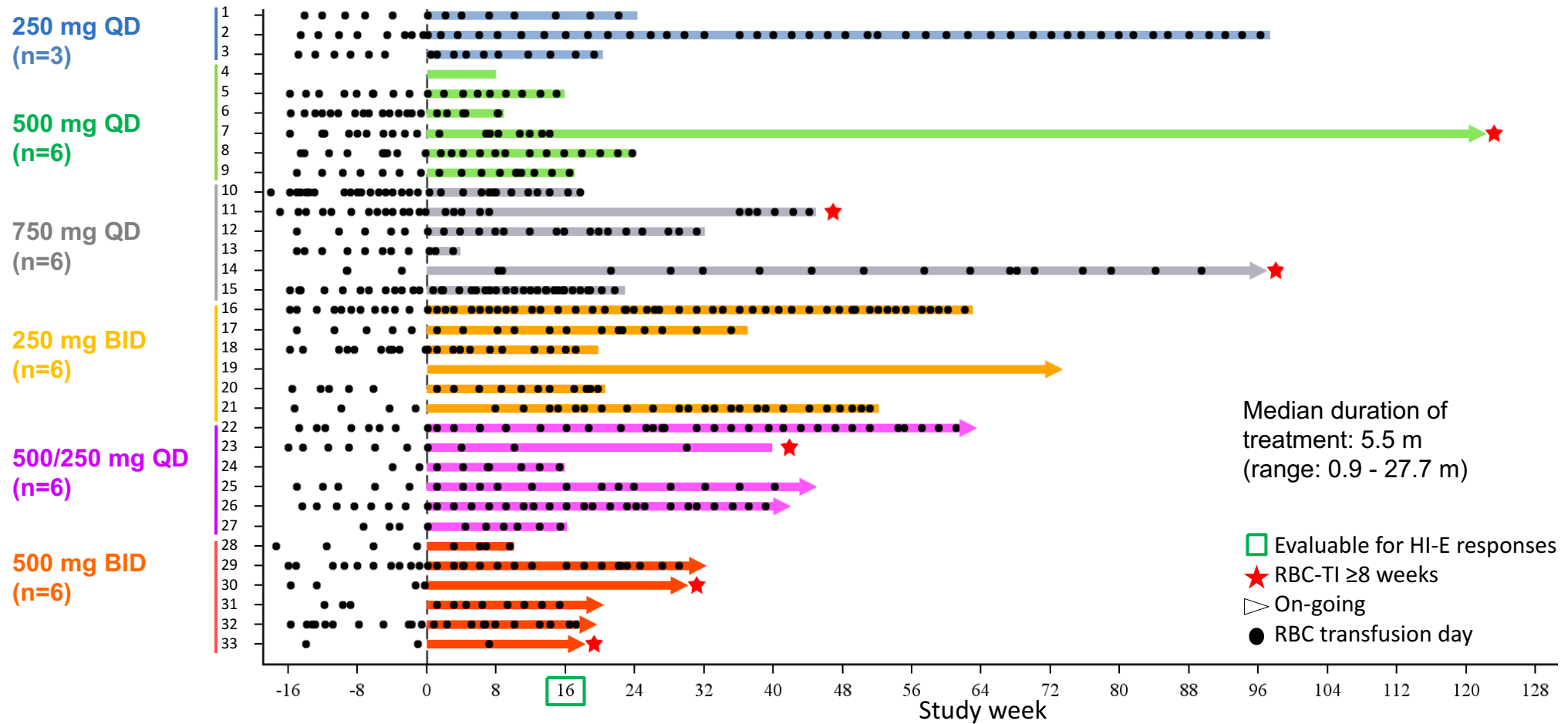
1. Sallman DA, et al. *Front Oncol.* 2016;6. 2. Lamagna C et al. *Ann Rheum Dis* 2020;79 (suppl 1). 3. Yan L et al. *Ann Rheum Dis* 2020;79 (suppl 1).

# Patient Characteristics (2)

	All patients (n=33)
<b>Median no. prior therapies (range)</b>	<b>3 (1 - 8)</b>
• Prior hypomethylating agent (HMA)	22 (67%)
• Prior luspatercept	25 (76%)
• Prior erythropoiesis stimulating agent (ESA)	24 (73%)
• Prior imetelstat	2 (6%)
<b>High transfusion burden (HTB)</b> (≥ 8u RBCs/prior 16 weeks)	<b>20 (61%)</b>
<b>Low transfusion burden (LTB)</b> (3-7u RBCs/prior 16 weeks)	<b>11 (33%)</b>
<b>Non-transfused (NT)</b>	<b>2 (6%)</b>
<b>Mean baseline ANC, 10<sup>9</sup>/L (range)</b>	<b>2.4 (0.3 - 5.4)</b>
• ANC <1.0 x 10 <sup>9</sup> /L	5 (15%)
<b>Mean baseline platelet count, 10<sup>9</sup>/L (range)</b>	<b>183 (32 - 524)</b>
• Plts < 100 x 10 <sup>9</sup> /L	7 (21%)

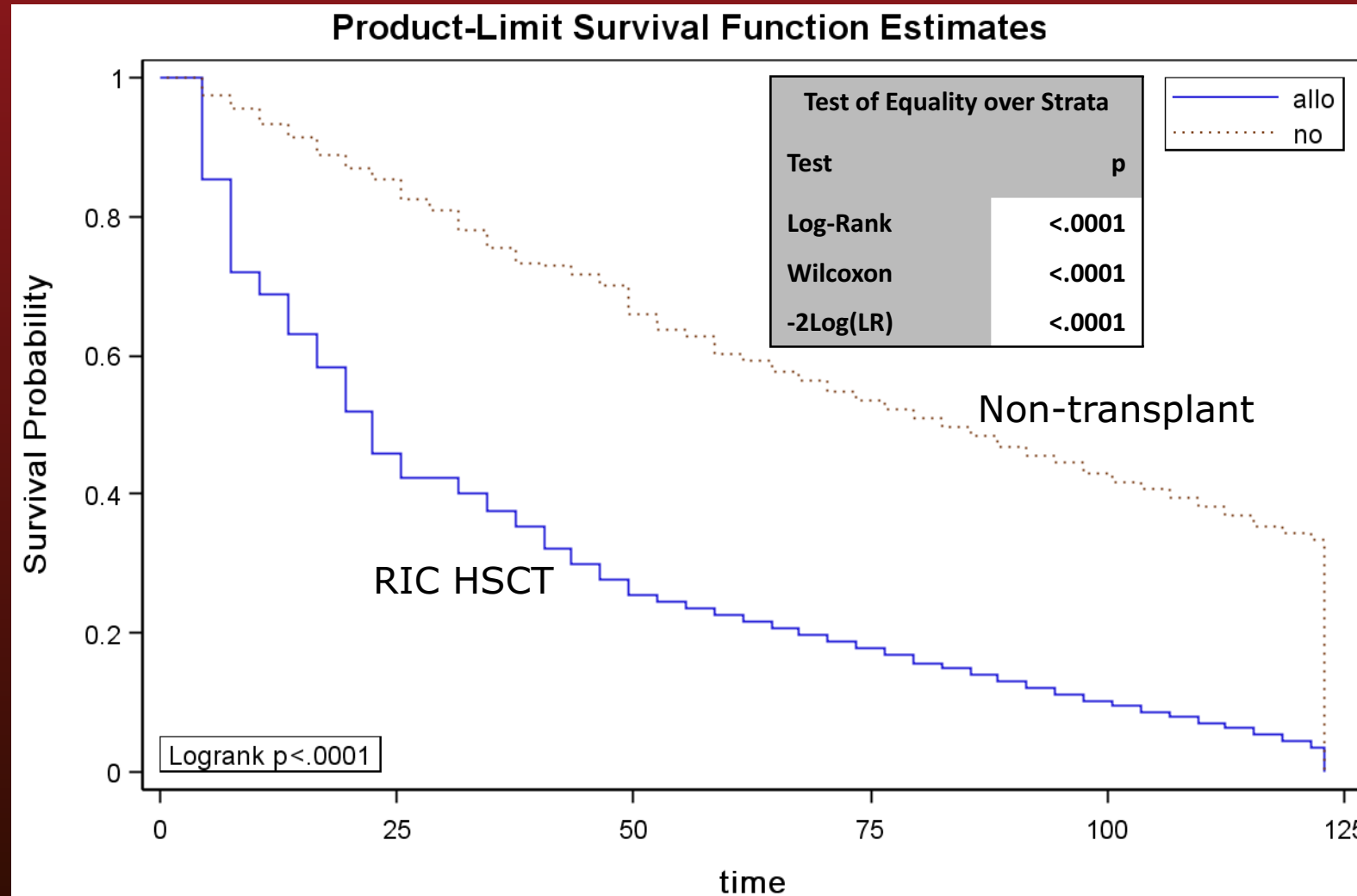


# RBC Transfusion Events by Dose Group

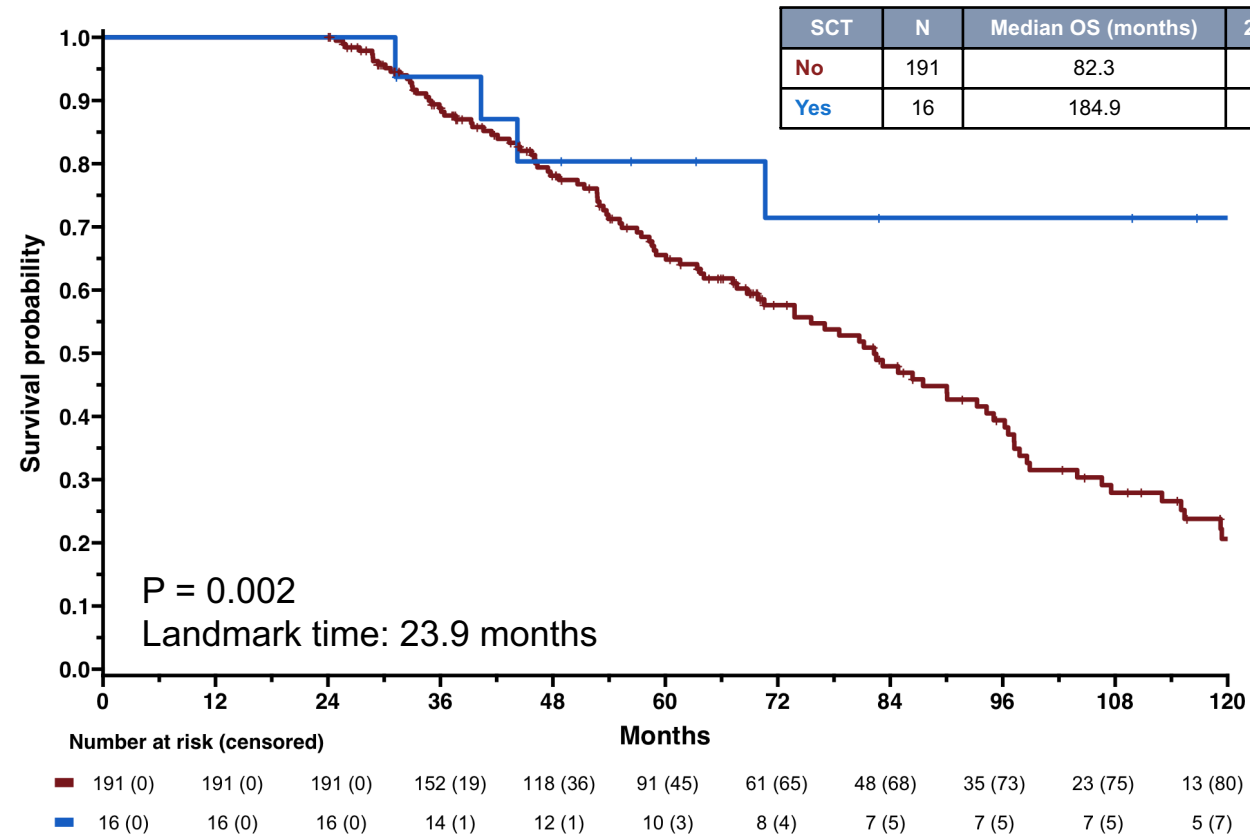


- 6/18 (33%) evaluable TD patients receiving ≥500 mg QD achieved RBC-TI >8 weeks; 4 >16 weeks; 3 >24 weeks
- Median time to onset of RBC-TI: 1.9 months
- Median duration of RBC-TI: 22.9 weeks (9 - 104.3)

# Monte Carlo – Low/int-1 IPSS Survival Estimates

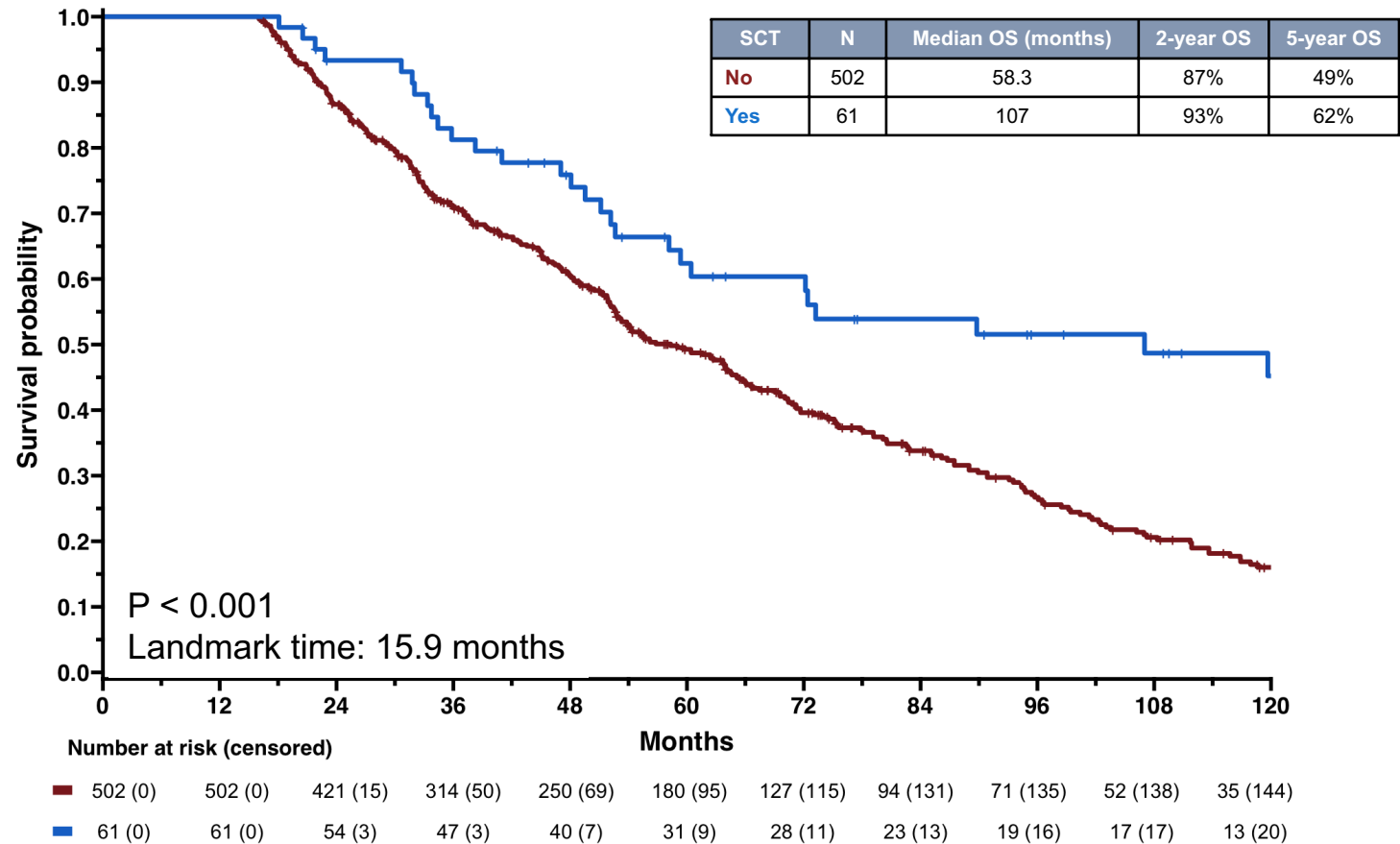


# Landmark OS: IPSS-R Very Low Risk



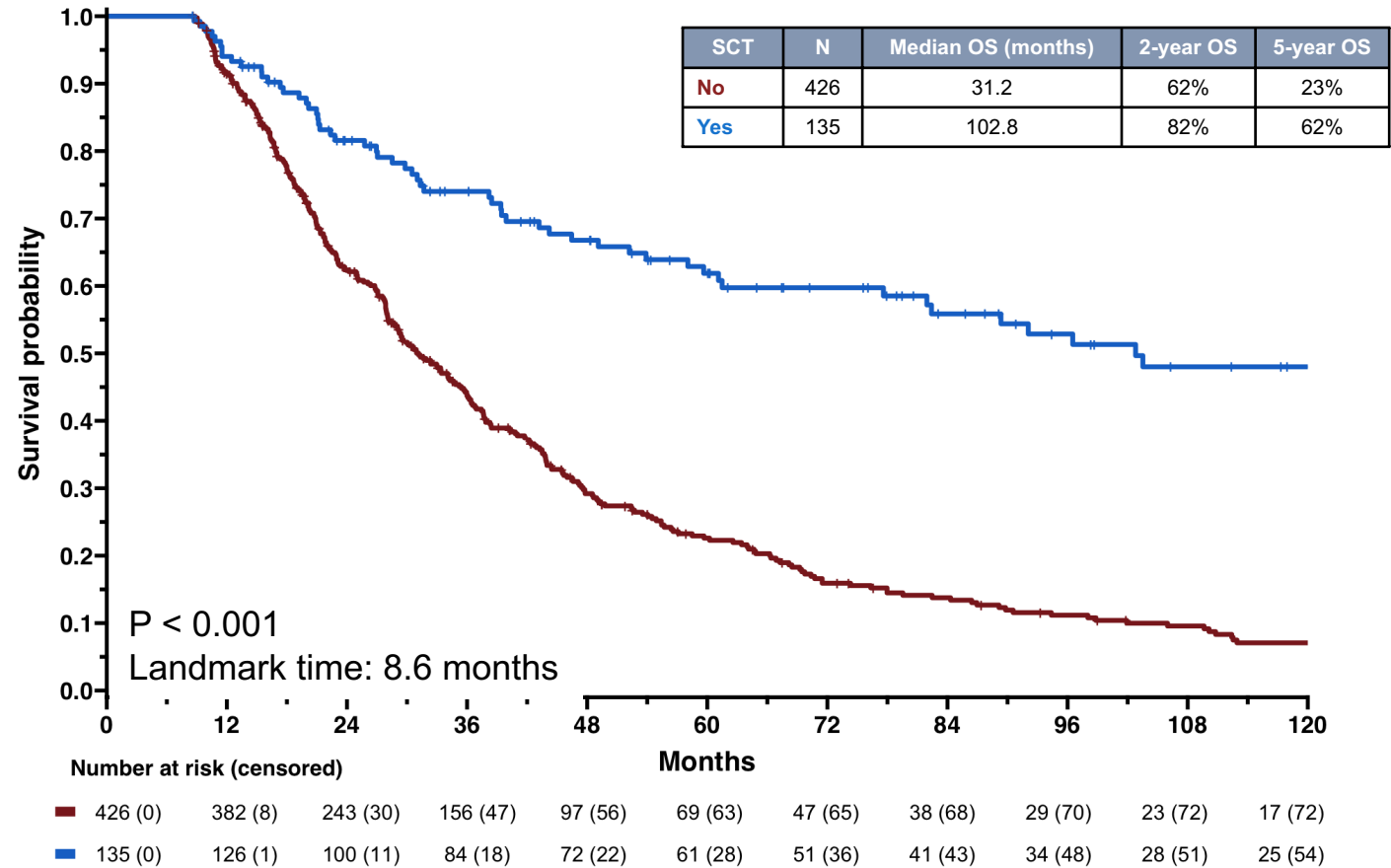
Bazinet et al EHA 2024

# Landmark OS: IPSS-R Low Risk



Bazinet et al EHA 2024

# Landmark OS: IPSS-R Intermediate Risk



Bazinet et al EHA 2024

# Treatment algorithm 2025 LR MDS in the US

Entity	First line	Second line
Del5q- MDS isolated anemia	<b>Lenalidomide</b>	ESA, luspa, HMA, alloSCT
Isolated anemia, very low risk features	ESA <b>Luspatercept</b>	Imetelstat, HMA, ESA, len, alloSCT
RARS post ESA	<b>Luspatercept</b>	Imetelstat, HMA, len, alloSCT
Other lower risk MDS (bilineal cytopenia)	<b>HMA</b>	alloSCT
IDH1, IDH2, p53, SF3B1	<b>Consider targeted approach, ivosidenib</b>	

Based on NCCN guidelines

# Suggested sequences in LR MDS anemia

Scenario	1st Line	Beyond
Del5q MDS	Lenalidomide (independent of epo level)	Sequence other drugs
Epo < 200, RS-, SF3B1-	Luspatercept or ESA	Reverse order, imetelstat, HMA, lenalidomide, alloSCT, clinical trial
Epo > 200, RS+, SF3B1+	Luspatercept	Imetelstat, HMA, lenalidomide, alloSCT, clinical trial
Epo > 500	Imetelstat	HMA, alloSCT, clinical trial
Anemia + other cytopenia	HMA	AlloSCT, other, clinical trial
IDH1, IDH2	Ivosidenib, enasidenib, luspatercept, ESA	? imetelstat, HMA, lenalidomide, alloSCT, clinical trial

# **Other trials in LR MDS in clinical trials**

- **Luspatercept**
- **IRAK4 inhibitors**
- **Imetelstat**
- **Canakinumab**
- **KER-050**
- **NLPR3 inhibitors**
- **Momelotinib**
- **IDH1 inhibitors**

# Conclusions

- **Molecular data helps identify true lower risk MDS**
- **Development and approval of active new agents for LR-MDS**
- **Next:**
  - **Targeting CCUS**
  - **Combination strategies**
  - **Targeting platelets**
  - **Role of SCT**
  - **Modulation of comorbidities**

# Thank you

**Guillermo Garcia-Manero**

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**MD Anderson Cancer Center**

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