

How did therapy for “lord of the rings” become therapy for all lower risk MDS?

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Conceptual classification of MDS: RSK classification

Chronic phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB- no adverse mutations

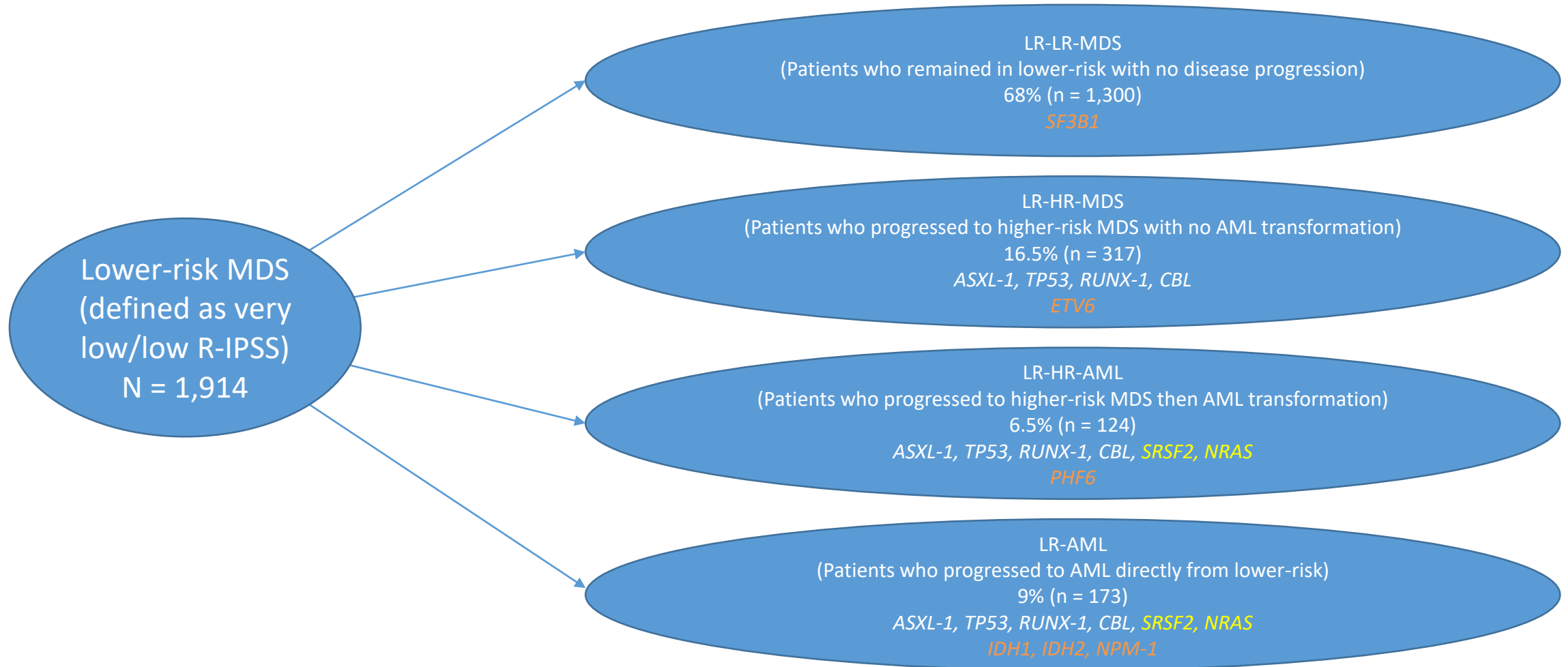
Accelerated phase MDS

- MDS-EB (5-19% myeloblasts) (cutoff to be refined)
- Bi-allelic *TP53* MDS
- MDS-f

AML-MDS related (AML-MR)

- $\geq 20\%$ myeloblasts (cutoff to be refined) with prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations.

Natural history of lower-risk MDS and the major mutations commonly found in each cohort

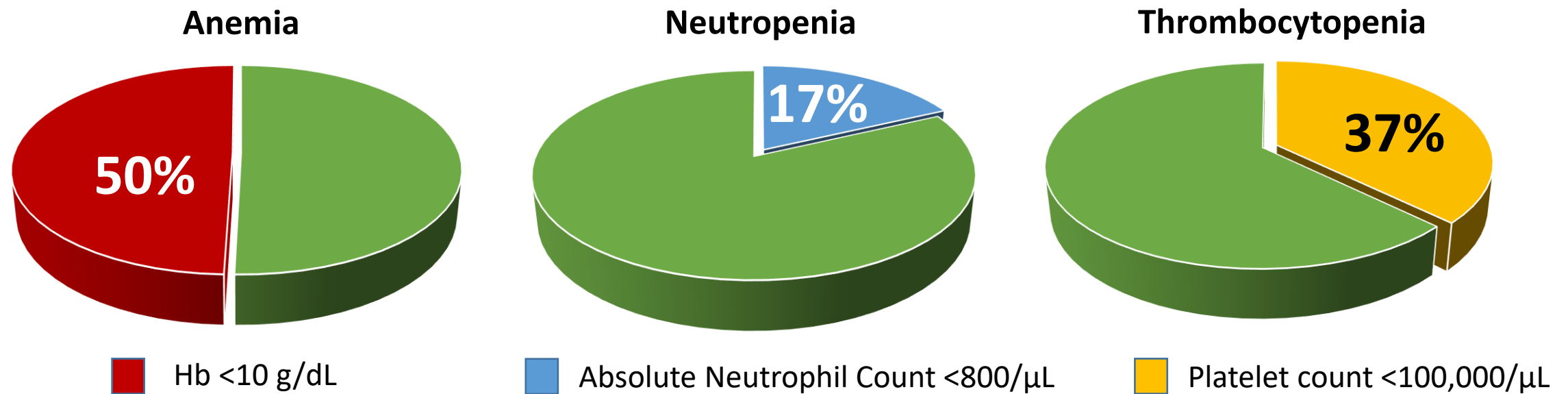


Anemia is the hallmark of lower risk MDS

- Lower-risk MDS is characterized foremost by anemia¹
- 50% of MDS patients will need RBC transfusions during the course of their disease²

Frequency of cytopenias in patients with Lower-risk MDS:^{3,4}

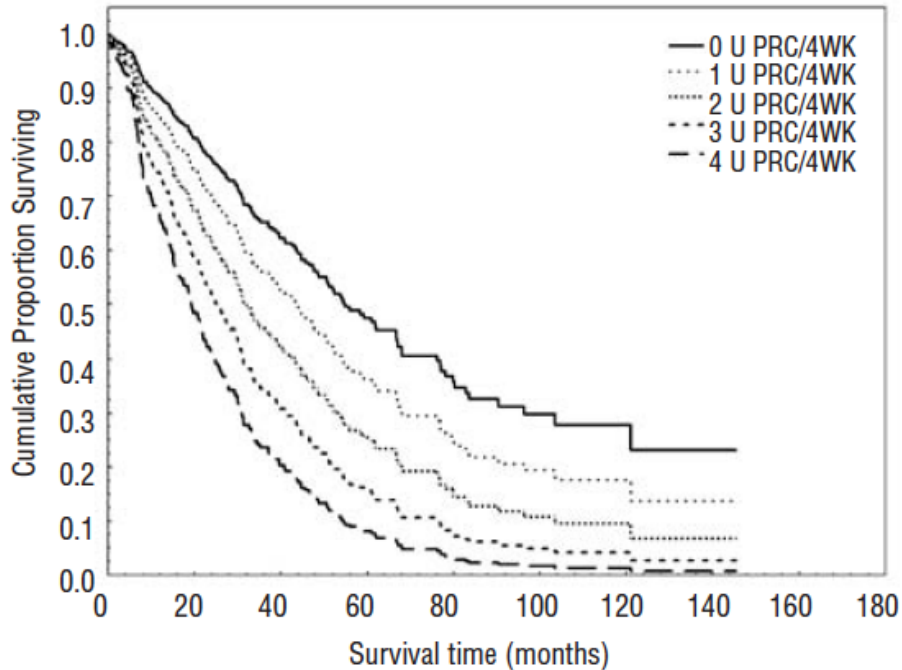
- Data from FISiM Italian registry



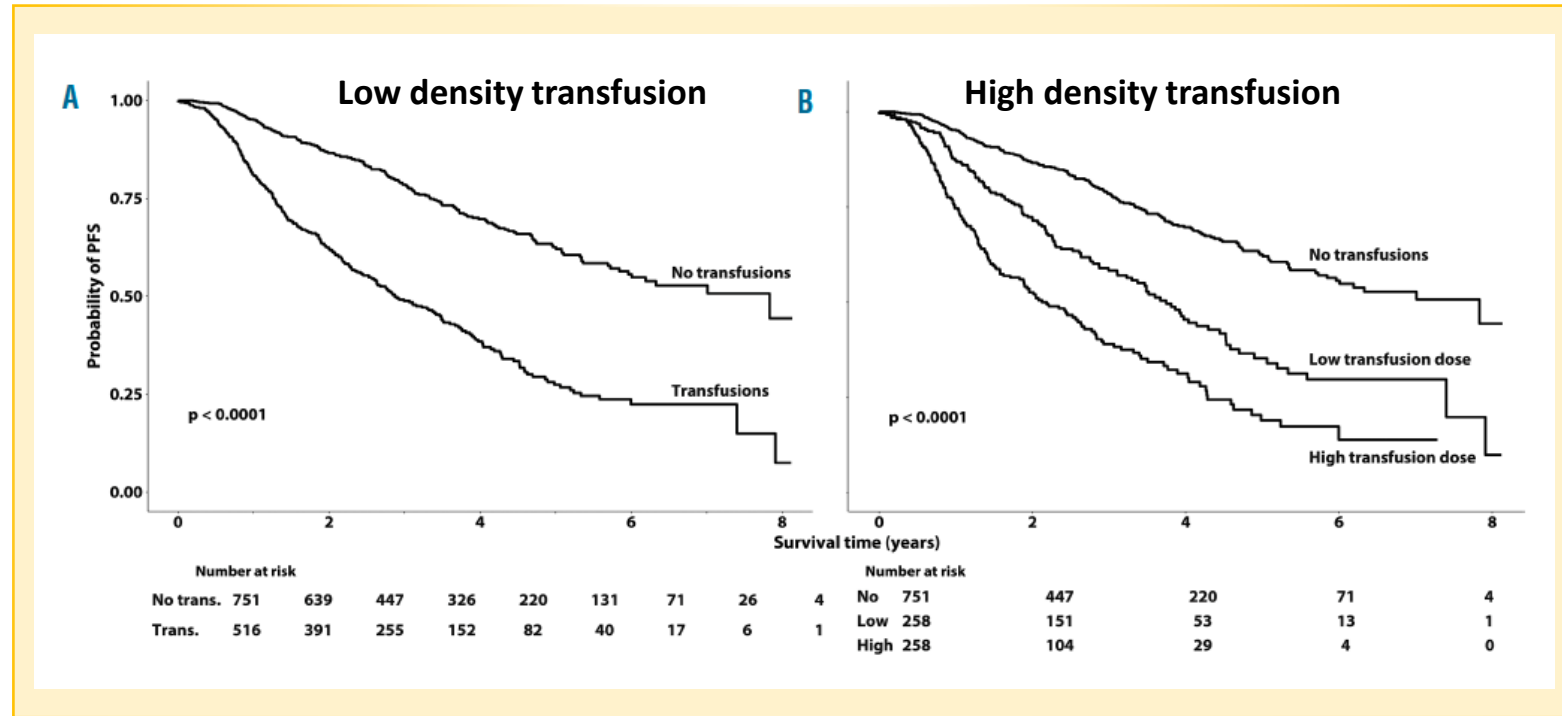
1. Fenaux P, et al. *Br J Haematol.* 2019;189(6):1016-1027; 2. Germing U, et al. *Hemasphere.* 2019;3(6):e314;
3. Lanino L, et al. *Am J Hematol.* 2023; 10.1002/ajh.26960; 4. Santini V. *Hemato.* 2022;3(1):153-162

Transfusion Dependency Negatively Affects Survival

Cumulative probability of survival among patients with MDS¹



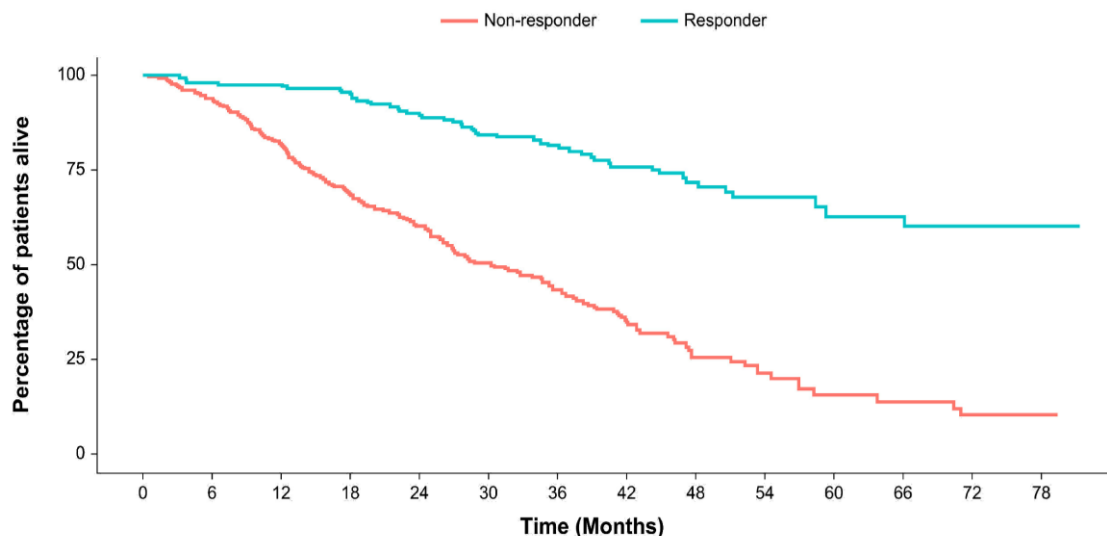
PFS and risk of progression according to transfusion status²



Negative effect of transfusion burden and density on PFS already visible at low transfusion burden of 3 units/16 weeks²

Overall survival according to transfusion independence in patients with LR-MDS with del(5q) and non-del(5q) treated with lenalidomide (MDS003, MDS004 and MDS005 studies)

Overall survival by achievement of transfusion independence



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Non-responder	582	332	251	220	177	149	100	56	27	19	9	8	6	3
Responder	10	206	217	177	151	122	111	87	60	35	24	24	23	3

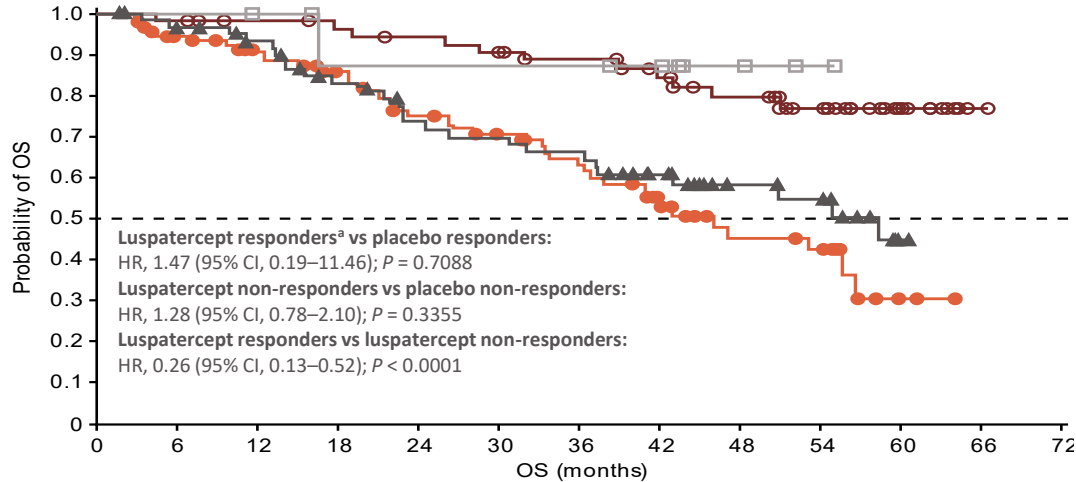
Pooled data from MDS-003, MDS-004 trials in del(5q) and MDS-005 in non-del(5q) patients

Relationship between TB and OS in in Univariate Analysis, 2 Time-Dependent Models, and Landmark Analysis

	Univariate analysis		Time-dependent TB		Time-dependent RBC-TI		Landmark RBC-TI (at week 17)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Time-dependent ever RBC-TI (yes vs. no)	0.50 (0.39–0.65)	<.0001	N/A	N/A	0.48 (0.37–0.62)	<.0001	N/A	N/A
RBC-TI at landmark (yes vs. no)	0.55 (0.42–0.72)	<.0001	N/A	N/A	N/A	N/A	0.57 (0.44–0.75)	<.0001

Overall survival and progression-free survival of patients following luspatercept treatment in the MEDALIST trial

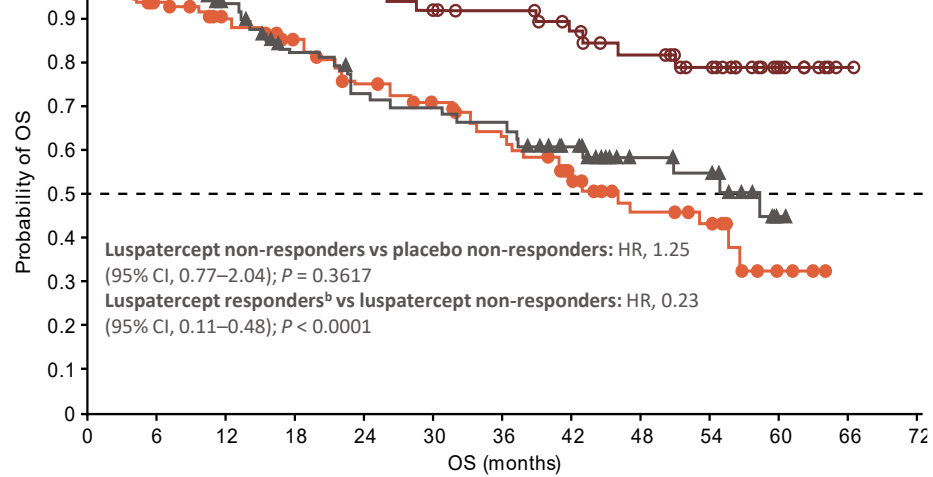
Kaplan–Meier estimates of OS by RBC-TI ≥ 8 weeks during weeks 1–24 response and treatment arm in the ITT population



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Luspatercept responders	58	57	54	52	50	47	44	38	33	24	10	1	0
Luspatercept non-responders	95	82	73	65	54	48	41	25	17	15	2	0	0
Placebo responders	10	10	9	7	7	7	7	6	3	1	0	0	0
Placebo non-responders	66	61	55	46	40	38	36	28	18	15	1	0	0

- Luspatercept responders (events 11/58), median NA months (95% CI, NA–NA)
- Luspatercept non-responders (events 40/95), median 46.1 months (95% CI, 36.3–56.6)
- Placebo responders (events 1/10), median NA months (95% CI, 16.6–NA)
- ▲— Placebo non-responders (events 26/66), median 58.3 months (95% CI, 37.0–NA)

Kaplan–Meier estimates of OS by mean increase in Hb ≥ 1 g/dL response during weeks 1–24



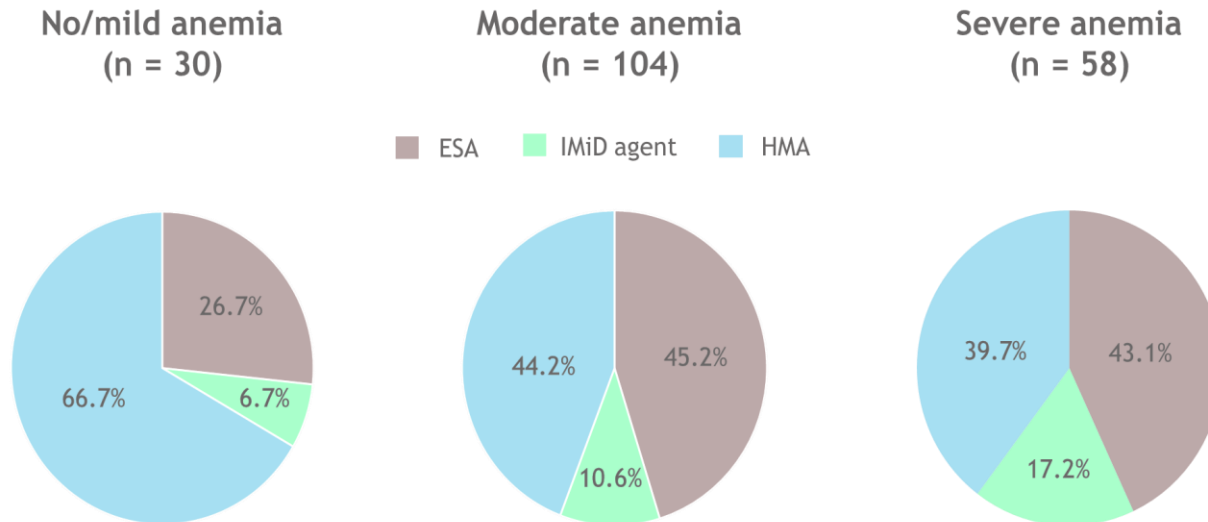
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Luspatercept responders	54	54	51	49	47	44	42	36	31	23	9	1	0
Luspatercept non-responders	99	85	76	68	57	51	43	27	19	16	3	0	0
Placebo responders	6	6	6	6	6	6	6	5	3	1	0	0	0
Placebo non-responders	70	65	58	47	41	39	37	29	18	15	1	0	0

- Luspatercept responders (events 9/54), median NA months (95% CI, NA–NA)
- Luspatercept non-responders (events 42/99), median 46.1 months (95% CI, 36.3–56.6)
- Placebo responders (events 0/6), median NA months (95% CI, NA–NA)
- ▲— Placebo non-responders (events 27/70), median 58.3 months (95% CI, 37.0–NA)

Primary outcome: Transfusion independence ≥ 8 weeks during weeks 1-24; data cut: January 15, 2022. OS was defined as time from randomization to death from any cause. ^aResponders were defined as patients with an absence of any RBC transfusion ≥ 8 weeks during the first 24 weeks of double-blind treatment. ^bResponders were defined as patients who achieved mean Hb increase ≥ 1 g/dL during weeks 1-24 of double-blind treatment

Initial treatments by baseline anemia

Patient characteristics from the Connect[®] Myeloid Disease Registry: 531 patients with LR-MDS (mean age 74.0 years, 66.5% male) were enrolled; 215 patients (40.6%) were classified as low-risk, and 314 (59.2%) were classified as Int-1 risk by IPSS



Results:

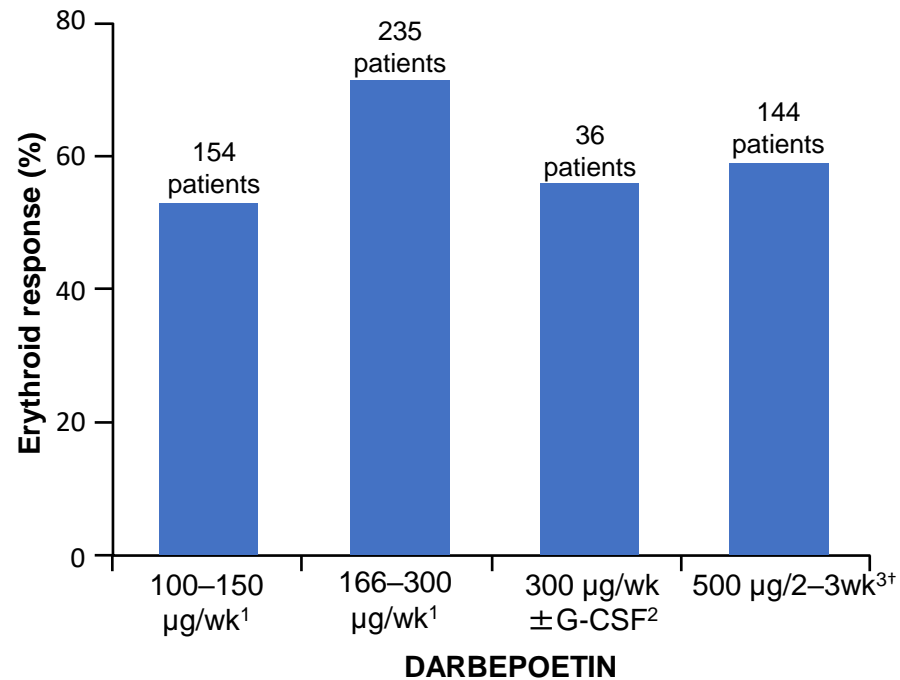
- 330 (62.1%) patients received no treatment at baseline, including:
 - 163 (49.4%) with no/mild anemia
 - 122 (37.0%) with moderate anemia
 - 45 (13.6%) with severe anemia
- Of the 330 patients, 38 (11.5%) died without receiving any treatment

Safety results:

- Death occurred in 213 (40.1%) patients
- Approximately half of the patient deaths were MDS-related

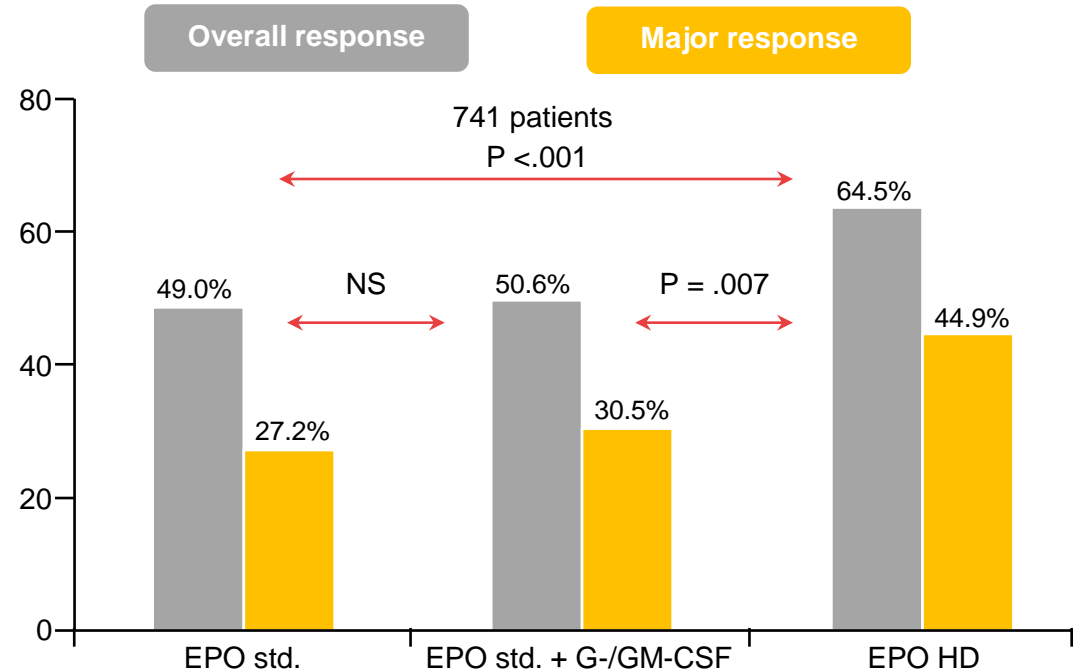
Meta-analysis of erythroid response to ESAs

Erythroid response with various darbepoetin strategies^{1-3*}



Higher dosing regimens of both epoetin alfa (weekly dose 60-80 K IU) and darbepoetin alfa (weekly dose 150–300 mcg) correlate with higher erythroid response rates⁵

Comparison of the pooled estimates of erythroid response with different EPO strategies (N = 741)⁴

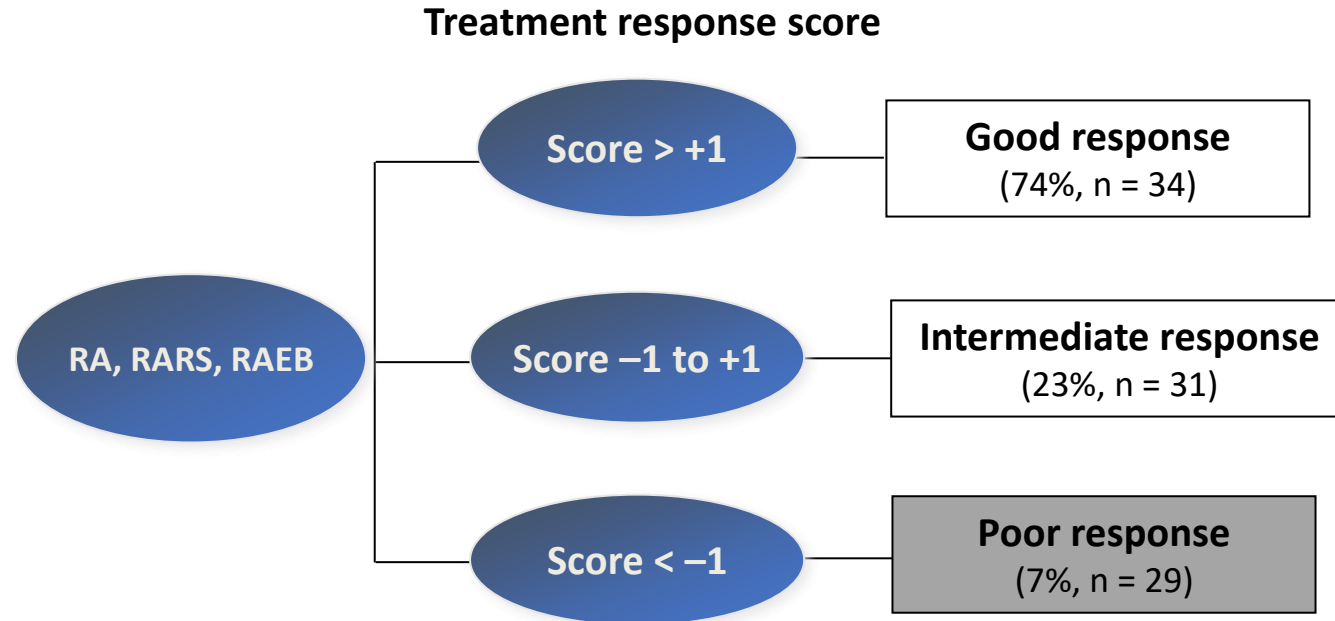


*This figure is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

[†]Every 3 weeks initially; after 6 weeks, poor responders received darbepoetin alfa 500 µg every 2 weeks.

1. Moyo V, et al. *Ann Hematol.* 2008;87(7):527-536; 2. Nilsson-Ehle H, et al. *Eur J Haematol.* 2011;87(3):244-252; 3. Gabrilove J, et al. *Br J Haematol.* 2008;142(3):379-393; 4. Mundle S, et al. *Cancer.* 2009;115(4):706-715; 5. Santini V. *Oncologist.* 2011;16(Suppl. 3):35-42.

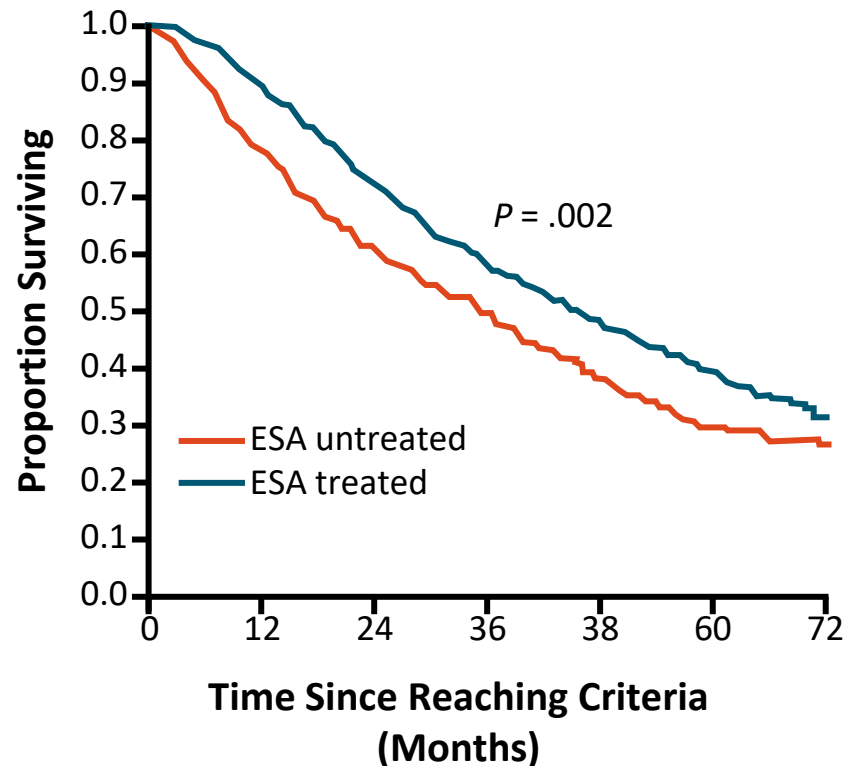
When would you give ESAs?



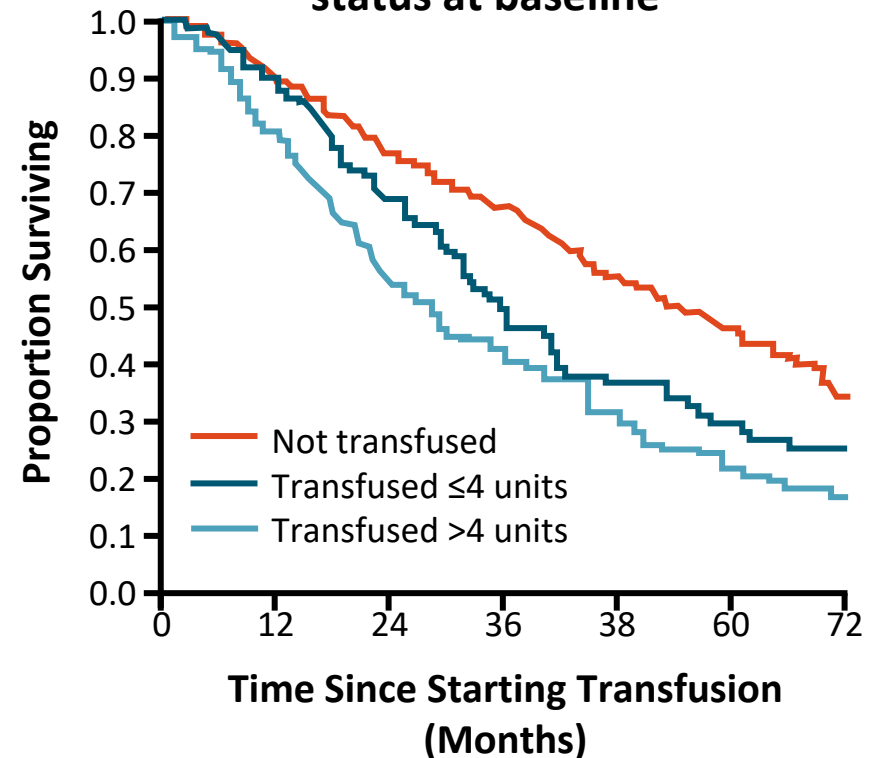
Epo level	<100	+2
U/L	100–500	+1
	>500	-3
Transfusion	<2 units/m	+2
U RBC/month	= or >2 units/m	-2

EUMDS Registry: ESAs provide OS benefit in LR-MDS

OS: Propensity Score Matched



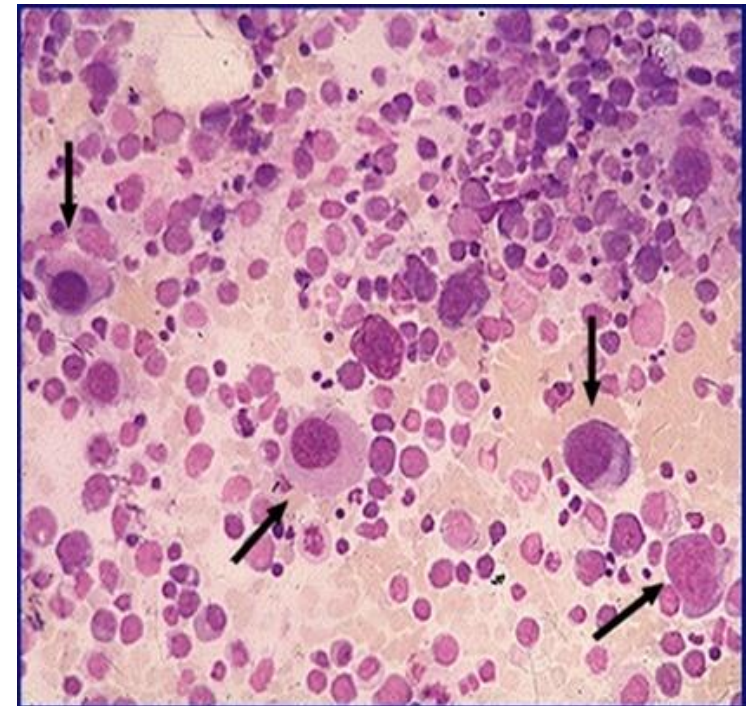
OS: ESA treated, stratified by RBC transfusion status at baseline



- Prospective, non-interventional longitudinal study
- Newly diagnosed patients with IPSS low or intermediate-1 MDS

5q- Syndrome: Clinical Characteristics

- First described by Van den Berghe in 1974.
- Isolated del(5q) as sole cytogenetic abnormality
- Female predominance
- Median age at diagnosis: 68 yrs
- Macrocytic anemia, mild leukopenia, normal or increased platelet count.
- Erythroid hypoplasia accompanied by megakaryocytic dysplasia with small oligo- or mononuclear forms, less than 5% myeloblasts are the hallmark features in the bone marrow biopsy and aspirate



Abstract # 1001 *TP53* Gene allelic State in Myelodysplastic Syndromes (MDS) with Isolated 5q Deletion

- 18.7% of MDS-del5q presented *TP53* mutations.
- 72.7% were classified as *TP53*-monoallelic
- The most recurrent mutations were ***SF3B1*** (21%), *DNMT3A* (18%), *TP53* (18%), *TET2* (14%), *ASXL1* (10%), *CSNK1A1* (6%) and *JAK2* (6%)
- MDS-del5q with *TP53*-multihit mutations presented worse OS and higher risk to AML evolution compared to *TP53*-wt and *TP53*-monoallelic MDS-del5q
- ***TP53*-monoallelic MDS with a *TP53* VAF >20% showed similar prognosis to *TP53*-multihit patients** (median OS of 43.7 and 55.2 months, and AML evolution at 60 months of 36.7% and 40.4%, respectively).
- A risk score (MDS-del5q score) for AML evolution :
 - **additional chromosomal abnormality, 2 points**
 - ***TP53*-multihit, 2 points**
 - **BM blast >2%, 2 points**
 - **platelets $\leq 100 \times 10^9/L$, 3 points**
 - ***SF3B1*-mutation, 1 point.**
- Three risk-groups were defined: ≤ 1 points, intermediate-risk if 2 points and high-risk if ≥ 3 points of the MDS-del5q score
- AML evolution at 60 months of 11.5%, 23.3% and 43.7% of low, intermediate, and high-risk MDS-del5q; $p < 0.05$)

Lenalidomide in MDS-del(5q)

Phase II MDS 003 Trial

FDA Approval: 12/17/2005



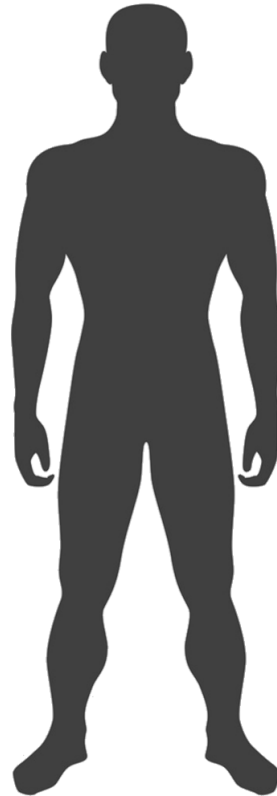
Patient Population

- ✓ Low-risk, or intermediate-risk MDS (IPSS)
- ✓ 5q31 deletion ± additional cytogenetic abnormalities
- ✓ Transfusion-dependent anemia



Most Common Grade 3–4 AEs with Lenalidomide

- Neutropenia (55%)
- Thrombocytopenia (44%)
- Anemia (7%)
- Leukopenia (6%)
- Rash (6%)
- Fatigue (3%)
- Febrile neutropenia (1%)



Lenalidomide

N = 148

67%



Transfusion Independence
by week 24

76%



Total transfusion response
by week 24



4.6wk

Median time to response

Long-Term Outcomes

Median Follow-Up 3.2 yrs

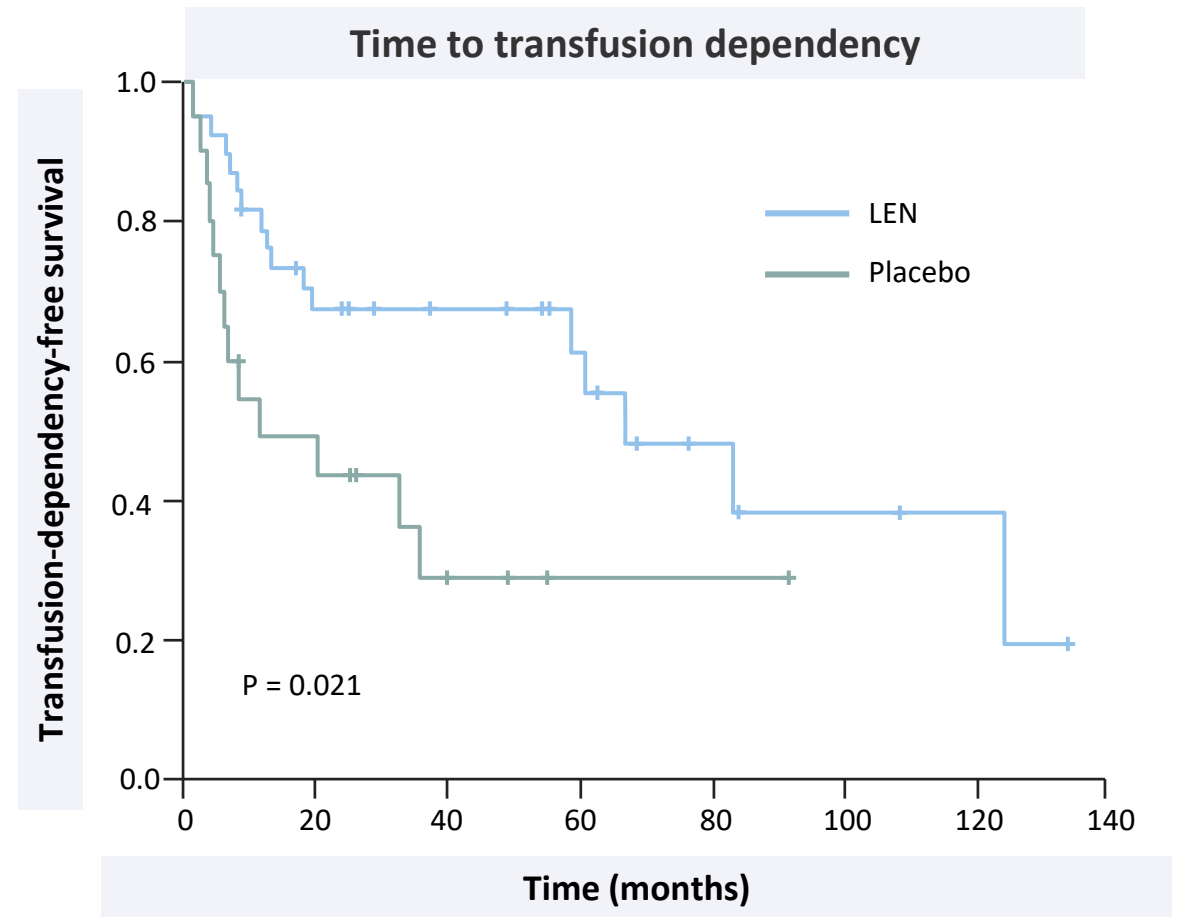


2.2 years

Median duration of transfusion
independence

Sintra-REV: Phase 3, multicenter trial investigating LEN versus placebo in non-transfusion-dependent LR-MDS del(5q) patients

- Patients were randomized 2:1 to receive LEN 5 mg/day (n = 40) or placebo (n = 21) on days 1 to 28 of every 28-day cycle
- Treatment phase: 108 weeks
- Follow-up phase: 108 weeks
- Median follow up: 60.6 months (IQR: 32.3–73.9)
- **Primary endpoint** (time to transfusion dependency):
 - LEN – 66.3 months (95% CI: 37.0, 95.5)
 - Placebo – 11.6 months (HR 0.414; 95% CI: 0.196, 0.875; P = 0.021)



Lenalidomide Discontinuation: HARMONY Alliance study (n=118)

- 42% of patients lost RBC-TI
- 48 patients were re-treated with LEN because of loss of response. Forty-two patients were evaluable for response and 28 of them (67%) achieved RBC-TI again

Prognostic factors for event-free survival on multivariate analysis

Variables	HR	95,0% CI		p value
		Lower	Upper	
Age at diagnosis*	1.04	1.01	1.07	0.005
RBC unit/8 weeks >4 at lenalidomide start	1.28	1.05	1.56	0,013
IPSS-R very low vs low/intermediate	0.33	0,16	0.70	0.004
Lenalidomide cycles \geq 12	0.55	0.32	0.95	0.031
Hemoglobin level at lenalidomide stop*	0.82	0.69	0.98	0.028

Anemia Management: Luspatercept

Phase III MEDALIST Trial

FDA Approval: 04/06/2020

Patient Population

- ✓ Very-low-risk, low-risk, or intermediate-risk MDS (IPSS-R) with ring sideroblasts
- ✓ Receiving regular RBC transfusions

Most Common Grade 3–4 AEs with Luspatercept

- Fatigue (5%)
- Asthenia (3%)
- Back pain (2%)
- Nausea (1%), headache (1%), arthralgia (1%), dyspnea (1%), bronchitis (1%), UTI (1%)

Luspatercept N = 153

38%

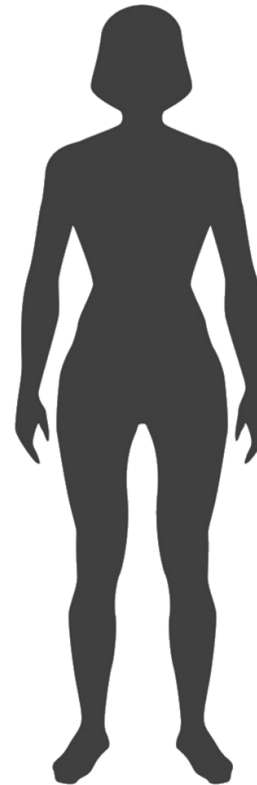
Transfusion Independence
≥ 8 Weeks (Weeks 1–24)

28%

Transfusion Independence
≥ 12 Weeks (Weeks 1–24)

33%

Transfusion Independence
≥ 12 Weeks (Weeks 1–48)



Placebo N = 76

13%

Transfusion Independence
≥ 8 Weeks (Weeks 1–24)

8%

Transfusion Independence
≥ 12 Weeks (Weeks 1–24)

12%

Transfusion Independence
≥ 12 Weeks (Weeks 1–48)

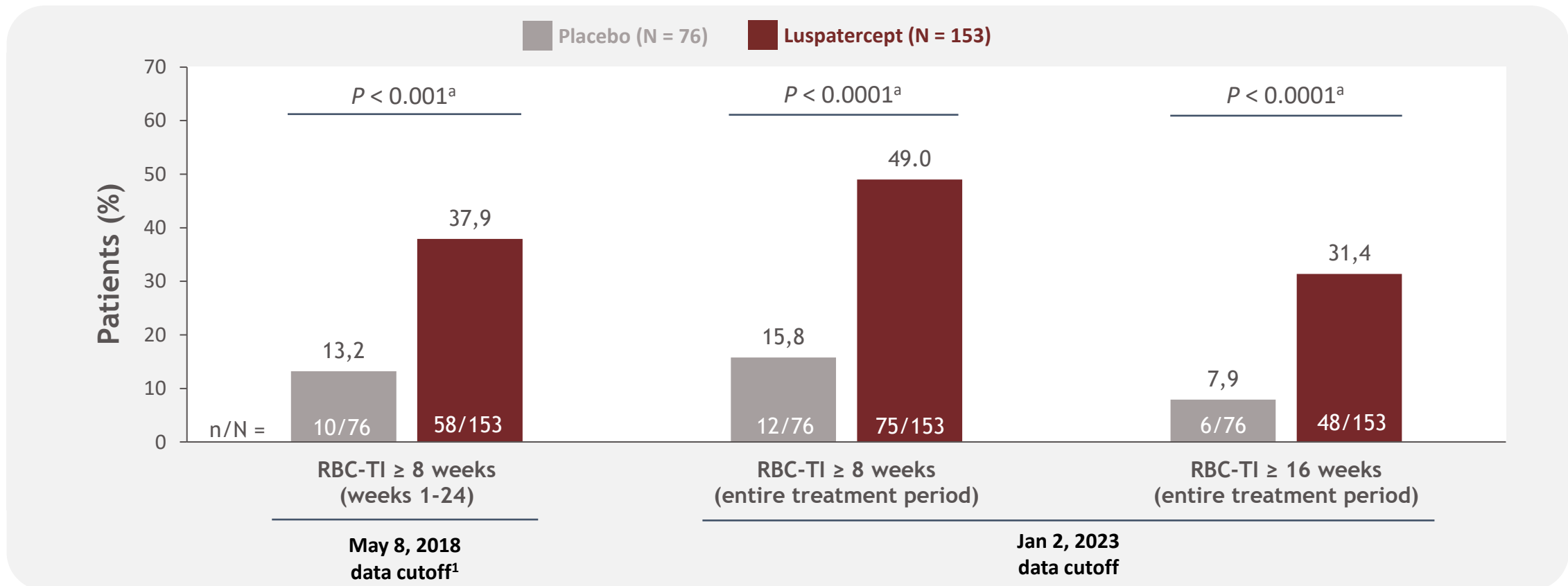


Oral Abstract 915:
Long-Term Data

$P < .001$
For All Comparisons

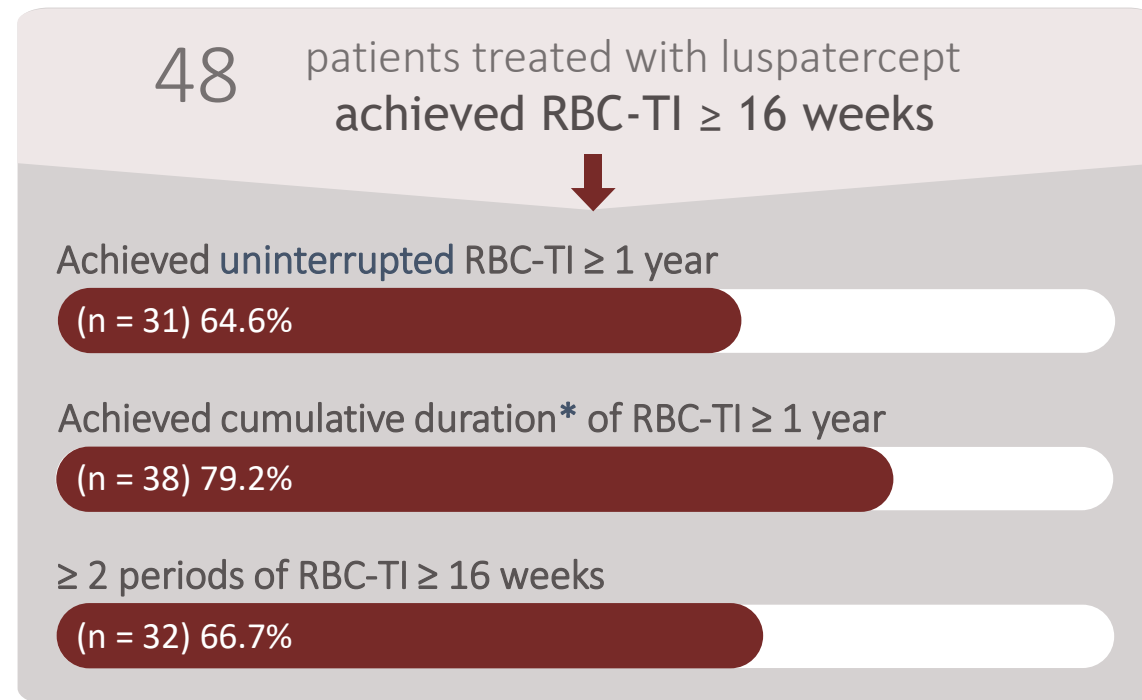
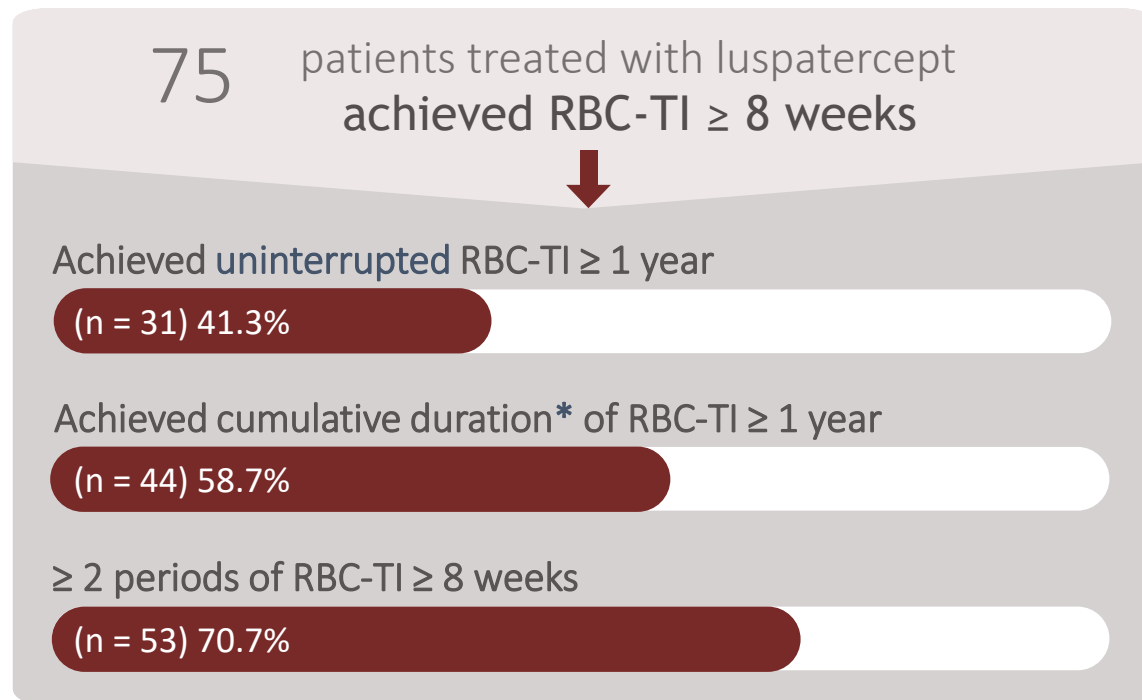
Treatment and follow-up duration and rates of RBC-TI

- As of January 2, 2023, the median (range) duration of:
 - **Treatment** was 50.9 (5.9–332.9) weeks for luspatercept and 24.0 (9.0–103.0) weeks for placebo
 - **Follow-up** was 39.9 (2.8–76.0) months for luspatercept and 38.7 (1.7–68.6) months for placebo



^aCalculated by Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 RBC units vs < 6 RBC units per 8 weeks) and baseline IPSS-R score (Very low or Low vs Intermediate). 1. Fenaux P, et al. *N Engl J Med* 2020;382:140-151.

Duration of RBC-TI response



*Cumulative duration of RBC-TI was defined as the sum of all respective response durations for responders over the entire treatment period

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve patients with transfusion-dependent lower-risk myelodysplastic syndromes: full analysis of the COMMANDS trial

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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^a
- 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)^b
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^c
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

^aMDS patients with del(5q) were excluded; ^b2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; ^cClinical 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: patient baseline characteristics

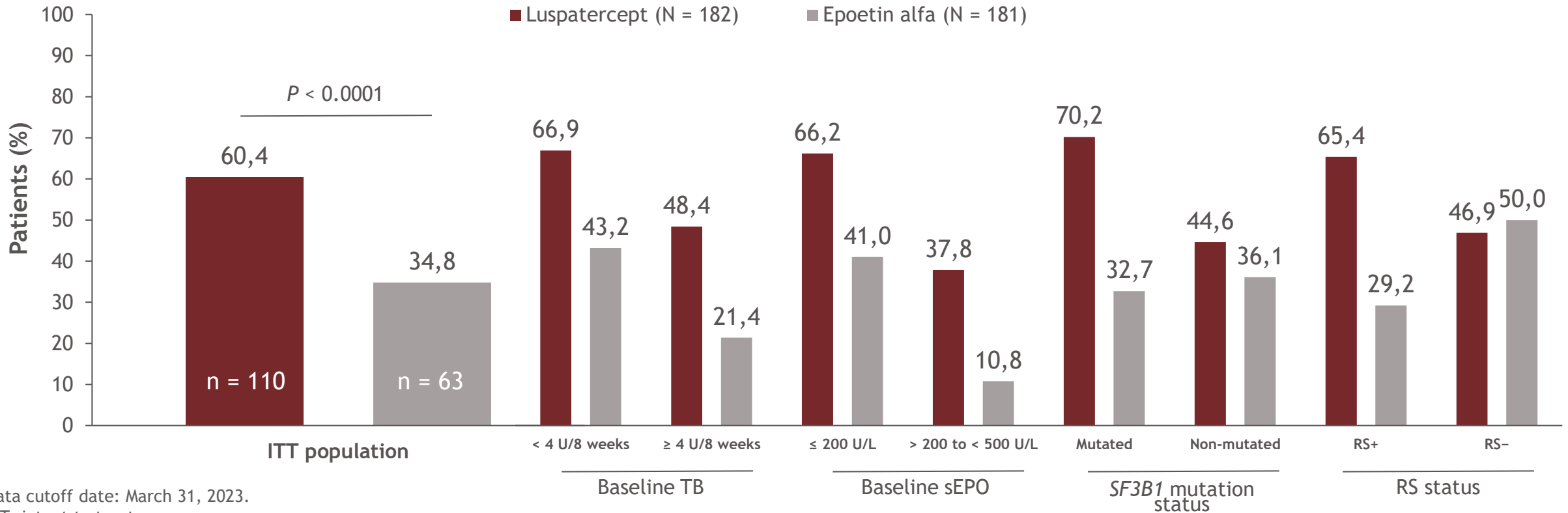
	Luspatercept (n = 182)	Epoetin alfa (n = 181)	Total (N = 363)
Age, median (range), years	74.0 (46-93)	74.0 (31-91)	74.0 (31-93)
Sex, female, n (%)	73 (40.1)	89 (49.2)	162 (44.6)
Hb, median (range), g/dL	7.80 (4.7-9.2)	7.80 (4.5-10.2)	7.80 (4.5-10.2)
Baseline TB, median (range), RBC U/8 weeks	3.0 (1-10)	3.0 (0-14)	3.0 (0-14)
Baseline TB category, n (%)			
< 4 U/8 weeks	118 (64.8)	111 (61.3)	229 (63.1)
≥ 4 U/8 weeks	64 (35.2)	70 (38.7)	134 (36.9)
ECOG performance status, n (%)			
0	74 (40.7)	69 (38.1)	143 (39.4)
1	104 (57.1)	94 (51.9)	198 (54.5)
2	4 (2.2)	18 (9.9)	22 (6.1)
Time since original MDS diagnosis, median (range), months	7.97 (-0.4-243.1)	5.13 (-0.3-171.6)	6.05 (-0.4-243.1)
sEPO category, n (%)			
≤ 200 U/L	145 (79.7)	144 (79.6)	289 (79.6)
> 200 to < 500 U/L	37 (20.3)	37 (20.4)	74 (20.4)
SF3B1 mutation status, n (%)			
SF3B1 mutated	114 (62.6)	101 (55.8)	215 (59.2)
SF3B1 non-mutated	65 (35.7)	72 (39.8)	137 (37.7)
Missing	3 (1.6)	8 (4.4)	11 (3.0)
RS status, n (%)			
RS+	133 (73.1)	130 (71.8)	263 (72.5)
RS-	49 (26.9)	50 (27.6)	99 (27.3)
Missing	0	1 (0.6)	1 (0.3)

Data cutoff date: March 31, 2023.

ECOG, Eastern Cooperative Oncology Group; SF3B1, splicing factor 3B subunit 1; TB, transfusion burden.

COMMANDS: achievement of primary endpoint in ITT population and subgroups

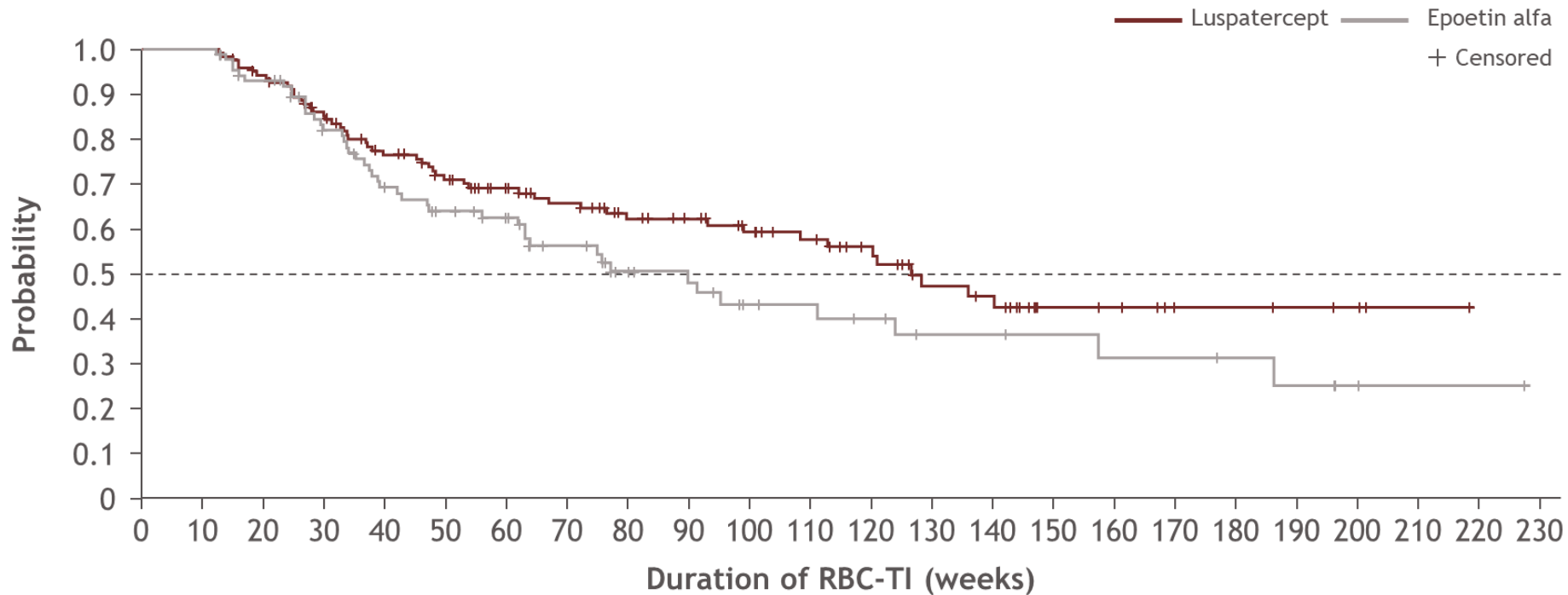
- The primary endpoint was achieved by 110 (60.4%) patients in the luspatercept arm versus 63 (34.8%) patients in the epoetin alfa arm ($P < 0.0001$)
 - Subgroup analysis of the primary endpoint showed greater response rates with luspatercept regardless of baseline TB, sEPO category, or *SF3B1* mutation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



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

COMMANDS: 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) <i>P</i> = 0.0147



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

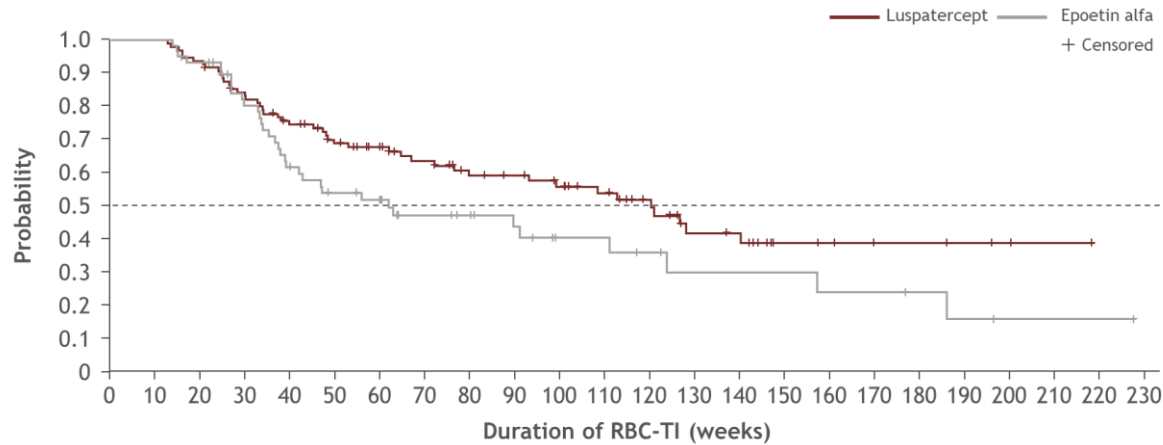
Data cutoff date: September 28, 2023.

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)

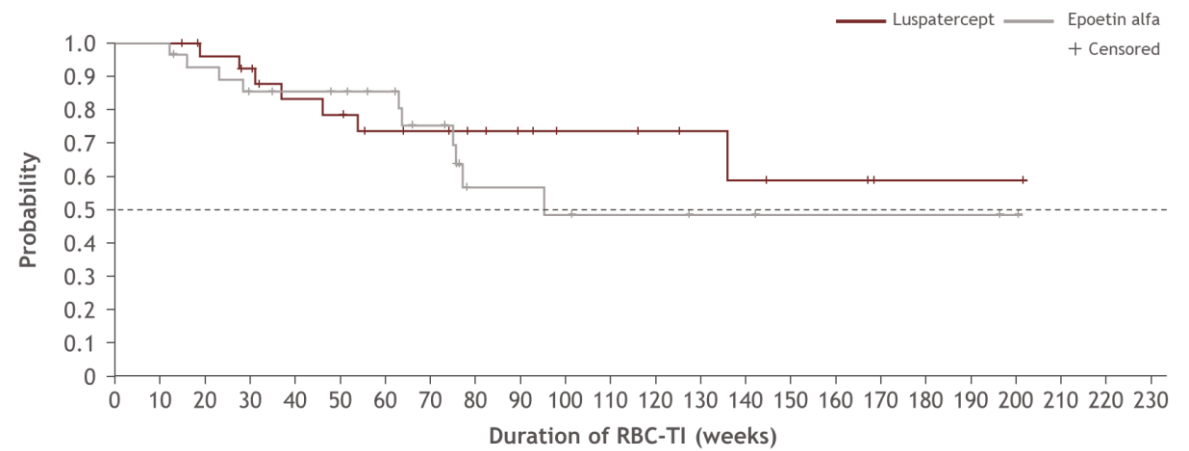
Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
RS+	120.1 (76.4-NE)	61.9 (38.9-123.9)	0.650 (0.415-1.018)
RS-	NE (135.9-NE)	95.1 (74.9-NE)	0.709 (0.269-1.866)

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		

Data cutoff date: September 28, 2023.

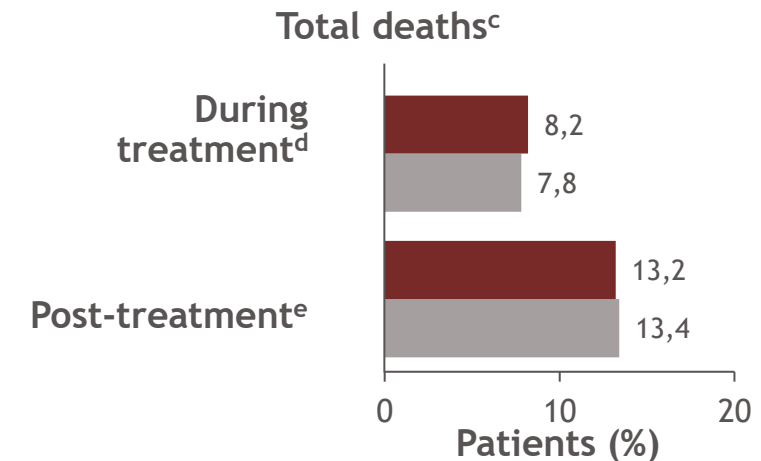
COMMANDS: summary of safety^a

- 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
- Similar proportions of patients in the luspatercept and epoetin alfa arms died at any time during the study
- Rates of progression to AML^b were low (2.7% vs 3.3% of patients for luspatercept versus epoetin alfa)

Most common TEAEs in ≥ 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,^b 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.

^aAssessed in the safety population; ^bAssessed in the ITT population; ^cTotal number of deaths includes number of deaths during treatment period and post-treatment period; ^dAny death that occurred on or after first dose of treatment until 42 days after the last dose of treatment; ^eAny death that occurred after 42 days of the last dose date of treatment.

Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes

Baseline characteristics (n=28)	% (n)
Age (median)	72 (51-94)
Gender (male)	68(19)
Race (white)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dl	8 (6.6-9.4)
Platelets (mean) x10 ⁹ /L	259 (16-814)
ANC (mean) x10 ⁹ /L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n=18)
RBC transfusion Burden	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Prior ESA treatment	89 (24)
Prior HMA treatment	42 (12)
Prior Lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

	% (n)
Overall response (n=28)	36 (10)
Hgb increase more than 1.5 g/dl in NTD or Hgb increase more than 1.5 g/dl with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	14 (4/28)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	4 (1/28)
Response in NTD (n=3)	
Hgb increase more than 1.5 g/dl	33 (1/3)
Response in LTB (n=13)	
Hgb increase more than 1.5 g/dl and RBC-TI	38 (5/13)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	15 (2/13)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	23 (3/13)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	0
Response in HTB (n=12)	
Hgb increase more than 1.5 g/dl and RBC-TI	33 (4/12)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	17 (2/12)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	8 (1/12)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	8 (1/12)

Predictors of response included:

- Prior response to luspatercept monotherapy/or frontline combination compared to primary luspatercept failure.
- Endogenous serum epo levels < 500
- *SF3B1* mutation.
- HMA/Len treatment naïve.

CONTINUOUS TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS STIMULATING AGENTS IN IMERGE PHASE 3

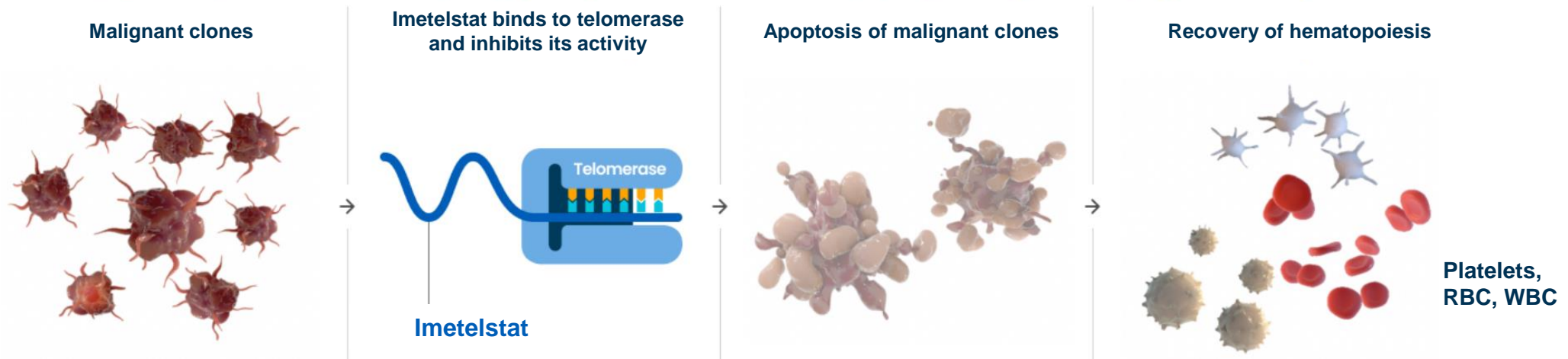
Uwe Platzbecker,¹ Valeria Santini,² Pierre Fenaux,³ Mikkael A. Sekeres,⁴ Michael Robert Savona,⁵ Yazan F. Madanat,⁶ Maria Diez-Campelo,⁷ David Valcárcel-Ferreiras,⁸ Thomas Illmer,⁹ Anna Jonášová,¹⁰ Petra Bělohávková,¹¹ Laurie Sherman,¹² Tymara Berry,¹² Souria Dougherty,¹² Sheetal Shah,¹² Qi Xia,¹² Lixian Peng,¹² Libo Sun,¹² Ying Wan,¹² Fei Huang,¹² Annat Ikin,¹² Shyamala Navada,¹² Rami S. Komrokji,¹³ Amer M. Zeidan¹⁴

¹Department of Hematology, Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany; ²MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; ³Service d'Hématologie Séniors, Hôpital Saint-Louis, Université de Paris 7, Paris, France; ⁴Division of Hematology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; ⁵Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; ⁶Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; ⁷Hematology Department, The University Hospital of Salamanca, Salamanca, Spain; ⁸Hematology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; ⁹Hematology Private Practice, Dresden, Germany; ¹⁰1st Medical Department - Hematology, General Hospital, Prague, Czech Republic; ¹¹4th Department of Internal Medicine - Haematology, Charles University Hospital, Hradec Kralove, Czech Republic; ¹²Geron Corporation, Parsippany, NJ, USA; ¹³Moffitt Cancer Center, Tampa, FL, USA; ¹⁴Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA

09/06/2023

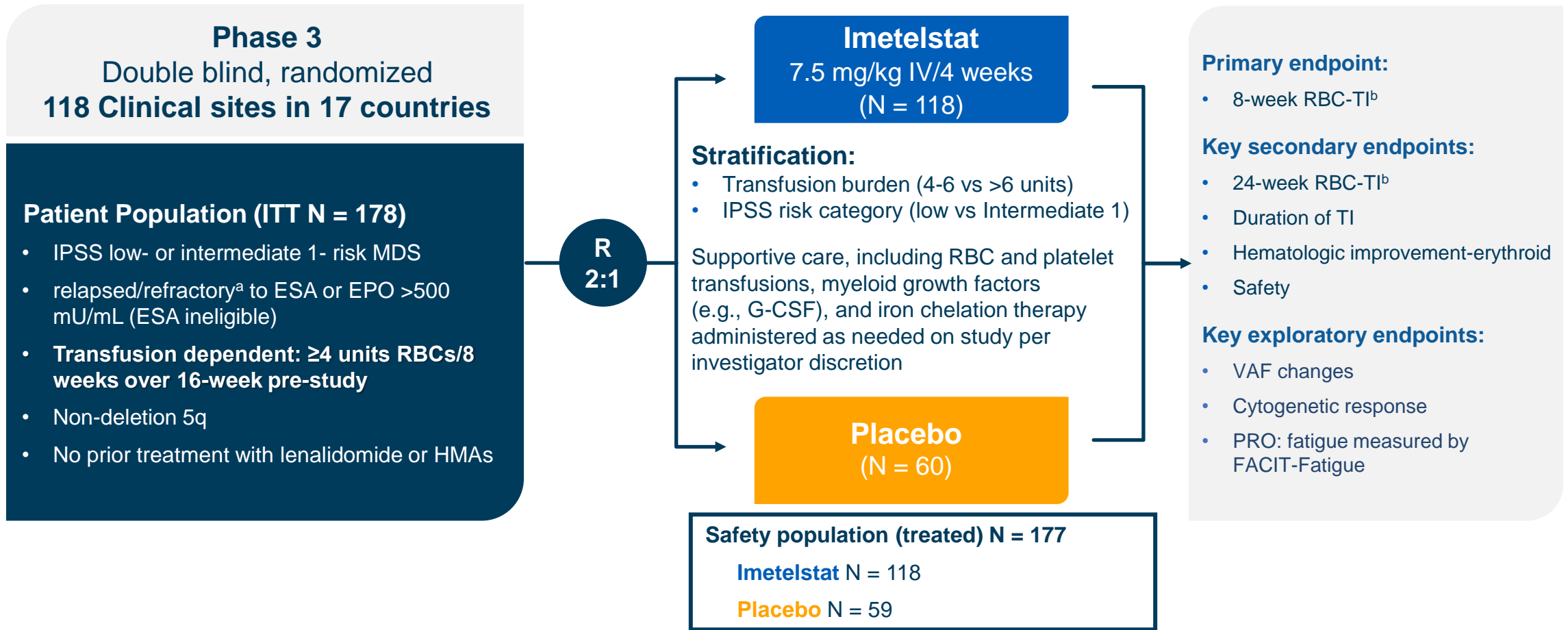
Session: s417 MPN and MDS Targeting red cells and platelets

Imetelstat in Lower Risk MDS



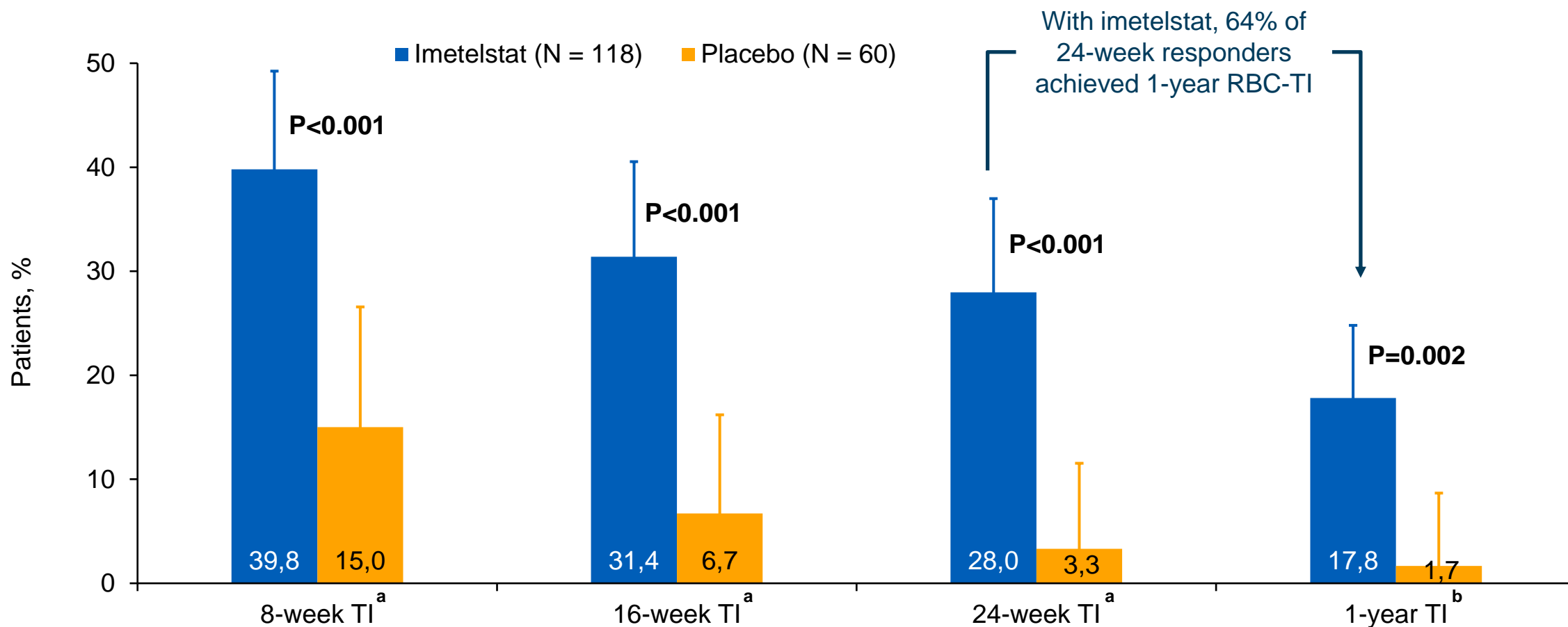
- Imetelstat is a first-in class direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis¹⁻⁴
- In the phase 2 part of the IMerge study (NCT02598661), patients with LR-MDS who were heavily RBC transfusion dependent, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA achieved durable and continuous RBC-TI when treated with imetelstat⁵
 - Specifically, 8-week RBC-TI rates were 42% with a median TI duration of 86 weeks
- This analysis reports phase 3 results from IMerge in the same patient population

IMerge Phase 3 Trial Design (MDS3001; NCT02598661)



^aReceived ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 units, epoetin beta ≥30,000 units or darbepoetin alfa 150 µg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 units/8 weeks or transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. ^bProportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI)
EPO, erythropoietin; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hgb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; R, randomization; RBC, red blood cell; TI, transfusion independence, VAF, variant allele frequency.

Higher Rates of Longer-Term Duration of RBC TI Observed With Imetelstat vs Placebo, Including 1-year RBC TI With Additional 3 Month Follow-up

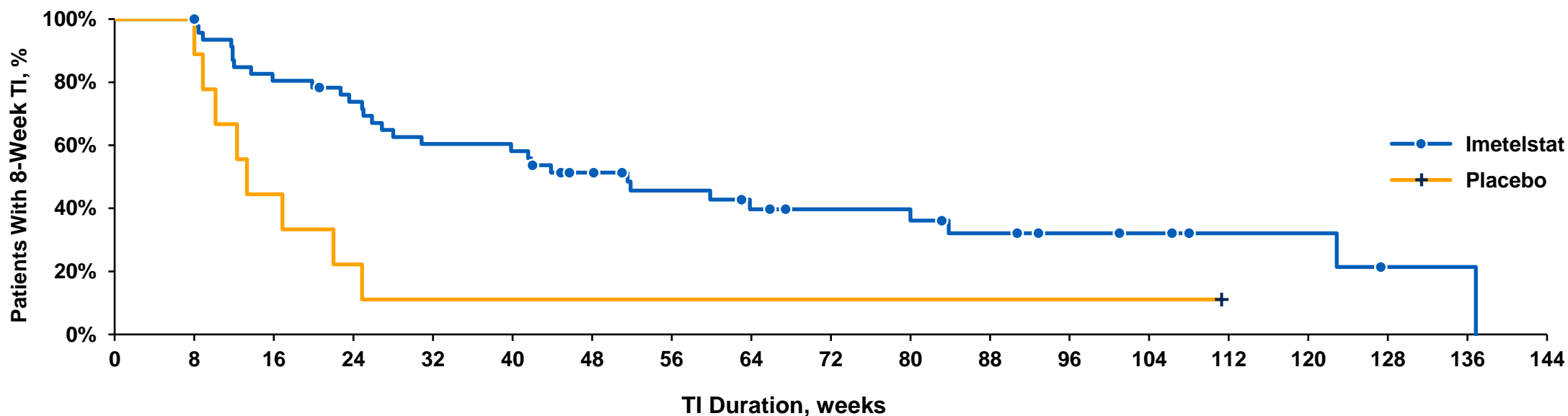


^aData cutoff: October 13, 2022. ^bData cutoff: January 13, 2023.

P-values were determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥ 4 to ≤ 6 vs. >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline International Prognostic Scoring System risk category (low vs. intermediate-1) applied to randomization. RBC, red blood cell; TI, transfusion independence.

Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)	HRa (95%CI)	P-Value
Median duration of RBC-TI, weeks (95% CI)	51.6 (26.9–83.9)	13.3 (8.0–24.9)	0.23 (0.09–0.57)	<0.001



Patients, N

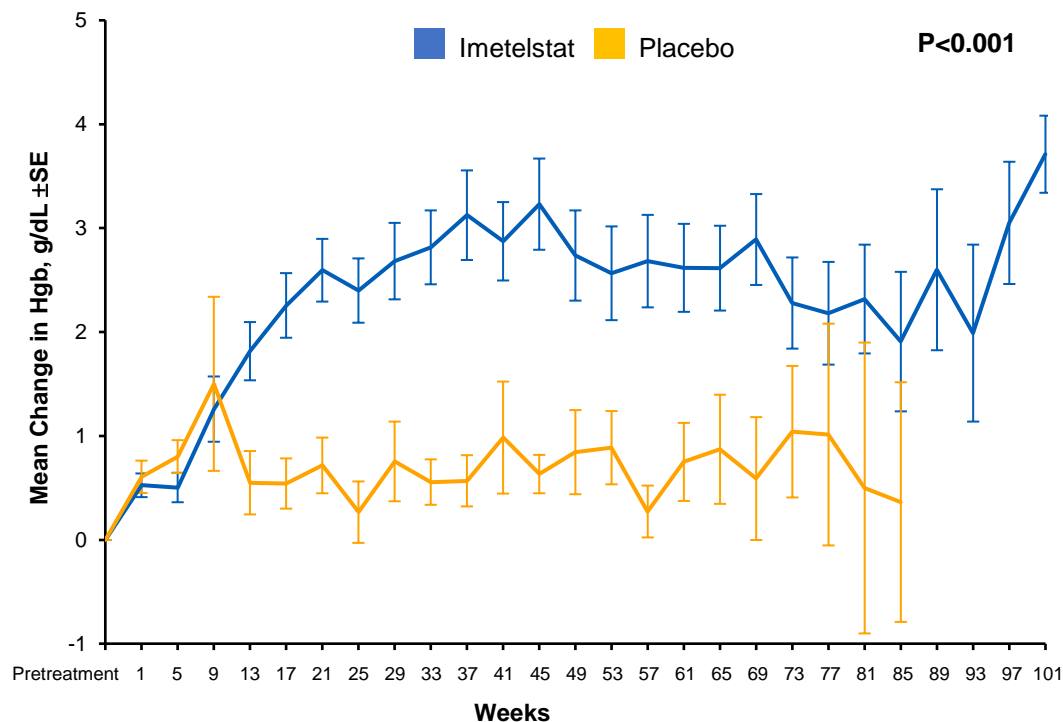
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

Data cutoff: October 13, 2022.

^aHR (95% CI) from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≥ 4 to ≤ 6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. ^bP value (2-sided) for superiority of imetelstat vs placebo in HR based on stratified log-rank test. HR, hazard ratio; IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

Significant and Sustained Increase in Hemoglobin Among Patients Treated With Imetelstat

Mean Change in Hgb Over Time^b



Patients, N

	118	59	53	54	47	42	48	48	43	43	31	37	31	35	32	25	26	24	23	21	19	18	11	11	9	9	5	
Imetelstat	60	37	29	17	16	18	15	8	10	10	11	7	3	9	8	9	7	7	5	5	4	2	4					
Placebo																												

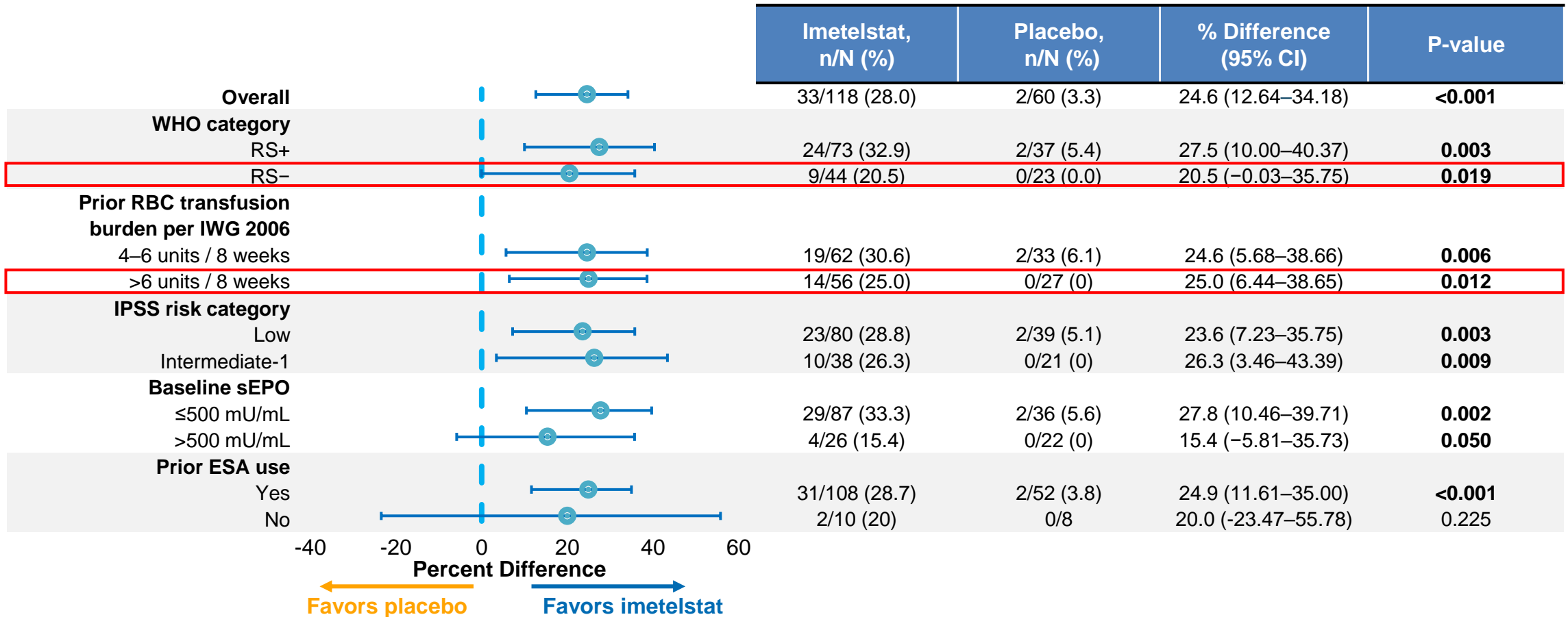
8-Week TI Responders ^a	Imetelstat (N = 47)	Placebo (N = 9)
Median Hgb rise, g/dL (range)	3.6 (-0.1 to 13.8)	0.8 (-0.2 to 1.7)
Median Hgb peak, g/dL (range)	11.3 (8.0–21.9)	8.9 (7.9–9.7)

Data cutoff: October 13, 2022.

^aAmong patients achieving 8-week TI, analysis performed during TI. Hgb rise is defined as the maximum Hgb value in the longest TI interval excluding the first 2 weeks minus the pretreatment Hgb level. ^bMean changes from the minimum Hgb of the values that were after 14 days of transfusions in the 8 weeks prior to the first dose date are shown. P-value based on a mixed model for repeated measures with Hgb change as the dependent variable, week, stratification factors, minimum Hgb in the 8 weeks prior to the first dose date, treatment group, and treatment and week interaction term as the independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

Hgb, hemoglobin; RBC, red blood cell; SE, standard error; TI, transfusion independence.

Comparable 24-Week RBC TI Rate Across Key LR-MDS Subgroups



- Similar trends were observed across subgroups for 8-week RBC TI rates

Data cutoff: October 13, 2022.

P-values were determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs. intermediate-1) applied to randomization.

IPSS, International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TI, transfusion independence.

Consistent With Prior Clinical Experience, the Most Common AEs Were Hematologic

- Grade 3–4 thrombocytopenia and neutropenia were the most frequently reported AEs, most often reported during Cycles 1–3
 - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low grade
- No cases of Hy’s Law or drug-induced liver injury observed
 - The incidence of grade 3 liver function test laboratory abnormalities was similar in both treatment groups

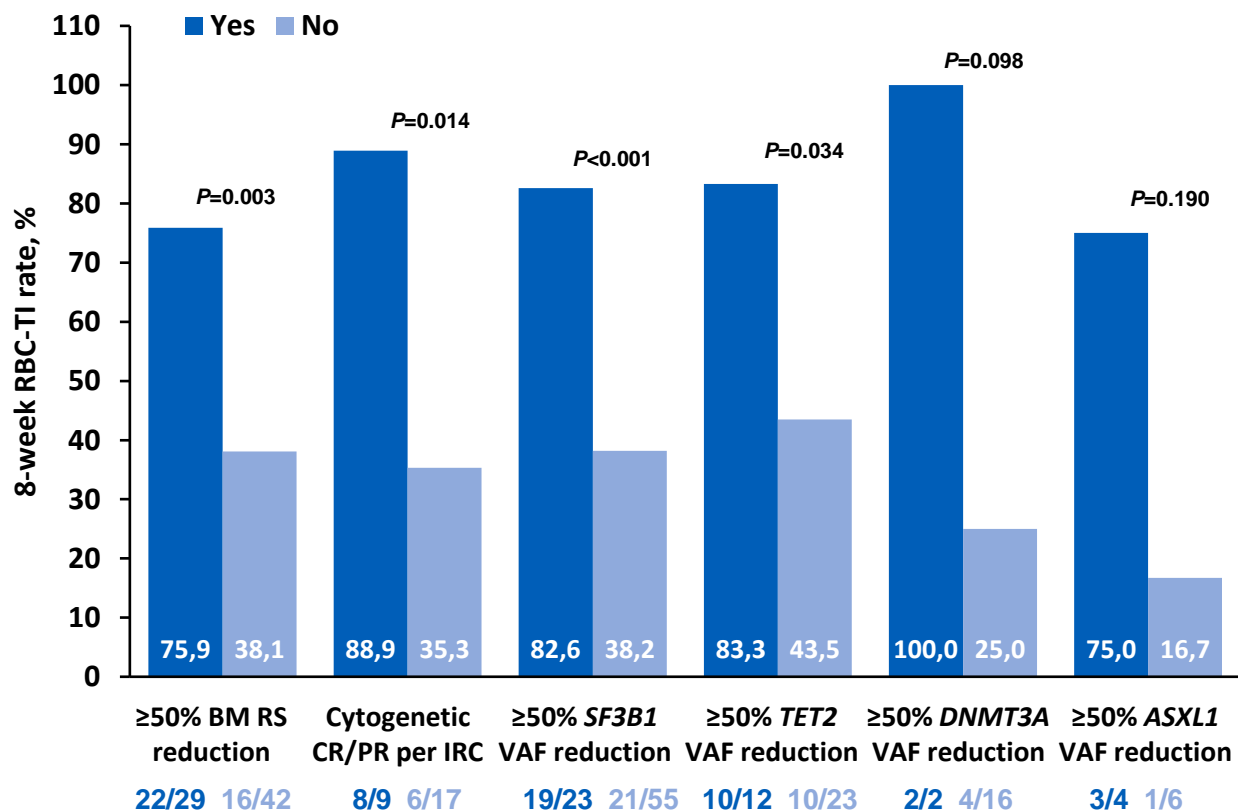
AE (≥10% of patients), n (%)	Imetelstat (N = 118)		Placebo (N = 59)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)
Leukopenia	12 (10)	9 (8)	1 (2)	0
Other				
Asthenia	22 (19)	0	8 (14)	0
COVID-19	22 (19) ^a	2 (2) ^b	8 (14) ^a	3 (5) ^b
Headache	15 (13)	1 (1)	3 (5)	0
Diarrhea	14 (12)	1 (1)	7 (12)	1 (2)
ALT increased	14 (12)	3 (3)	4 (7)	2 (3)
Edema peripheral	13 (11)	0	8 (14)	0
Hyperbilirubinemia	11 (9)	1 (1)	6 (10)	1 (2)
Pyrexia	9 (8)	2 (2)	7 (12)	0
Constipation	9 (8)	0	7 (12)	0

Data cutoff: October 13, 2022.

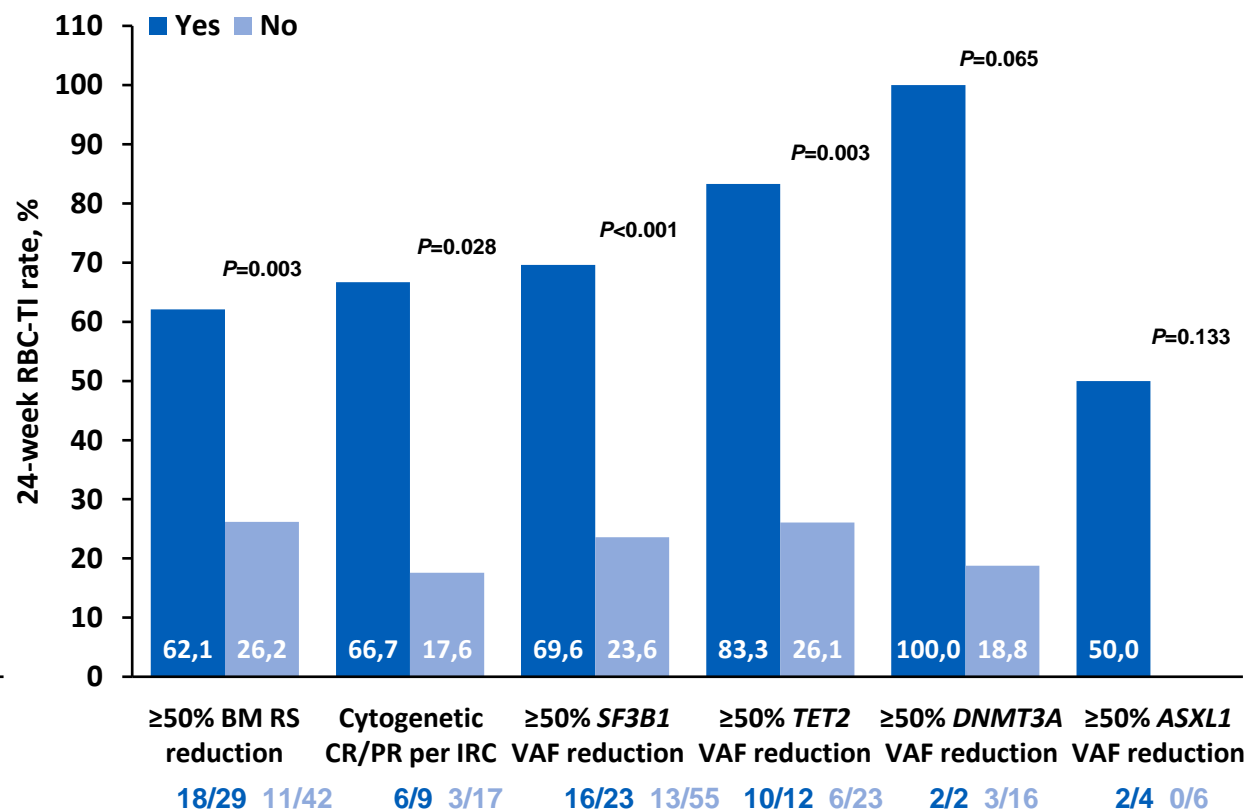
^aIncluded COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. ^bOnly COVID-19 pneumonia events were grade 3–4 COVID-19. AE, adverse event; ALT, alanine aminotransferase.

8-Week and 24-Week RBC-TI Correlated With Reduction in RS+ Cells, Cytogenetic Responses, and VAF Reduction in Patients Treated With Imetelstat

8-Week RBC-TI Correlations



24-Week RBC-TI Correlations



Note: P value calculated using Fisher exact test between yes vs no in each outcome.

ASXL1, additional sex combs like-1; BM, bone marrow; CR, complete response; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IRC, independent review committee; PR, partial response; RBC, red blood cell; RS, ring sideroblasts; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

Low-dose HMAs in Lower-Risk MDS: Response Rates

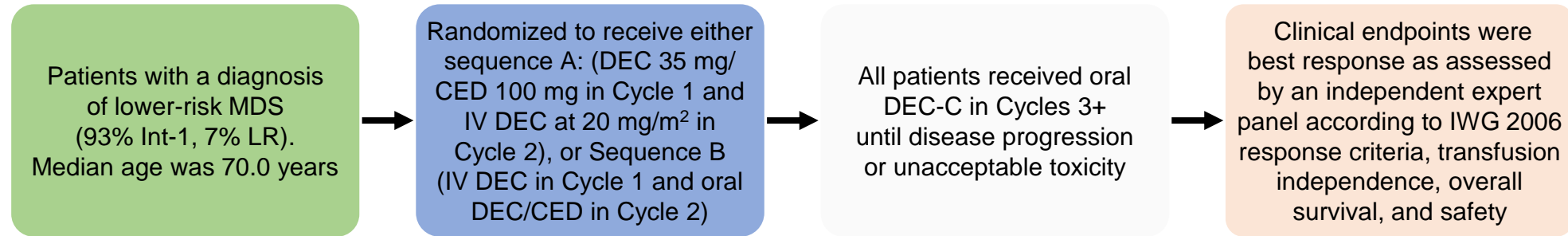
Response, %	Decitabine (n = 70)	Azacitidine (n = 39)	P value
ORR	70	49	0.03
CR	37	36	0.90
mCR	9	5	NR
HI	24	8	NR
	(n = 28)	(n = 16)	
CCyR	25	6	0.12
PCyR	36	19	
CCyR + PCyR	61	25	0.02

Response, %	Decitabine (n = 70)	Azacitidine (n = 39)	P value
Blasts ≥ 5%	(n = 21)	(n = 11)	
ORR	100	36	< 0.001
CR	57	18	
Blasts < 5%	(n = 45)	(n = 27)	
HI: ≥ 1 lineage	36	48	
HI: all lineages	22	26	
TD at baseline	(n = 38)	(n = 19)	
TI at response	32	16	0.20

- Strongest predictors of response included BM blasts ≥ 5%, MDS/MPN or CMML diagnosis, high MDA LR-MDS score, and IPSS Intermediate-1 risk

This symposium may include information about investigational products and/or uses that are not approved for use in any country or in the country of your residence.

ASCERTAIN Study: A Longer-term Follow-up in LR-MDS



- **CR rate was 23% and marrow CR was 26%**
 - 13% had hematologic improvement
- **ORR was 57%**
- **Safety profile was consistent with that of decitabine**
 - TEAEs of CTCAE \geq Grade 3, included cytopenias (neutropenia [59%], thrombocytopenia [58%], anemia [48%], leukopenia [26%]), febrile neutropenia (32%), and pneumonia (19%)

CED, cedazuridine; CR, complete remission; DEC, decitabine;
DEC-C; decitabine/cedazuridine; ORR, overall response rate.

This symposium may include information about investigational products and/or uses that are not approved for use in any country or in the country of your residence.

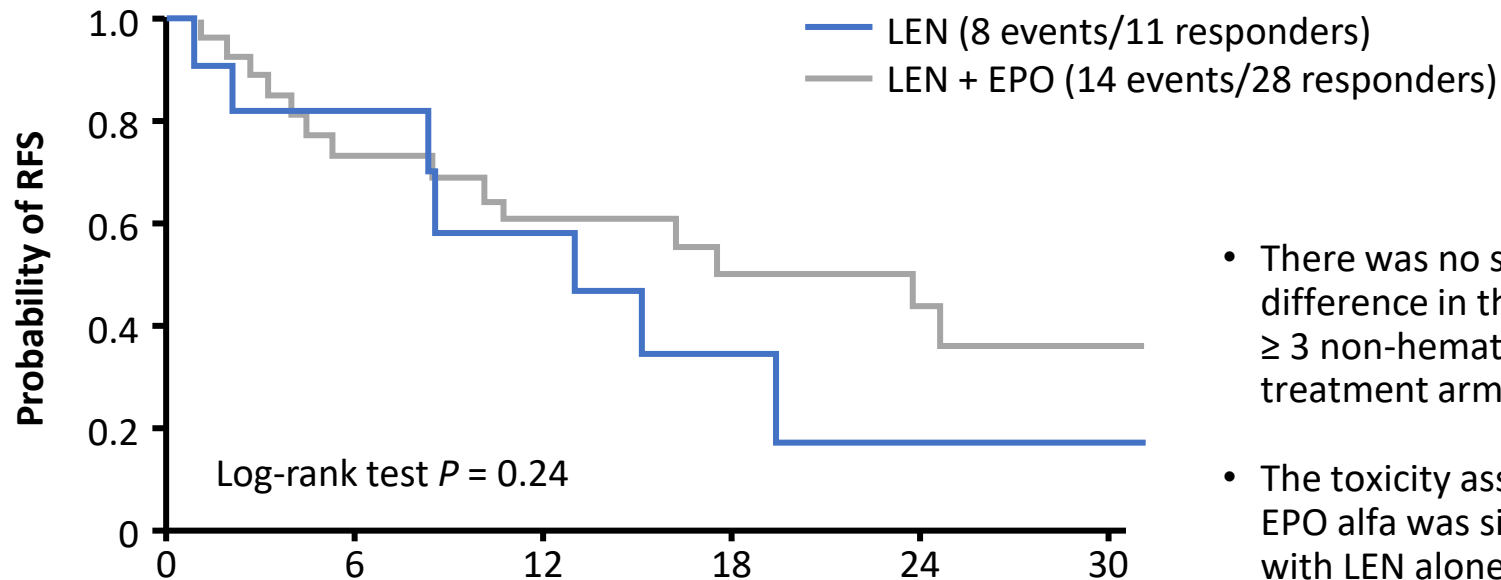
Immunosuppressive Therapy (IST)

- One course ATG ± CSA
- Positive variable for IST response^{1,2}
 - Age is the strongest variable for response
 - HLA-DR 15 status
 - Short Duration of disease.
 - Low transfusion burden
 - Trisomy 8
 - Hypoplastic MDS
 - PNH clone
- Negative predictors of response
 - Bone marrow fibrosis
 - Del(5q)
 - SF3B1
- Responses are durable and trilineage responses are observed³

1. Saunthararajah Y et al. *Blood*. 2002;100(5):1570-1574; 2. Sloan EM et al. *J Clin Oncol*. 2008;26(15):2505-2511; 3. Sloan E et al. ASH 2004. Abstract 1431.

Phase III ECOG 2905 Study of Lenalidomide ± EPO Alfa in Lower-risk MDS Non-del(5q) Refractory to Erythropoietin: RFS

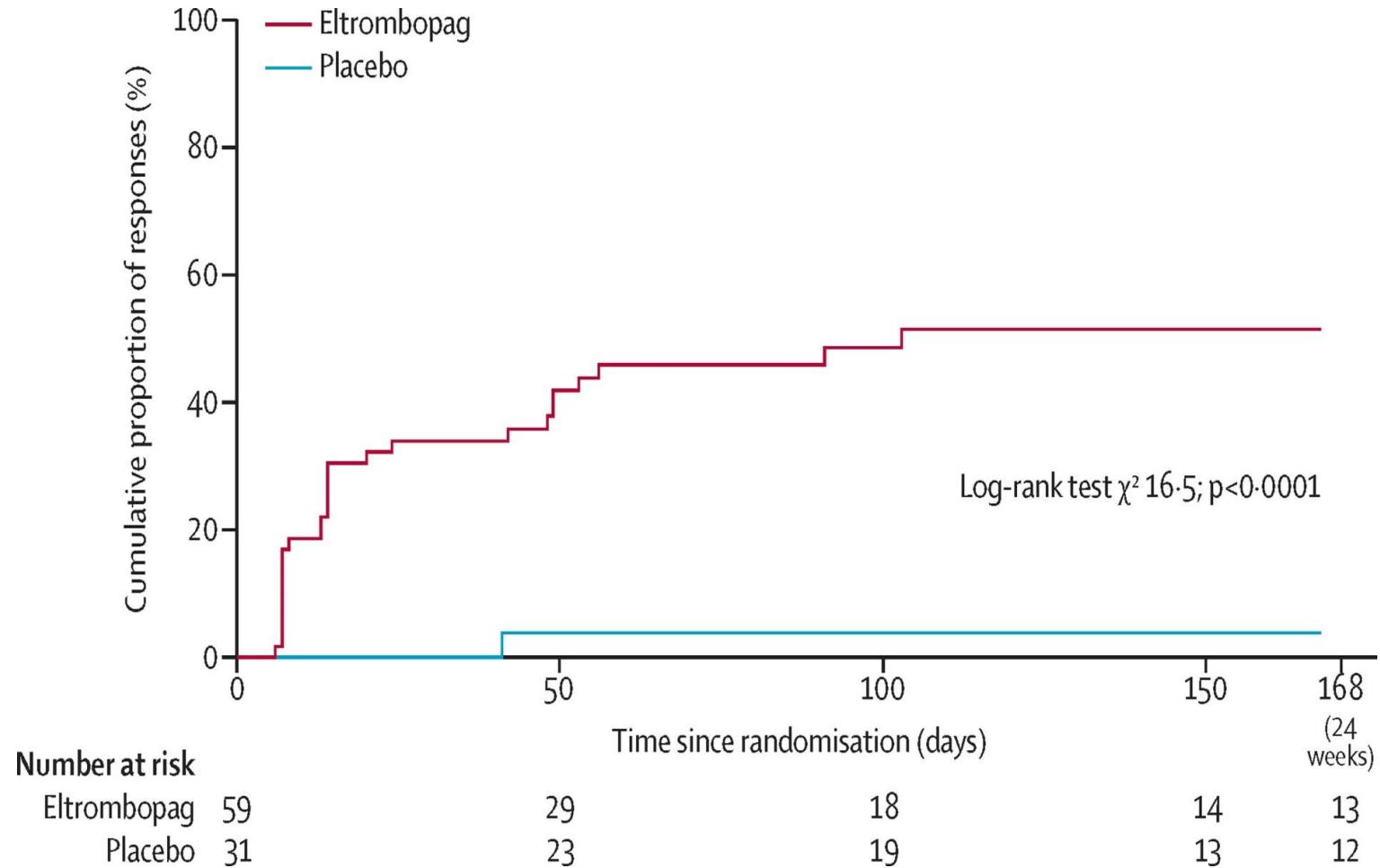
Randomized, Phase III trial of patients with Low- or Intermediate-1 risk by IPSS; symptomatic anemia either untransfused with hemoglobin < 9.5 g/cL or RBC-TD (N = 247; n = 195 evaluable)



- There was no statistically significant difference in the frequency of Grade ≥ 3 non-hematologic AEs between treatment arms
- The toxicity associated with LEN and EPO alfa was similar to treatment with LEN alone

Patients at risk, n		Months from major erythroid response					
	0	6	12	18	24	30	
LEN	11	8	5	2	1	1	
LEN + EPO	28	18	13	10	6	5	

Eltrombopag Responses



Targeting R/R *IDH1/IDH2*^{mut} MDS with ivosidenib/enasidenib

IDIOME: phase 2 study of Ivo in 3 cohorts (N=26)¹

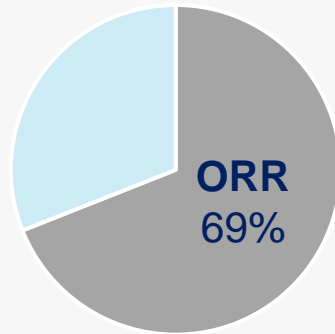
- **A:** HR-MDS, failed AZA (n=13)
- **B:** Untreated HR-MDS (n=11)
- **C:** LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

Differentiation syndrome, n=4,
febrile neutropenia, n=1



Ivosidenib in R/R *IDH1/IDH2*^{mut} MDS³

Updated results of a phase 1 dose-escalation study (500 mg QD)

Efficacy outcomes	N=16	Safety outcomes	N=16
ORR	81%	Grade ≥3 AEs	69%
CR	44%	Grade ≥3 TRAEs	13%
mCR	31%	SAEs	44%
PR	6%		
HI	69%		
12-month duration CR+PR	60%		

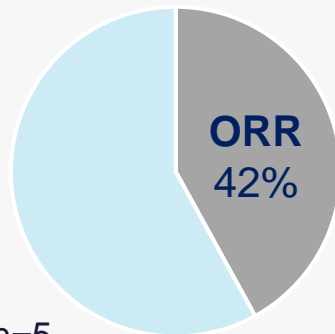
IDEAL: phase 2 study of Ena in 3 cohorts (N=26)²

- **A:** HR-MDS, failed AZA (n=11)
- **B:** Untreated HR-MDS (n=9)
- **C:** LR-MDS, failed ESA (n=6)

Median follow-up: 8.6 months

Median OS: 17.3 months

Differentiation syndrome, n=3;
nausea/diarrhea, n=4; thrombocytopenia, n=5

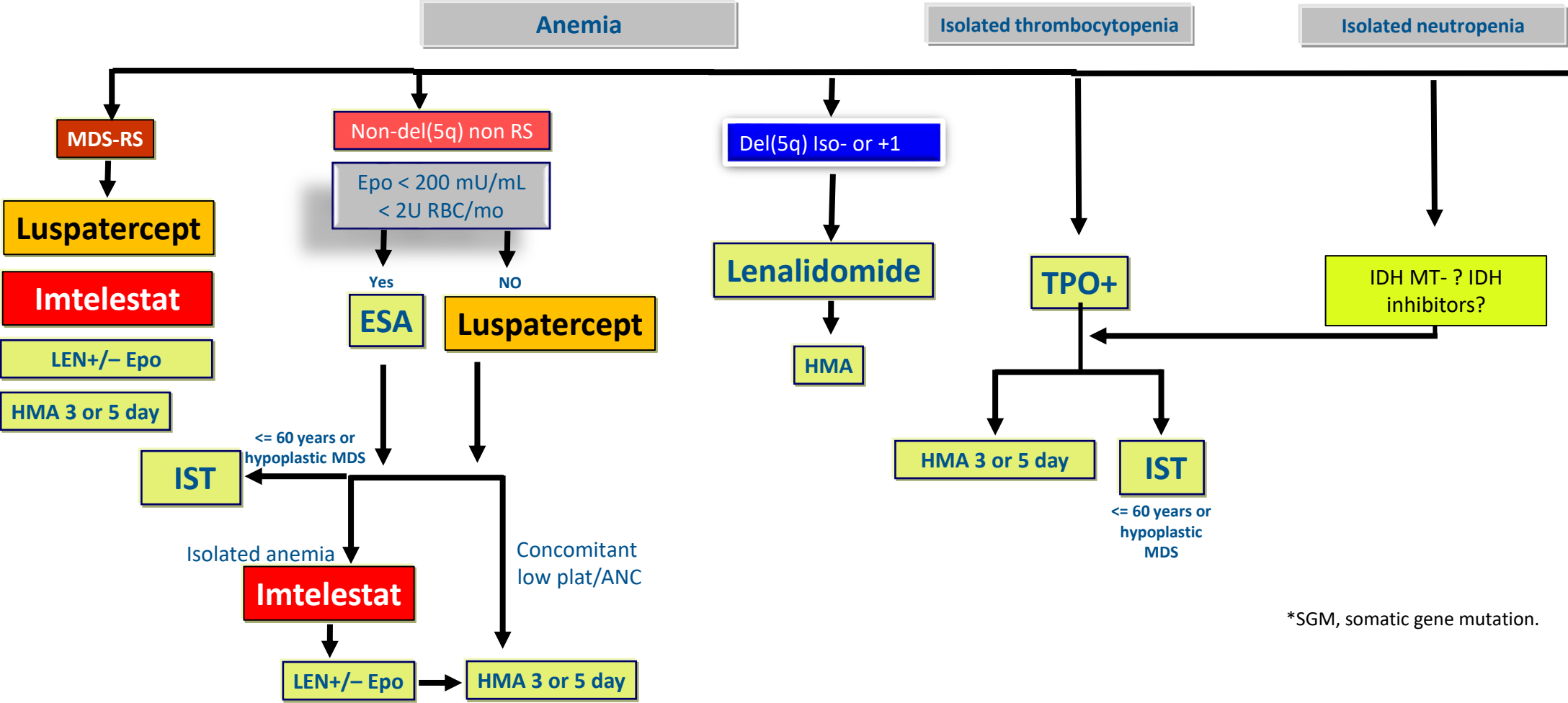


- Both studies reported 50% response in LR-MDS

1. Sebert M, *et al.* ASH 2021. Abstract 62 (oral presentation);

2. Ades L, *et al.* ASH 2021. Abstract 63 (oral presentation); 3. Sallman DA, *et al.* ASCO 2022. Abstract 7053 (Poster 284)

How would I Manage LR-MDS in 2024



*SGM, somatic gene mutation.

- Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features by IPSS-M.
- Iron chelation should be considered in patients with evidence of iron overload.

Thank You
Rami.Komrokji@moffitt.org

Moffitt MDS team: Only perfect counts !!!

Acknowledgements:

- Our patients and their caregivers
- Moffitt MDS team