

# **Treatment of anemia in MDS: selecting the right strategy for the right patient**

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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**

# 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?**

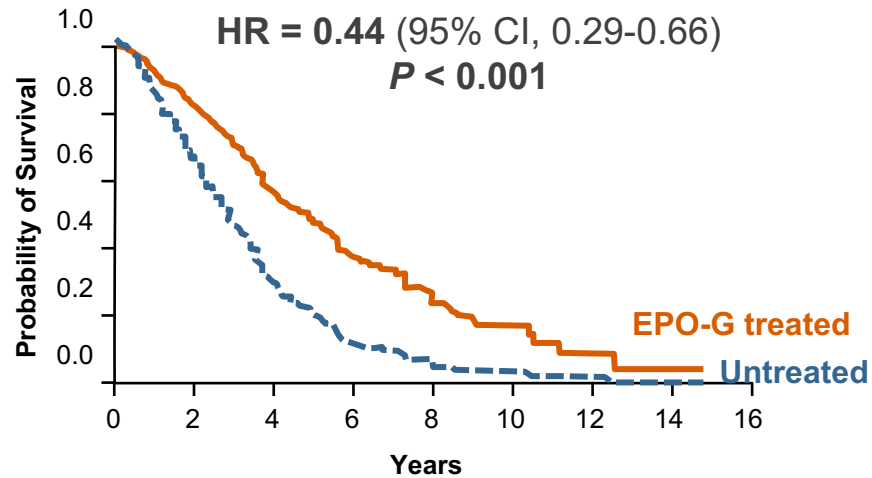
# Treatment algorithm 2025 LR MDS in the US

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>	

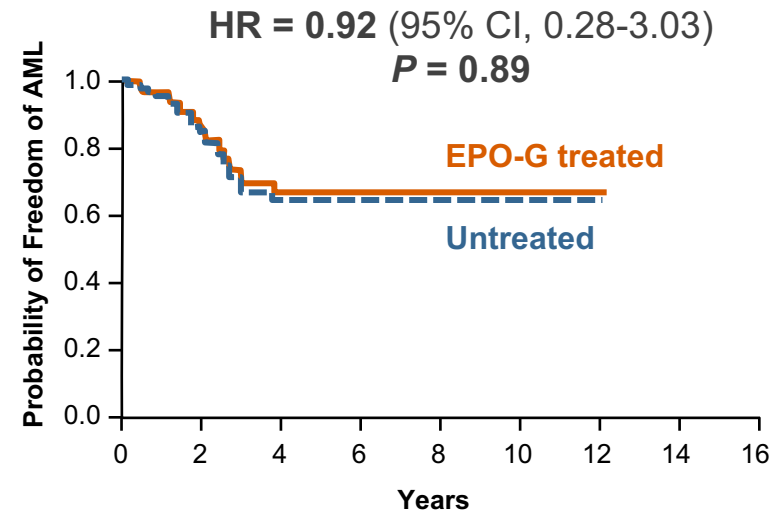
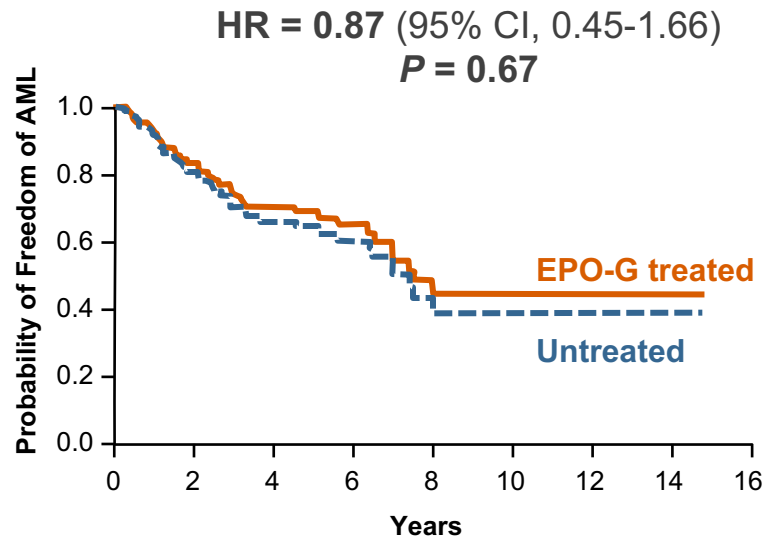
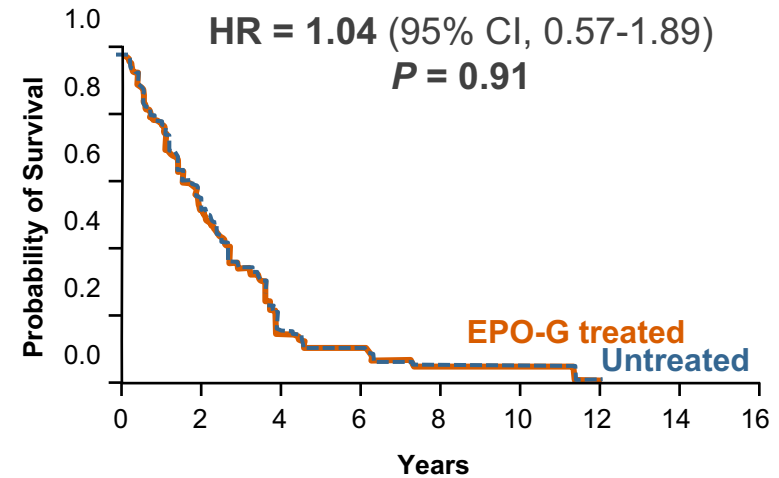
Based on NCCN guidelines

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

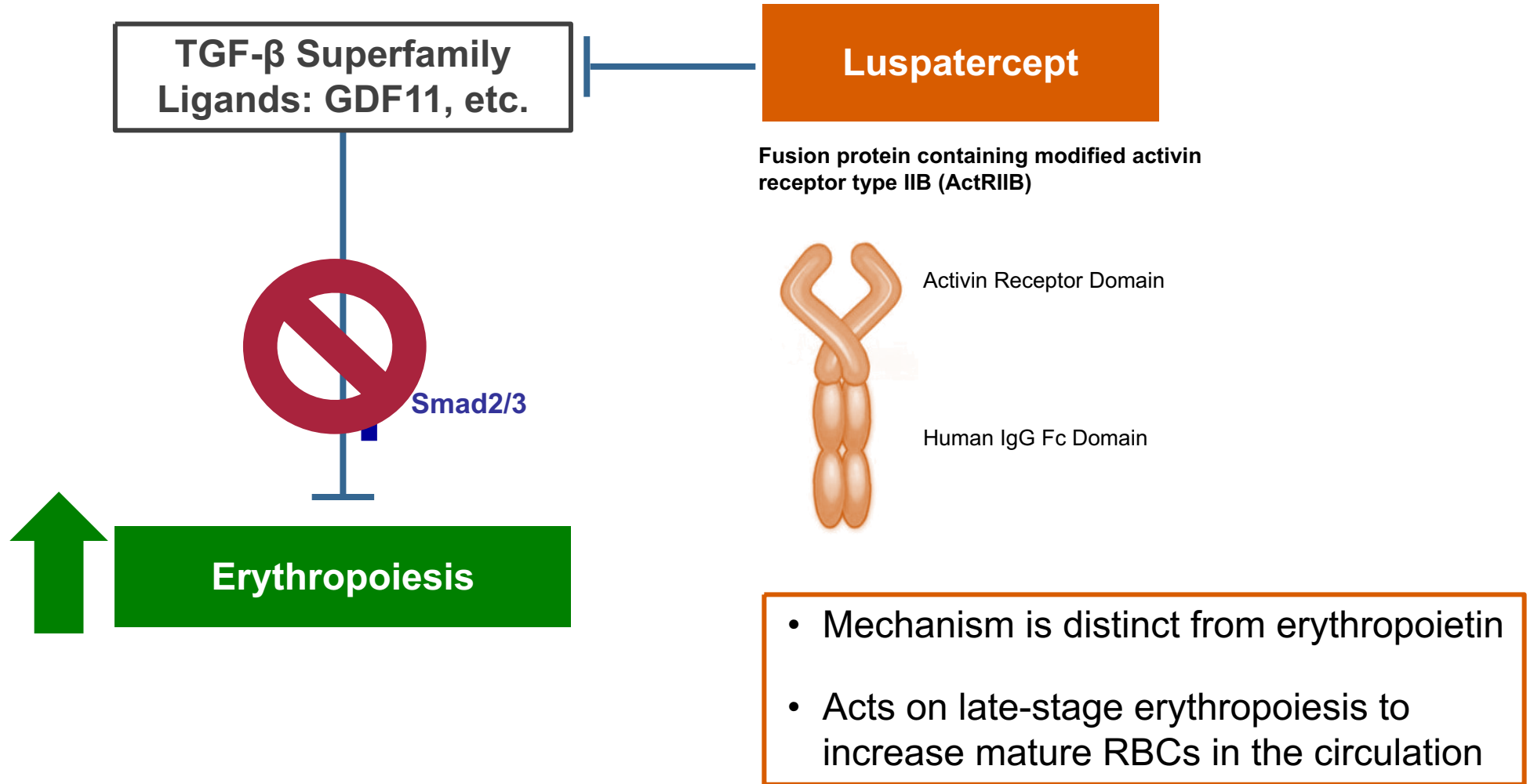
$\leq 1$  Unit PRBC per Month



$\geq 2$  Units PRBC per Month



# Luspatercept in MDS: Background



# 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)

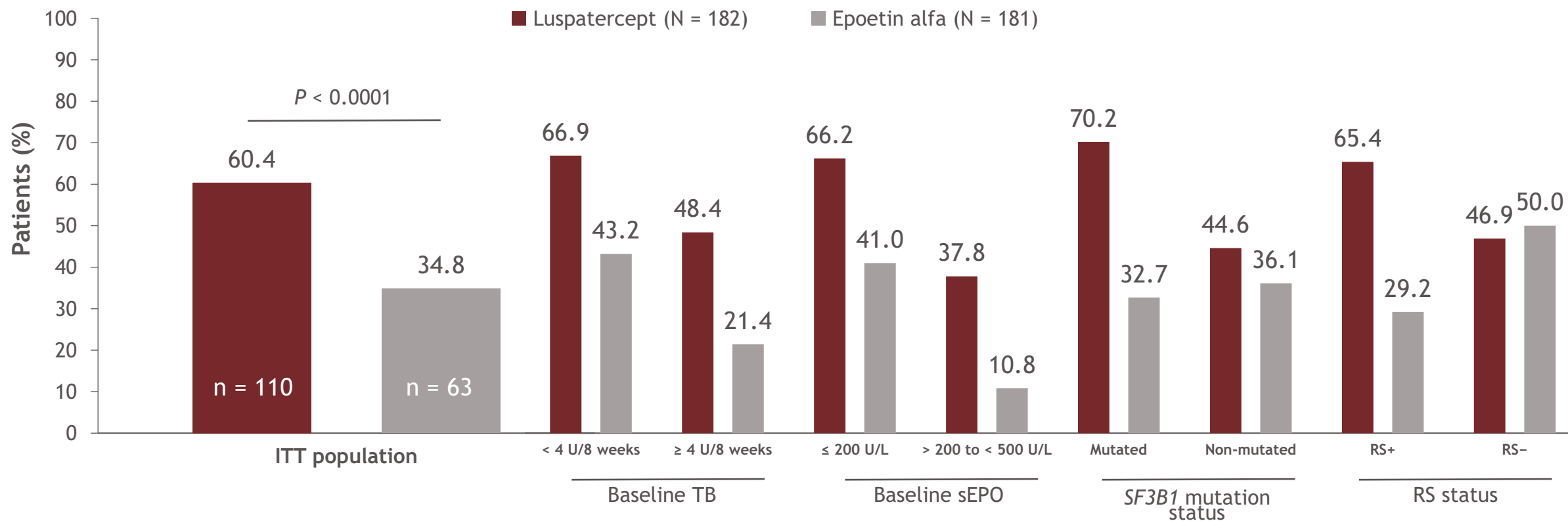
## Safety assessment

- 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.

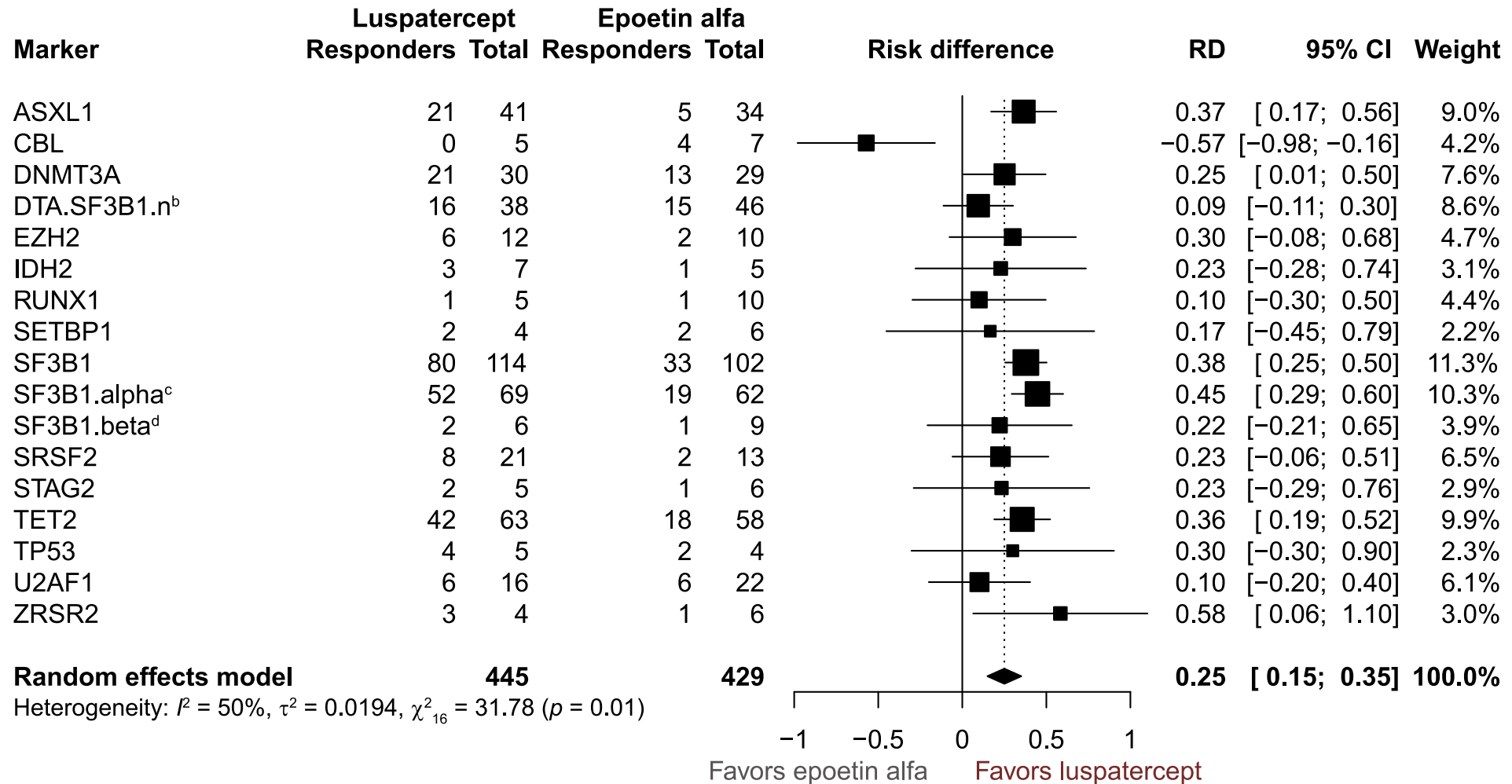
# COMMANDS: achievement of primary endpoint in ITT population and subgroups

- 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.

# 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.

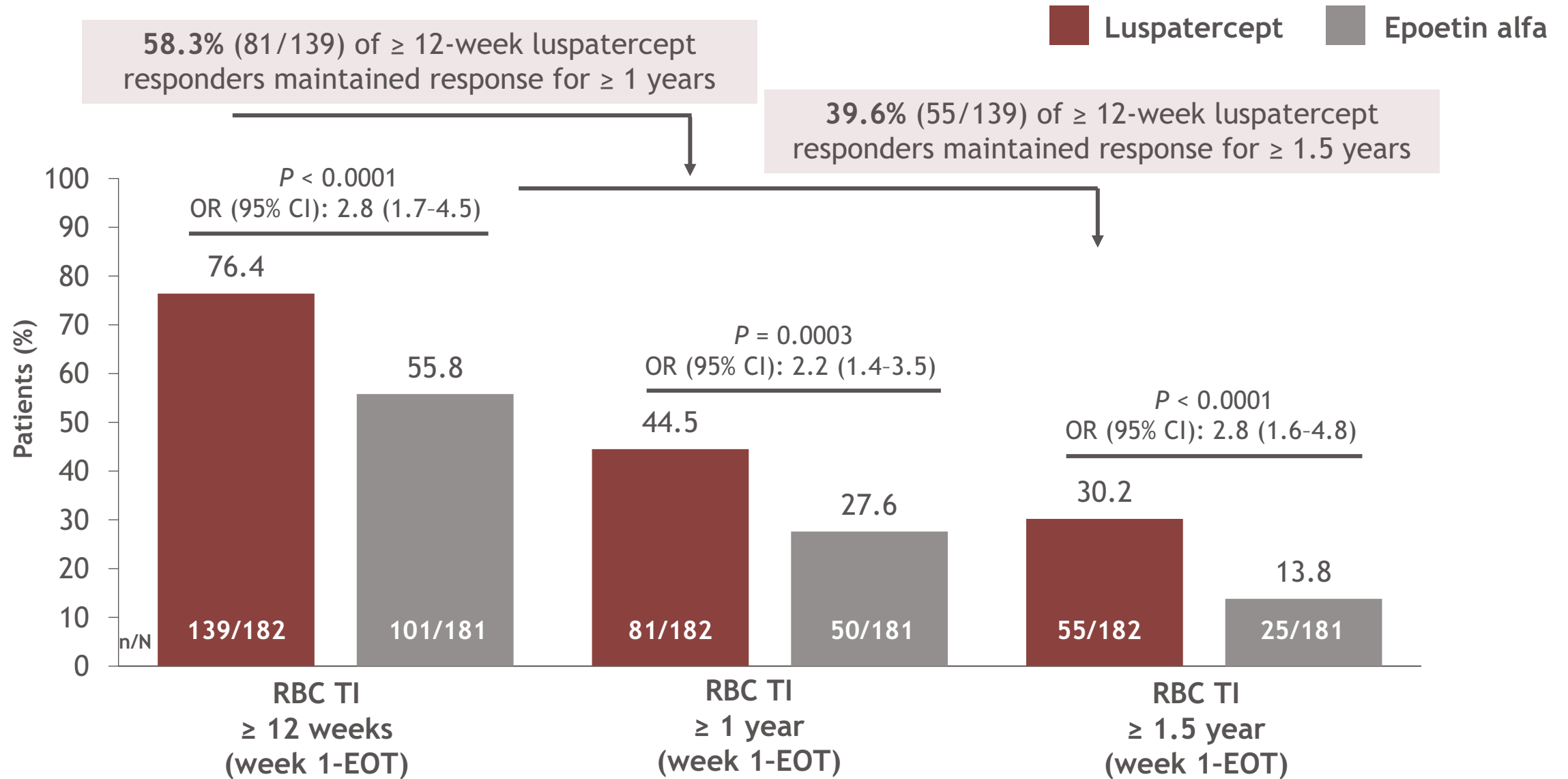
MDS, myelodysplastic syndromes; mut, mutation; RD, risk difference; wt, wild type.

# 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

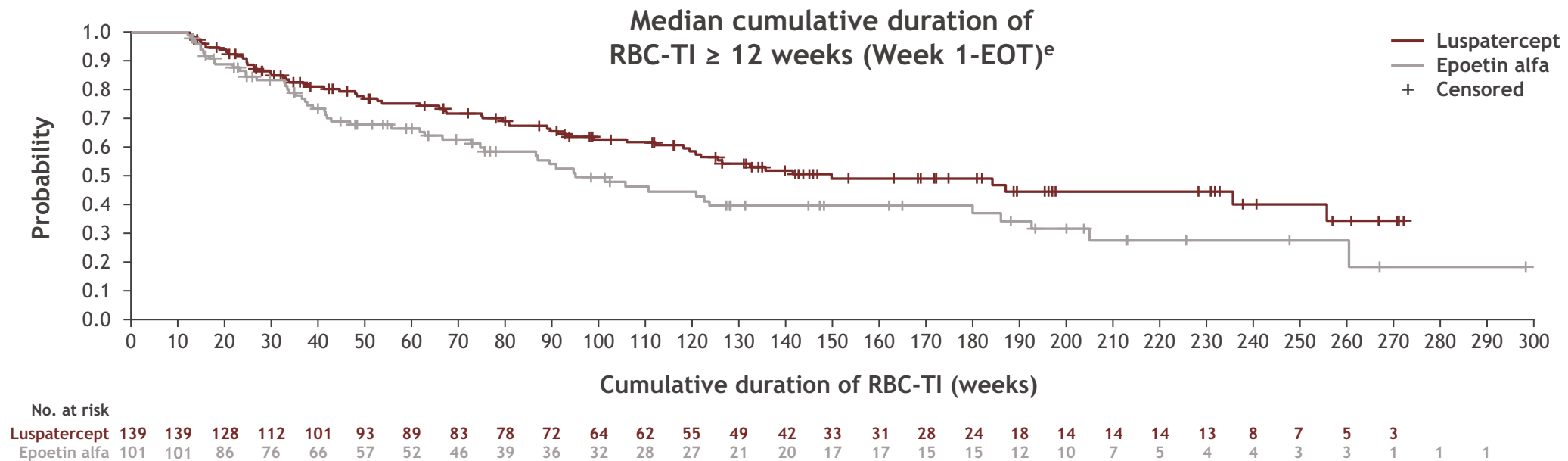
[Guillermo Garcia-Manero](#),<sup>1</sup> [Matteo Giovanni Della Porta](#),<sup>2</sup> [Amer M. Zeidan](#),<sup>3</sup> [Rami S. Komrokji](#),<sup>4</sup> [Veronika Pozharskaya](#),<sup>5</sup> [Shelonitda Rose](#),<sup>5,\*</sup> [Karen L. Keeperman](#),<sup>5</sup> [Yinzhi Lai](#),<sup>5</sup> [Sameer 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



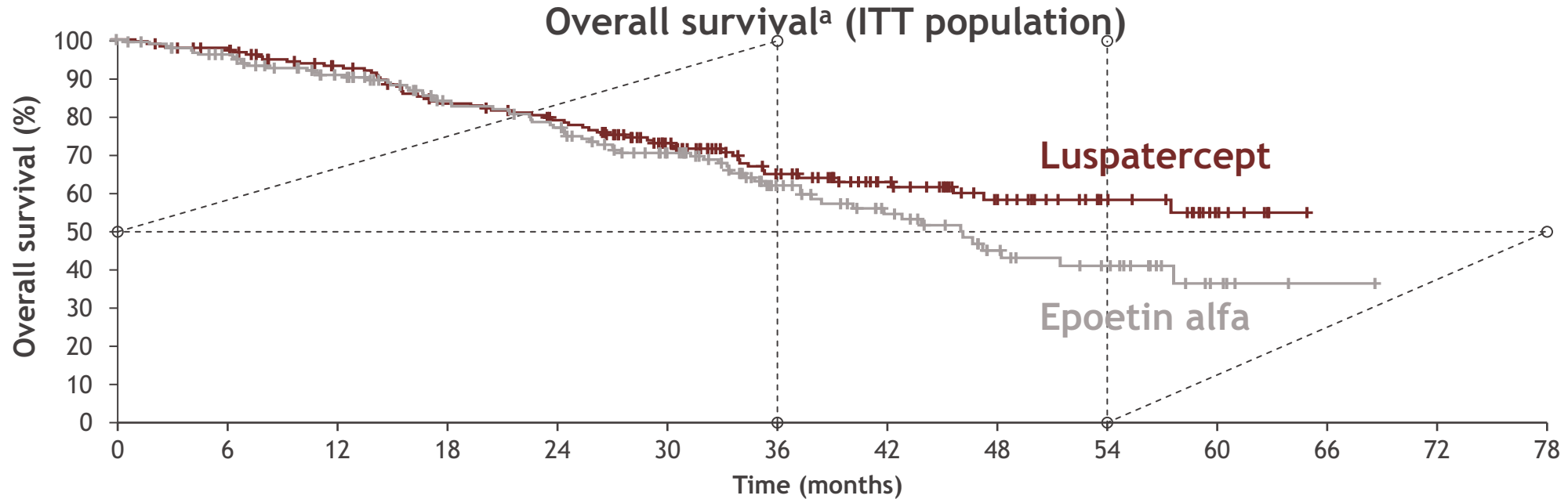
Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

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	1			
Epoetin alfa	181	166	144	120	109	87	55	39	24	17	5				

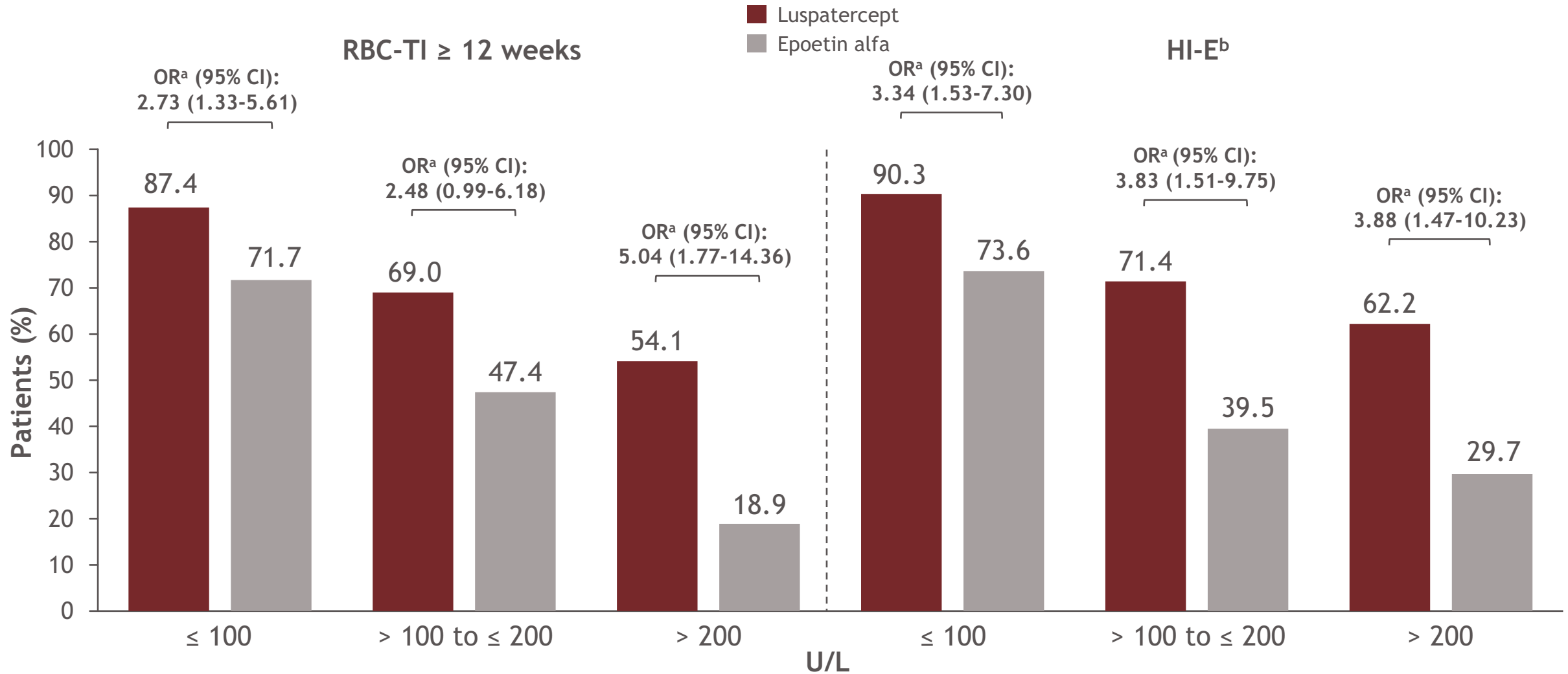
	Luspatercept	Epoetin alfa	HR (95% CI) <sup>b</sup>
Median OS, <sup>c</sup> months	NR	46.0	0.805 (0.565-1.146)
Piecewise analysis Deaths, n/N (%), ≥ 36 months	6/68 (8.8)	15/55 (27.3)	0.330 (0.128-0.853); P = 0.0221

# 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

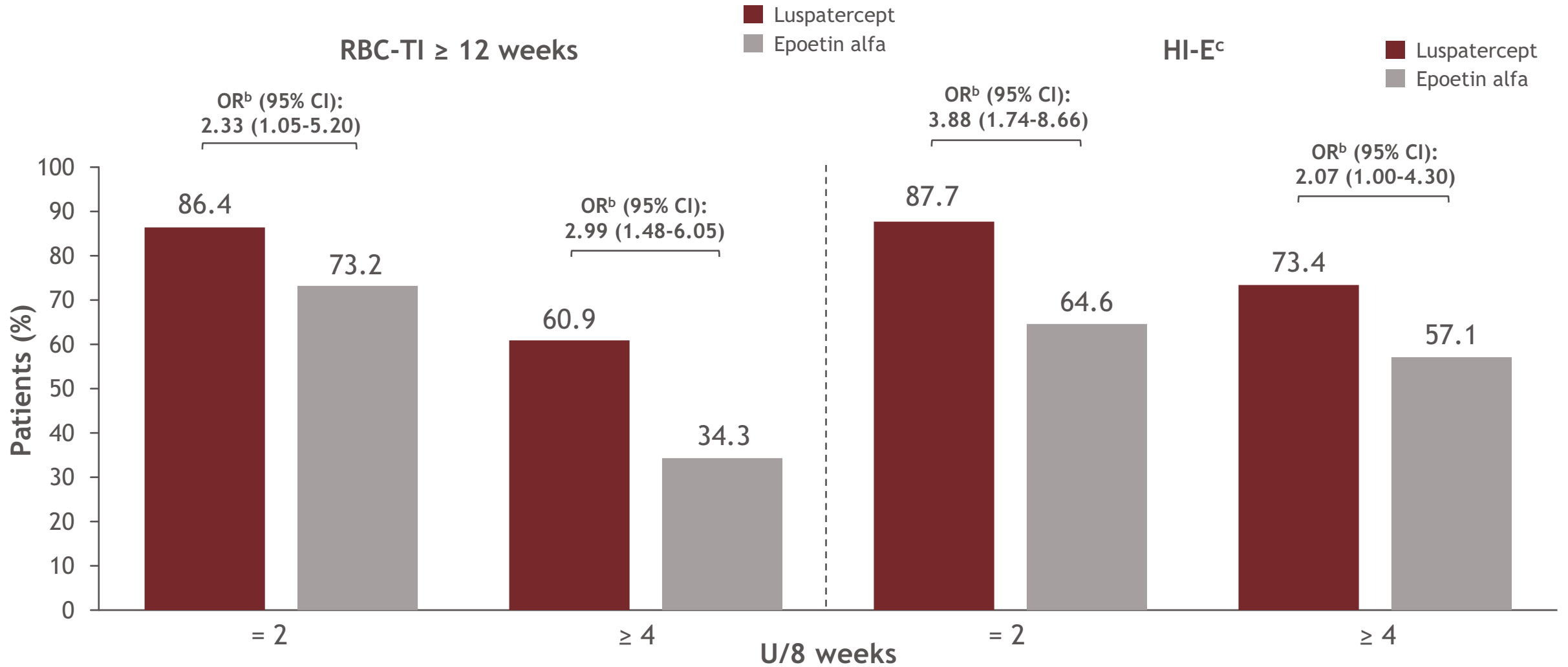
# Achievement of RBC-TI $\geq 12$ weeks and HI-E (Week 1-EOT) with luspatercept and epoetin alfa, stratified by baseline sEPO



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>

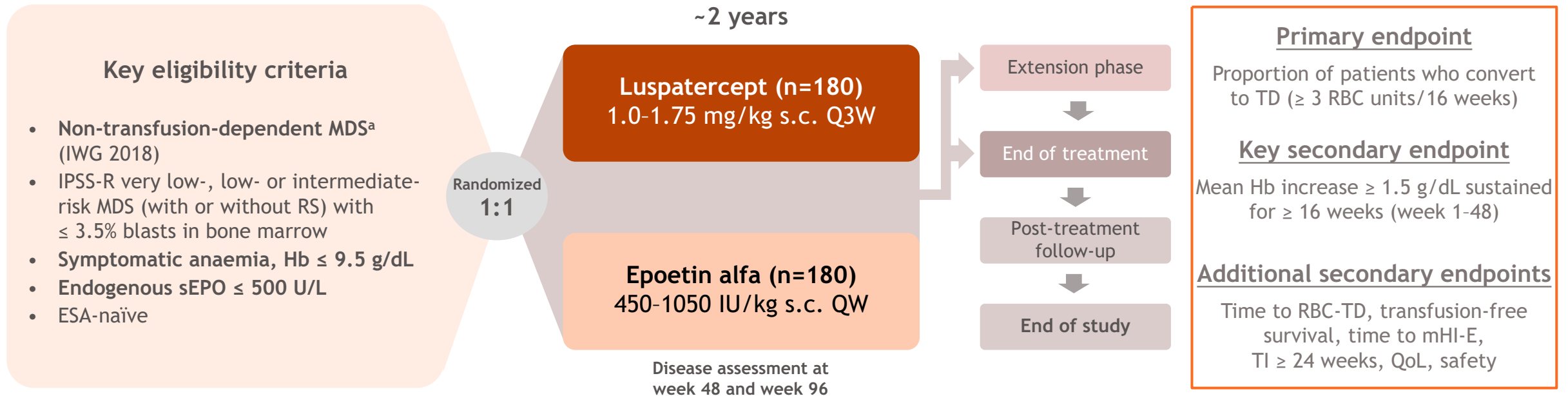


Data cutoff: February 7, 2025. Median (range) follow-up was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

<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.

# Luspatercept: Wait for transfusion dependency?

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



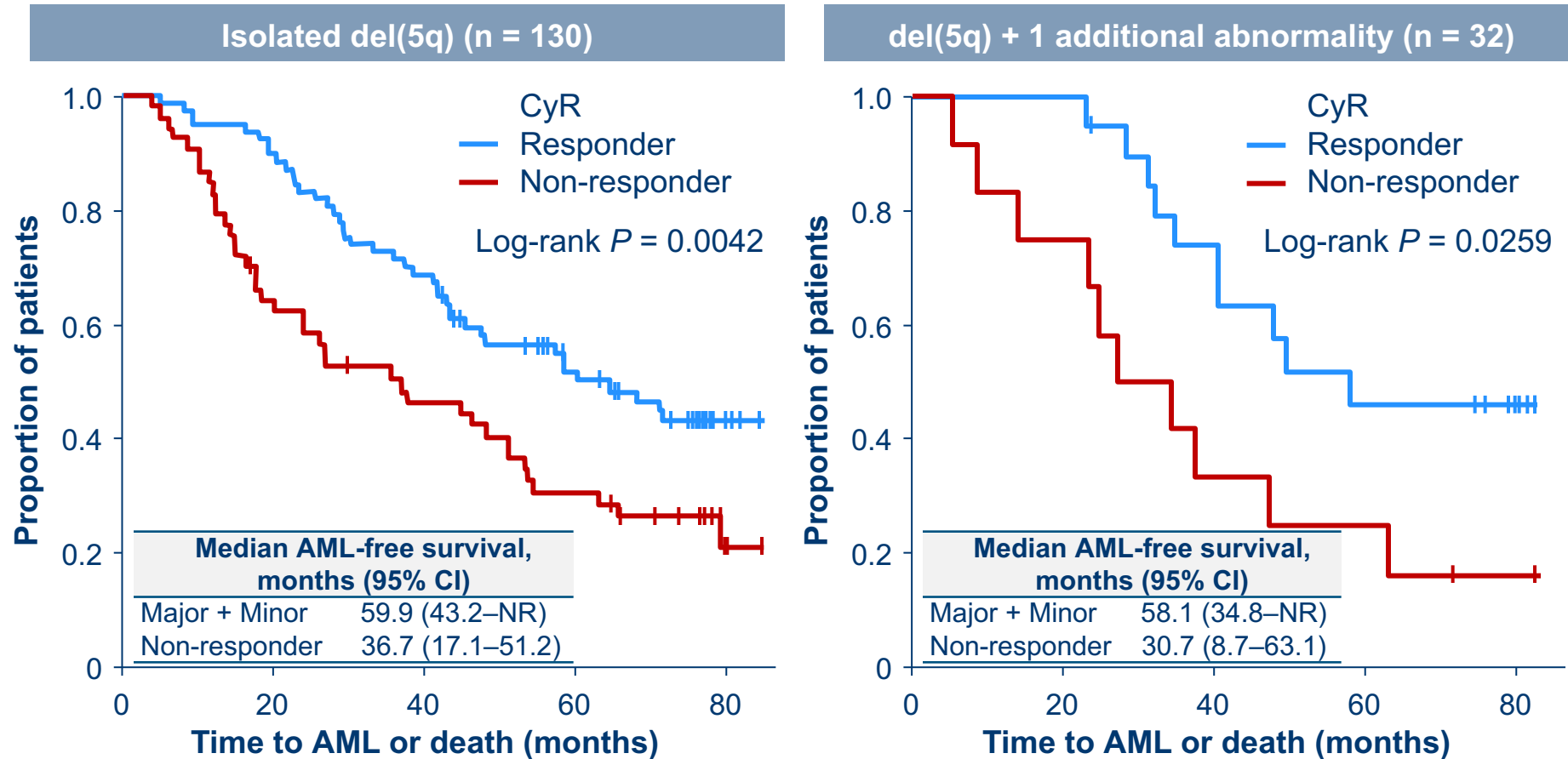
Luspatercept is not approved in Europe for patients with NTD anemia caused by lower-risk MDS

<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.

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

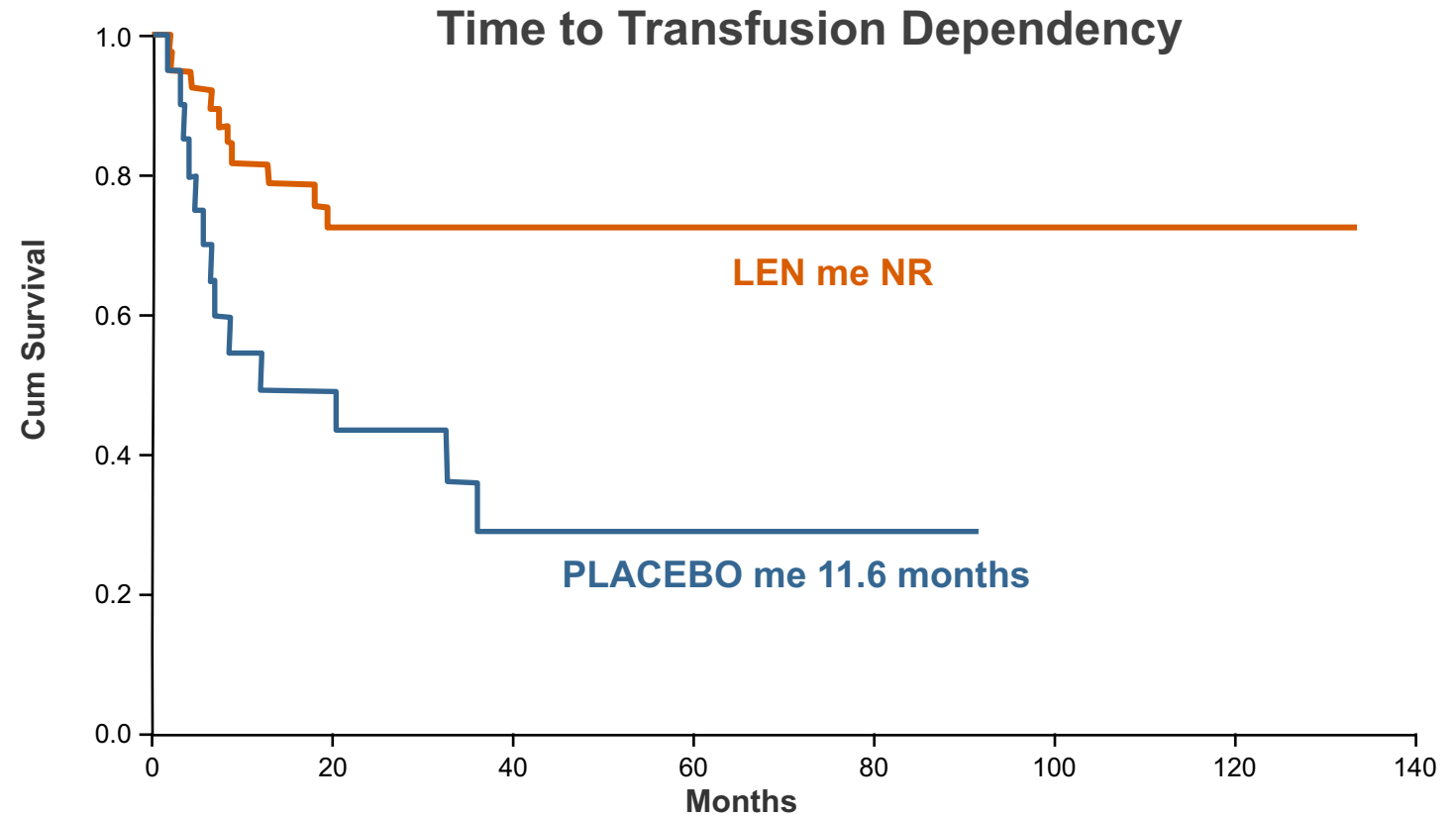


For the risk of AML transformation or death, CyR was associated with a 41% reduction (95% CI 0.38–0.92;  $P = 0.019$ ) in patients with isolated del(5q) and a 58% reduction (95% CI 0.17–1.02;  $P = 0.056$ ) in patients with del(5q) + 1 additional abnormality, compared with no CyR

# Sintra-Rev Trial

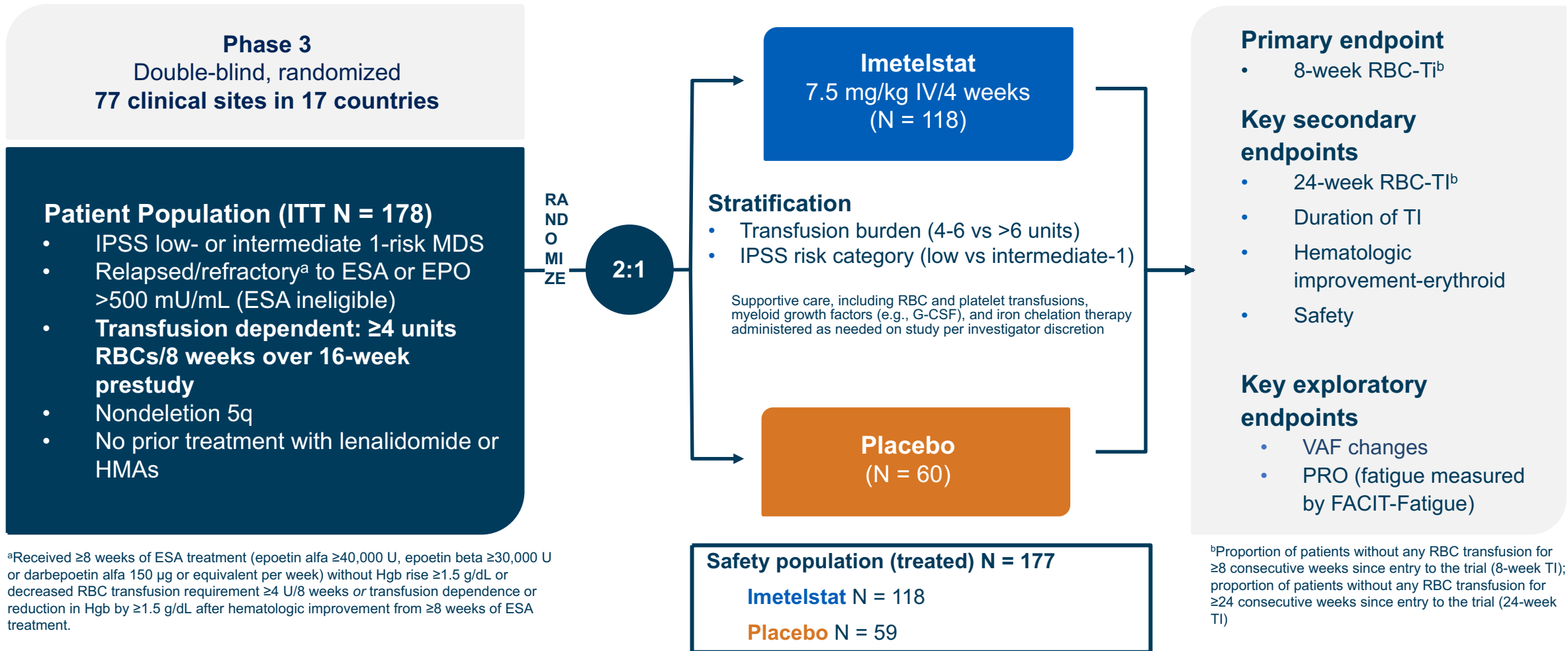
## Primary Objective: Efficacy (ITT, N=61)

- **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),  $P = 0.005$

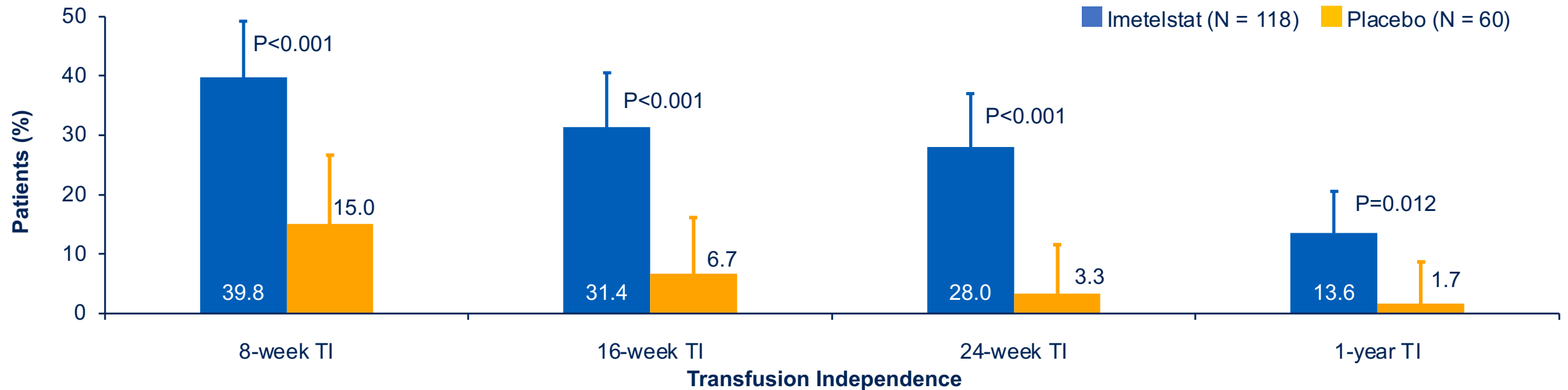


Median follow up 5.05y (0.3-11): 5.2 vs 4.85,  $P = ns$

# 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>

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<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

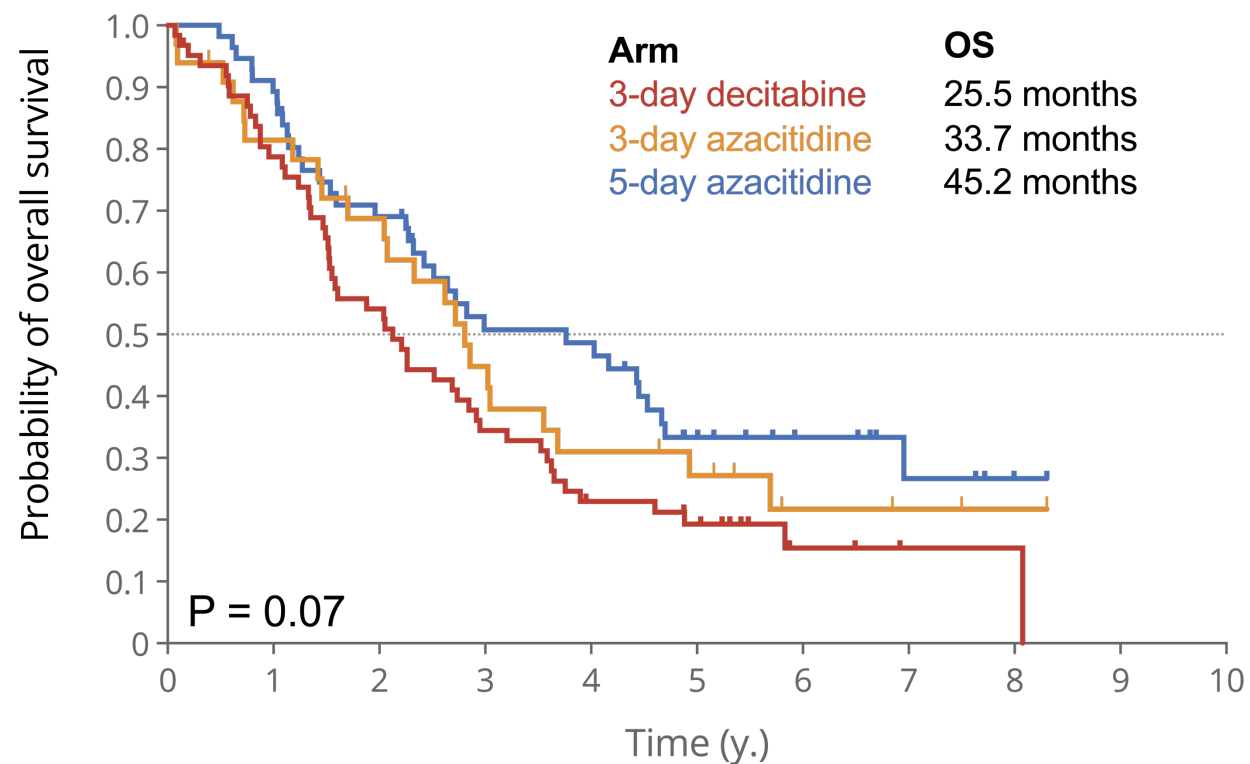
3-day decitabine, 20 mg/m<sup>2</sup>  
3-day azacitidine, 75 mg/m<sup>2</sup>  
5-day azacitidine, 75 mg/m<sup>2</sup>  
Best supportive care

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**.

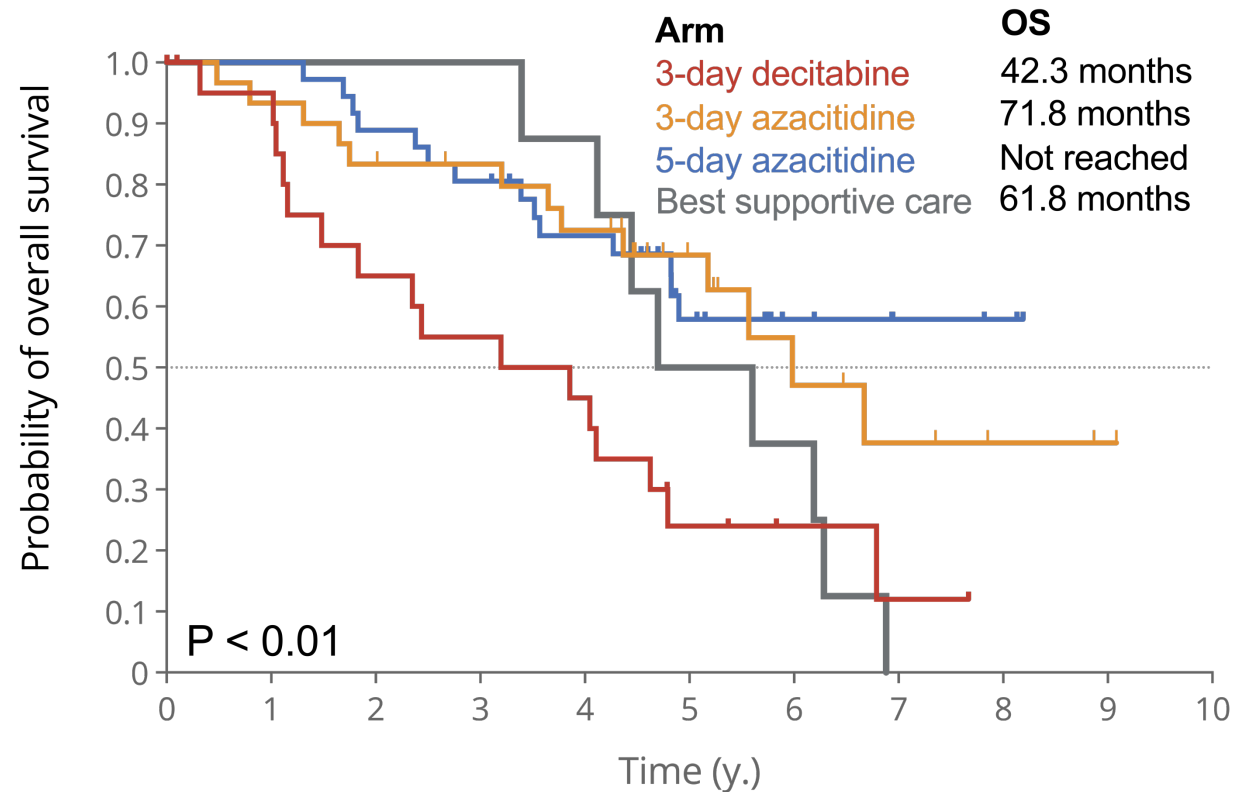
# Overall Survival

## 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

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# 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)

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# 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).**

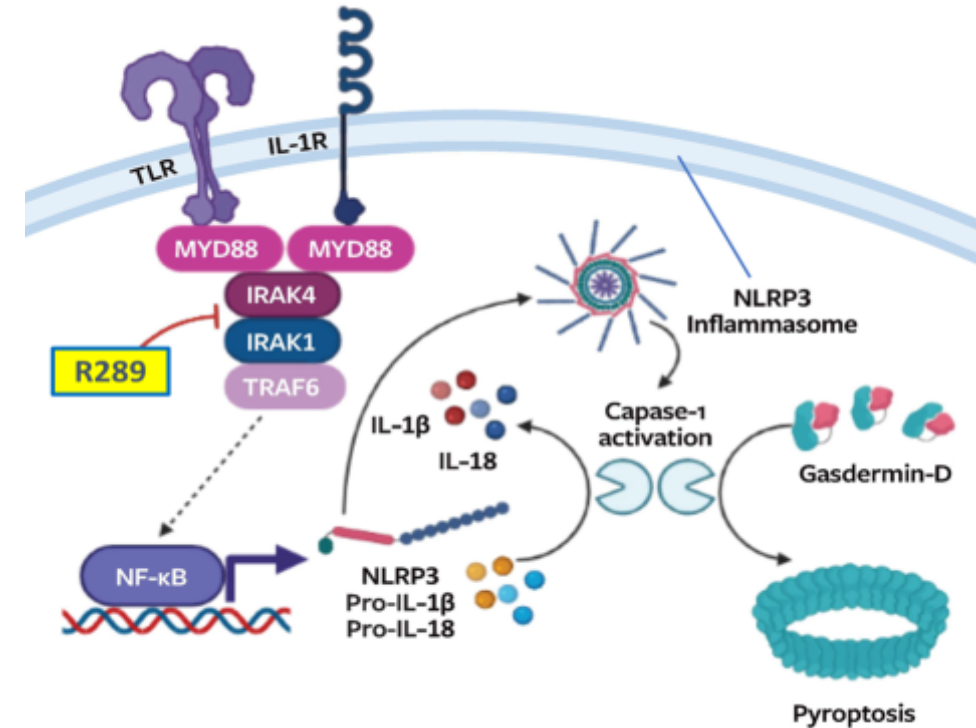


Fig 1: TLR/IL-1R Signaling Pathway

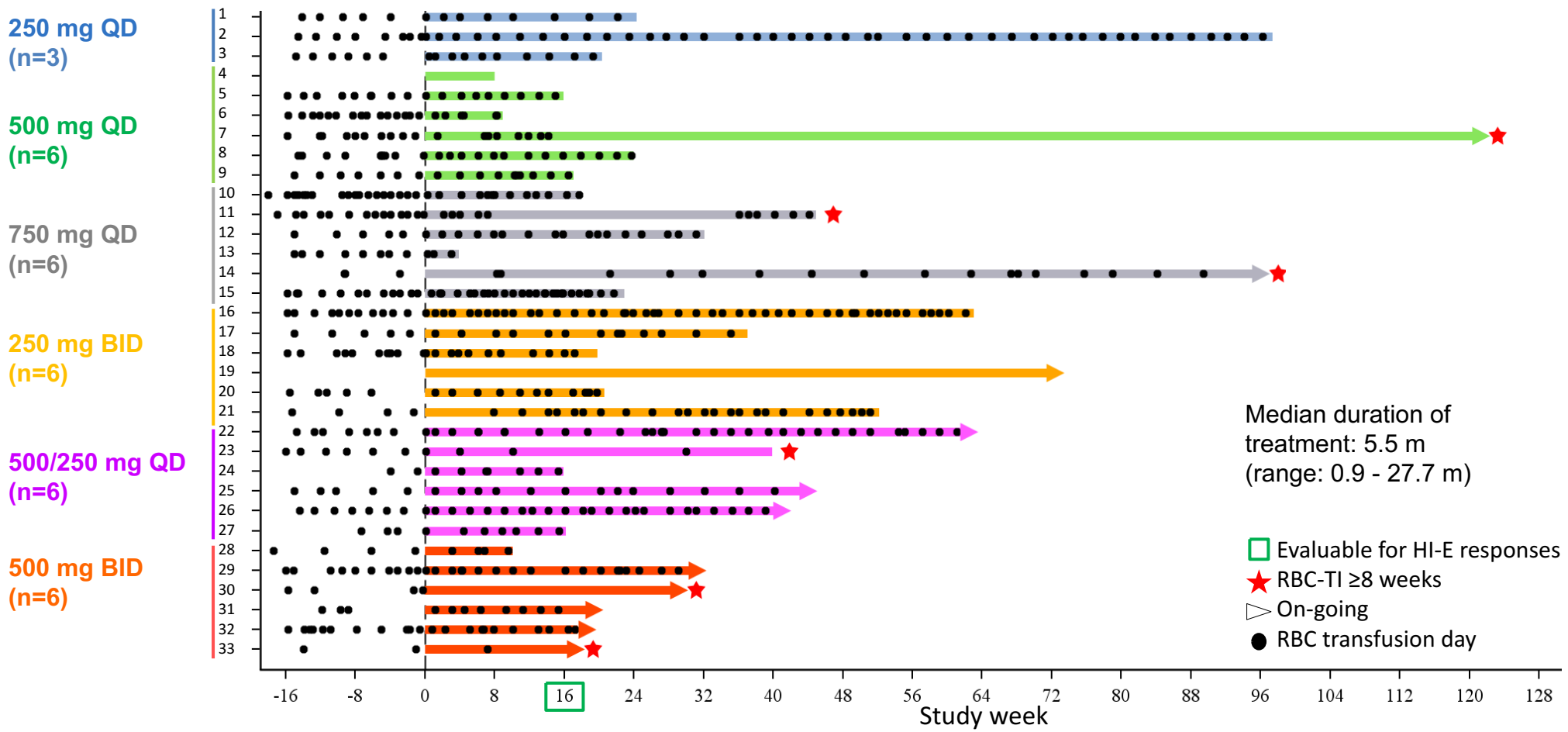
1. Sallman DA, et al. *Front Oncol.* 2016;6. 2. Lamagna C et al. *Ann Rheum Dis* 2020;79 (suppl 1). 3. Yan L et al. *Ann Rheum Dis* 2020;79 (suppl 1).

# 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%)

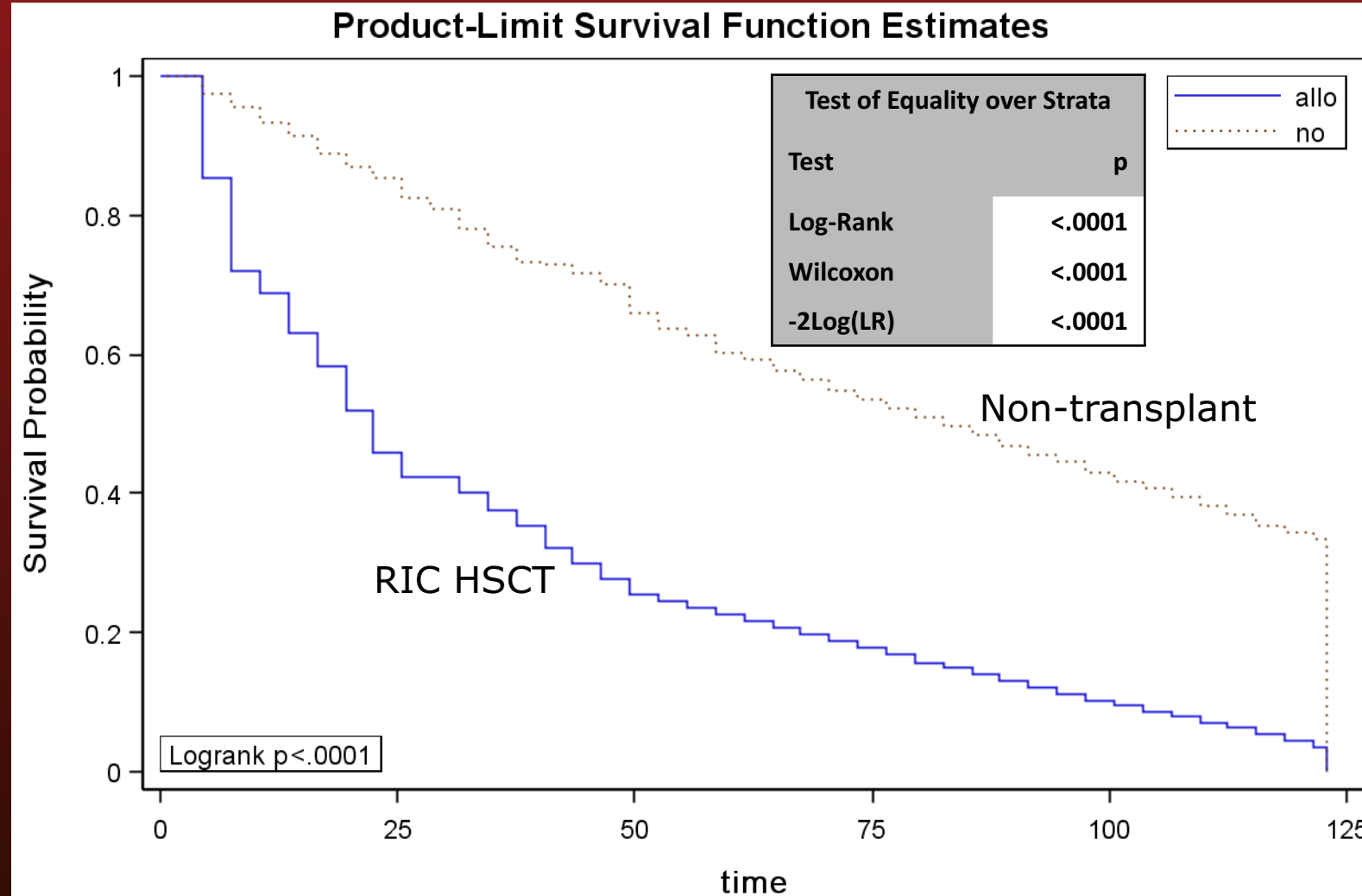


# RBC Transfusion Events by Dose Group

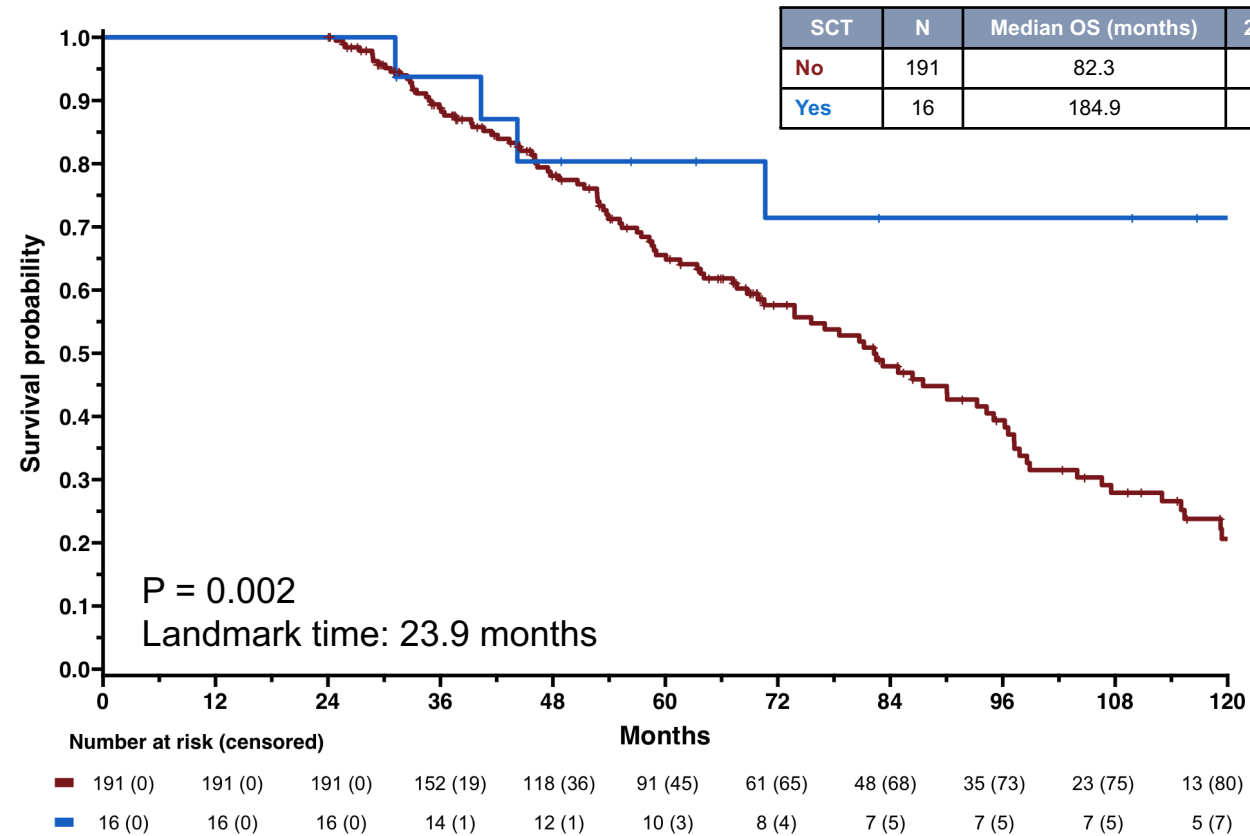


- 6/18 (33%) evaluable TD patients receiving ≥500 mg QD achieved RBC-TI >8 weeks; 4 >16 weeks; 3 >24 weeks
- Median time to onset of RBC-TI: 1.9 months
- Median duration of RBC-TI: 22.9 weeks (9 - 104.3)

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

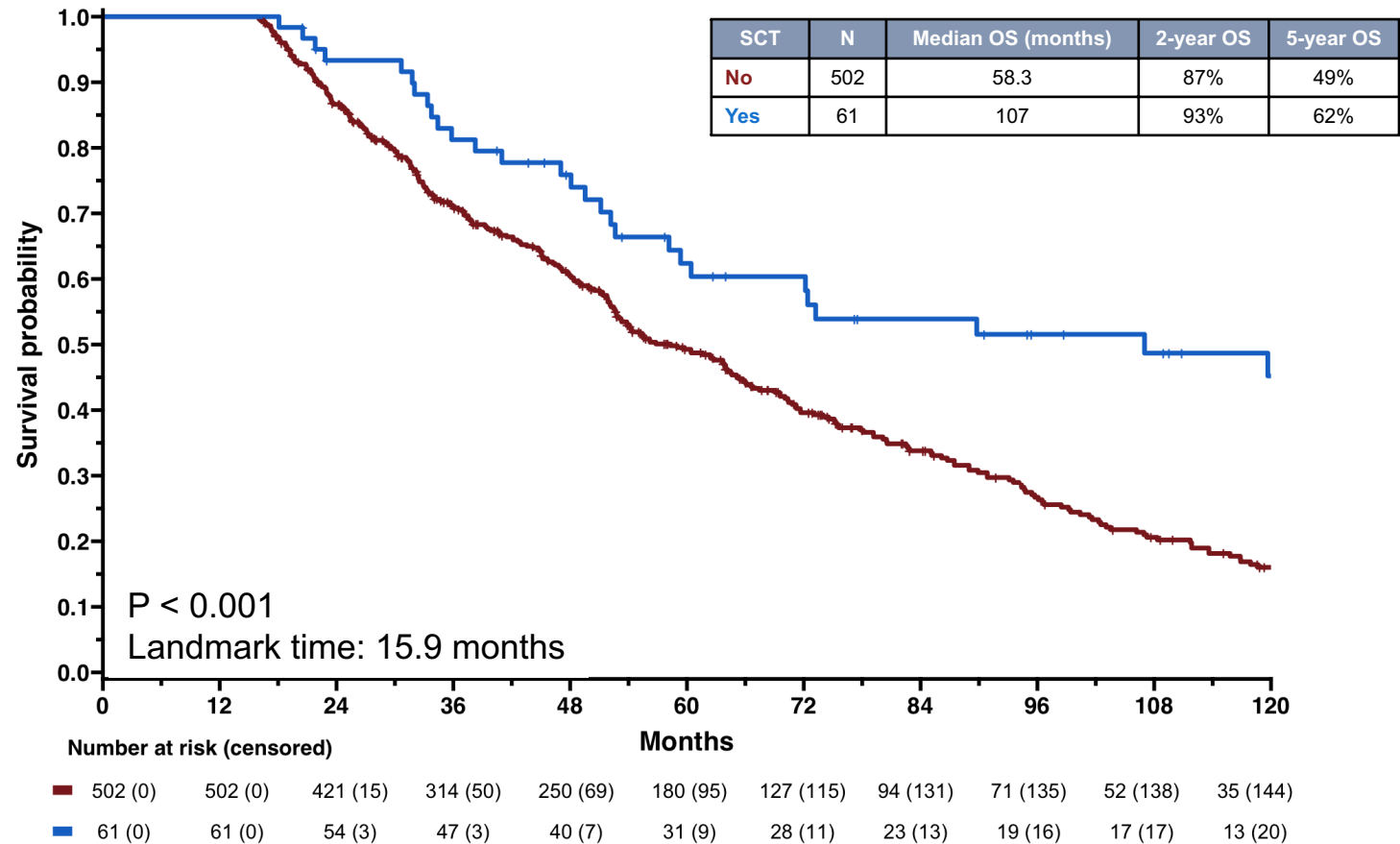


# Landmark OS: IPSS-R Very Low Risk



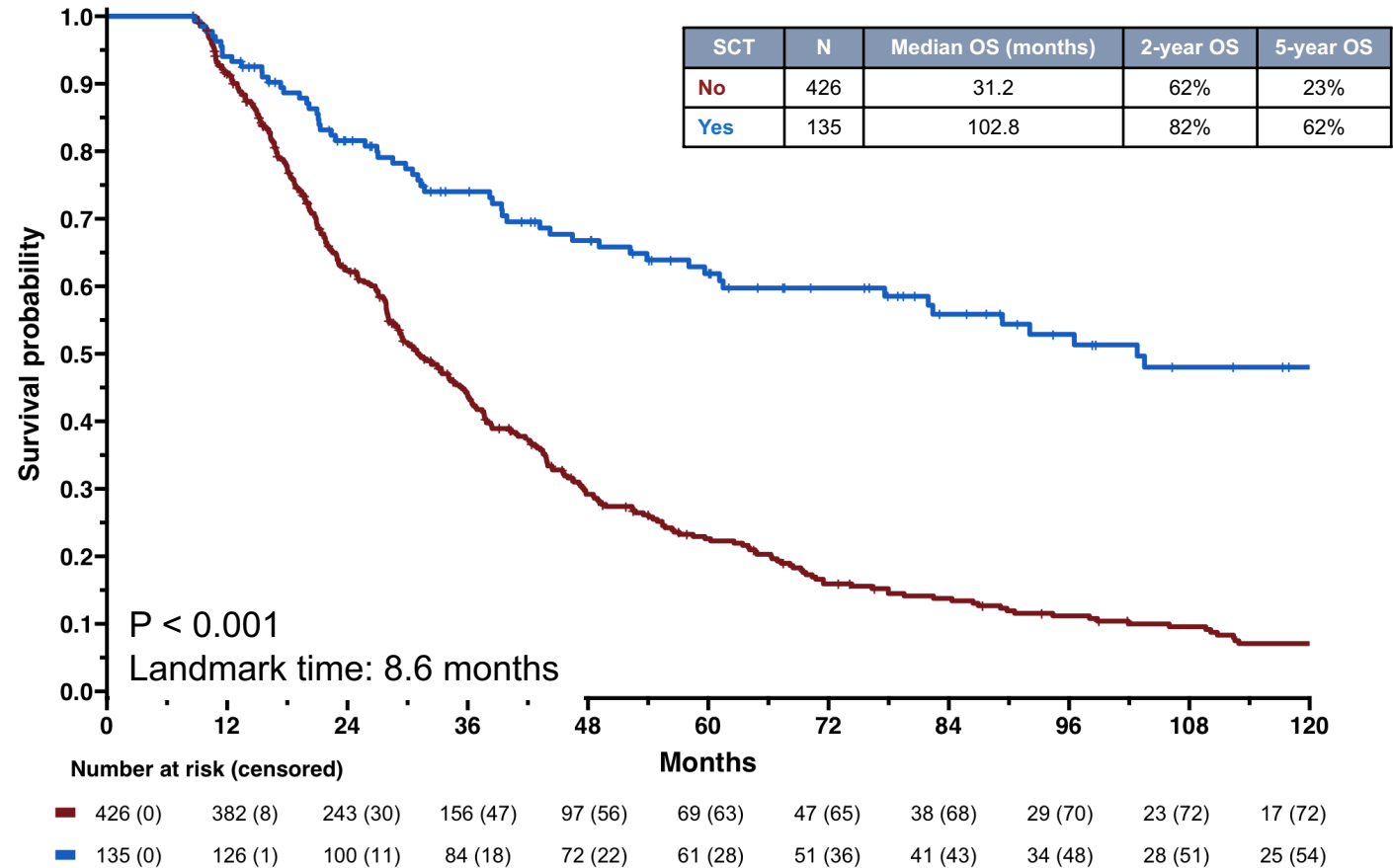
Bazinet et al EHA 2024

# Landmark OS: IPSS-R Low Risk



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# Landmark OS: IPSS-R Intermediate Risk



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# 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

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